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**ASSOCIATION OF ARTERIAL HYPERTENSION, DIABETES
MELLITUS AND INFLAMMATION WITH CANCER
INCIDENCE AND MORTALITY**

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ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
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Chapter 1

Introduction

1.1 Specific aims

Cancer is a major public health problem worldwide and is the second leading cause of death. The last release of the GLOBOCAN database (September 2018) predicts 18 million cancer cases and 9.6 million cancer related deaths for 2018 (1). The traditional focus and goal of cancer epidemiology has been the determination of the incidence and mortality rates of cancer in different populations and subgroups, as well as the identification of risk factors for the purpose of disease prevention and control through primary prevention and screening interventions. From an epidemiologic perspective, a risk factor is anything that increases or decreases the probability that an individual will develop cancer. These risk factors can include exogenous factors such as demographic characteristics, lifestyle or behavioural factors and endogenous factors such as genetic mutations that have been identified as predisposing a person for cancer development. Most cancers undoubtedly arise from a combination of endogenous and exogenous factors that interact to define an individual's risk for developing cancer. The main goal of this thesis is the investigation of potential associations between hypertension, T2DM and inflammation and cancer incidence. The choice of these particular risk factors is based on their high prevalence and potential implication for cancer development. The following specific aims were designed to answer the aforementioned goal:

1. Examine the association of blood pressure with the development of incident cancer at all anatomical sites:
 - a. Estimate hazard ratios (HRs) using delayed-entry Cox proportional hazards models for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean

blood pressure (MBP), hypertension and antihypertensive treatment in relation to cancer risk by anatomical site.

- b. Test for statistical interactions according to age, sex, body mass index (BMI), smoking status, alcoholic beverages intake and use of antihypertensive treatment.
- c. Perform sensitivity analyses, excluding the first two years of follow-up.

For this aim we used data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which is a prospective cohort of more than 500,000 participants in 10 European countries.

2. Investigate the association of type 2 diabetes (T2DM) and the risk of developing cancer:
 - a. Conduct the evidence search process of the relevant literature in Pubmed.
 - b. Perform an umbrella review of the evidence across systematic reviews and meta-analyses of relevant observational studies. Calculate the summary effect and the 95% confidence interval using both fixed and random effects inverse variance weighted methods. Assess the between study heterogeneity with the Cochran's Q test and the I^2 metric of inconsistency. Assess possibility for existence of bias. Grade the strength of evidence..
 - c. Assess the methodological quality of all the meta-analyses included in this study using the AMSTAR tool, an 11-item scale from which positive responses are summed to obtain an overall quality score.
 - d. Conduct an additional umbrella review of Mendelian randomization studies that assessed cancer incidence according to genetic instruments for T2DM, fasting insulin, glucose levels or glycated haemoglobin (HbA1C).

3. Examine the potential association between inflammation and colorectal cancer, through assessment of the pre-diagnostic interleukin-6 (IL-6) concentrations and the subsequent risk of colorectal cancer:
 - a. Estimate matched odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) using conditional logistic regression models in a nested case-control study within the CLUE II cohort of Washington County, MD, USA.
 - b. Perform a meta-analysis of prospective epidemiological studies to summarize the evidence and study its heterogeneity.

For this aim we used data from the CLUE II cohort and searched the relevant literature in Pubmed.

This proposed dissertation was designed to provide insight into the contribution of established (T2DM and inflammation) and suspected (hypertension) risk factors for carcinogenesis, to investigate potential biases of the existing literature and to present potential unbiased evidence for associations between T2DM and cancer.

The following sections of the introduction provide information on the process of cancer and the descriptive epidemiology of cancer with a focus on inflammation in general, hypertension and T2DM).

1.2 Carcinogenesis

Carcinogenesis is not a distinct event but rather a process that occurs over time. It is a cumulative continuum of discrete cellular changes resulting in uncontrolled proliferation and

growth. Thus, the development of fully malignant cancers requires many independent events. Eight Hallmarks of cancer have been proposed, defined as ‘distinctive and complementary capabilities that enable tumour growth and metastatic dissemination’(2, 3):

1. Sustaining proliferative signalling
2. Evading growth suppressors
3. Resisting cell death
4. Enabling replicative mortality
5. Induced angiogenesis
6. Tissue invasion and metastasis
7. Deregulating cellular energetics
8. Avoiding immune destruction

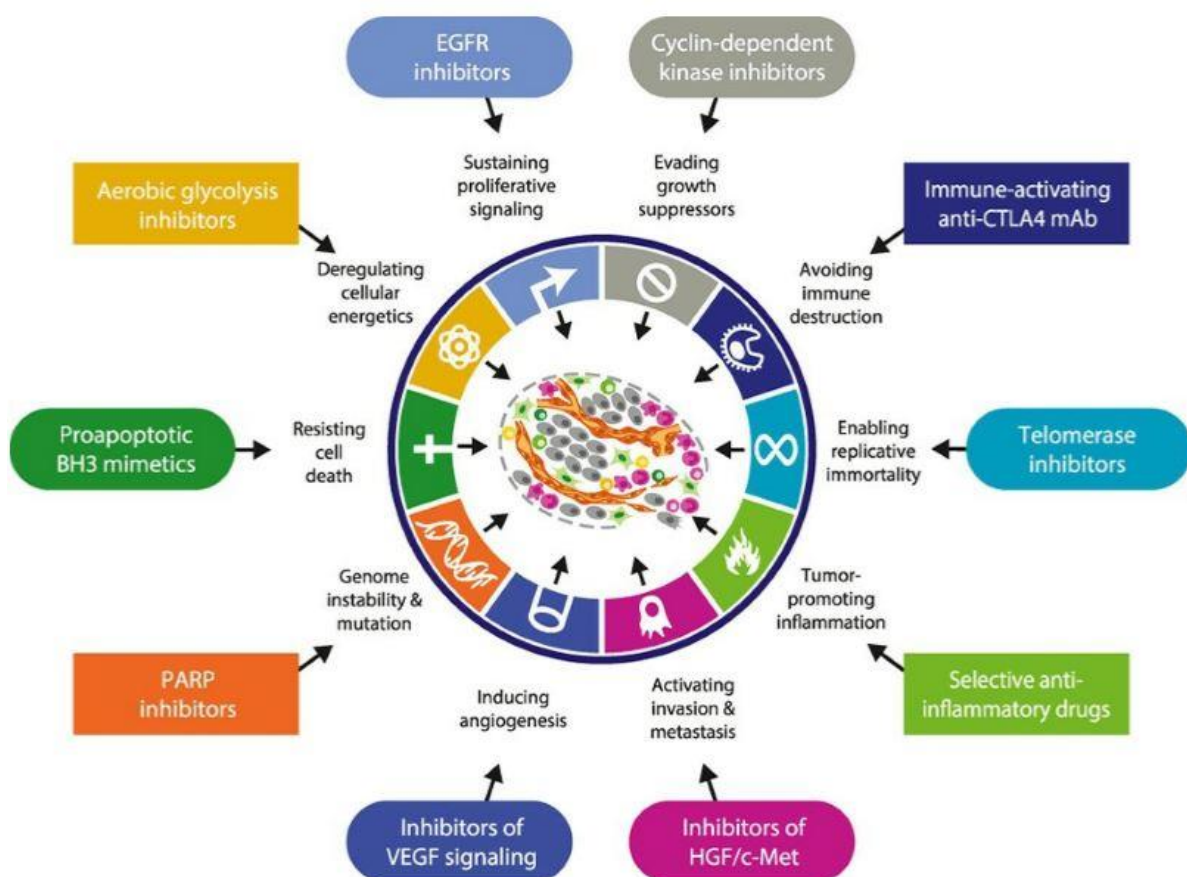


Figure 1: The hallmarks of cancer

The first three of these “acquired capabilities” involve mutations within the mitogenic signaling, cell cycle, and cell-death pathways. The fourth category involves the acquisition of cellular immortality in tumors. Normal cells are limited in the number of times that they can divide, even when they are provided with all of the normal mitogenic stimuli required for cell division. In contrast, many cancer cells have apparently limitless potential to divide. One fundamental mechanism that limits human cell division involves the ends of chromosomes, which are called “telomeres.” Telomeres normally protect the ends of chromosomes, and they shorten with each cell division. Thus, the length of a cell’s telomeres reflects the number of divisions it has undergone. Eventually the telomeres are shortened to a point at which they can no longer protect the chromosome ends; this leads to a condition termed “crisis” and, ultimately, to cell death. Unlike normal cells, cancer cells maintain their telomere length during cell division. This usually results from expression of the enzyme telomerase that adds DNA back to the telomere. Telomerase activity can be detected in 85 to 90% of cancers, and the remaining tumors maintain their telomeres through a mechanism involving recombination.

The fifth capability of induced angiogenesis reflects the fact that tumors often outgrow their blood supply and must actively recruit vasculature to grow. In normal tissues, the development of new blood vessels is highly regulated by both positive and negative signals. Tumor cells promote angiogenesis by upregulating the pathways that promote blood vessel formation (e.g., increased expression of growth factors such as vascular endothelial and fibroblast growth factors) and by reducing the activity of inhibitory pathways. The sixth hallmark is tissue invasion and metastasis, which is critically important because metastasis accounts for most cancer fatalities. Specific gene products are associated with the ability of tumor cells to

metastasize to different organ sites. The last two emerging hallmarks are deregulating cellular energetics and avoiding immune destruction.

Moreover, there are further enabling characteristics of cancer cells that facilitate the acquisition of these hallmarks. The first characteristic is genomic instability, which drives the acquisition of the multiple mutations required for multistep tumorigenesis. Mammalian cells use three major DNA repair pathways to maintain genomic integrity. Mutations that disrupt these pathways cause genetic instability and are associated with diseases characterized by cancer predisposition. Ultraviolet light-induced nucleotide dimers and other DNA adducts are recognized and repaired by the nucleotide excision repair (NER) pathway. DNA recombination repair is involved in the restoration of double-stranded breaks induced by ionizing radiation and radiomimetic agents. Finally, the DNA mismatch repair pathway (MMR) corrects errors during DNA replication by removing the mismatched strand and enabling subsequent repair of the DNA. Microsatellite instability (MSI) is resulting from the accumulation of mismatch mutations in the genome, especially at regions of repetitive DNA known as microsatellites, driven by an underlying defect in the MMR pathway (Figure 2).

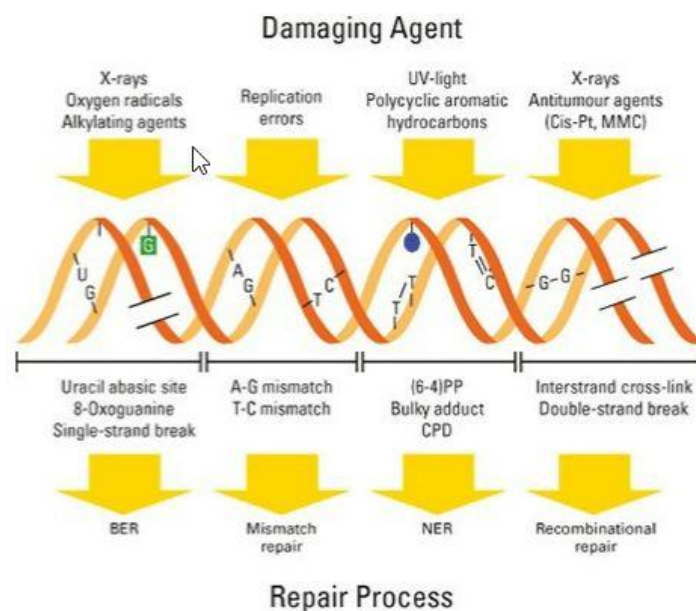


Figure 2: DNA lesions and repair mechanisms

The second enabling characteristic concerns epigenetic effects. Epigenetic gene regulation, or epigenetics, refers to heritable, higher-order processes that can profoundly influence gene expression without mutating DNA. Chromatin is highly dynamic and undergoes remodeling via two central epigenetic processes, histone modification and DNA methylation (4). DNA is compacted into chromatin by winding around proteins called “histones,” which maintain the DNA in nucleosomal complexes (Figure 3). Histones are modified covalently (e.g., acetylation, methylation, phosphorylation, and ubiquitylation) by changes in subunit composition (e.g., replacement of core histones by specialized histones) and by repositioning. Each of these modifications renders DNA more or less accessible to RNA polymerase (Figure 3)(5, 6) . Histone methylation occurs on lysine residues and is controlled by opposing methylating and demethylating enzymes: methylation on some sites facilitates transcription, whereas on others transcription is repressed (7) . Histone acetylation is also regulated by groups of opposing enzymes: acetylation is found in actively transcribed genes, whereas histone deacetylation correlates with repression. Epigenetic regulation also involves DNA modifications, most commonly cytosine methylation within cytosine–guanosine (CG) dinucleotides(8) . DNA regions that contain many CGs are termed “CpG islands,” and their methylation represses transcription. Indeed, promoter methylation is one way that cancer cells inactivate tumor suppressor genes. There is widespread cross talk between epigenetic modifications of DNA and histones, and genomewide analyses are revealing how complex epigenetic “marks” establish differential gene expression (4, 9).

The third enabling characteristic is tumour promoting inflammation, which reflects the rapidly advancing concept that inflammatory responses can actually facilitate tumour initiation and progression (2, 3).

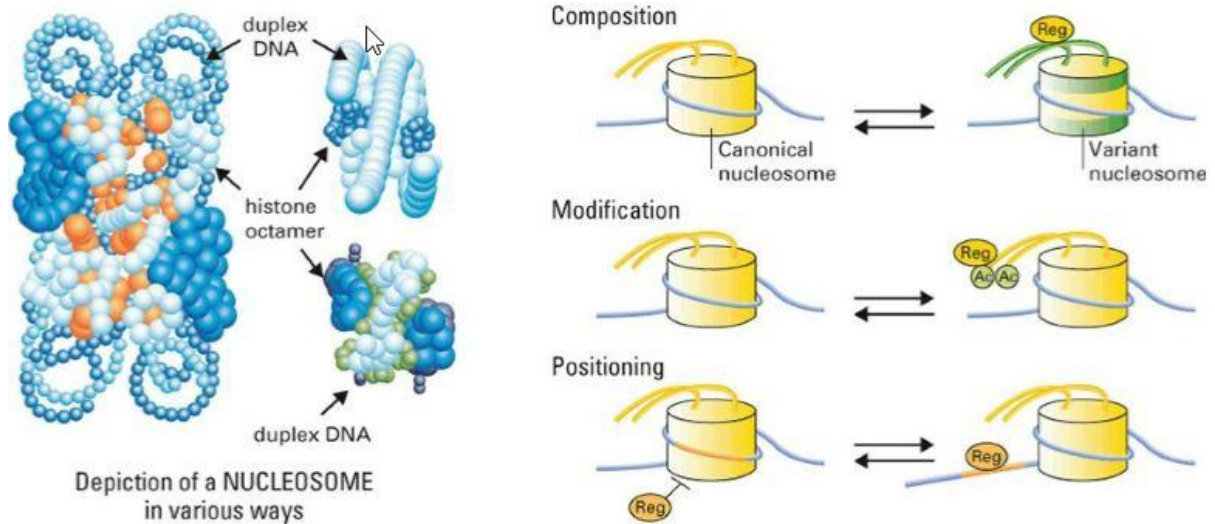


Figure 3: Nucleosome structure and regulation

The process through which a normal cell is divided in two equivalent daughter cells is called cell cycle. Cells cycles are divided into four phases that coordinate cell growth, DNA replication and cell division. G1 phase is a period of growth between mitosis and the onset of DNA synthesis during which the cells integrate mitogenic signals and commit to the onset of DNA replication. S phase is the period of DNA synthesis during which a cell replicates its genomic complement. G2 phase follows the S phase and is a second period of growth. It is critically important that cells execute the cell-division cycle faithfully, and mutations in the genes that regulate the cell cycle are among the most common genetic changes in cancer cells (10, 11). Progression through the cell cycle is promoted by cyclin-dependent kinases (CDKs), which are regulated positively by cyclins and negatively by CDK inhibitors (CDKIs). The different steps of human cell cycle are presented graphically in figure 4.

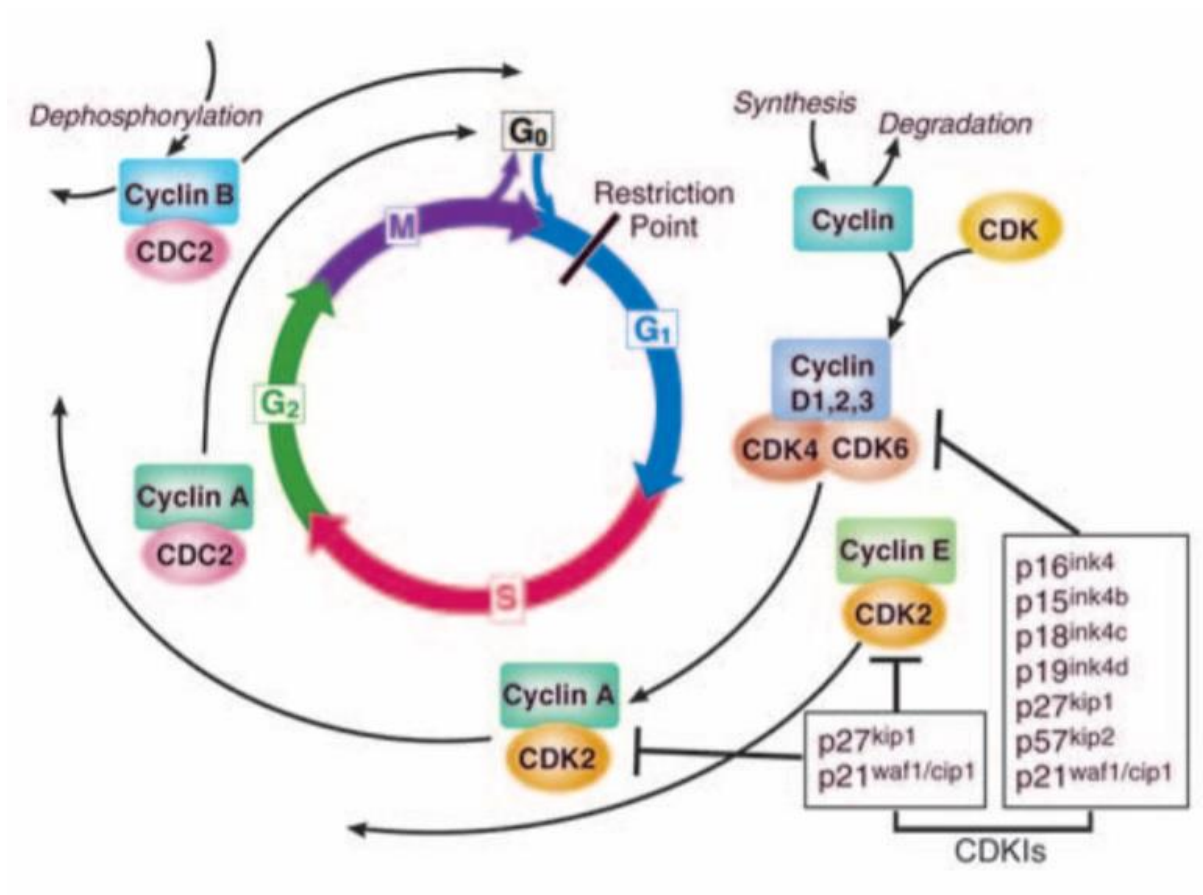


Figure 4: The cell cycle (12)

The best known G₁ CDK substrate is the retinoblastoma protein (pRb), and the Rb pathway is muted in most cancers. Early in the G₁ phase, unphosphorylated pRb sequesters E2F transcription factors and represses the expression of cell-cycle genes. As the cycle progresses, Rb becomes phosphorylated by cyclin CDKs, which releases E2F and promotes the transcription of genes that drive cell proliferation (figure 5)

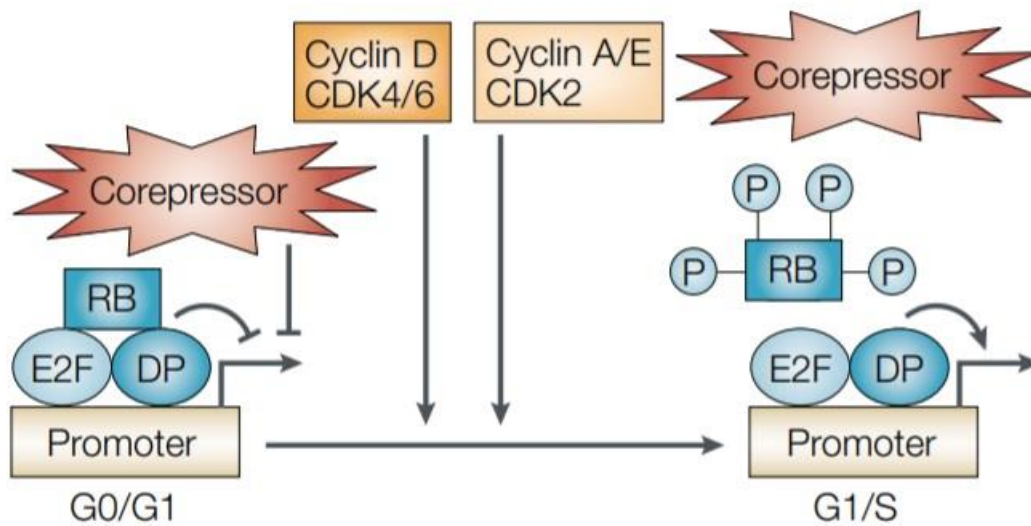


Figure 5: Rb and E2F function (13)

There are three types of genes that act as regulators of the cell cycle and based on their functions they can be classified as proto-oncogenes, tumour-suppressor genes, and DNA repair genes, and mutations in these can accelerate or obstruct carcinogenesis.

Oncogenes are a group of muted genes (eg. Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER-2), Rat Sarcoma (RAS), Rapidly Accelerated Fibro sarcoma (RAF), MYC, B-Cell Lymphoma 2 (BCL-2), Anaplastic Lymphoma Kinase (ALK), Breakpoint Cluster Region/Abelson Murine Leukemia (BCR/ABL)), which can contribute to neoplasia when their functions are altered. To date, several hundred human genes have been implicated as proto-oncogenes, genes that have the potential to be converted into oncogenes. These normal cellular genes (proto-oncogenes) are involved in the regulation of proliferation and differentiation. The conversion of a proto-oncogene to an oncogene is called activation. Dominant oncogenes sustain gain-of-function mutations in cancers and can be activated by numerous mechanisms such as translocation (14), amplification

(15) and point mutations (16). In each instance the genetic aberration results in a proto-oncogene that is now free of its normal regulatory constraints (17).

Tumour suppressor genes are recessive oncogenes that can suppress tumorigenicity and are involved in cell cycle checkpoint control, mitogenic signalling pathways, protein turnover, DNA damage, hypoxia, and other stress responses (18). TP53 is the most frequently mutated human tumour suppressor gene (19-21). When the p53 protein is activated by signals such as DNA damage, the outcome can be cell-cycle arrest, apoptosis or cellular senescence. P53 accomplishes these outcomes by activating transcription of its target genes. Tumours most commonly inactivate TP53 through loss-of-heterozygosity, which leaves a single normal copy of the gene, followed by intragenic point mutations, which inactivate the remaining allele by altering critical function domains of the resulting p53 protein. Other known tumour suppressor genes include Breast Cancer (BRCA), Retinoblastoma (Rb), Adenomatous Polyposis Coli (APC), Neurofibromatosis type 1(NF-1), Neurofibromatosis type 2(NF-2), Phosphatase and Tensin homolog (PTEN), Von Hippel Lindau (VHL), Multiple Endocrine Neoplasia 1 (MEN1) genes.

Finally, mammalian cells also have DNA repair genes that they use to maintain genomic integrity. Mutations of these genes are associated with diseases characterized by sensitivity to DNA-damaging agents, such as ionizing radiation, UV light and genotoxic chemicals. There are three major pathways. The first one is the nucleotide excision repair pathway that recognizes and repairs ultraviolet light-induced nucleotide dimers and other DNA adducts (22). The second pathway is the DNA recombination repair that is involved in the restoration of double-stranded breaks induced by ionizing radiation and radio mimetic agents (23-26). Finally, the DNA mismatch repair pathway corrects errors during DNA replication by removing the mismatched strand and enabling subsequent repair of the DNA (27).

1.3 Descriptive epidemiology of cancer

Cancer incidence and mortality are rapidly growing worldwide. The reasons are complex but reflect both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development. Therefore, there are large heterogeneities between developed and non-developed regions. In developed regions, mortality from most cancers is going down and the incidence is also going down for some cancers, such as stomach, liver, cervical, cancers of lip and oral cavity, sarcoma Kaposi, breast, colorectal and prostate cancer. In the non-developed words cancer incidence but also cancer mortality is going up. The International Agency for Research on Cancer (IARC) recently published the updated report on global cancer incidence and mortality based on GLOBOCAN estimates (1). It was estimated that there would be 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 2018, at a global level. For both sexes combined, it was estimated that nearly one-half of the cases and over one-half of the cancer deaths in the world would occur in Asia in the year 2018, in part because close to 60% of the global population resides there. Europe accounts for 23.4% of the total cancer cases and 20.3% of the cancer deaths, followed by the Americas' 21% of incidence and 14.4% of mortality worldwide. For both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), colorectal cancer (10.2%), and prostate cancer (7.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. By sex, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in males, followed by prostate and colorectal cancer for incidence, and liver and stomach cancer for mortality. Among females,

breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer for incidence, and vice versa for mortality; cervical cancer ranks fourth for both incidence and mortality. Figure 6 shows the distribution of cases and deaths by world area in 2018.

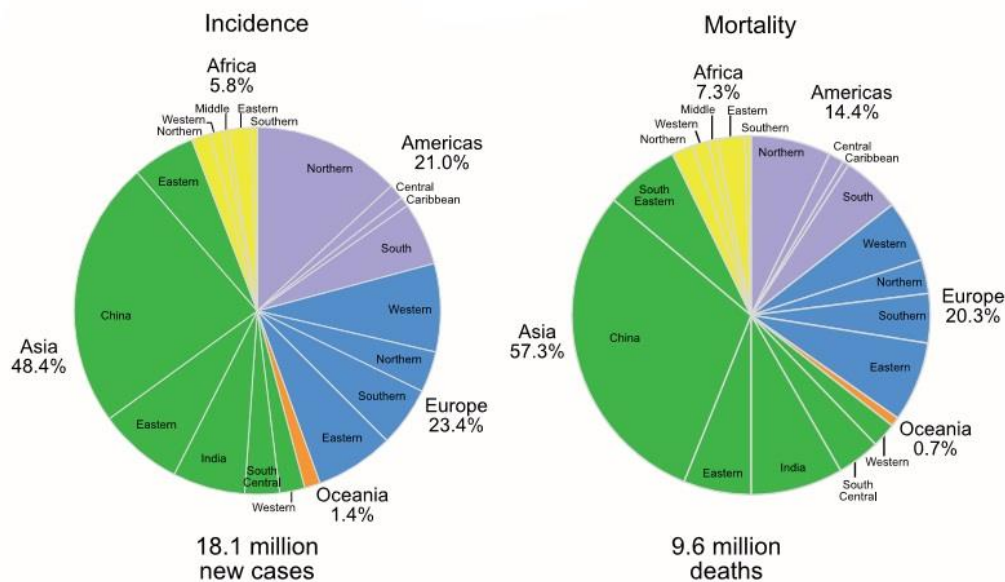


Figure 6: Pie Charts presenting the Distribution of Cases and Deaths by World Area in 2018 for both Sexes (1)

1.4 Inflammation and cancer

It has long been perceived that cancer is linked to inflammation. Chronic inflammation predisposes to different forms of cancer. The forms of chronic inflammation which predispose to cancer include infectious agents, such as hepatitis B, hepatitis C (hepatocellular carcinoma), Epstein-Barr virus (lymphoma and stomach cancer), Human Papilloma virus (cervical cancer, cancer of lip and oral cavity, cancer of anus), human herpes virus 8 (Kaposi's sarcoma) and *Helicobacter pylori* (stomach cancer).

Furthermore, there are several other occupational carcinogens related to cancer via systemic inflammation, such as asbestos (mesothelioma, lung, and larynx cancer) and radon (lung cancer), ionizing radiation (breast, lung, esophageal, bladder, sarcoma, brain tumors, leukaemia, multiple myeloma, thyroid cancer), cumulative exposure to ultraviolet radiation (skin cancer), smoking (lung, oropharyngeal, esophageal, bladder, kidney, ureter, pancreas, stomach, liver, cervix and ovary cancer), alcohol consumption (oropharyngeal, esophageal, stomach, breast, liver and colorectal cancer), adiposity (oesophageal adenocarcinoma, multiple myeloma, and cancers of the gastric cardia, colon, rectum, biliary tract system, pancreas, breast, endometrium, ovary, and kidney) and finally metabolic syndrome components of which are hypertension and insulin resistance.

Asbestos, which is prominent among construction workers, pipefitters, and shipyard workers, has been closely linked to the incidence of mesothelioma, lung cancer, and probably gastrointestinal tract malignancies. The various types of asbestos are divided into two major groups: serpentine, represented by chrysotile, the most common form of asbestos in the Western world; and rodlike amphiboles, which include crocidolite, the most oncogenic type of asbestos. Carcinogenic effects of asbestos appear to result from its physical properties rather than from its chemical structure, with long, rodlike fibers of narrow diameter being more likely to induce tumors in laboratory animals. The fibers cause mutagenic changes by several different mechanisms, including direct physical effects on chromosomes; the production of hydroxyl radicals and superoxide anions leading to DNA strand breaks and deletions; stimulation of EGFR autophosphorylation, activation, and signal transduction; and increased production of inflammatory cytokines (28).

Another classic exposure has been radon inhalation, which occurs in uranium miners and potentially from exposure to radon in the home. Radon is a naturally occurring, chemically

inert gas that is a decay product of uranium. Radon increases the risk of lung cancer. The biological mechanism by which radon and its decay products induce lung cancer is not entirely known. Some effects derived from exposure to alpha particles include mutations, chromosomal aberrations, generation of reactive oxygen species (ROS) or modifications during the cell cycle, such as delay in mitosis and inhibition of apoptosis, regulation of cytokines and increased protein production associated with cell cycle regulation and carcinogenesis (29).

Exposure to ionizing radiation is associated with an increased risk of breast, lung, esophageal, and bladder cancers, leukemia, sarcoma, and brain tumors. It has also been linked to thyroid cancer when there is exposure to radioactive iodine, as in the aftermath of the Chernobyl nuclear accident, which released radioactive iodine into the atmosphere. The most prominent source of such exposure stemmed from the atomic bomb explosions in August 1945 in Japan, and much of what we know about radiation dosimetry, latency, and carcinogenic effects comes from the careful and meticulous studies undertaken in the wake of those events. The other major source of radiation exposure is therapeutic radiation, mainly in the treatment of malignancies, hence the observation of second malignancies as a consequence (30).

Cigarette smoke contains thousands of constituents, many of which are carcinogenic. Two of the major classes of nicotine-related inhaled carcinogens include the polycyclic aromatic hydrocarbons and *N*-nitrosamines, which are metabolized to nitrosamine ketone and *N'*-nitrosonornicotine. Both compounds are activated by the cytochrome P450 enzyme system and exert carcinogenic effects through the formation of DNA adducts. The distribution of benzo(a)pyrene diol epoxide adducts along the exons of the *TP53* gene occurs preferentially in codons 157, 248, and 273, which are the same mutational hot spots of *TP53*. Nitrosamine ketone has been postulated to be one factor that leads to the increased incidence of adenocarcinomas, because it predominantly induces these tumors in

mice (31).

Alcohol ingestion is responsible for an estimated 5 to 10% of cancer cases in Europe and the United States, specifically for cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast (32). The mechanisms by which it causes cancer vary from site to site. The classical association of alcohol with carcinogenesis has been in the upper aerodigestive tract, where it has acted as a tumor promoter in association with tobacco use in the etiology of squamous cell malignancies. Another tumor linked to alcohol consumption is hepatocellular carcinoma (HCC). HCC occurs in this context in heavy drinkers, as the causal chain involves the development of cirrhosis (33). One of the most important effects of alcohol may be through breast cancer, in which even modest consumption is associated with elevated risk. The Nurses' Health Study found a 30% increased risk of breast cancer for women who drank 1.5 to 2 drinks per day (relative risk [RR], 1.28; 95% CI, 0.97, 1.69) (34). This effect appears to be due to increased estrogen and androgen levels in women consuming moderate levels of alcohol, though other plausible mechanisms have been proposed (35).

Specifically, the effect of obesity on the incidence and mortality of cancer is well recognised (36, 37). An umbrella review published in 2017 evaluated the strength and validity of the evidence for the association between adiposity and risk of developing or dying from cancer and found strong associations for 11 cancers (oesophageal adenocarcinoma, multiple myeloma, and cancers of the gastric cardia, colon, rectum, biliary tract system, pancreas, breast, endometrium, ovary, and kidney) (38). The International Agency for Research on Cancer (IARC) of the World Health Organization, a widely accepted source of the classification of cancer-causing agents, has linked 13 cancers to obesity with sufficient evidence that an elevated risk exists for those with excess BMI (esophageal adenocarcinoma, gastric cardia adenocarcinoma, colorectal cancer, liver cancer, gallbladder cancer, pancreas cancer,

postmenopausal breast cancer, uterine cancer, ovarian cancer, renal cell carcinoma, meningioma, thyroid cancer, multiple myeloma) and an additional 3 (fatal prostate cancer, male breast cancer, diffuse large B-cell lymphoma) for which there is limited evidence of a link (39).

The molecular mechanisms that link adiposity and cancer risk are not fully understood, though three hormonal systems the insulin and insulin-like growth factor (IGF) axis, sex steroids, and adipokines are the most studied candidates. The insulin–cancer hypothesis postulates that chronic hyperinsulinemia is associated with decreased concentrations of insulin-like growth factor binding protein1 (IGFBP-1) and IGFBP-2, leading to increased availability of IGF-I and concomitant changes in the cellular environment that favour tumour formation (40). For postmenopausal breast cancer, the increase in risk might be explained by the higher rates of conversion of androgenic precursors to oestradiol through increased aromatase enzyme activity in adipose tissue. For endometrial cancer, the increase in risk might be explained by more than one system: increased oestradiol not only increases endometrial cell proliferation and inhibits apoptosis, but might also stimulate the local synthesis of IGF-I in endometrial tissue. Furthermore, chronic hyperinsulinaemia might promote tumorigenesis in oestrogen-sensitive tissues, through reduction of blood concentrations of sex-hormone-binding globulin, and thus increase of the bioavailable oestrogen (41). Finally adiponectin, the most abundant adipokine which is secreted mainly from visceral fat adipocytes is inversely correlated with BMI. Mean circulating concentrations are higher in women than men. In terms of tumour development, this insulin-sensitising agent is antiangiogenic and anti-inflammatory, and inhibits tumour growth in animals. Inverse associations between adiponectin concentrations and cancer risk have also been reported in some studies in humans (42).

Strong evidence of the role of inflammation in cancer has been provided by studies showing that long-term therapy with anti-inflammatory drugs resulted in decreased number of relapses

or fewer appearances of new tumors. Several meta-analyses have demonstrated the potential role of aspirin use in primary cancer prevention (43-47). A large population based cohort study found that the risk of colorectal cancer was decreased among users of non-aspirin Non Steroid Anti-inflammatory Drugs (NSAIDs) (48). Also, a systematic review including 19 case-control studies with more than 20,000 cases, showed that regular use of aspirin or other NSAIDs was consistently associated with a decreased risk of colorectal cancer (49). Furthermore, a re-analysis of patient data of 8 randomized trials of daily aspirin use, taken for prevention of cardiovascular disease, found that aspirin users had reduced risk of death due to several common cancers and that the benefit increased with duration of treatment (44). Also, a re-analysis of patient data from 5 large randomized clinical trials of daily aspirin use demonstrated that aspirin prevents distant metastasis and this could account for the early reduction in cancer deaths in trials of daily aspirin versus control (50). These data indicate that anti-inflammatory drugs could prevent gastro-intestinal and other solid-organ cancers and suggest that an inflammatory component is present in the micro-environment of most neoplastic tissues, including those not etiologically related to an obvious inflammatory process.

Chronic inflammatory conditions demonstrating extensive associations with cancer include Crohn's disease and ulcerative colitis, collectively referred to as inflammatory bowel disease (IBD). IBD exhibited associations with gut malignancies, the primary system targeted by its inflammation. In fact, the classic pathology of IBD – granulomatous and transmural gut mucosal inflammation in Crohn's disease and primarily distal mucosal and submucosal inflammation in ulcerative colitis – may be a result of a unique milieu of inflammatory mediators experienced in each condition. This abnormal immune response appears to be the result of multifaceted immune dysregulation. For example, genetic mutations in patients with IBD have been isolated and linked to aberrancies in autophagy and eradication of antigenic

material, subsequently causing abnormally high levels of inflammation. Moreover, unlike the typical immunosuppressive gut environment of unaffected people, patients with IBD appear to lose immune tolerance for normal gut flora, again creating an environment of chronic inflammation. This loss of tolerance extends to the adaptive immune systems of patients with IBD, which appear to be sensitized to self-antigens and release interleukins (IL) and interferons that eventually lead to local tissue damage. Resultant chronic inflammation is likely the source of increased cancer risk observed in patients with IBD (51, 52). A similar chronic inflammatory condition includes acid reflux for oesophageal adenocarcinoma (53).

Furthermore evidence suggests that several other auto-immune diseases are associated to cancer, such as rheumatoid arthritis (Hodgkin and non-Hodgkin lymphoma), Sjogren syndrome (non-Hodgkin lymphoma and thyroid cancer), systemic lupus erythematosus (non-Hodgkin lymphoma, vagina/vulva, head/neck, leukemia, thyroid, liver/gallbladder, kidney, anal, cervix, oesophagus, lung and pancreas cancer), systemic sclerosis (lung and breast cancer), polymyositis and dermatomyositis (endometrial, nasopharygeal, ovarian, lung, colon), Antineutrophil Cytoplasmatic Antibody associated vasculitis (non melanoma skin cancer, leukemia, bladder, lymphoma, liver, lung cancer)(54).

At present, cancer biology is constantly shifting from a “cancer cell centric” view to a more inclusive concept that places cancer cells within a network of stromal cells that are comprised of fibroblasts and vascular cells and inflammatory immune cells that all act together to form the tumour microenvironment (TME). Inflammation, irrespectively of its occurrence in the context of a chronic inflammatory disease or in the appearance of a tumour inflammation, has a great effect on the composition of the TME and particularly on the plasticity of both tumour and stromal cells. Thus, our current view of inflammatory processes in the immune system during carcinogenesis can be distilled to the following: immunity exerts antitumorogenic

function through immunosurveillance and immunological sculpting of tumour heterogeneity. At the same time inflammation can promote cancer by blocking anti-tumour immunity, shaping the TME toward a more tumour-permissive state and by exerting direct tumour-promoting signals and functions onto epithelial and cancer cells. So, it is clear that immune system can play significant pro- and anti-tumourigenic roles at all stages of tumourigenesis (55-59).

Key features of cancer related inflammation include leucocyte infiltration, mostly tumour associated macrophages; the presence of cytokines such as TNF- α , IL-1, IL-6 or chemokines such as CCL2 and CXCL8 (figure 7); and the occurrence of angiogenesis and tissue remodelling. The molecular and cellular pathways that link inflammation and cancer have been identified (60). In the intrinsic pathway, activation of different classes of oncogenes drives the expression of inflammation related programmes which guide the construction of an inflammatory environment. In the extrinsic pathway inflammatory conditions promote cancer development.

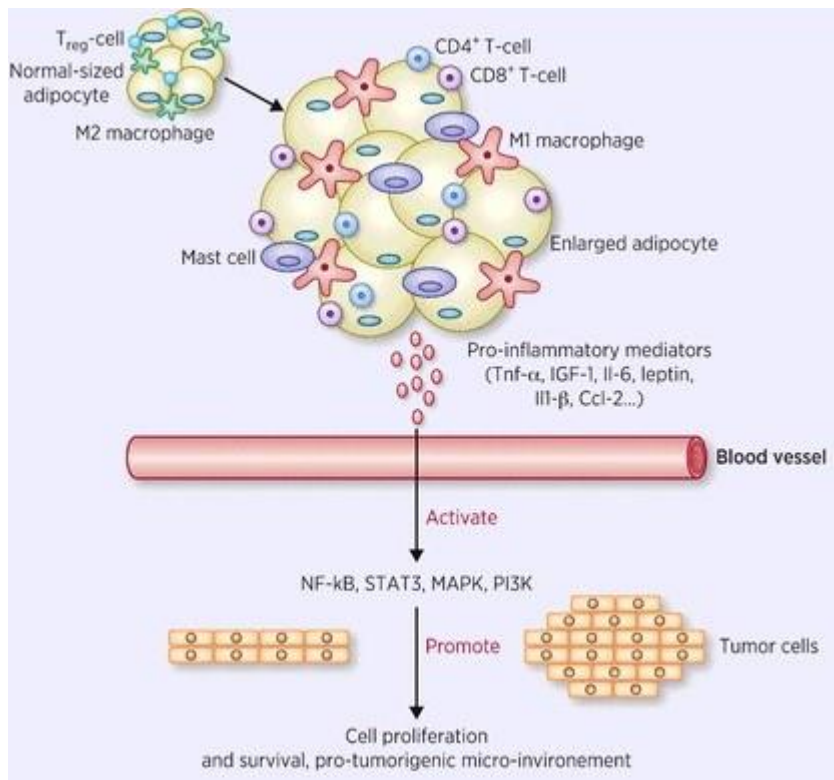


Figure 7: Inflammation and cancer mechanisms

1.5 Hypertension and cancer

Hypertension is a worldwide public health challenge and a major cause of premature death. According to the World Health Organisation (WHO), an estimated of 1.13 billion people globally have hypertension, most (two-thirds) living in low- and middle-income countries. One in four men and one in five women had hypertension in 2015 and fewer than one in five people had the problem under control. One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 25% by 2025 (61).

Although the association between blood pressure and cancer risk has been investigated, the results are controversial. Arterial hypertension is closely linked with renal cell

cancer development, as confirmed by several studies (62-64), but evidence for other cancers is equivocal (65).

For renal cancer, most studies reported an association with a history of long-term hypertension, and cohort studies with blood pressure measurements taken at baseline generally reported a dose-response of increasing risks with rising levels of blood pressure (62, 66, 67). Users of anti-hypertensive medications also were associated with an elevated risk of renal cell cancer, but an independent effect from that of hypertension *per se* has not been established (68-70). In a Swedish cohort study with sequential blood pressure measurements, renal cell cancer risk increased with further elevation of blood pressure and decreased with reduction of blood pressure over time, suggesting a tumour-promoting effect for hypertension and that effective control of blood pressure may reduce renal cell cancer risk (66).

A meta-analysis based of 10 longitudinal studies in a total of 47 119 participants showed that hypertension was related to a 23% increased risk of cancer mortality (71), but most of this risk was due to renal cell carcinoma. Moreover, a large study consisting of over half a million participants from the Metabolic Syndrome and Cancer Project with a median follow-up of 12 years found a small increase of total cancer risk in men with elevated BP level and a higher risk for cancer mortality in both sexes(72). Another meta-analysis of 18 prospective studies with 8097 kidney cancer cases from 3 628 479 population showed that history of hypertension was associated with 67% increased risk of kidney cancer (64). Furthermore, recent meta-analyses of observational studies have supported weak higher risks for other cancers as well, such as endometrial and colorectal cancer (73, 74).

The biological mechanisms underlying the relationship between hypertension and kidney cancer remain unclear, but are hypothesized to involve chronic renal hypoxia and lipid peroxidation with formation of reactive oxygen species (75, 76). Hypertensive individuals may

suffer chronic renal hypoxia caused by the transcription of hypoxia-inducible factors that promote tumor cell proliferation and angiogenesis (77). Individuals with elevated hypertension also exhibit increased lipid peroxidation, which has been implicated in the pathogenesis of kidney cancer (78, 79). Experimental studies suggest that lipid peroxidation of the proximal renal tubules play a critical role in chemically induced renal carcinogenesis (80-82). Byproducts of lipid peroxidation have been shown to react with renal DNA to form adducts (83). Misrepair of the DNA damaged by these adducts leading to mutations in proto-oncogenes and/or tumor suppressor genes, which is a critical step in the generation and progression of changing a normal cell to a malignant phenotype (75).

Both hypertension and cancer are possible consequences of similar risk factors, such as cigarette smoking, diabetes, obesity, alcohol consumption, physical inactivity, and environmental/occupational exposure (84, 85). For example, obesity, diabetes, hypertension, and cancer have a complex relationship, which is mediated by several common factors such as diet, body fat distribution, physical activity, hyperglycemia, insulin and insulin-like growth factor signaling, adipokines, sex hormones, inflammation, and oxidative stress (84). Regarding cigarette smoking, carcinogens, irritants, proinflammatory stimuli, and oxidizing agents contained in cigarette are thought to play an important role in the development of both cancer and hypertension (84). Furthermore, environmental factors such as heavy metals exposure have also been linked to increased risk of cancer and hypertension (86, 87).

1.6 Diabetes mellitus and cancer

Diabetes mellitus type 2 is a chronic metabolic disease, whose prevalence in the past three decades has risen dramatically in countries of all income levels. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and the global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. In 2016, an estimated 1.6 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose in 2012. Almost half of all deaths attributable to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016 (88).

Long-standing T2DM is an established risk factor for pancreatic cancer. This association may be secondary to consequences of peripheral insulin resistance, pancreatic β -cell dysfunction, or hyperglycemia itself. (89). Furthermore T2DM has been associated with several other cancers including breast, colorectal, endometrial, gallbladder and liver cancer (90). A retrospective, population-based cohort study of 1,027 patients with T2DM from the Center for Diabetes Treatment of the "Pius Brînzeu" Emergency Hospital in Timisoara, Romania showed that diabetes was associated with increased risk of malignant neoplastic disorders, especially pancreatic cancer, colorectal cancer, breast cancer and prostate cancer (91). The Nurses' Health Study enrolled women in 1976 and followed them biennially to determine potential risk factors for cancer, amongst other diseases. In 2003, the investigators reported a 17% increased risk of breast cancer incidence (HR 1.17, CI 1.01–1.35) in women with diabetes, compared with women without diabetes, independently of age and obesity. This association was stronger for postmenopausal women and women with estrogen receptor (ER)-positive breast cancer (92). The CPS II cohort followed patients for 26 years and found an increased risk of death from liver, pancreatic, colon, and breast cancer in diabetic men and women. In

addition, an increased mortality was seen from endometrial cancer in women, oral cavity and pharyngeal cancer and bladder cancer in men (93). Several meta-analyses have also been performed and have found an association with risk of pancreatic cancer (94), biliary tract cancer (95), and esophageal cancer in men (96); breast and endometrial cancer in women (97); and kidney and colorectal cancer in men and women (98, 99). Furthermore, studies on cancer mortality have demonstrated that patients with diabetes have greater cancer mortality compared with the nondiabetic patients (100).

Diabetes may influence the process of carcinogenesis by several mechanisms, including hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretagogues), hyperglycemia, or chronic inflammation. Insulin and insulin-like growth factor (IGF) receptors form a complex network of cell surface receptors. Most cancer cells express insulin and IGF-I receptors; the A isoform of the insulin receptor is commonly expressed. The A receptor isoform can stimulate insulin-mediated mitogenesis, even in cells deficient in IGF-I receptors (101). The insulin receptor is also capable of stimulating cancer cell proliferation and metastasis. Because most glucose uptake in cancer cells is constitutively high and independent of insulin binding to its receptor (102), the effects of insulin receptor activation on neoplastic cells may relate more to cell survival and mitogenesis than to enhanced glucose uptake. Multiple signaling pathways are activated after insulin receptors or IGF-I receptors interact with their ligands. By phosphorylating adaptor proteins, most notably the insulin receptor substrate (IRS) family, the initial kinase event is linked to downstream signalling pathways (103). Once activated, these signaling pathways may stimulate multiple cancer phenotypes including proliferation, protection from apoptotic stimuli, invasion, and metastasis, potentially enhancing promotion and progression of many types of cancer cells. Moreover, hyperglycemia allows IGF-I to stimulate vascular smooth

muscle cell proliferation and migration, which is a hallmark of cancer (104). Apart from the direct effects of insulin on cancer cells, it is possible that hyperinsulinemia could promote carcinogenesis indirectly through its effects on IGF-I. Insulin reduces the hepatic production of IGF binding protein (IGFBP)-1 and possibly IGFBP-2 with resultant increases in the levels of circulating free, bioactive IGF-I (40, 105-107). IGF-I has more potent mitogenic and anti-apoptotic activities than insulin and could act as a growth stimulus in preneoplastic and neoplastic cells that express insulin, IGF-I, and hybrid receptors (108). Human tumours commonly over-express these receptors.

Many cancers depend on glycolysis for energy, creating a high requirement for glucose, since ATP generation by glycolysis requires far more glucose than oxidative phosphorylation. Indeed, this forms the basis for FDG-PET imaging of cancers, which detects tissues with high rates of glucose uptake. Therefore it is possible that untreated hyperglycemia facilitates neoplastic proliferation. Direct data concerning dose-response characteristics of cancers to glucose are sparse, but it is relevant that most cancers have highly effective upregulated, insulin-independent glucose uptake mechanisms and therefore may not derive a further growth advantage from hyperglycemia (109). *In vivo* models showing reduced tumour growth in the setting of type 1 diabetes (110) suggest that hyperglycemia does not lead to increased neoplastic growth, at least in the setting of insulin deficiency. Studies relating hyperglycemia to cancer do not necessarily indicate that glucose mediates the relationship; rather, hyperglycemia may serve as a surrogate for a causative factor such as hyperinsulinemia.

Adipose tissue is an active endocrine organ producing free fatty acids, interleukin-6 (IL-6), monocyte chemoattractant protein, plasminogen activator inhibitor-1 (PAI-1), adiponectin, leptin, and tumour necrosis factor- α (111). Each of these factors might play an etiologic role in regulating malignant transformation or cancer progression. In some cases, the role for these

molecules is well known. For example, the plasminogen system has been linked to cancer with expression of PAI-1 linked to poor outcome in breast cancer (112). Activation of signal transducer and activator of transcription protein (STAT) signalling, via cytokines such as IL-6, is known to enhance cancer cell proliferation, survival, and invasion while also suppressing host anti-tumour immunity (113). Similarly, data from animal studies support the epidemiologic results that relate obesity with cancer mortality. Certain cancers tend to behave more aggressively when animals overeat and less aggressively when animals are calorically restricted (114). These studies provide evidence that diet-induced changes in IL-6 and/or insulin may mediate the effect of diet on neoplasia.

Chapter 2

Blood pressure and risk of cancer in the European Prospective Investigation into Cancer and Nutrition (this work has been published in International Journal of Cancer in July 2019)(115)

2.1 INTRODUCTION

Hypertension and cancer are complex multifactorial conditions. Hypertension is a worldwide public health challenge, with systolic blood pressure (SBP) above 115mmHg ranked as the leading risk factor for the global burden of disease in 2017 (116). The global age-standardised prevalence of raised blood pressure (SBP \geq 140mmHg or diastolic BP DBP \geq 90mmHg) in adults was estimated as \geq 20% in 2015 (117). However, whilst hypertension is a major risk factor for coronary heart disease and stroke, the evidence is much weaker for an association with cancer (72).

A meta-analysis of ten longitudinal studies published in 2002 found that individuals with hypertension had higher risk of total cancer mortality: odds ratio OR=1.23 (95% confidence interval (CI) 1.11-1.36), largely explained, based on 13 case-control studies, by a positive association for renal cell carcinoma (RCC) mortality: OR=1.75 (1.61-1.90) (71). The results of subsequent studies have confirmed that hypertension is associated with a higher incidence of RCC (63, 64, 118, 119). Whilst, hypertension has not attracted much attention as a risk factor for other cancers, recent meta-analyses of observational studies, although summarising only 5 to 12 prospective studies and with large between-study heterogeneity, have reported higher risks for endometrial, prostate, postmenopausal breast and colorectal cancer,

comparing hypertensive with normotensive participants (73, 74, 120-122). Further, the largest to date prospective study examining the association of individual components of the metabolic syndrome (including BP measurements) and cancer in over half a million participants from Norway, Sweden and Austria: the Metabolic syndrome and Cancer project (Me-Can) (123), reported positive associations of high BP with the risk of cancers in locations other than the kidney in both men (oropharynx, colon, rectum and anus, lung with larynx and trachea, bladder, malignant melanoma, non-melanoma skin cancer) and women (liver, pancreas, corpus uteri, cervix, malignant melanoma) (72).

It is not clear whether the association of hypertension with cancer is causal or it could, at least partially, be explained by reverse causality or other biases. It is, however, possible that risk factors and mechanisms of pathogenesis are shared by the two conditions. For example, it has been hypothesized that predisposition to cancer is increased by chronic inflammation (124) and vascular inflammation could be involved in the pathogenesis of hypertension (125). Lipid peroxidation, associated with hypertension and obesity, has also been proposed as a mechanism responsible for higher risk of RCC (126). Further, experimental studies have implicated a potential role of the renin-angiotensin-aldosterone system (which regulates BP) in the biological processes of cellular proliferation, inflammation, angiogenesis, and tissue remodeling (127). Studies in mice have also provided preliminary evidence that blockade of the angiotensin II type 1 receptor attenuates the growth and metastatic potential of RCC (128).

In the context of the above considerations, the aim of our study was to further explore the association between hypertension and cancer. We examined whether measured SBP and DBP were associated with the risk of incident cancer at all anatomical sites in the large and well-established European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, after taking into account obesity smoking and other lifestyle and dietary factors (for both men

and women) and indicators of sexual maturation and reproductive life (for women), which could be potential confounders or shared risk factors for cancer and hypertension.

2.2 MATERIALS AND METHODS

2.2.1 Study population

EPIC is an ongoing, multicentre, prospective cohort study designed to investigate the associations between diet, lifestyle, and various medical and environmental risk factors with the incidence of cancer and other diseases. The source population (the majority aged between 25 and 70 years at the time of enrolment) and data collection methods have been described in detail previously (129). Approval for this study was obtained from the ethical review boards of the International Agency for Research on Cancer and from all the EPIC participating centres. Written informed consent was obtained from all participants before entry into the study.

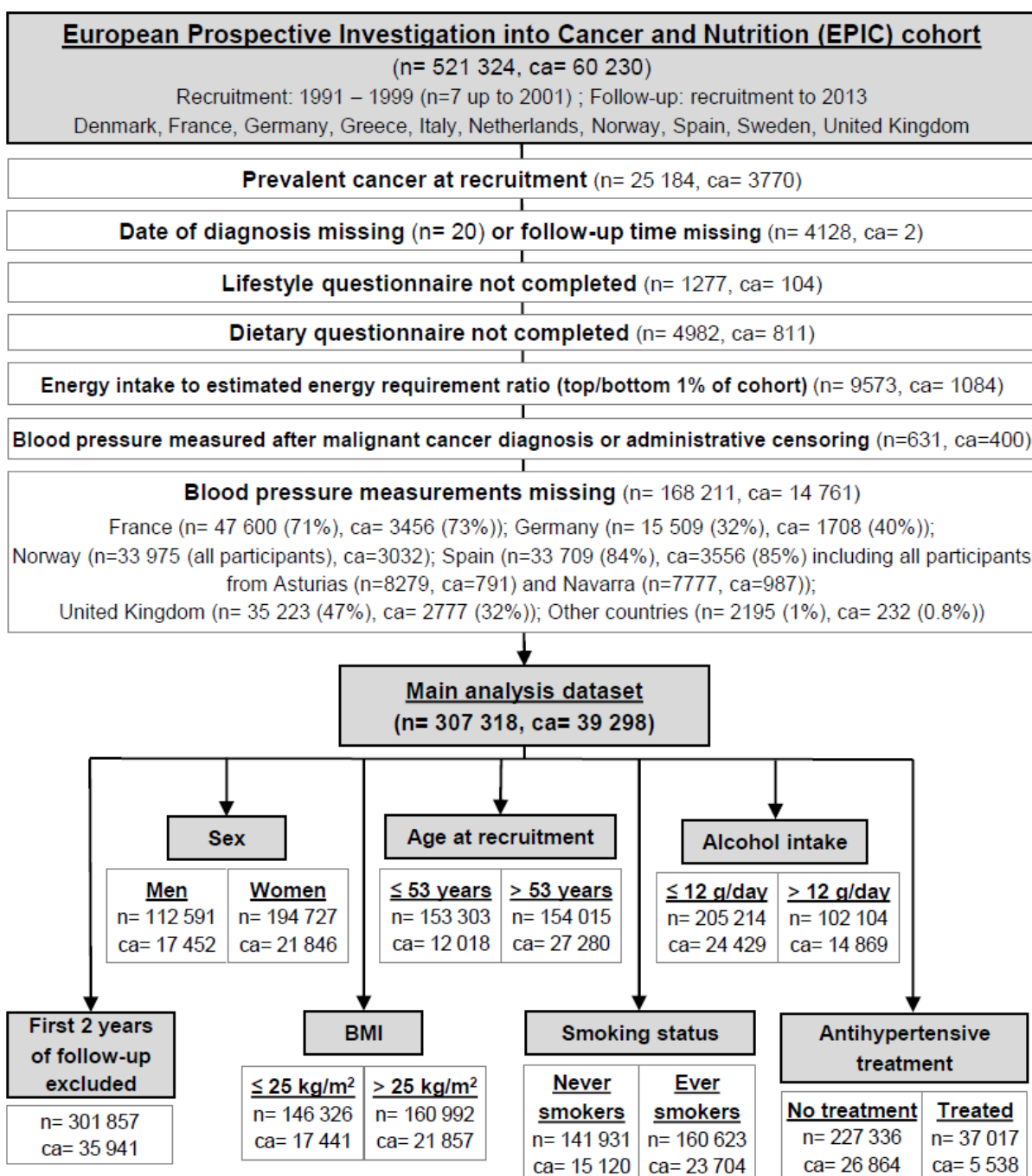


Figure 8: Flow diagram for EPIC participants included in the current study. Abbreviations: n, number of participants; ca, number of cancer cases.

2.2.2 Assessment of blood pressure and other variables

SBP and DBP were measured in millimeters of mercury (mmHg) by trained personnel. Measurements were obtained during a visit to an EPIC centre and within 6 months of recruitment in 91.5% of participants, except in France: all measurements obtained at the blood-

collection visit, 3.8 years (standard deviation (SD) 1.3) after recruitment; Granada: 39.2% after 2.0 (0.9) years; San Sebastian: 78.4% after 1.6 (0.7) years; Oxford: 29.3 % after 0.8 (0.2) years. Two readings (1-5 minutes apart) were performed with a standard mercury manometer or oscillometric device on the right arm in a sitting position (after at least 5 minutes initial resting time). The average value was used as the exposure variable, assuming differences are due to random measurement error. Exceptions were the Danish and Swedish centres, where one single measurement was taken in the supine position. Mean BP (MBP) was defined as $(1/3)*SBP+(2/3)*DBP$ (130) and not as the mean of SBP and DBP (mid-BP), used in the Me-Can study (72) . Self-reported information on treatment with antihypertensive medication (at baseline and/or in the past) was available for 264,353 participants (86.9%), of which 37,017 (14%) were receiving or had received treatment.

Information on socio-demographics, lifestyle characteristics, medical history and dietary intake was collected via questionnaires at the time of recruitment. Weight and height were measured at recruitment using a standardised protocol, except for part of the Oxford cohort and France, where height and weight were self-reported. Body mass index (BMI) was calculated as $weight/height^2$ (kg/m²). Food and nutrient intakes were estimated from country-specific baseline dietary questionnaires (129). A physical activity index was derived as previously described (131).

2.2.3 Assessment of cancer

Incident cancer cases were identified through population cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden and the United Kingdom. In France, Germany and Greece, a combination of methods was used including health insurance records, cancer pathology registries and active follow-up of study participants and their next of kin. Cancer

incidence data were coded according to the International Classification of Diseases for Oncology (ICD-O) (132). The presented analyses are focused on the first primary neoplasm. Participants subsequently diagnosed with a second (or third) cancer, were censored at the date of diagnosis of the first cancer. We considered a joint group of any cancer and location (ICD-O behavioral code 3 (malignant, primary site)) and separate groups for all major anatomic sites (excluding rare morphologies), with further subdivisions for specific locations or major morphologies (Supplementary Table 1).

2.2.4 Statistical analyses

Hazard ratios (HRs) (95% CIs) were estimated using delayed-entry Cox proportional hazards models, with age at recruitment (5-year categories) and EPIC centre (n=25) as stratification variables. Origin of time was the date of birth, aligning individuals by birth cohort. Entry time was the date of BP measurement. Time of censorship was the date of first incidence of cancer (recruitment to 2013), or death, or last complete follow-up, whichever occurred first.

The main analyses examined the following exposures: SBP and DBP (considered in separate models and each as a continuous (per 10mmHg) variable); hypertension (defined as a dichotomous (yes/no) variable, according to BP measurements ($SBP \geq 140$ mmHg, or $DBP \geq 90$ mmHg) or self-reported information, and antihypertensive treatment in hypertensive individuals (a binary variable defined according to self-reported antihypertensive treatment (yes/no) for individuals fulfilling the hypertension criteria specified above). The latter analysis aimed to examine potential associations of antihypertensive drugs, as exogenous chemicals, and cancer. Although the results for hypertension (yes/no) would be useful for meta-analyses, the risk estimates per 10 mmHg, based on the complete range of SBP and DBP, would be more informative than a dichotomous simplification. The secondary analyses examined SBP and DBP as categorical variables, with categories based on the definitions of the American (ASH)

(133) and the European Society of Hypertension (ESH) (134) (supplementary Table 1), and MBP, as a continuous variable and also categorised using cohort-wide quartiles (cut-points at 88.8, 96.7, 106.0 mmHg). To test for trend, BP categories were analyzed as continuous variables, after assigning participants an ordinal score.

All statistical models were adjusted for the categorical variables listed in Table 1. Missing values were assigned to separate categories. For pre-menopausal breast cancers, analyses were restricted to participants with pre-menopausal status at recruitment (if known), or under the age of 46 (for unknown menopausal status) and were not adjusted for menopausal status or age at menopause. If breast cancer diagnosis was before 46 years of age, participants were considered “cases”, otherwise they were censored at 46 years, if not censored by age 46 for death, loss to follow-up or other cancer. For post-menopausal breast cancer, analyses were restricted to participants with physiological or surgical menopause at recruitment, or with age ≥ 55 years (for unknown menopausal status).

Additionally, associations of BP with cancer were examined in strata according to age (cut-point at 53 years, the cohort-wide median), sex, BMI (cut-point at 25kg/m²), smoking status (ever smokers vs never smokers), alcoholic beverages intake (cut-point at 12g ethanol/day, the largest ethanol unit used in Europe) and use of antihypertensive treatment in individuals with available information for the stratifying factor. Likelihood ratio tests, comparing nested models with and without the addition of interaction terms, were used to test for statistical interactions on multiplicative scale. BP categories were included in the interaction models as ordinal variables. Examining potential biological interactions was beyond the scope of this study.

Sensitivity analyses were also performed, excluding the first two years of follow-up (to explore possible reverse causation). Crude estimates of HR (omitting the adjustment variables,

but retaining the stratification by age at recruitment and study centre) were calculated to examine the influence of adjustment.

All analyses were performed with STATA version 13 software. Plots and data summaries were generated in R version 3.4.3.

2.3 RESULTS AND DISCUSSION

2.3.1 Characteristics of study participants

The study cohort consisted of 307,318 individuals (63.4% women), with a mean age 52.5 (SD=9.9) years at recruitment. During an average follow-up of 13.7 (SD=4.4) years, 39,298 incident cancers were diagnosed, with major anatomical sites: breast (n=8,154 cases), prostate (n=5,848), colorectum (n=4,625) and lung (n=3,229). Mean SBP was 131.5mmHg (SD=19.7) and mean DBP was 81.1mmHg (SD=10.9). BP measurements and numbers of cancer cases are summarised by country in Supplementary Table 2. Participants with higher SBP or DBP were older, more likely to be men, to have low education or physical activity level, to have higher BMI, to have diabetes mellitus and to consume more alcohol and red meat, but less fruit and vegetables. Women with higher SBP or DBP were less likely to have ever used oral contraceptives. Cohort characteristics are summarised by BP categories in Supplementary Table 3.

Table 1: Baseline demographic, lifestyle and reproductive characteristics by hypertension and treatment status

Characteristics (men and women)	Total	No hypertension	Hypertension	Untreated hypertension	Treated hypertension
Cohort size	307318	174179	133139	73714	37017
Female	194727 (63.4)	117264 (67.3)	77463 (58.2)	41779 (56.7)	23736 (64.1)
Age at recruitment, years	52.5 (9.9)	49.8 (9.8)	56.1 (8.7)	54.9 (8.6)	57.8 (7.6)
Body Mass Index, kg/m²	25.8 (4.2)	24.8 (3.7)	27.1 (4.5)	26.7 (4.3)	28.2 (4.7)
Alcohol intake, g/day	12.4 (17.1)	11.2 (15.2)	13.9 (19.2)	15.4 (20.2)	12.3 (18.0)
Fruit consumption, g/day	230.6 (176.7)	235.2 (182.3)	224.6 (169.0)	226.3 (172.6)	230.9 (164.4)
Vegetable consumption, g/day	200.9 (145.4)	205.0 (149.9)	195.6 (139.2)	190.9 (138.4)	195.9 (143.6)
Red meat consumption, g/day	48.2 (36.3)	46.5 (35.7)	50.5 (37.0)	53.1 (37.7)	47.4 (34.0)
Blood pressure, mmHg					
Systolic blood pressure	131.5 (19.7)	119.4 (10.9)	147.3 (17.4)	146.7 (15.9)	147.9 (20.0)
Diastolic blood pressure	81.1 (10.9)	75.2 (7.5)	88.8 (9.8)	88.6 (9.1)	89.0 (10.6)

Diabetes					
Self-reported diabetes	8588 (2.8)	2516 (1.4)	6072 (4.6)	2410 (3.3)	3067 (8.3)
Missing information	30147 (9.8)	16247 (9.3)	13900 (10.4)	615 (0.8)	657 (1.8)
Smoking status					
Never smoker	141931 (46.2)	80450 (46.2)	61481 (46.2)	33057 (44.8)	18603 (50.3)
Former smoker	86314 (28.1)	45575 (26.2)	40739 (30.6)	21901 (29.7)	11154 (30.1)
Current smoker (≤ 20 pack-years)	32226 (10.5)	21711 (12.5)	10515 (7.9)	6539 (8.9)	2716 (7.3)
Current smoker (> 20 pack-years)	34907 (11.4)	19428 (11.2)	15479 (11.6)	9777 (13.3)	3655 (9.9)
Missing information	11940 (3.9)	7015 (4.0)	4925 (3.7)	2440 (3.3)	889 (2.4)
Physical activity					
Inactive	67194 (21.9)	32680 (18.8)	34514 (25.9)	16013 (21.7)	11191 (30.2)
Moderately inactive	100295 (32.6)	57476 (33.0)	42819 (32.2)	23828 (32.3)	12268 (33.1)
Moderately active	70977 (23.1)	42530 (24.4)	28447 (21.4)	16954 (23.0)	7300 (19.7)
Active	62152 (20.2)	36956 (21.2)	25196 (18.9)	15696 (21.3)	6021 (16.3)
Missing information	6700 (2.2)	4537 (2.6)	2163 (1.6)	1223 (1.7)	237 (0.6)
Education					
None	9377 (3.1)	3478 (2.0)	5899 (4.4)	2863 (3.9)	2973 (8.0)
Primary school completed	90254 (29.4)	43392 (24.9)	46862 (35.2)	25274 (34.3)	14288 (38.6)
Technical/professional school	77398 (25.2)	43025 (24.7)	34373 (25.8)	18676 (25.3)	9033 (24.4)
Secondary school	53830 (17.5)	35179 (20.2)	18651 (14.0)	11377 (15.4)	4730 (12.8)
Longer education (inc. University)	67606 (22.0)	43999 (25.3)	23607 (17.7)	14246 (19.3)	5875 (15.9)
Missing information	8853 (2.9)	5106 (2.9)	3747 (2.8)	1278 (1.7)	118 (0.3)
Age at first menstrual period *					
< 12 years	27085 (13.9)	16544 (14.1)	10541 (13.6)	5521 (13.2)	3116 (13.1)
≥ 12 and < 15 years	125828 (64.6)	76353 (65.1)	49475 (63.9)	27400 (65.6)	15450 (65.1)
≥ 15 years	32391 (16.6)	17996 (15.3)	14395 (18.6)	7842 (18.8)	4618 (19.5)
Missing information	9423 (4.8)	6371 (5.4)	3052 (3.9)	1016 (2.4)	552 (2.3)
Age at first full term pregnancy*					
≤ 21 years	36839 (18.9)	20636 (17.6)	16203 (20.9)	8514 (20.4)	5607 (23.6)
> 21 and ≤ 30 years	106230 (54.6)	62619 (53.4)	43611 (56.3)	23884 (57.2)	13515 (56.9)
≥ 30 years	15709 (8.1)	9715 (8.3)	5994 (7.7)	3391 (8.1)	1689 (7.1)
Missing information	35949 (18.5)	24294 (20.7)	11655 (15.0)	5990 (14.3)	2925 (12.3)
Full-term pregnancies *					
None	25571 (13.1)	16963 (14.5)	8608 (11.1)	4966 (11.9)	2397 (10.1)
One	28796 (14.8)	17156 (14.6)	11640 (15.0)	6350 (15.2)	3656 (15.4)
Two	75357 (38.7)	45696 (39.0)	29661 (38.3)	16246 (38.9)	9280 (39.1)
Three	33031 (17.0)	18740 (16.0)	14291 (18.4)	7483 (17.9)	4664 (19.6)
Four or more	14897 (7.7)	7360 (6.3)	7537 (9.7)	3601 (8.6)	2832 (11.9)
Missing information	17075 (8.8)	11349 (9.7)	5726 (7.4)	3133 (7.5)	907 (3.8)
Menopausal status *					
Pre-menopausal	58190 (29.9)	45853 (39.1)	12337 (15.9)	7856 (18.8)	2450 (10.3)
Post-menopausal	96806 (49.7)	46876 (40.0)	49930 (64.5)	25486 (61.0)	16640 (70.1)
Peri-menopausal or unknown	33371 (17.1)	21490 (18.3)	11881 (15.3)	6918 (16.6)	3292 (13.9)
Surgical post-menopausal	6360 (3.3)	3045 (2.6)	3315 (4.3)	1519 (3.6)	1354 (5.7)
Reproductive characteristics (women)	Total	No hypertension	Hypertension	Untreated hypertension	Treated hypertension
Age at menopause *					
< 40 years	4301 (2.2)	2106 (1.8)	2195 (2.8)	1067 (2.6)	769 (3.2)
≥ 40 and ≤ 46 years	18912 (9.7)	9058 (7.7)	9854 (12.7)	4754 (11.4)	3650 (15.4)
> 46 and ≤ 50 years	31996 (16.4)	15578 (13.3)	16418 (21.2)	8510 (20.4)	5579 (23.5)
> 50 and ≤ 56 years	29427 (15.1)	13238 (11.3)	16189 (20.9)	8327 (19.9)	5619 (23.7)
> 56 years	1997 (1.0)	753 (0.6)	1244 (1.6)	595 (1.4)	469 (2.0)
Missing or not applicable	108094 (55.5)	76531 (65.3)	31563 (40.7)	18526 (44.3)	7650 (32.2)
Oral contraceptive use *					
Never	82568 (42.4)	43393 (37.0)	39175 (50.6)	20706 (49.6)	12755 (53.7)
Former	91622 (47.1)	58870 (50.2)	32752 (42.3)	18294 (43.8)	9916 (41.8)
Current	10050 (5.2)	7434 (6.3)	2616 (3.4)	1829 (4.4)	594 (2.5)
Missing information	10487 (5.4)	7567 (6.5)	2920 (3.8)	950 (2.3)	471 (2.0)
Hormone replacement therapy *					
Never	129049 (66.3)	79952 (68.2)	49097 (63.4)	26920 (64.4)	14842 (62.5)
Former	16259 (8.3)	8638 (7.4)	7621 (9.8)	3937 (9.4)	2598 (10.9)

Current	30133 (15.5)	17724 (15.1)	12409 (16.0)	6596 (15.8)	3891 (16.4)
Missing information	19286 (9.9)	10950 (9.3)	8336 (10.8)	4326 (10.4)	2405 (10.1)

* Reproductive characteristics in women; Categorical variables: number of individuals (percentage from total number in category (for reproductive factors in women only)); Continuous variables: mean (standard deviation).

2.3.2 Associations with the risk of malignant cancers

Results from all analyses are included in Supplementary Table 4. The presentation below focuses on SBP and DBP examined as continuous variables in adjusted models. Forest plots with estimates of HR (95% CI) for SBP and DBP in the total dataset are shown in Figure 9; for hypertensive status and antihypertensive treatment in Figure 10 and for sub-groups determined by sex, BMI, age at recruitment, smoking status, alcohol and antihypertensive treatment are shown in Supplementary Figure 1. There were positive associations of BP with malignant cancers in several locations and with some specific morphologies. Analyses of BP categories were largely in agreement with the findings for BP examined on a continuous scale. The main findings are presented below, within the context of large published studies and meta-analyses. Anatomical sites and cancers, for which there was no overall association, are presented in Supplementary Results and Discussion.

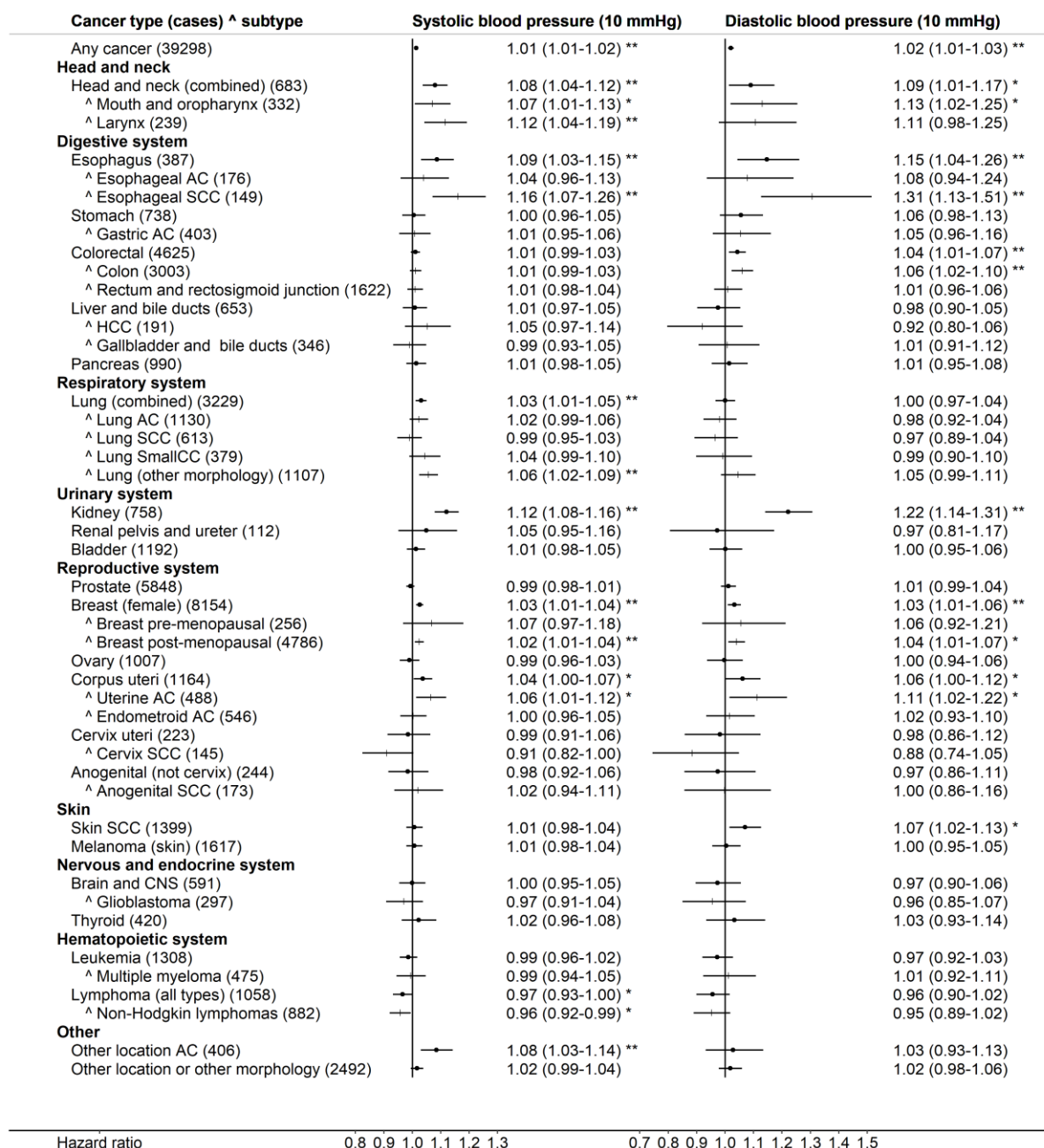


Figure 9: Forest plot of hazard ratios for continuous systolic and diastolic blood pressure. Abbreviations: AC, adenocarcinoma; CNS, central nervous system; HCC, hepatocellular carcinoma; SCC, squamous cell carcinoma; SmallCC, small cell carcinoma; Vertical order, determined by body system (bold), followed by the main anatomical locations and the relevant specific locations or morphologies marked with ^ symbols (other locations, not included in those specified, are shown last); Hazard ratios, estimates (95% confidence intervals) (per 10 mmHg higher blood pressure) derived from Cox proportional hazards models, stratified by study center and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors listed in Table S2). For cervical AC (n=37) : HR=0.96 (0.79–1.17) for SBP and HR=0.84(0.59–1.19) for DBP and for other morphology in the cervix (non-SCC and non-AC) (n=41) :HR=1.28 (1.10–1.48) for SBP and HR=1.53(1.17–2.01) for DBP (considered only in the main analyses and excluded to avoid the larger confidence intervals dominating the plot); *p < 0.05, **p < 0.005

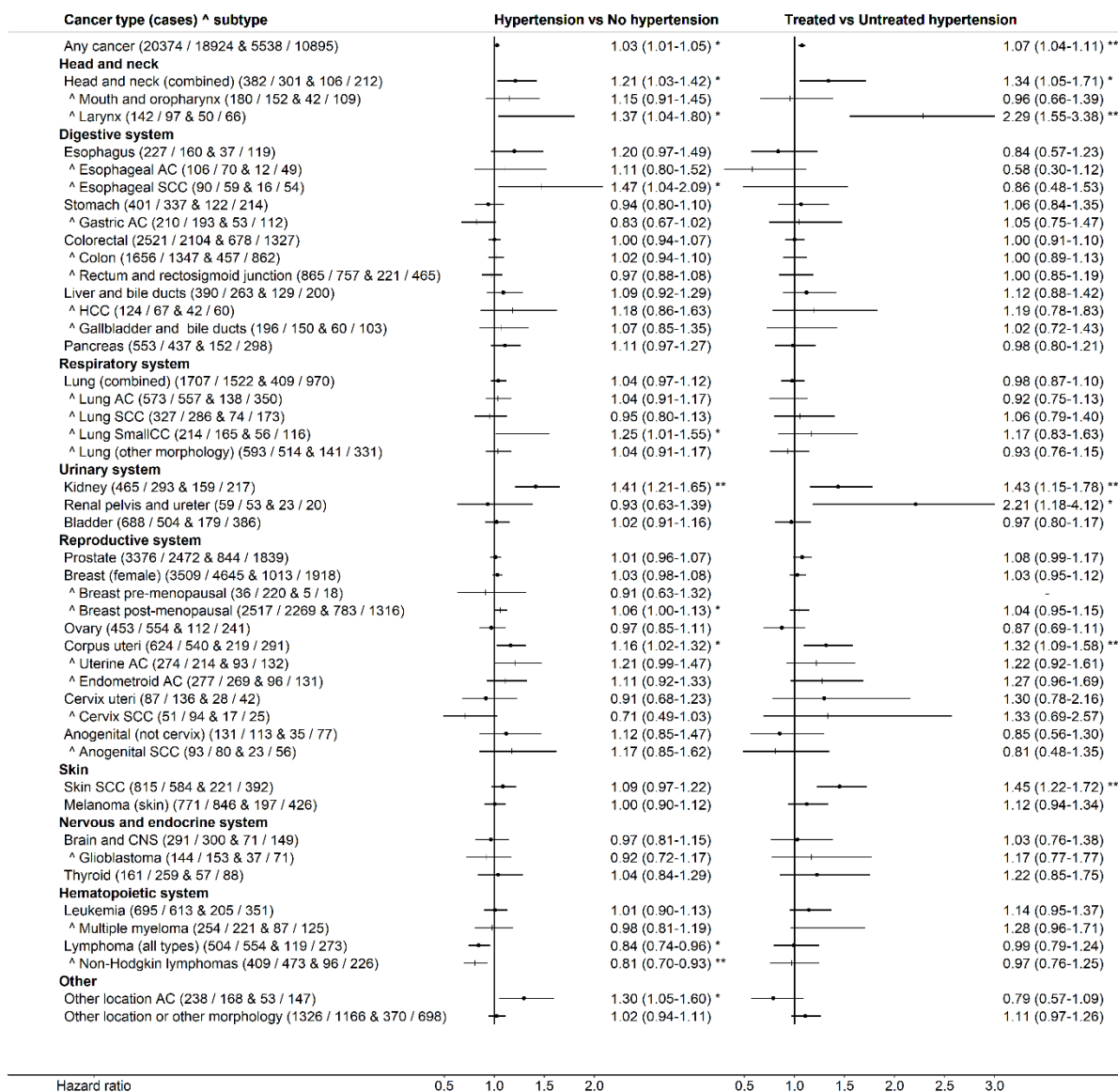


Figure 10: Forest plot of hazard ratios for dichotomous hypertension and antihypertensive treatment. Abbreviations: AC, adenocarcinoma; CNS, central nervous system; HCC, hepatocellular carcinoma; SCC, squamous cell carcinoma; SmallCC, small cell carcinoma; Hypertension, defined as systolic blood pressure (SBP) ≥ 140 mm Hg, or diastolic BP (DBP) ≥ 90 mm Hg at the BP measurement visit, or self-reported history of hypertension; Antihypertensive treatment status, either self-reported or no treatment assumed, if there was self-reported absence of diagnosis of hypertension; Cases, numbers per group (hypertension/no hypertension and treated/untreated hypertension); Vertical order, determined by body system (bold), followed by the main anatomical locations and the relevant specific locations or morphologies marked with ^ symbols, as per Fig. 2 (other locations, not included in those specified, are shown last); Hazard ratios, estimates (95% confidence intervals) (per 10 mm Hg higher BP) were derived from Cox proportional hazards models, stratified by study center and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors listed in Table S2. For cervical AC ($n = 37$): HR = 1.23 (0.58–2.06) and for other morphology in the cervix (non-SCC and non-AC) ($n = 41$): HR = 1.82 (0.92–3.63) (considered only in the main analyses and omitted from the plot to avoid the larger confidence intervals dominating the plot); * $p < 0.05$, ** $p < 0.005$

3.2.2.1 Kidney cancer and cancers of the renal pelvis and ureter

The results of the current analyses confirmed our previous findings (118) of a positive association of BP with the risk of RCC: HR=1.12 (1.08-1.17) for SBP and HR=1.23 (1.14-1.32) for DBP (Figure 9). We found no evidence for a difference between men (with n=431 cases) and women (n=327) (Supplementary Figure 1A,B). As cancers of the renal pelvis and ureter are mainly of transitional cell morphology, i.e. different than the parenchymal cell morphology of RCC, they were considered as a negative control and, indeed, there was no association with BP in the total dataset (n=112). There was, however, an indication for a positive association with SBP in the subgroup with BMI>25kg/m² (n=63): HR=1.16 (1.03-1.32). The risk was also higher in treated compared to untreated hypertensive individuals: HR=2.21 (1.18-4.12) (Figure 10), although for a small number of cases.

The association of hypertension with a higher risk of RCC is well established. In 1999, Grossman et al. reported a higher risk for users of diuretics relative to nonusers: OR=1.55 (1.42-1.71), based on a meta-analysis of 9 case-control studies, and more than a two-fold increased risk, based on three cohort studies (135). In 2007, a meta-analysis of 18 studies reported a higher risk of RCC among hypertensive patients (estimated pooled OR=1.62 (1.24-2.12)), also for treatment with diuretics and, in women, with non-diuretic drugs (119). At the same time, Weikert et al. reported, based on 250 cases in the EPIC study, that high SBP and DBP are associated with a higher risk of RCC, both in men and women and found that individuals receiving antihypertensive treatment had higher risk only if hypertension was poorly controlled (118). Earlier, Heath et al. had reported in a large cohort high age-adjusted risk-ratio in women: RR=3.1 (1.5-4.3), but not in men: RR=0.8 (0.4-1.3) receiving antihypertensive medication, including diuretics (136) and Grossman et al. had reported from a meta-analysis of seven case-control studies a high risk in women: averaged OR=2.01 (1.56-2.67), but slightly lower risk in men OR=1.69 (1.34-2.13), but with heterogeneity between the

studies (135). However, Haggström et al. reported for the Me-Can project a higher risk only in men (n=592): HR=1.39 (1.24-1.56) per 10mmHg higher mid-BP, but not in women (n=263): HR=1.05 (0.89-1.24) (72), with similar findings for SBP and DBP examined separately (137). Nevertheless, a more recent meta-analysis of 18 prospective studies, with a total of 8097 cases, has confirmed an association of history of hypertension with kidney cancer: risk ratio estimate RR=1.67 (1.46-1.90) and an association also of SBP and DBP in both men and women (64), in agreement with our findings. A potential relationship between hypertension and the risk of renal pelvis and ureter cancer is less well studied, but an early case-control study reported a positive association for hypertension history longer than 5 years: OR=1.3 (1.0-1.8) and, in agreement with our findings, among users of antihypertensive drugs: OR=2.4 (1.1-4.9) (138). However, as antihypertensive treatment may be related to the type and severity of hypertension, it is difficult to separate their effects in an observational study.

2.3.2.2 Cancers of the upper aero-digestive tract and lung

We found a positive association of BP with the risk of esophageal carcinoma, but more specifically with squamous cell carcinoma (SCC) (n=149): HR=1.16 (1.07-1.26) for SBP and HR=1.31 (1.13-1.51) for DBP and not with esophageal adenocarcinoma (AC) (n=176) (Figure 9). We also found a weak positive association for head and neck cancers (89% of which were SCC morphology): HR=1.08 (1.04-1.12) for SBP and HR=1.09 (1.01-1.17) for DBP (similarly for mouth and oropharynx and for larynx). For mouth and oropharynx, the positive associations were statistically significant only in women, in individuals older than 53 years at recruitment and for alcohol intake>12g/day and for head and neck cancers and esophageal SCC only for alcohol intake>12g/day and not below. There were, however, fewer cases among never smokers and the 95% CIs were too wide to make meaningful conclusions for smoking (Supplementary Figure 1G,H).

For lung cancer, there was no overall evidence for association of BP with SCC, AC or small cell carcinoma morphologies (Figure 9). In subgroup analyses, we observed an inverse association of DBP with lung AC among individuals with BMI>25kg/m² (n=528): HR=0.90 (0.83-0.98) and a positive association of SBP with lung SCC in individuals receiving antihypertensive treatment (n=74): HR=1.14 (1.01-1.28). A weak positive association of SBP with the risk of total lung cancer was mainly accountable for by other morphologies (predominantly unclassified or large cell): HR=1.06 (1.02-1.09).

Our findings for esophageal cancer are in agreement with the similarly-sized Me-Can project, for which Stocks et al. reported a positive association of mid-BP with total esophageal cancer (n=285): HR=1.33 (1.13–1.57) per 10mmHg higher BP (72). Lindkvist et al. further showed that this was accountable for by a higher risk of SCC (n=184): HR=1.30 (1.17-1.44) and not AC (n=114): HR=1.03 (0.89-1.19), with no major differences between subgroups of never, former and current smokers (139). For head and neck cancers, Stocks et al. did report for the Me-Can project an association of mid-BP with the risk of cancers of the lip, oral cavity and pharynx, but only in men (n=561): HR=1.31 (1.15-1.48) per 10mmHg increase, and not in women (n=177): HR=1.05 (0.85-1.28). They also found a positive association for the combined group of cancer of the larynx, trachea and lung in men (n=2810): HR=1.09 (1.03-1.16) but not in women (n=905): HR=1.00 (0.92-1.10) (72). Our study includes a similar number of lung cancer cases (n=3229), but we have examined separately cancer of the larynx and individual lung morphologies. Whilst smoking is a major risk factor for both esophageal and lung SCC cancers and can also lead to hypertension, as shown in an animal model (140) and some epidemiological studies (141, 142), we could find a positive association with hypertension only for esophageal and not for lung SCC, after adjustment for smoking. If there was any residual confounding by smoking, it is likely that we would have observed a positive association for lung, as well as for esophageal SCC. In fact, we could find no positive association of

hypertension with lung SCC even without adjustment for confounders (crude HRs in Supplementary Figure 2). Further, a positive association for esophageal AC was observed only in unadjusted analyses but was lost after adjustment for confounders, indicating that the adjustment, has removed, to a great extent, the confounding by smoking. This leads us to conclude that smoking is not likely to explain the association of high BP with the risk of SCC in the upper aero-digestive tract. Alcohol, however, may have an influence (Supplementary Figure 1I,J), but further investigations are needed to clarify our observations.

2.3.2.3 Gastric and colorectal cancers

We could not find association of BP with the risk of gastric cancer (n=738) (including gastric AC (n=403)) in the total cohort (Figure 9). We only found a positive association for gastric AC among individuals receiving antihypertensive treatment (n=53): HR=1.22 (1.06-1.40) for SBP and HR=1.65 (1.27-2.15) for DBP. We also found a weak positive association of DBP with the risk of cancer of the colon (n=3003) (75% of which had AC (code 8140/3) morphology): HR=1.06 (1.02-1.10) for DBP, similarly for men and women (Supplementary Figure 1B), but not the rectum and rectosigmoid junction (n=1622) (81% AC) (Figure 9). There was also a weak positive association of SBP with the risk of colorectal cancer (similarly for colon and rectum (including rectosigmoid junction)) in men, but not in women (in men colon (n=1304): HR=1.03 (1.00-1.06) and rectum (n=876): HR=1.03 (0.99-1.07)). We also found a positive association in the subgroup analyses for participants with BMI>25kg/m² (colon: n=1813, rectum: n=966) and for the participants who reported alcohol intake>12g/d (colon: n=1091, rectum: n=685) (Supplementary Figure 1C,D,I,J).

Our data are broadly compatible with results from previous large studies, which suggest that high BP is associated with the risk of colorectal cancer in men but not in women. In 2001 Tenenbaum et al. reported, in a cohort of patients with stable angina or previous myocardial

infarction, higher risk of colon cancer (n=96) in individuals receiving diuretics compared to nonusers: HR=2.0 (1.2-3.2) (143). More recently, in a large case-control study in Italy, Pelucchi et al. found that history of treated hypertension was associated with colorectal cancer risk in men (n=1310) OR=1.24 (1.03-1.48) but not in women (n=946) OR=0.87 (0.71-1.06) (144). Stocks et al., considering SBP, DBP and mid-BP in a prospective study (Me-Can), also reported a positive association for cancer of the colon in men (n=1747): HR=1.10 (1.03-1.19) per 10mmHg higher mid-BP but not in women (n=1265): HR=0.95 (0.88-1.02) (145) (72), with similar findings for cancer of the rectum and anus (72). Esposito et al., have subsequently reported in a meta-analysis based on 9 studies, a RR=1.09 (1.01-1.18) for high BP, although considering jointly men and women (74). For gastric AC, Lindkvist et al., similar to our total cohort results, could not find in the Me-Can project evidence supporting an association with mid-BP (n=1210), but they did not consider antihypertensive treatment (146).

2.3.2.4 Breast cancer

In our study, representing a cohort with the largest to date number of breast cancer cases, we found a weak but statistically significant positive association with both, SBP and DBP (n=8154): HR=1.03 (1.01-1.04) for SBP and HR=1.03 (1.01-1.06) for DBP. The association was similar for post-menopausal cancers (n=4786), but the number of pre-menopausal cancers was considerably smaller and the 95% CIs were too wide to permit conclusions. In sub-group analyses, the positive association of SBP with the risk of post-menopausal breast cancer was retained only in ever smokers (n=2180) and there was some suggestion for a positive association of SBP with pre-menopausal breast cancer in women with alcohol intake \leq 12g/day (n=201) (Supplementary Figure 1G,I).

Literature reports on breast cancer are conflicting. In an early case-control study in Italy, Soler et al. described a higher risk of breast cancer in women with treated hypertension

(n=3,406): OR=1.2 (1.1-1.4) and more specifically in post-menopausal (n=2184), at age 55 years or older (n=1580), in drinking women (n=2,400) and at BMI>25kg/m² (n=1266) and not in pre- and peri-menopausal women (147). However, Bjorge et al. in the Me-Can project did not find associations of SBP or DBP with the risk of incident breast cancer (n=4,862), however they reported a higher risk of breast cancer mortality for age≥60 years (123). Similarly, Largent et al., defining high BP as treated hypertension in the California Teachers Study cohort (n=4,151), found a higher risk associated with antihypertensive treatment longer than 5 years: HR=1.18 (1.02-1.36) (148), but no association with hypertension overall. However, in the largest to date meta-analysis (n=11,643), Han et al. (in agreement with an earlier meta-analysis (74) and with our findings) have reported a higher risk of breast cancer in hypertensive women, based on 18 retrospective case-control studies: RR 1.29 (1.14-1.47) and on 12 prospective studies: RR=1.07 (1.01-1.14), but only for post-menopausal women (13 studies): RR=1.20 (1.09-1.31) and not for pre-menopausal (9 studies): RR=0.97 (0.84-1.12) (122).

2.3.2.5 Endometrial cancer

For cancers located in corpus uteri, we found a weak positive association, which could be traced only to AC morphology (code 8140/3): HR=1.06 (1.01-1.12) for SBP and HR=1.11 (1.02-1.22) for DBP, but not to the endometrioid morphology (code 8380/3): HR=1.00 (0.96-1.05) for SBP and HR=1.02 (0.93-1.10) for DBP (Figure 9). In sub-group analyses, the association for AC morphology was retained only at BMI>25kg/m² and in never smokers (Supplementary Figure 1C,D,G,H). The differences between morphologies, however, would need further clarification, as the relative proportions of the two morphologies differed considerably between the individual countries in the EPIC cohort (Supplementary Table 2).

Large European case-control and cohort studies (n>700 in each), although not accounting for specific morphologies, have consistently reported, in agreement with our

findings, a higher risk of endometrial cancer with high BP (147, 149, 150), especially in obese women (149, 150), while a relatively smaller case-control study in the United States (n=469) found a higher risk only in women receiving thiazide diuretics (151). Nevertheless, recent meta-analyses, have corroborated a positive association: RR=1.32 (1.12-1.56) (6 prospective studies, 1,1469 cases) (73), RR=1.81 (1.08–3.03) (5 studies, 3,112 cases) (120).

2.3.2.6 Cervical cancer

For cervical SCC (n=145), but not for total cervical cancers (n=223), we found an inverse association (Figure 9), which was especially pronounced in women with BMI>25kg/m² (n=68): HR=0.81 (0.71-0.93) for SBP and HR=0.74 (0.57-0.95) for DBP (Supplementary Figure 1C,D), whilst we found no evidence for association of BP with cervical AC (n=37) and a positive association for the remaining morphologies (n=41): HR=1.28 (1.10-1.48) for SBP and HR=1.53 (1.17-2.01) for DBP, which would have contributed to absence of an overall association for total cervical cancers, but with a small number of cases, this could be a chance finding.

In contrast to our findings, Stocks et al. reported a higher risk of total cervical cancer in the Me-Can study (n=424): HR=1.17 (1.01-1.34) per 10mmHg higher mid-BP (72). Further, Ulmer et al. examined individual morphological subtypes and reported, similar to esophageal cancer, a positive association for cervical SCC (n=337): HR=1.28 (1.05-1.57) per SD higher mid-BP, but not for cervical AC (n=59): HR=1.09 (0.65-1.83) (152).

2.3.2.7 Prostate cancer

Our study, based on a reasonably large number of incident cases (n=5,848), provided no evidence for association of SBP or DBP with the risk of prostate cancer: HR=0.99 (0.98-

1.01) for SBP and HR=1.01 (0.99-1.04) for DBP, except for some weak inverse association, mainly with SBP, which was found only in never smokers (n=1937): HR=0.97 (0.95-1.00).

Contrary to our findings, the CONOR study (n=1974) (153) has reported a weak positive association between SBP and DBP and the risk of prostate cancer and recent meta-analyses have confirmed this (74, 121). Based on 10 studies (n=4343), Esposito et al. reported RR=1.15 (1.01-1.30) (74) and Gacci et al. (7 studies) reported RR=1.10 (1.01-1.19) (121). However, the Me-Can study (n=6673) (154) found only a positive association of SBP and DBP with prostate cancer death, while Stocks et al. reported in the Swedish Construction Workers cohort an inverse association with the risk of total prostate cancer (n=10,002) and non-aggressive tumours (n=2817), but a positive association of DBP with the risk of aggressive tumours (n=2402) (155). In the light of these discrepancies, it would be important to examine further the impact of cancer aggressiveness or grading in EPIC, but this was beyond the scope of the current study.

2.3.2.8 Blood and lymphoid cancers

Our data revealed an inverse association of BP with the risk of all-type lymphomas (n=1058), and specifically with non-Hodgkin lymphomas (n=882): HR 0.96 (0.92-0.99) for SBP and borderline for DBP: HR=0.95 (0.89-1.02), whilst we found no evidence for association with leukaemia (n=1308), or specifically with multiple myeloma (n=475) (Figure 9).

In the Me-Can study, Nagel et al. considered a total of 2,751 cases of myeloid and lymphoid neoplasms and their results did not support associations with mid-BP, except for a suggestion, based on a small number of cases (n=46), for an inverse association with the risk of T-cell non-Hodgkin lymphomas in men: HR=0.54 (0.29-1.01) (156). Lymphoid cells are closely involved in inflammatory processes and recent studies have specifically linked T-cell

subtypes with vascular remodelling and the development of hypertension (157), so there may be some mechanistic explanation, but this would need a more detailed investigation.

2.3.2.9 Skin cancer

We found evidence for a positive association with the risk of skin SCC for DBP (n=1399): HR=1.07 (1.02-1.13) and for antihypertensive treatment among hypertensive individuals: HR=1.45 (1.22-1.72).

The Me-Can project also reported higher risk of skin SCC, but only in men (n=566): HR=1.11 (0.95–1.31) for one SD higher mid-BP and not in women (n=286): HR=0.95 (0.76-1.19) (156). Several studies have also reported higher risk in association with antihypertensive drugs, especially diuretics (158), but there were no sufficient treatment details in EPIC to explore further.

2.3.3 Sensitivity analyses

Excluding the first two years of follow-up did not have material influence on the findings (Supplementary Figure 2), except for abolishing the inverse association for cervical SCC (without changing it to positive), which may be the result of selection bias introduced by the exclusion. However, crude HRs (unadjusted) (Supplementary Figure 3) had indicated some associations, which were lost or mitigated after adjustment for confounders. Thus, crude HRs indicated positive associations of SBP and DBP not only with esophageal SCC or the endometroid cancer morphology in corpus uteri, but also of the AC morphology in both locations, and further positive associations of DBP with gastric cancer (total and AC morphology) and of SBP, not only DBP, with cancers of the rectum and rectosigmoid junction, as well as with colon cancer. Additionally, crude HRs indicated positive associations of SBP

and DBP with bladder cancer, of SBP with liver cancer (accountable for only by HCC) and of DBP with multiple myeloma. In addition, in the absence of adjustment for confounders a weak inverse association was observed for SBP with prostate cancer (SBP only) and DBP with lung AC. Associations observed only in crude and not in adjusted HR estimates suggest that the differences in the selection of adjustment variables in our and other studies may be responsible for some of the discrepancies in the findings. Of note, we have included adjustment for dietary factors, information on which was either not available or not included in the analyses in other published studies. This may be of particular relevance to cancers of the gastrointestinal tract. Similarly, we have used detailed information on reproductive factors in women, although adjustment did not affect our findings for breast and cervical cancers (Supplementary Figure 3).

2.3.4 Strengths and limitations

Our study has several strengths and limitations. Major advantages are the prospective design and the large sample size, including several European countries. Furthermore, BP was measured by trained personnel and was not self-reported. Detailed information on lifestyle, diet and, in women, reproductive history and hormonal treatments was also available, enabling adjustment for potential confounders and shared risk factors.

The main limitation of our study is that BP was measured only at one timepoint. Moreover, specific information on the type of antihypertensive medications in treated individuals was unavailable. Theoretically, antihypertensive treatment could lead to a lower “observed” BP, i.e. measured during the investigation, compared to the “underlying” BP, i.e. the BP that could be reached without treatment. If high BP is causally associated with cancer, controlling BP would mitigate the association, but if high BP and cancer share common mechanisms, the association would remain when BP is controlled, unless treatment targets the

mechanism of BP development. In practice, however, a single timepoint measurement may not be representative of the commonly “observed” BP and this applies to untreated and treated individuals alike. Individuals receiving treatment are also likely to have a more sustained high BP, confirmed by a doctor. Treated individuals in our study showed, indeed, considerably higher SBP (mean difference 19.8mmHg (95% CI 19.6-20.1)) and DBP (9.5mmHg (9.4-9.6)) compared to cohort participants without antihypertensive treatment and even showed marginally higher SBP (1.2mmHg (1.0-1.4)) and DBP (0.4mmHg (0.3-0.5)) compared to untreated hypertensive individuals (self-reported or with “observed” high BP (Table 1)). Therefore, when there was a positive association for both hypertension and antihypertensive treatment, as for kidney cancer, we could not discriminate associations related to the severity and duration of high BP from association related to the administration of antihypertensive medication (Figure 10). Nevertheless, a positive association only for treated compared to untreated hypertension, as for cancers of the renal pelvis and ureter, might be more suggestive of the involvement of treatment (Figure 10). There is a growing body of literature evaluating associations between antihypertensive medication and cancer development, but with overall inconclusive findings. An involvement of drugs in cancer pathogenesis is possible, because they are exogenous chemical compounds administered often for very long time (85), but we have not reviewed this literature, because our study could not contribute reliably to the debate.

Finally, information about potential confounders and shared risk factors was self-reported, which may have contributed to misclassification bias and there are always potentially unmeasured risk factors, which may result in residual confounding.

2.4 CONCLUSIONS

The results of our study, involving over 300,000 participants, are largely compatible with published studies. We confirmed a positive association between BP and RCC and

additionally found a positive association of BP with malignant cancers in several anatomical sites, including postmenopausal breast and colon cancers, and with specific morphologies, i.e. SCC in the upper aero-digestive tract and the skin or AC in corpus uteri and other unspecified locations. We also found an inverse association of BP with the risk of non-Hodgkin lymphomas and cervical SCC. These associations, however, are mainly weak and future research is required to clarify potential shared mechanisms. Admittedly, observations based on smaller number of cases could be chance findings, but they could also give some directions for further studies.

Chapter 3

Type 2 diabetes and cancer: an umbrella review of observational and Mendelian randomisation studies (this work is under review at Diabetes Care journal)

3.1 INTRODUCTION

The number of individuals living with diabetes has increased dramatically over the past decades. In 2014, there were more than 420 million people living with diabetes; reflecting a four-fold increase in prevalence since 1980, with the largest increases observed in low- and middle-income countries(159). Compelling evidence for a causal link between type 2 diabetes mellitus (T2DM) with renal disease(160), coronary heart disease(161) and stroke(160) has led to the development of specific prevention approaches within these patient groups(162). T2DM has also been associated with several cancers including breast, colorectal, endometrial, gallbladder, liver and pancreatic cancer(163). Cancer is also a leading cause of mortality and morbidity, with 18.1 million cases worldwide in 2018(164); accordingly, prevention of T2DM may reduce the burden of cancer. A recent study estimated 293,000 cancer cases to be attributable to all diabetes in 2012(165), with both conditions expected to increase over the coming decades.

Developing effective clinical and public health policy to address the concurrent increases in T2DM and cancer can be informed by robust evidence regarding site-specific cancer associations with T2DM and by understanding potential causal effects. A leading proposed mechanism underlying the T2DM-cancer association pertains to the possibility of hyperinsulinaemia activating cancer and/or growth promoting pathways(159, 166-169), while

one other hypothesis includes hyperglycaemia(170-173); however, these potential mechanisms have not been fully characterised. The association between T2DM and cancer has been widely examined in observational research; however, these studies are vulnerable to several biases, including residual confounding, reporting bias(174), and T2DM diagnosis classification bias. Our previous umbrella review of meta-analyses of observational studies on T2DM and cancer concluded that only a minority of reported associations had strongly statistically significant results with no suggestion of bias(163). Subsequently, several meta-analyses on T2DM and cancer have been published. Thus, we performed an updated umbrella review of observational evidence investigating T2DM in relation to cancer incidence or mortality, and extended the analysis to include evidence from Mendelian randomisation (MR) studies.

3.2 METHODS

3.2.1 Eligibility of observational studies

For this update to our previous umbrella review (163), we searched PubMed from January 2014 to May 2018 for systematic reviews or meta-analyses of epidemiological studies using the following algorithm: “(diabetes) AND (cancer OR carcinoma OR neoplasia OR tumor OR neoplasm OR maligna*) AND (meta-analysis OR systematic review)”. A manual review of references from eligible systematic or narrative reviews was also performed. The titles, abstracts, and full texts of the resulting papers were examined in detail by two authors (JP-S and AK), and discrepancies were resolved by consensus.

We included systematic reviews and meta-analyses of cohort studies or combined cohort and case-control studies in humans. We excluded studies in which T2DM was not the exposure of interest and cancer incidence or mortality were not the outcomes of interest, and meta-

analyses of prognostic studies associating T2DM and outcomes among patients with cancer. Where meta-analyses did not present comprehensive study-specific data, such as relative risks (RR), 95% confidence intervals (CI) and number of cases or total population, we examined the primary studies and extracted this data for all comparisons. When we identified more than one meta-analysis per outcome, the meta-analysis with the highest quality assessment score was selected to avoid duplication; if both had the same quality score, the study with the larger numbers of cohorts and cases was retained. The 'duplicate' meta-analyses were evaluated separately in a sensitivity analysis. The methodological quality of all the systematic reviews and meta-analyses included in this study was assessed with the AMSTAR tool, 11-item questionnaire from which positive responses are summed to obtain an overall quality score (high: ≥ 8 , moderate: 4-7, low: < 4). (175). The quality evaluation was performed by SC and reviewed by KKT.

From each eligible systematic review or meta-analysis, we extracted the name of the first author, year of publication, exposure, outcome, and meta-analytic estimate in duplicate by two study authors (JP-S and NP/GM). From each individual study in a meta-analysis, we extracted the name of first author and publication year, epidemiological design, number of cases and total population, maximally-adjusted relative risk (e.g., hazard ratio or standardized incidence/mortality ratio in prospective or retrospective cohort studies, respectively and odds ratios in case-control studies) and 95% confidence intervals.

3.2.2 Data analysis of observational studies

For each exposure and outcome pair, we calculated the summary effect and the 95% confidence interval using both fixed and random effects inverse variance weighted methods

(176). The heterogeneity between studies was assessed with the Cochran's Q test (177) and the I^2 metric of inconsistency (178). The I^2 metric (0-100%) is the ratio of variance between studies over the sum of the variances within and between studies. Large inconsistency could reflect either genuine heterogeneity between the studies or some form of bias. We additionally calculated 95% prediction intervals for the summary random effect estimates, which further account for between study heterogeneity and represent the range of estimates that future studies would lie in (179). We examined whether smaller studies gave higher risk estimates compared to larger studies, based on the Egger's regression asymmetry test ($P \leq 0.10$) and whether the random effects summary estimate was larger than the point estimate of the largest study (i.e., smallest standard error) in the meta-analysis. We assessed the presence of excess significance bias by comparing the observed number of studies with nominally statistically significant results (i.e., $P < 0.05$) in the published literature to the expected number of studies with significant results (180). The expected number of significant studies in each meta-analysis was calculated from the sum of the statistical power estimates for each component study, calculated with an algorithm from a non-central t distribution (181, 182). The power estimates of each component study depend on the plausible effect size for the tested association, which was assumed to be the effect of the largest study in each meta-analysis (183). Excess significance for individual meta-analyses was determined at $P \leq 0.10$ (180).

3.2.3 Grading the evidence of observational studies

The strength of the evidence for observational associations between T2DM and cancer were categorized as strong, highly suggestive, suggestive, weak or not suggestive using the aforementioned criteria (184, 185). These criteria are outlined with corresponding results in detail in supplemental Table 6. Briefly, 'strong association' referred to meta-analyses with a

random effects model p value smaller than 10^{-6} (a threshold that might substantially reduce false positive findings⁽¹⁸⁶⁻¹⁸⁸⁾), more than 1,000 cancer cases, I^2 values below 50%, 95% prediction intervals not containing the null value, and no indication of small study effects or excess significance bias. Similarly, a 'highly suggestive association' required a random effects model p value smaller than 10^{-6} , more than 1,000 cancer cases, and the largest study included being nominally significant ($p < 0.05$). Meta-analyses with 'suggestive' associations had a random effects p-value smaller than 10^{-3} , and more than 1,000 cases. All other meta-analyses with a nominally significant p-value for the random effects model were classified as 'weak association'. We ran a main analysis including both cohort and case control studies and a sensitivity analysis including cohort studies only. All statistical analyses were performed using Stata version 13 (College Station, TX) (189), and all P values were two-tailed.

3.2.4 Eligibility and analysis of Mendelian randomization studies

We conducted an additional search for MR studies evaluating potential causal associations between T2DM and cancer. We additionally considered fasting insulin, fasting glucose and HbA1C as exposures, given their potential role as a mediator or as a primary mechanism in the T2DM-cancer association (159, 166-173). We therefore used the following search algorithm in PubMed, from inception to February 22nd 2019: “(diabetes OR insulin OR glucose OR HbA1c) AND (cancer OR carcinoma OR neoplasia OR tumor OR neoplasm OR maligna*) AND (mendelian randomisation OR mendelian randomization)”. The titles, abstracts, and full texts of the resulting papers were examined in detail by two authors (NP and DG), and discrepancies were resolved by consensus.

We included MR studies that assessed cancer incidence according to genetic instruments for T2DM, fasting insulin or glucose levels or HbA1C. From each eligible MR study, we extracted the name of the first author, year of publication, specific exposure studied, choice of genetic instruments, percentage of variance in the exposure explained by the instruments, outcome, sample size (cases and controls), main MR analysis approach, main result and additional sensitivity analyses. This was done in duplicate by two study authors (NP and DG). T2DM is a binary trait (i.e. an individual either has the diagnosis or does not), and therefore only a proportion of the individuals with the genetic variants used to instrument its effects will actually have the condition(190). Furthermore, unlike T2DM, genetic variants used in MR analysis to proxy its effects may have lifelong cumulative consequences that begin from conception(191). Given the resultant limitations in using MR to estimate the effect of T2DM on risk of cancer(190, 192), only the statistical significance and direction of associations were assessed(191, 193). Evidence was categorized as either ‘present’ or ‘not present’, with studies considered as providing evidence of a causal effect if they had a statistically significant effect estimate ($p < 0.05$) with further evaluation that this finding was not entirely attributable to possible bias related to pleiotropic effects of the genetic variants used as instruments(191).

3.3 RESULTS

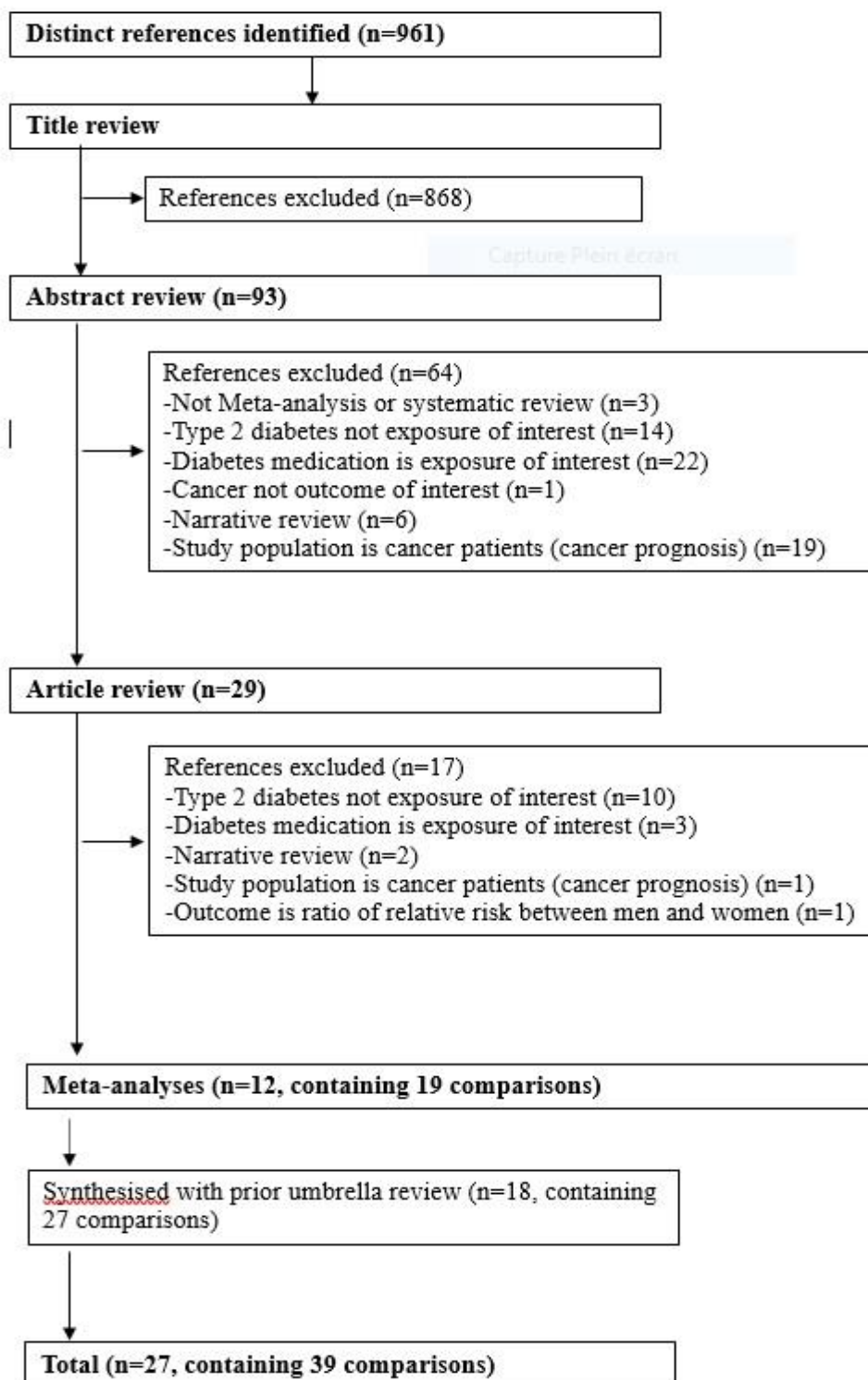


Figure 11: Flow diagram of selection process of meta-analyses of observational studies of type 2 diabetes and cancer

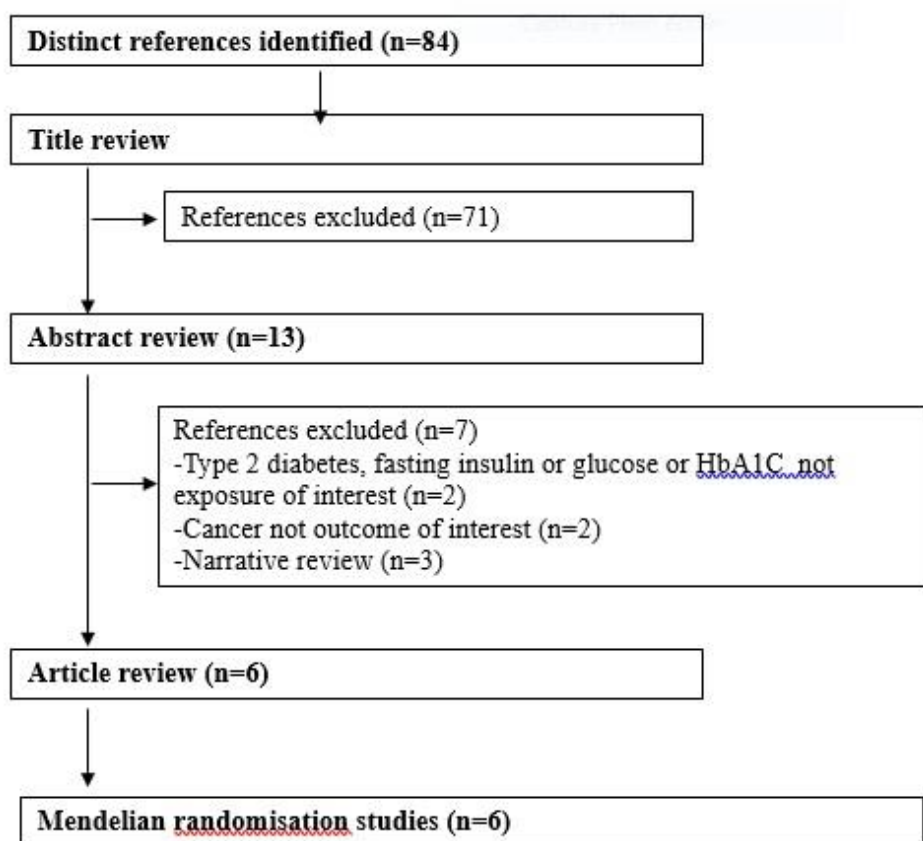


Figure 12: Flow diagram of selection process of meta-analyses of Mendelian randomization studies of type 2 diabetes and cancer

3.3.1 Observational studies

Of the 961 articles initially identified in PubMed, 12 publications reporting on 17 meta-analyses met our criteria selection. When combined with findings from the prior period covered in the previous umbrella review (163), 27 publications reported on meta-analyses that met our selection criteria: 39 associations for the main (n=29) and sensitivity (duplicate) analysis (n=10) (figure 11), which included associations of T2DM with risk of incidence (n=25) or death (n=9) or incidence or death (n=5) from oral cancer(194), esophageal(96), gastric(195),

colorectal(196, 197), hepatocellular(198, 199), cholangiocarcinoma(200), biliary tract(95), gallbladder(201), pancreatic(202, 203), lung(204), breast(205, 206), endometrial(207), ovarian(208), localised prostate(209) total prostate(210), kidney(211), bladder(212, 213), thyroid(214, 215) cancer, non-Hodgkin's lymphoma(216), myeloma(216), leukaemia(216) and glioma(217). There were 5 to 57 studies combined per meta-analysis with a median of 11 studies. All meta-analyses included more than 1,000 cases, with the exceptions of cholangiocarcinoma incidence (n=674) and hepatocellular carcinoma mortality (n=292).

Out of the 29 meta-analyses in the main analysis, the summary random effects estimates were significant at $P \leq 0.05$ in 23 meta-analyses (79%). When we used $P \leq 10^{-6}$ as a threshold for significance, only six (gallbladder, breast, hepatocellular, colorectal, endometrial and pancreatic cancer incidence) meta-analyses produced significant summary results using the random effects method (Figure 13). All these six associations suggested increased risks of cancer in individuals with T2DM. Most (n=22, 76%) of the largest study effects in each meta-analysis were nominally significant at $P \leq 0.05$. The effects of the largest studies were more conservative than the summary effects of the meta-analysis in 14 (48%) of the 29 meta-analyses. The results from random effects and fixed effects models were similar in all studies except two (breast cancer mortality, myeloma incidence) where the p value was significant in the fixed effects, but not the random effects model. (Supplemental Table 6).

The Q test showed significant heterogeneity ($P \leq 0.10$) for 23 (79%) meta-analyses and 21 (72%) comparisons had an I^2 statistic $> 50\%$ (Figure 13). There was moderate to high heterogeneity ($I^2 = 50-75\%$) in seven meta-analyses and high heterogeneity ($I^2 > 75\%$) in 14 meta-analyses (incidence of bladder, gastric, hepatocellular, kidney, lung, leukaemia, multiple myeloma, non-Hodgkin's lymphoma, pancreatic, and total prostate cancer; and mortality from breast, colorectal, gastric and hepatocellular cancer). When we calculated 95% prediction

intervals, in only five associations was the null value excluded (colorectal, endometrial, thyroid cancer incidence, and oral and endometrial cancer mortality) (Supplemental Table 6).

There was evidence for the presence of small study effects according to the Egger's test ($P < 0.10$) for the meta-analyses of lung, pancreatic and localised prostate cancer (incident only), and glioma and bladder cancer (incidence and mortality combined). However, only the bladder cancer incidence/mortality had adequate statistical power ($n = 10$ studies) for the Egger's test (21). Five (17%) meta-analyses (on incidence of bladder and pancreatic cancer, hepatocellular, and non-Hodgkin's lymphoma, and bladder cancer mortality) had evidence of a significant excess of "positive" studies when the plausible effect was assumed to be equal to the effect of the largest study in each meta-analysis (Supplemental Table 6).

In our evaluation of evidence grade, only the association between T2DM and risk of colorectal cancer incidence was supported by strong evidence (summary random effects RR, 1.27; 95% CI, 1.21-1.34), with strongly statistically significant results and no suggestion of bias (Supplemental Table 7). Highly suggestive evidence was detected for T2DM and greater risk of hepatocellular, gallbladder, pancreatic, breast and endometrial cancer incidence. 'Suggestive' evidence was found for the positive association between T2DM and biliary tract and thyroid cancer (incidence), endometrial and oral cancer (mortality), and bladder and esophageal cancers (incidence/mortality), and for the inverse association for localised prostate cancer. However, it is worth noting that associations with thyroid cancer incidence and oral and endometrial cancer satisfied all criteria for a 'suggestive' grading with the exception of the random effects p value. The remaining 10 associations under study were only supported by weak evidence.

There were 10 duplicate meta-analyses which were included in a separate sensitivity analysis (supplemental Table 8). Findings in the duplicates were consistent in evidence grade

for four associations. Most notably, duplicate studies for breast and thyroid cancer incidence had weak and not suggestive associations respectively compared to highly suggestive and suggestive associations respectively in the main analysis. When including cohort studies only, the evidence grade was altered in just two associations; breast cancer incidence (from highly suggestive to suggestive) and glioma incidence/mortality (weak to not significant) (Supplemental Table 9). Grade of evidence in all other associations remained the same.

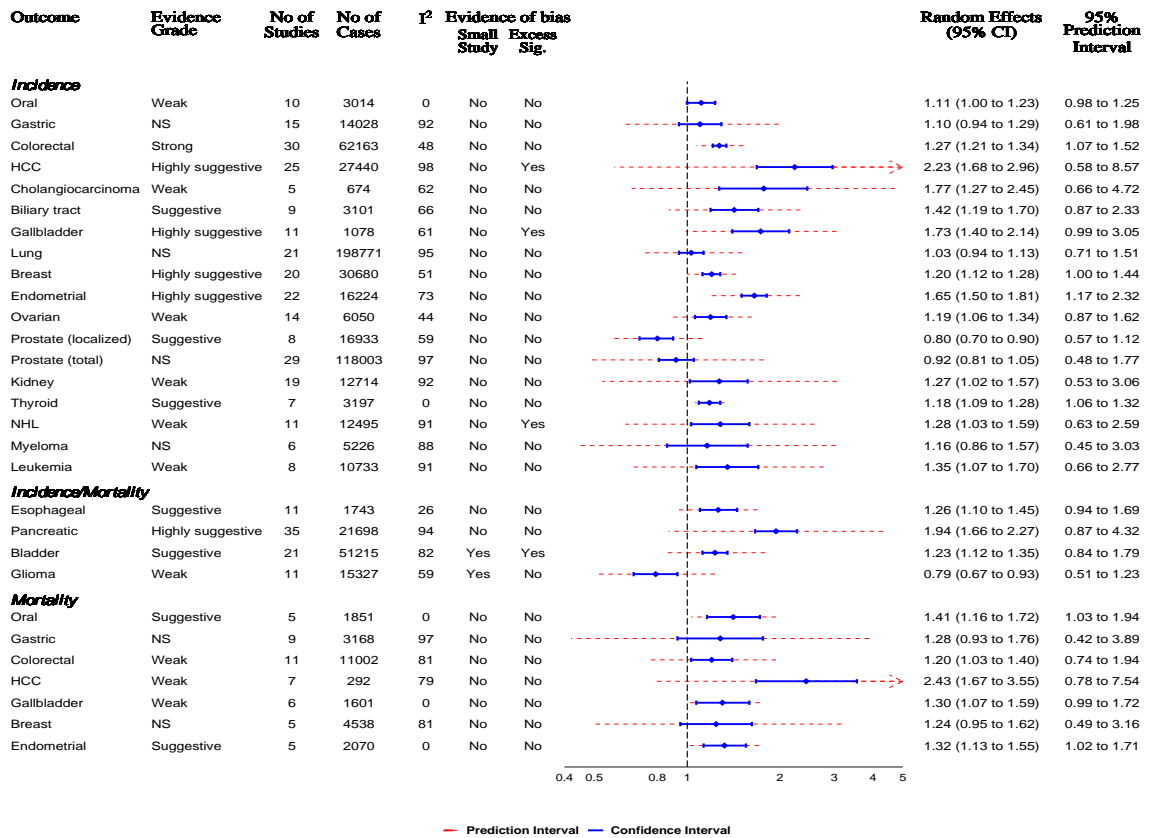


Figure 13: Summary random effects estimates with 95% confidence and prediction intervals from 29 meta-analyses of type 2 diabetes and cancer incidence, mortality or both

3.3.2 Mendelian randomization studies

Of the 84 articles initially identified in the PubMed search, four MR studies assessed a causal effect of T2DM(pancreatic(218), endometrial(219), renal cell(220), glioma(221)), while six MR studies assessed a causal effect of fasting insulin or fasting glucose with risk of cancer (pancreatic(218), lung(218) breast(222), endometrial(223), renal cell carcinoma(220) and glioma(221)) (Table 2, Figure 14-13). The methodological approaches employed varied between studies, although consideration was consistently offered to potential bias arising from the pleiotropic effect of genetic variants through pathways unrelated to the exposure under consideration (i.e. T2DM, fasting glucose or insulin).

A causal effect of genetically-determined fasting glucose was identified for squamous cell lung cancer (fasting glucose) only, with no other association for total lung or any other cancer outcomes for fasting glucose or T2DM. However, higher levels of fasting insulin were causally associated with increased risk of (total and oestrogen receptor positive) breast cancer, endometrial cancer, pancreatic cancer and renal cell carcinoma. For all of these associations, consistent results were achieved in sensitivity analyses performed to investigate possible bias related to pleiotropic variants in the main analysis. Of all the cancers investigated, only for glioma (including the glioblastoma multiforme and non-glioblastoma multiforme subtypes specifically) there was no MR evidence that higher levels of fasting insulin increased risk.

Triangulation of the evidence from both observational and MR studies suggest consistently positive associations between T2DM (observational) and fasting insulin (MR) for breast, endometrial and pancreatic cancer. The evidence for renal cell carcinoma was less concordant – weak observational evidence, but a positive association for fasting insulin using MR. The largest divergence in findings across the different study types was in lung cancer, specifically squamous cell carcinoma which had a positive association with fasting insulin in

MR, but negative findings in the observational findings, though the latter study type did not disaggregate into pathophysiological subtype.

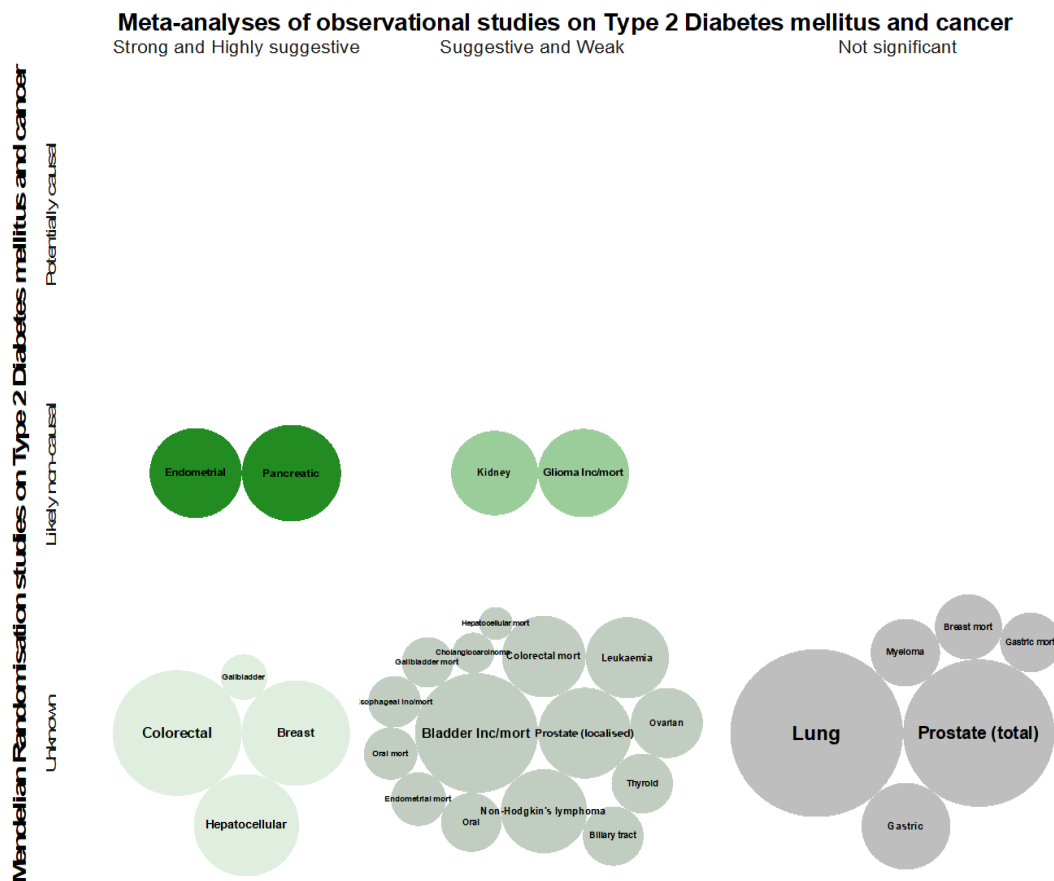


Figure 14: Triangulation of evidence from observational and Mendelian randomization studies assessing the association between type 2 diabetes and site-specific cancers. *Legend: Bubble size corresponds to the number of cases in the corresponding meta-analysis (more cases->larger bubble). Unless stated as incidence/mortality (i.e. both), is incidence, *=mortality*

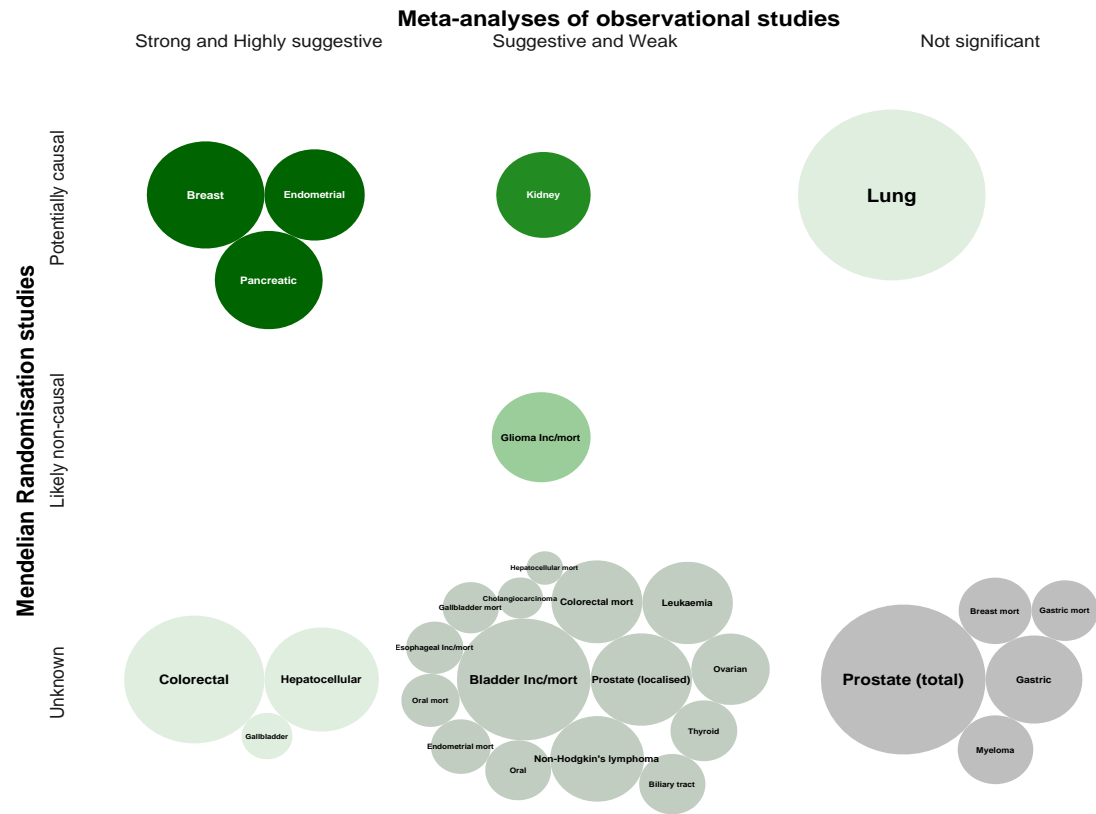


Figure 15: Triangulation of evidence from observational and Mendelian randomization studies assessing the association between fasting insulin and site-specific cancers

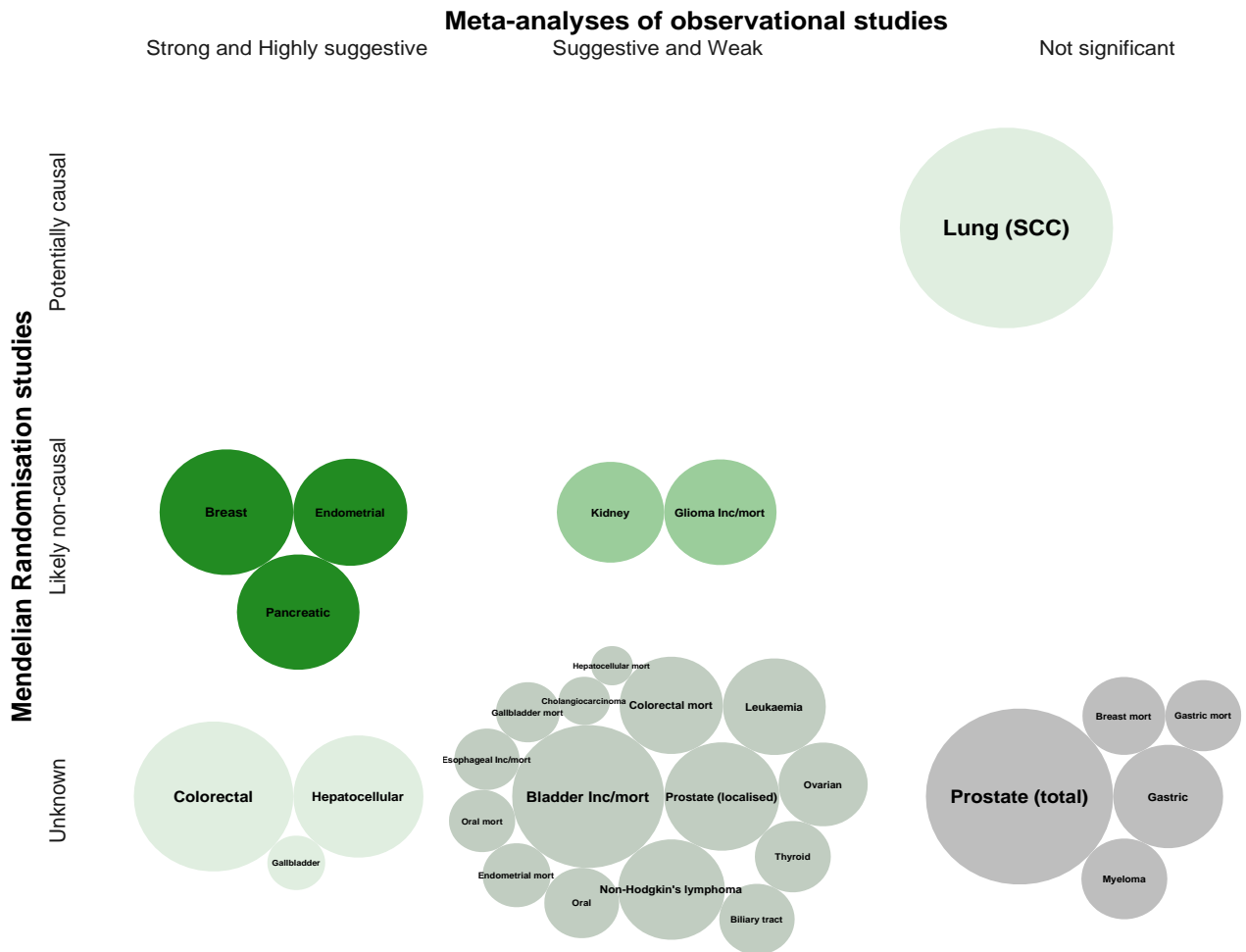


Figure 16: Triangulation of evidence from observational and Mendelian randomization studies assessing the association between fasting glucose and site-specific cancers

Table 2. Description of 6 Mendelian randomization studies of type 2 diabetes, fasting insulin and/or fasting glucose and cancer incidence in umbrella review

Study	Exposure	Cancer site	Instrument selection approach	Percentage variance explained	Outcome sample size (cases /controls)	Main MR analysis	Result (per SD-unit change in exposure)	Sensitivity analyses	MR evidence supporting a causal effect
Carreras-Torres, 2017	Type 2 diabetes mellitus (log OR)	Pancreatic	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.2$	5.7	7,110 cases and 7,264 controls	Likelihood-based MR	1.03 (0.95, 1.11; 0.47)	Exclude SNPs associated with BMI; weighted median MR; MR-Egger; stratification by sex and study	No
Nead, 2015	Type 2 diabetes mellitus (log OR)	Endometrial	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding variants at the FTO locus	~5	1,287 cases and 8,273 controls	Inverse-variance weighted MR	0.91 (0.79, 1.04; 0.16)	Investigation of unweighted instrument score associations with potential confounders; outlier SNP exclusion	No
Johansson, 2019	Type 2 diabetes mellitus (log OR)	Renal cell	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.1$	5.7	10,784 cases and 20,406 controls	Likelihood-based MR	0.99 (0.93, 1.05; 0.74)	MR-PRESSO; weighted-median MR; MR-Egger; leave-one-out analysis; stratification by sex and study	No
Disney-Hogg, 2018	Type 2 diabetes mellitus (log OR)	Glioma	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.01$	1.6	12,488 cases and 18,169 controls	Generalised summary data-based MR	1.04 (0.97, 1.11; 0.29)	HEIDI-outlier test; GBM and non-GBM	No
Carreras-Torres, 2017	Fasting insulin	Pancreatic	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding ($r^2 \geq 0.2$)	1.2	7,110 cases and 7,264 controls	Likelihood-based MR	1.66 (1.05, 2.63; 0.03)	Exclude SNPs associated with BMI; weighted median MR; MR-Egger; stratification by sex and study	Yes
Carreras-Torres, 2017	Fasting insulin	Lung	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.01$	1.2	29,266 cases and 56,450 controls	Likelihood-based MR	1.63 (1.25, 2.13; 3.2 x 10 ⁻⁴)	Weighted-median MR; MR-Egger; stratification by histology and smoking status	Yes, overall and in ever smokers
Shu, 2018	Log fasting insulin	Breast	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.1$ and BMI or WHR (adjusted for BMI) related SNPs ($r^2 < 0.8$)	0.27	98,842 cases and 83,464 controls	Inverse-variance weighted MR	1.71 (1.26, 2.31; 5.09 x 10 ⁻⁴)	MR-Egger; stratification by genotyping array, age, menopausal status, ER status and family history of breast cancer	Yes, overall and ER+

Nead, 2015	Log fasting insulin	Endometrial	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding variants at the FTO locus	~1	1,287 cases and 8,273 controls	Inverse-variance weighted MR	2.34 (1.06, 5.14; 0.03)	Investigation of unweighted instrument score associations with potential confounders; outlier SNP exclusion	Yes
Johansson, 2019	Fasting insulin	Renal cell	$P \leq 5.0 \times 10^{-8}$, European ancestry, $r^2 \geq 0.1$	1.2	10,784 cases and 20,406 controls	Likelihood-based MR	1.82 (1.30, 2.55; 5 x 10 ⁻⁴)	MR-PRESSO; weighted-median MR; MR-Egger; leave-one-out analysis; stratification by sex and study	Yes
Disney-Hogg, 2018	Fasting insulin	Glioma	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.01$	1.2	12,488 cases and 18,169 controls	Generalised summary data-based MR	1.32 (0.71, 2.46; 0.37)	HEIDI-outlier test; GBM and non-GBM	No
Carreras-Torres, 2017	Fasting glucose	Pancreatic	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.2$	4.8	7,110 cases and 7,264 controls	Likelihood-based MR	0.94 (0.72, 1.21; 0.61)	Exclude SNPs associated with BMI; weighted median MR; MR-Egger; stratification by sex and study	No
Carreras-Torres, 2017	Fasting glucose	Lung	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.01$	4.8	29,266 cases and 56,450 controls	Likelihood-based MR	1.1 (0.96, 1.26; 0.19)	Weighted-median MR; MR-Egger; stratification by histology and smoking status	Squamous cell carcinoma only
Shu, 2018	Fasting glucose	Breast	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.1$, BMI or WHR (adjusted for BMI) related SNPs ($r^2 < 0.8$)	2.3	98,842 cases and 83,464 controls	Inverse-variance weighted MR	1.02 (0.91, 1.14; 0.75)	MR-Egger; stratification by genotyping array, age, menopausal status, ER status and family history of breast cancer	No
Nead, 2015	Fasting glucose	Endometrial	$P \leq 5.0 \times 10^{-8}$, European ancestry	Not provided	1,287 cases and 8,273 controls	Inverse-variance weighted MR	1.00 (0.67, 1.50; 0.99)	Investigation of unweighted instrument score associations with potential confounders; outlier SNP exclusion	No
Johansson, 2019	Fasting glucose	Renal cell	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.1$	4.8	10,784 cases and 20,406 controls	Likelihood-based MR	0.92 (0.76, 1.12; 0.43)	MR-PRESSO; weighted-median MR; MR-Egger; leave-one-out analysis;	No

								stratification by sex and study	
Disney-Hogg, 2018	Fasting glucose	Glioma	$P \leq 5.0 \times 10^{-8}$, European ancestry, excluding $r^2 \geq 0.01$	4.8	12,488 cases and 18,169 controls	Generalised summary data-based MR	1.00 (0.78, 1.30; 0.97)	HEIDI-outlier test; GBM and non-GBM	No

3.4 DISCUSSION

Our study provides a comprehensive update in observational evidence between T2DM and cancer risk across 21 different sites and is substantially enhanced by the inclusion of MR studies, which provide insight into potential causation and mechanisms underpinning the observed associations. The most robust observational evidence of association between T2DM and increased risk of cancer were observed with colorectal, breast, endometrial, gallbladder, hepatocellular and pancreatic cancer, while MR studies supported a causal association between genetically determined fasting insulin concentrations and risk of endometrial, breast, pancreas and renal cancer. Fasting insulin was not associated with glioma in an MR analysis, consistent with the observational evidence that suggests a potential inverse association, albeit at an evidence grade judged to be weak.

This updated umbrella review advances previous work; specifically, narrowing prediction intervals for thyroid cancer incidence and endometrial cancer mortality, finding significant associations in both, whereas previously not. Further, this study included oral cancers, finding suggestive associations with mortality, but not incidence. The major advancement of this study is the inclusion of MR studies providing a more comprehensive overview of potential mechanisms and causal relationships to our understanding of diabetes-cancer associations. The opportunity to draw upon genetic data from large-scale, international consortia in MR studies allows for triangulation of evidence using distinct methodological approaches that make orthogonal underlying assumptions and suffer distinct sources of bias(224). In particular, the MR findings of our study contribute to hypothesised pathways through which T2DM may be associated with different cancers. MR findings in the present study support a causal effect of fasting insulin levels, rather than T2DM per se, on risk of breast, endometrial, pancreatic and renal cell cancer, consistent with leading hypothesis to date(166, 225, 226), and with findings from meta-analysis of observational studies for T2DM. There are important other potential mechanisms, not considered here, that may have a significant role, such as such as chronic inflammation, circulating adipokines and dysregulation of sex hormone activity(227), especially if the cancer risk in patients with diabetes is not independent of BMI.

Some associations warrant further specific discussion regarding the strength of observational evidence, as the stringency of the evidence grading system adopted(185, 228, 229) has implications for interpreting the findings for these sites specifically.. The associations with strong or highly suggestive evidence of a causal association, have similarly strong associations with high BMI. Given the negative MR findings of T2DM, this could suggest a crucial role of BMI/adiposity in mediating the excess cancer risk in this patient group. Breast and endometrial cancers were just below the threshold for having ‘strong’ evidence, owing to high levels of heterogeneity (and prediction interval including the null for breast cancer). Taken together with the positive MR results for fasting insulin, further work to elicit the underlying mechanism, the role of oestrogen and potential mediation of BMI could allow more precise risk stratification and screening opportunities in this patient group. Finally, associations for pancreatic and hepatocellular carcinoma, while not passing the stringent threshold for ‘strong’ evidence, owing to high heterogeneity and smaller number of cases per study, reflective of their relatively less common incidence, seem compelling. The MR evidence for fasting insulin (pancreatic) is supportive and the associations for both cancers are consistently approximately double in patients with T2DM compared to the non-T2DM population. The observational evidence for renal carcinoma yielded a random effect result that would meet a conventional significance test (HR 1.27, 95%CI 1.02 – 1.57) and did not include small study effects or excess significance, but was graded as weak due to high heterogeneity and a random effects p value below the more stringent standard of this study. The MR study found a positive association between fasting insulin and renal carcinoma.

The evidence provided by our study has clinical and public health implications, particularly for the cancer sites where evidence from both observational and MR studies is most robust (endometrial, breast, and pancreas). Both T2DM and cancer have increased in prevalence over the past three decades and are expected to increase further. High BMI, a shared risk factor for both of these conditions, has experienced similar, though not identical trends. The global burden of cancer attributable to all diabetes is expected to increase 30% in women and 20% in men over the next two decades(165). Therefore, this will be an increasingly important

clinical and public health priority. Secondary prevention measures, reducing the risk of complications, are vital to reducing morbidity and mortality in patients with T2DM. Reductions in mortality in these patients in the United States(230) has led to a broader set of sequelae, including cancer. Further research is needed to characterise the mechanisms and/or predictive characteristics of fasting insulin in relation to cancer risk, which could inform the development of clinical guidelines for early screening. Secondly, these results highlight the overlapping nature of T2DM and cancer, which jointly occupy an increasing share of the global disease burden(231). Population-based strategies that target the largest modifiable drivers of T2DM and cancer (poor diet, alcohol, tobacco and physical inactivity) through altering the environment to favour affordable, health promoting behaviours are the most effective and most equitable approach(232) and must be implemented without delay.

Our study was deliberately systematic and broad in its search in attempt to capture all studies investigating the association between T2DM and cancer however there was limited granularity in cancer subtype, sex and issues such as menopausal status and HRT use in the meta-analyses selected. We examined whether smaller studies gave higher risk estimates compared to larger studies, which is an indication of either publication bias, true heterogeneity or chance (90, 233) and generated prediction intervals which provide a range for the association in a potential new study. The MR framework has several advantages and is complimentary to traditional epidemiology; it is able to overcome the confounding and reverse causation bias that limits the ability to draw causal inference in traditional observational research by using genetic variants that are randomly allocated at conception as instruments to proxy the effect of the exposure under consideration(234).

Limitations of this analysis include the accuracy of diabetes status. Self-reported T2DM status is the norm in observational studies, and is 99% specific, but just 66% sensitive compared to medical records(235). Mis-classification bias is likely given 46% of all estimated diabetes prevalence is in undiagnosed individuals. Ideally, studies incorporate clinical diagnosis of diabetes and more granular detail regarding duration since diagnosis, long term glucose control (HbA1c) and treatment regimens(236) however most studies lack this

information. While our literature search was systematic, and our results consistent with duplicate independent meta-analyses, there is a risk of incomplete search. With respect to evidence grading, both asymmetry and excess significance tests offer hints of bias, not definitive proof thereof, but our estimates are likely to be conservative as a negative test result does not exclude the potential for bias. In addition, the quality of the meta-analyses, including heterogeneity and small study effects, varied. Finally, we confined the analysis to T2DM as there were very few studies, of variable quality available considering associations between Type 1 diabetes and cancer (237). Finally, our study, and the studies captured in the umbrella review do not include use of anti-diabetes medications hence we cannot exclude mediating effects of such treatment in the effects observed in our findings.

The MR approach itself has its own limitations. For this analysis we assessed studies using genetic instruments for type 2 diabetes and fasting insulin and glucose. Type 2 diabetes is a binary outcome and as such corresponding genetic instruments will only relate to its incidence in a fraction of the considered populations (termed ‘compliers’). As such, MR effect estimates that consider T2DM as the exposure can be biased(190, 192), with genetic variants used as instruments may exert effects throughout an individual’s life course, while T2DM typically arises in later life(238) therefore the lack of association with cancer risk must be interpreted with caution. In contrast, fasting insulin is a continuous trait, and it is more plausible that its genetic instruments will uniformly affect fasting insulin levels across individuals in the outcome population. Thus, this ‘monotonicity’ assumption of MR will be held, and resultant effect estimates will be less susceptible to bias(191, 192). These potential sources of bias may in part explain the discrepancy in MR results when considering either T2DM or fasting insulin as the exposure. Additionally, MR approaches vary, with no standardised or widely applicable reporting framework currently in use, which may result in more subtle bias related to methodological nuances(239). Importantly, the accumulation of data from future genome-wide association studies will enable investigation into other potential mechanisms underpinning the risk of cancer in patients with diabetes.

3.5 CONCLUSION

There is mounting evidence of a causal association between patients with diabetes and an increased risk of common cancers. Understanding the mechanistic pathways underlying this risk, and potential mediation by high BMI is crucial to allow evidence-based prevention policies.

CHAPTER 4

Interleukin-6 and risk of colorectal cancer: results from the CLUE II cohort and a meta-analysis of prospective studies (this work has been published in Cancer Causes Control in October 2015)(240)

4.1 INTRODUCTION

Interleukin-6 (IL-6) is a multifunctional cytokine produced by a variety of hematopoietic and non-hematopoietic cells (241). It exerts a pro-inflammatory role by acting either on a trans-membrane type 1 cytokine receptor or by binding to a soluble IL6 receptor (sIL6R). IL-6 up-regulates several acute-phase proteins such as C-reactive protein (CRP), fibrinogen, α 1-antitrypsin and serum amyloid A (241, 242). There is ample mechanistic evidence suggesting an involvement of IL-6 in colorectal cancer (CRC) development. In vivo experiments on wild-type mice have demonstrated that IL-6 is significantly augmented at the colonic tumor microenvironment, and the growth of colon tumours has been shown to be suppressed when the mice were treated with antibodies against IL6R (243). However, results from prospective epidemiological studies regarding the association of circulating IL-6 concentrations and risk of subsequent colorectal cancer development have generally not observed strong relationships (244-248). We have previously shown that CRP concentrations were associated with a two-fold higher risk of colorectal cancer in the CLUE II cohort (249). This report further examines the potential association between inflammation and colorectal cancer by testing an upstream to CRP biomarker, IL-6, and includes a meta-analysis of prospective epidemiological studies to summarize the evidence and study its heterogeneity.

4.2 MATERIALS AND METHODS

4.2.1 Study population

Colorectal cancer cases and controls were identified among members of the prospective CLUE II cohort. The CLUE II cohort enrolled participants from May through October 1989 primarily in Washington County, Maryland and neighboring counties or states. The aim of the cohort was to investigate potential lifestyle and serologic risk factors for cancer and heart disease. The cohort consisted of 32,894 individuals, 25,076 of whom were residents of Washington County. For this analysis, the study participants were restricted to 22,887 adult (≥ 18 years old) Washington County residents, of whom 59% were female and 98% were white reflecting the demographics of the county at the time. All participants provided a blood sample, and completed a brief medical and lifestyle exposure history questionnaire at baseline. Self-administered questionnaires were mailed to participants in 1996, 1998 and 2000 to collect and/or update information on family history of cancer, medical conditions, medication use, and lifestyle exposures. Loss to follow-up was less than 5% among cohort members who were over 45 years old at baseline, which is the age range of the majority of the cases and the pool of cohort members eligible to be selected as age-matched controls. All participants provided informed consent, and the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health approved the study.

4.2.2 Selection of colorectal cancer cases and controls

Participants were eligible to be selected as a case or a control if they were cancer-free (except possibly for non-melanoma skin cancer or cervix in situ) in 1989 or earlier. A total of 173 colorectal cancer cases were identified from 1990 through mid-2000 via linkage with the Washington County Cancer Registry and, since 1992, with the Maryland State Cancer Registry. The Maryland Cancer Registry is certified by the North American Association of Central Cancer Registries as being more than 95% complete. Compared with the Maryland Cancer Registry, the Washington County Cancer Registry captured 98% of the colorectal cancer cases diagnosed in Washington County residents in 1998. Ninety-eight percent of the cases were pathologically confirmed. A total of 124 cases had colon cancer and 48 cases had rectal cancer (1 case with missing tumour location), 68 cases had stage I or II disease and 55 cases had stage III or IV disease (50 cases were missing stage information). Ninety-nine percent and 80% of the colon and rectal cancer tumours were

adenocarcinomas, respectively. For each case, up to two controls (345 controls in total because one case was matched to only one control) matched on age (± 1 year), sex, race, date of blood draw (± 2 weeks), and time since last meal (0-1, 2-3, 4-5, 6-7, ≥ 8 hours) were selected if they were known to be alive at the time that the case was diagnosed.

4.2.3 IL-6 assessment

IL-6 concentrations were measured in the archived plasma specimens collected in 1989 by an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) in the laboratory of Dr. Rifai at Children's Hospital, Boston, MA. A total of 24 quality control samples (approximately equal to 5% of the total sample) aliquoted from pooled plasma were arranged in triplets among the cases and the two controls, and each triplet was run adjacently. The laboratory was blind to the case-control and quality control sample status. The mean intra-pair coefficient of variation was 4.3%. C-reactive protein (CRP) concentrations were also available and details of its measurement and quality control statistics are provided elsewhere (249).

4.2.4 Covariate assessment

Self-reported current weight and height, weight at age 21, schooling years, and history of smoking were collected at baseline in 1989. Body mass index (BMI) was calculated at baseline and at age 21 as weight in kilograms divided by height in meters squared. Participants were asked whether they had used any medications in the 48 hours prior to blood draw. Any medication that contained aspirin or non-aspirin non-steroidal anti-inflammatory drugs were coded as non-steroidal anti-inflammatory drugs (NSAIDs). Use of anti-diabetic and cholesterol-lowering medication was also recorded. Women were asked if they ever used oral contraceptives or hormone replacement therapy. Daily intake of alcohol (g/day) and red meat (g/day) were estimated from the food frequency questionnaire at baseline, which was an abbreviated version of the Block food frequency questionnaire comprised of 60 food items (250), and was returned by 94% of colorectal cancer cases and selected controls. Follow-up questionnaires in 1996, 1998 and 2000 ascertained whether

participants had a first-degree family history of colorectal cancer and a personal history of inflammatory bowel disease.

4.2.5 Statistical analysis

The distributions of baseline characteristics were compared between cases and controls using conditional logistic regression models, and across thirds of the IL-6 distribution among controls using linear and logistic regression models adjusted for age at recruitment and sex. Matched odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were estimated for the association of circulating IL-6 concentrations and risk of colorectal cancer using conditional logistic regression. IL-6 was modeled using continuous, after natural logarithm transformation, and categorical terms (thirds and fourths of the IL-6 distribution among controls) after inspecting non-parametric plots of IL-6 concentrations on colorectal cancer risk, where the pattern of risk changed approximately linearly with higher IL-6 concentrations in the logarithmic scale. The inferences were very similar using each of the latter IL-6 modeling approaches, thus the main results were presented using thirds and continuous variables (per 1 unit change in the natural logarithm transformed values). Linear trends were tested by entering into the model the ordinal IL-6 concentration variable with values corresponding to the thirds of the distribution among controls. Models were adjusted for known or suspected risk factors for colorectal cancer. The ORs accounting only for the matching variables were first estimated, and then models were adjusted for education (years of schooling), BMI at baseline (<25, ≥25-<30, ≥30 kg/m²), smoking status (never, former, current), NSAIDs or aspirin use (yes, no), family history of colorectal cancer (yes, no), use of diabetes treatment (yes, no) and ever use of female hormones (yes, no). None of the above confounders had any missing data. Analyses that included further adjustments for BMI at age 21, inflammatory bowel disease, cholesterol-lowering medications and daily intakes of red meat and alcohol gave very similar results and are not presented here. Furthermore, we conducted analyses according to tumor location (colon vs. rectum) and stage at diagnosis (I-II vs. III-IV), and heterogeneity according to these tumour characteristics was measured with the Cochran's Q test.

Stratified analyses were conducted according to age at recruitment (cut at the median: <66 vs. ≥66 years), sex, BMI at recruitment (<25, ≥25 kg/m²), use of aspirin or NSAIDs and ever cigarette smoking, because these variables are known to influence IL-6 concentrations and/or colorectal cancer risk. Tests for interaction were carried out by using the relevant exposure variables, indicator variables for the potentially modifying factors, and product terms of the two variables. The statistical significance of the interaction terms was evaluated by the Wald test. For these analyses, to preserve power, we broke the matched sets and performed unconditional logistic regression adjusting for the matching variables. Sensitivity analyses were performed after excluding colorectal cancer cases that developed within 2 or 5 years from the baseline blood draw to exclude the possibility that IL-6 concentrations were affected by extant cancers. To shed light on whether the association between IL-6 concentrations and colorectal cancer is independent of CRP, we further adjusted all models for CRP concentrations, and performed interaction (cut at the median: <0.2 vs. ≥0.2 mg/dL) and joint analyses for thirds of IL-6 and CRP. All p-values (P) were two-sided and all analyses were performed using STATA version 12 (College Station, TX).

4.2.6 Meta-analysis

A comprehensive search on PubMed was conducted from 1966 through April 2014 to identify prospective epidemiological studies investigating the association between prediagnostic concentrations of circulating IL-6 and the subsequent development of colorectal cancer. The following algorithm was used: “(c-reactive protein OR interleukin* OR tumor necrosis factor) AND (colorectal OR colon or rectal or large bowel) AND (cancer OR carcinoma OR neoplasia OR tumor OR adenoma OR neoplasm)”. A manual review of references from eligible studies was also performed. No language limitations were applied. Articles were excluded if (a) the research was not conducted in humans or was not original, (b) they were prognostic or diagnostic studies, (c) colorectal cancer was not the outcome of interest, and (d) circulating IL-6 was not the exposure of interest. The literature search, the review of the eligible studies and the data extraction was conducted independently by two investigators (CK and KKT), and discrepancies were resolved by consensus.

Maximally-adjusted relative risk (RR) estimates and 95% CIs for the association of the natural logarithm (ln) of IL-6 (per one unit change in ln pg/mL) with colorectal cancer were obtained from the original publications and additional risk estimates (especially by bowel location) were provided by several study authors (244, 245, 247, 248). Specifically, Chan et al. provided updated data with more cases and controls compared to the numbers in the published paper. After weighting the study specific ln RR estimates by the inverse of their variance, we calculated summary estimates and its 95% CIs using random effects models. Alternative analyses were based on fixed effects models. The meta-analysis was conducted for colorectal cancer risk and separately for colon and rectal cancer. Between-study heterogeneity was assessed with the I^2 statistic and the p-value from the Cochran's Q test, and small-study effects bias was evaluated using funnel plots and the Egger's regression asymmetry test. The methodological quality of the included studies was assessed independently by AK and KKT using the Newcastle-Ottawa scale, which accords a maximum of nine points to each study, with five or less points indicating a high risk of bias (251).

4.3 RESULTS

4.3.1 IL-6 concentrations and colorectal cancer in CLUE II

Table 3 compares the cases and controls with respect to several lifestyle, medical and dietary factors after taking into account the matched design using conditional logistic regression models. Compared to the controls, colorectal cancer cases were more likely to have a positive family history of colorectal cancer (P, 0.06), were less likely to have used aspirin or NSAIDs (P, 0.02), were more likely to have used diabetes medications (P, 0.03), and had higher concentrations of plasma IL-6 (median of 2.3 pg/mL in cases and 1.9 pg/mL in controls; P, 0.03) and CRP (P, 0.01).

Table 3. Baseline characteristics of colorectal cases and matched controls in the CLUE II cohort of Washington County, Maryland, 1989

Characteristics	Cases (n=173)	Controls (n=345)	P-value*
Age (y), mean (SD)	63.5 (11.3)	63.3 (11.4)	Matched
Men, n (%)	77 (44.5)	154 (44.6)	Matched
White, n (%)	168 (97.1)	337 (97.7)	Matched
First-degree family history of CRC, n (%)	17 (9.8)	18 (5.2)	0.06
Years of school completed, mean (SD)	11.5 (3.0)	11.9 (3.2)	0.16
BMI at recruitment (kg/m ²), mean (SD)	26.5 (4.4)	25.9 (3.9)	0.17
BMI at age 21 (kg/m ²), mean (SD)	21.9 (4.4)	21.4 (2.9)	0.11
Cigarette Smoking status, n (%)			
Current	21 (12.1)	42 (12.2)	0.44
Former	68 (39.3)	119 (34.5)	
Never	84 (48.6)	184 (53.3)	
Use (in the past 48h) of NSAIDs, n (%)	36 (20.8)	105 (30.4)	0.02
Ever use of female hormones, n (%)†	21 (21.9)	57 (29.8)	0.13
Use of diabetes medications, n (%)	14 (8.1)	12 (3.5)	0.03
Use of cholesterol-lowering medications, n (%)	17 (9.9)	20 (5.8)	0.08
History of inflammatory bowel disease, n (%)	2 (1.2)	3 (0.9)	0.75
Daily intake (g), mean (SD)‡			
Red meat	72.8 (58.9)	69.8 (73.1)	0.47
Alcohol	3.4 (9.6)	5.6 (15.6)	0.19
Plasma interleukin-6 (pg/mL), median (IQR)	2.3 (1.5-3.6)	1.9 (1.3-3.0)	0.03
Plasma C-reactive protein (mg/dL), median (IQR)	0.24 (0.13-0.55)	0.19 (0.09-0.37)	0.01

Abbreviations: SD, standard deviation; CRC, colorectal cancer; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug; IQR, inter-quartile range.

* Conditional logistic regression models accounting for the matched design. Highly skewed characteristics were transformed using the natural logarithm and were summarized using the median and IQR.

† Use of oral contraceptives or hormone replacement therapy based on 96 female cases and 191 matched controls.

‡ Based on the participants who completed the food frequency questionnaire (151 cases and 335 matched controls).

Table 4 shows baseline characteristics by concentration of IL-6 among controls after adjusting for age at recruitment and sex. Participants with higher IL-6 concentrations were on average older (P, 0.05), heavier (P, <0.01) and more likely to be men (P, 0.03). No statistically significant differences were observed for other covariates.

Table 4. Age and sex adjusted baseline characteristics according to thirds of circulating interleukin-6 among controls in the CLUE II cohort of Washington County, Maryland, 1989

Characteristics	Thirds of Interleukin-6 (pg/mL)			P-value*
	Lowest (≤ 1.40)	Second (1.41-2.56)	Third (≥ 2.57)	
Age (y), mean	61.5	63.9	64.4	0.05
Men, %	36.5	47.0	50.6	0.03
First-degree family history of CRC, %	3.2	8.0	4.4	0.67
Years of school completed, mean	12.3	11.8	11.7	0.15
BMI at recruitment (kg/m^2), mean	24.2	26.1	27.5	<0.01
BMI at age 21 (kg/m^2), mean	21.4	21.2	21.7	0.42
Ever cigarette smokers, %	45.2	44.4	49.5	0.54
Use (in the past 48h) of NSAIDs, %	30.0	32.8	27.3	0.65
Ever use of female hormones, % [†]	24.3	30.1	21.3	0.76
Use of diabetes medications, %	3.1	4.0	1.1	0.27
Use of cholesterol-lowering medications, %	5.6	4.9	5.6	0.99
Red meat (g/d), mean [‡]	67.4	68.6	73.3	0.54
Alcohol (g/d), mean [‡]	6.3	4.3	6.2	0.96

Abbreviations: CRC, colorectal cancer; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug.

* Linear or logistic regression models adjusted for age at recruitment and gender.

[†] Use of oral contraceptives or hormone replacement therapy based on 191 female controls.

[‡] Based on the participants who completed the food frequency questionnaire (335 controls).

Participants above the highest third of plasma IL-6 concentrations had an approximately 2-fold higher risk (OR, 2.09; 95% CI, 1.26-3.46; P-trend<0.01) of colorectal cancer compared with participants in the lowest third after taking into account the matching variables (Table 5). Further adjustment for education, smoking, BMI, aspirin/NSAIDs, diabetes medications, family history of colorectal cancer and female hormones, reduced the magnitude and statistical significance of the association (3rd vs. 1st third: OR, 1.76; 95% CI, 1.01-3.06; P-trend, 0.07). The fully-adjusted OR of colorectal cancer per 1 unit increase in the natural logarithm of IL-6 concentrations was 1.21 (95% CI, 0.94-1.56). Table 5 also shows the association of IL-6 with colorectal cancer by tumor location. Compared to participants in the lowest third of IL-6, participants in the highest third had a 2.48 times higher risk of colon cancer (OR, 2.48; 95% CI, 1.26-4.87; P-trend, 0.02), but no statistically significant association was observed for rectal cancer risk. When only adenocarcinoma tumors were considered among rectal cancer cases, the association remained identical (data not shown).

Table 5. Odds ratios (OR) and 95% confidence intervals (CI) of colorectal cancer according to thirds of the distribution of circulating interleukin-6 in the CLUE II cohort of Washington County, Maryland, 1989

	Thirds of Interleukin-6 (pg/mL)			P-value for trend*
	Lowest (≤ 1.40)	Second (1.41-2.56)	Third (≥ 2.57)	
Colorectal cancer				
Cases/controls, n	34/117	72/113	67/115	
OR (95% CI) [†]	1.00 (ref)	2.17 (1.35 - 3.51)	2.09 (1.26 - 3.46)	<0.01
OR (95% CI) [‡]	1.00 (ref)	1.87 (1.13 - 3.11)	1.76 (1.01 - 3.06)	0.07
Colon cancer				
Cases/controls, n	19/81	52/81	53/85	
OR (95% CI) [†]	1.00 (ref)	2.74 (1.50 - 5.01)	2.80 (1.50 - 5.25)	<0.01
OR (95% CI) [‡]	1.00 (ref)	2.55 (1.35 - 4.81)	2.48 (1.26 - 4.87)	0.02
Rectal cancer				
Cases/controls, n	15/36	19/32	14/28	
OR (95% CI) [†]	1.00 (ref)	1.42 (0.62 - 3.24)	1.18 (0.47 - 2.99)	0.65
OR (95% CI) [‡]	1.00 (ref)	0.90 (0.33 - 2.42)	0.77 (0.25 - 2.40)	0.65

* Interleukin-6 was entered into the model as a single ordinal variable with values corresponding to the thirds of its distribution among controls.

[†] From a conditional logistic regression model with the interleukin-6 concentration entered as a series of indicator variables corresponding to thirds of its distribution among the controls. Cases and controls were matched on age, sex, race, date of blood draw and time since last meal.

[‡] As in [†] but further adjusted for years of education, cigarette smoking status, body mass index at baseline, use of aspirin or non-steroidal anti-inflammatory drugs, use of diabetes medications, family history of colorectal cancer and use of oral contraceptives or hormone replacement therapy in women.

Table 6 shows the risk of colorectal and colon cancer according to a 1 unit increase in the natural logarithm of IL-6 concentrations in subgroup and sensitivity analyses. The OR of colon cancer per 1 unit increase in the natural logarithm of IL-6 concentrations was 1.50 (95% CI, 1.12-2.01), and it was statistically significantly different from the association observed for rectal cancer (OR, 0.77; 95% CI, 0.51-1.16; P-heterogeneity, 0.01). However, the associations did not differ by colorectal cancer stage or according to age at recruitment, sex, BMI, use of aspirin/NSAIDs and smoking status. The association of IL-6 concentrations with risk of colon cancer were slightly attenuated but remained statistically significant after excluding cases occurring within 2 or 5 years of the baseline blood draw or after adjusting for circulating CRP concentrations (Table 6). When we tested whether IL-6 and CRP concentrations might act synergistically to further increase the risk for colon cancer, no statistically significant multiplicative interaction was observed.

Table 6. Risk of colorectal cancer according to a 1-unit increase in the natural logarithm of interleukin-6 concentration in subgroups in the CLUE II cohort of Washington County, Maryland, 1989

	Cases/Controls	Odds Ratio (95% Confidence Interval)*	P-value for interaction/heterogeneity
All colorectal cancer	173/345	1.21 (0.94 - 1.56)	
Adjustment for CRP	172/343	1.17 (0.88 - 1.55)	
Stage I or II CRC	68/345	1.19 (0.84 - 1.67)	
Stage III or IV CRC	55/345	1.32 (0.87 - 2.01)	0.71†
Age<66 years	83/167	1.05 (0.73 - 1.52)	
Age≥66 years	90/178	1.43 (0.99 - 2.08)	0.45
Men	96/191	0.91 (0.63 - 1.32)	
Women	77/154	1.61 (1.11 - 2.35)	0.11
BMI<25 kg/m ²	69/152	1.70 (1.10 - 2.63)	
BMI≥25 kg/m ²	104/193	1.05 (0.76 - 1.44)	0.23
Users of aspirin/NSAIDs	36/105	1.01 (0.54 - 1.90)	
Nonusers of aspirin/NSAIDs	137/240	1.26 (0.94 - 1.68)	0.64
Never smokers	84/184	1.35 (0.95 - 1.93)	
Ever smokers	89/161	1.08 (0.73 - 1.60)	0.40
CRP<0.2 mg/dL	72/176	0.89 (0.57 - 1.38)	
CRP≥0.2 mg/dL	100/167	1.33 (0.95 - 1.87)	0.13
Joint third analysis IL-6/CRP			
Third 1 / third 1	17/65	1.00 (ref)	
Third 1 / third 2	10/37	0.96 (0.39 - 2.40)	
Third 1 / third 3	6/13	1.92 (0.61 - 6.07)	
Third 2 / third 1	18/31	2.07 (0.91 - 4.72)	
Third 2 / third 2	27/46	1.97 (0.94 - 4.14)	
Third 2 / third 3	27/36	2.69 (1.22 - 5.92)	
Third 3 / third 1	4/18	0.80 (0.23 - 2.75)	
Third 3 / third 2	23/32	2.60 (1.17 - 5.77)	
Third 3 / third 3	40/65	2.03 (0.97 - 4.28)	0.45
Exclude cases occurring within 2 years of baseline blood draw	135/345	1.12 (0.85 - 1.48)	
Exclude cases occurring within 5 years of baseline blood draw	82/345	1.09 (0.78 - 1.52)	
All colon cancer	124/345	1.50 (1.12 - 2.01)	0.01†
Adjustment for CRP	123/343	1.40 (1.01 - 1.94)	
Stage I or II CRC	48/345	1.53 (1.02 - 2.29)	
Stage III or IV CRC	46/345	1.40 (0.89 - 2.19)	0.77
Age<66 years	59/167	1.60 (1.02 - 2.52)	
Age≥66 years	65/178	1.39 (0.92 - 2.10)	0.17
Men	66/191	1.16 (0.75 - 1.81)	
Women	58/154	1.88 (1.23 - 2.87)	0.19
BMI<25 kg/m ²	49/152	1.89 (1.16 - 3.09)	
BMI≥25 kg/m ²	75/193	1.28 (0.88 - 1.86)	0.26
Users of aspirin/NSAIDs	28/105	1.15 (0.59 - 2.26)	
Nonusers of aspirin/NSAIDs	96/240	1.57 (1.12 - 2.20)	0.42
Never smokers	58/184	2.06 (1.34 - 3.18)	

Ever smokers	66/161	1.17 (0.76 - 1.80)	0.11
CRP<0.2 mg/dL	46/176	1.26 (0.72 - 2.21)	
CRP≥0.2 mg/dL	77/167	1.50 (1.03 - 2.19)	0.53
Joint third analysis IL-6/CRP			
Third 1 / third 1	8/65	1.00 (ref)	
Third 1 / third 2	5/37	1.04 (0.30 - 3.58)	
Third 1 / third 3	5/13	3.75 (1.00 - 14.0)	
Third 2 / third 1	9/31	2.24 (0.76 - 6.60)	
Third 2 / third 2	21/46	3.41 (1.35 - 8.62)	
Third 2 / third 3	22/36	5.09 (1.93 - 13.4)	
Third 3 / third 1	4/18	1.83 (0.48 - 7.02)	
Third 3 / third 2	17/32	4.08 (1.53 - 10.9)	
Third 3 / third 3	32/65	3.70 (1.46 - 9.33)	0.12
Exclude cases occurring within 2 years of baseline blood draw	98/345	1.44 (1.06 - 1.98)	
Exclude cases occurring within 5 years of baseline blood draw	61/345	1.46 (1.01 - 2.13)	

* From a logistic regression model according to a 1-unit increase in the natural logarithm of interleukin-6 concentration adjusted for the matching variables (age, sex, race, date of blood draw and time since last meal), and further adjusted for years of education, cigarette smoking status, body mass index at baseline, use of aspirin or non-steroidal anti-inflammatory drugs, use of diabetes medications, family history of colorectal cancer and use of oral contraceptives or hormone replacement therapy in women.

†P-values for heterogeneity using the Cochran's Q test comparing risk estimates by stage (I/II vs. III/IV) and anatomical location (colon vs. rectal) of colorectal cancer. The remaining p-values are for evaluating interactions in subgroup analyses by age, sex, BMI, aspirin/NSAID use, smoking and CRP, and are calculated using the Wald test.

4.3.2 Meta-analysis of IL-6 concentrations and colorectal cancer

Of the 6,484 articles initially identified in PubMed, six publications with results from seven prospective studies were selected for the meta-analysis including the current study in the CLUE II cohort (Figure 17). Five studies were conducted in the USA and two in the UK. The number of colorectal cancer cases ranged from 30 to 413, and all seven studies summed to 1,308 cases and 8,420 controls (Supplemental Table 10). Three studies had a cohort design, another three were nested case-control studies and one used a case-cohort design. The quality of the included studies was good with a median Newcastle-Ottawa quality score of 7 (Supplemental Tables 10 and 11). Circulating IL-6 concentrations were not statistically significantly associated with risk of colorectal cancer (Figure 18; 7 studies; per one unit change in ln IL-6; random-effects summary RR, 1.10; 95% CI, 0.94-1.28). There was small between-study heterogeneity (I^2 , 34%; P, 0.17), and

no evidence of small-study effects was detected by inspecting the funnel plot or using the Egger's regression asymmetry test (P, 0.77).

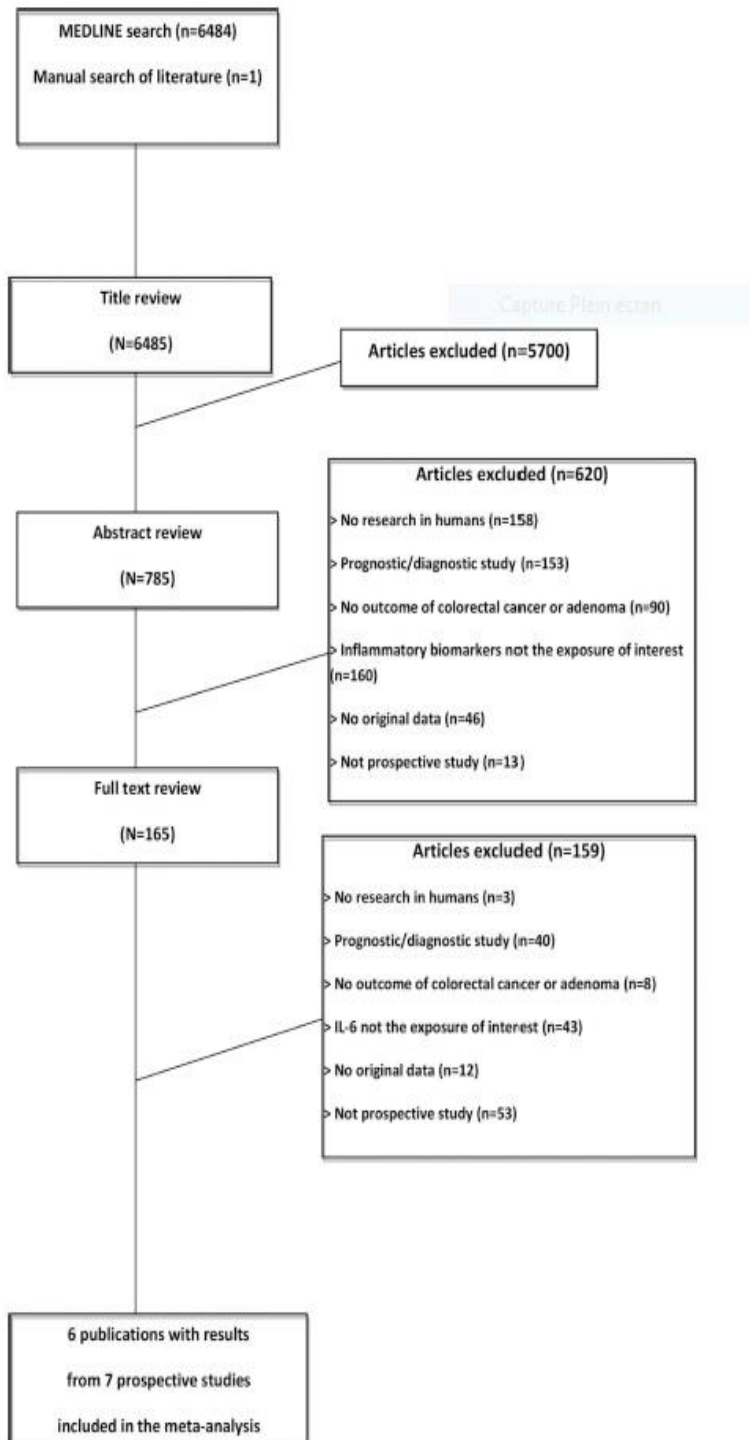


Figure 17: Flow diagram of the study selection process in the meta-analysis of IL-6 and colorectal cancer

A total of six studies provided results according to colorectal cancer location, which summed to 919 and 271 colon and rectal cancer cases, respectively. The summary association per one unit increase in ln IL-6 for colon cancer risk was positive and borderline statistically significant using the random-effects method (Figure 18; RR, 1.22; 95% CI, 1.00-1.49) with some evidence of between-study heterogeneity (I^2 , 46%; P, 0.10). The association was nominally statistically significant with the fixed-effects method (RR, 1.22; 95% CI, 1.06-1.40). However, for rectal cancer risk the association was statistically significantly inverse (RR, 0.69; 95% CI, 0.54-0.88) with no evidence of heterogeneity (I^2 , 0%; P, 0.81). The summary associations for colon and rectal cancer were statistically significantly different (P, <0.001). No evidence of small-study effects was detected in the colon cancer analysis (P, 0.81), but smaller studies tended to give larger estimates of effect size compared to larger studies for the rectal cancer analysis (P, 0.02).

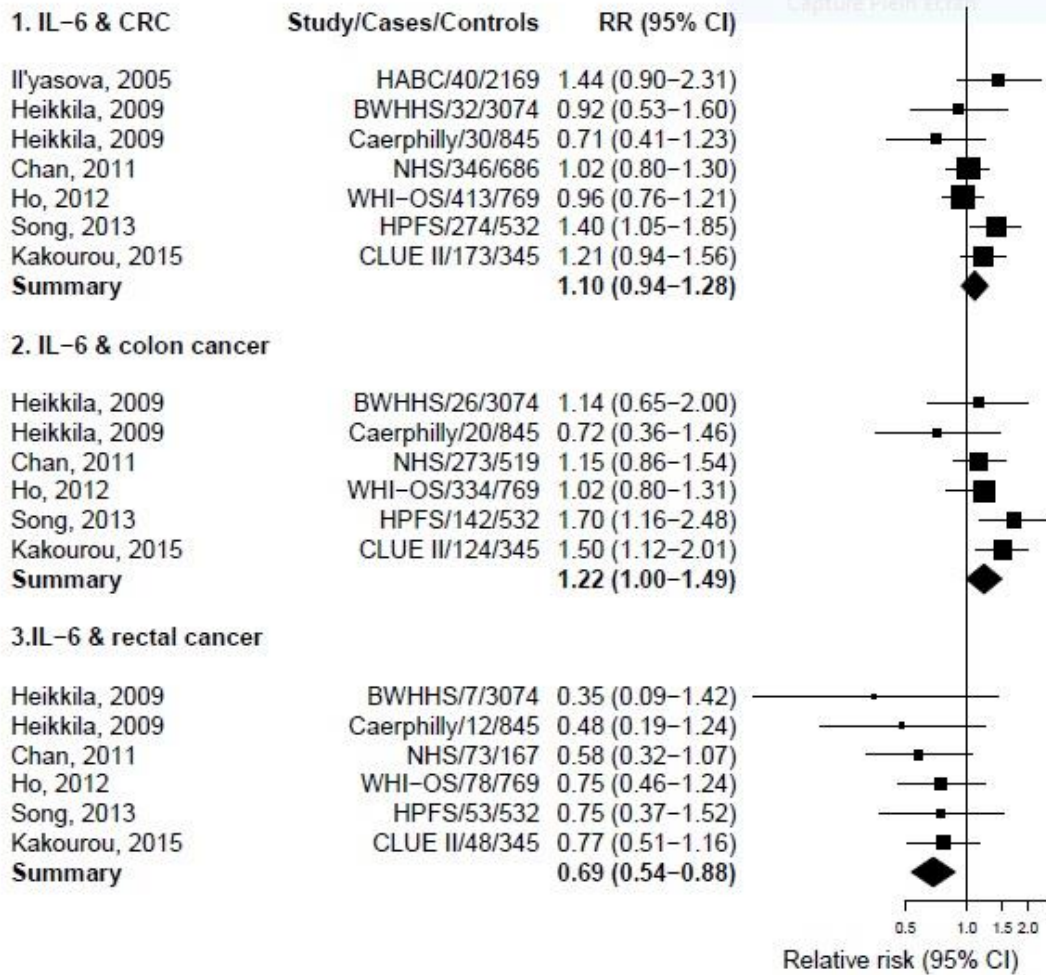


Figure 18: Forrest plot of the seven studies included in the meta-analysis of pre-diagnostic IL-6 concentrations and risk of colorectal, colon and rectal cancer

4.4 DISCUSSION OF THE RESULTS

Prediagnostic concentrations of circulating IL-6 were associated with the subsequent development of colon cancer in the prospective CLUE II cohort. This association did not differ according to the stage of disease, age, sex, CRP concentrations or by other potential modifying variables, and remained statistically significant after adjustment for CRP concentrations and after excluding cases that occurred within two or five years of follow-up, thus reducing the likelihood that the results could reflect presence of subclinical disease

at the time of blood collection. No association was observed between IL-6 and rectal cancer risk. The meta-analysis showed that higher IL-6 concentrations were associated with a borderline statistically significant higher risk of colon cancer but with a significant lower risk of rectal cancer.

The overall literature evidence for an association between IL-6 concentrations and risk of colorectal cancer is sparse, as only 6 prospective studies exist (244-248). Il'yasova and colleagues found that serum IL-6 concentrations were not statistically significantly associated with risk of colorectal cancer in the Health Aging and Body Composition Cohort (246). Similarly, no association was observed in two British prospective studies published in 2009 (244), but the latter three studies included small numbers of colorectal cancer cases (n=30-40). Chan et al. used 279 cases from the Nurses' Health Study but also did not observe a statistically significant association (248), and another large publication (413 cases) from the Women's Health Initiative observational cohort yielded a similar not significant finding (247). Only, a recent paper from the Health Professionals Follow-up Study observed a borderline significant increased risk of colorectal cancer with higher IL-6 concentrations, but this association did not remain significant when the first two years of follow-up were excluded (245). In the current paper from the CLUE II cohort, we also did not observe a statistically significant association between IL-6 concentrations and risk of colorectal cancer. When we synthesized the results of the latter seven studies in a meta-analysis, we observed a non-significant summary RR of 1.10 (95% CI, 0.94-1.28) per one unit change in ln IL-6. Very few reports have studied the association between IL-6 concentrations and risk of colorectal adenoma, and observed inconsistent findings (252, 253).

However, the association between IL-6 concentrations and colon cancer risk was statistically significant in the CLUE II cohort. Only one other study reported results by tumour location in the original publication (245), but several study authors sent us site-specific risk estimates after communicating with them. In four studies, the association of IL-6 concentrations and colon cancer risk was not statistically significant (244, 247, 248). However, the Health Professionals Follow-up Study (HPFS) observed a statistically significant increased risk of colon cancer with higher IL-6 concentrations (245). When we synthesized the results of the six studies in a meta-analysis, we observed a borderline statistically significant summary RR of 1.22 (95% CI, 1.00-1.49) per one unit change in ln IL-6 concentrations without substantial between-study

heterogeneity. It is important to note that the two cohorts (CLUE II and HPFS) that observed significant increased risks for IL-6 and colon cancer risk, also reported that those estimates were attenuated (the results in CLUE II remained significant) after excluding cases occurring within 2 or 5 years of the baseline blood draw. Future large prospective studies are warranted to confirm whether IL-6 concentrations are associated with colon cancer risk.

The association between IL-6 concentrations and rectal cancer risk was not statistically significant in the CLUE II cohort but the point estimate was below unity, and this finding was significantly different from the association observed for colon cancer risk. Five studies sent us results for rectal cancer risk and they were all quite homogeneous with estimates below unity without reaching statistical significance (244, 245, 247, 248). When we synthesized the results of the six studies, the summary association was statistically significantly inverse (RR, 0.69; 95% CI, 0.54-0.88). Findings suggesting possible inverse relationships between IL-6 concentrations and cancer risk are intriguing but have no easy explanations. Increased IL-6 concentrations may reflect both the level of inflammatory status and an attempt by the host to suppress tumour formation or growth. Another explanation may involve the biologic differences of the colon and the rectum, but when we excluded rare histologies (e.g., squamous cell carcinomas) from the rectal cancer analysis, the results remained identical. The inverse finding could be also due to chance or bias, because it was based on only 271 rectal cancer cases and we found evidence of small-study effects in the meta-analysis, where the smaller studies observed stronger inverse estimates, which offer a hint for possible publication and other selective reporting biases, but they may also reflect genuine heterogeneity, chance or other reasons for differences between small and large studies (233).

There is ample evidence suggesting an association between inflammation and colorectal neoplasia. Animal models and mechanistic studies implicate inflammation as a risk factor for colorectal cancer (254-256). In addition, patients with inflammatory bowel disease are at increased risk of developing colorectal cancer (257), and regular aspirin or NSAID use reduces colorectal cancer risk or adenoma recurrence (258-261). However, epidemiological studies of inflammatory biomarkers, like CRP and TNF- α , have observed mixed results (262-268). A meta-analysis that our team conducted in 2008 found that increased circulating

CRP concentrations were weakly associated with an increased risk of colorectal cancer (269). More recently, two prospective studies reported an increased risk of colorectal cancer with higher CRP concentrations (270, 271), whereas four other prospective studies reported no significant association (244, 245, 248, 272). An updated meta-analysis published in 2014 reported that CRP concentrations were weakly associated with an increased risk of colorectal and colon cancer, but not with rectal cancer risk (273). When we investigated whether increased CRP is marking colonic inflammation, we found no such association in a colonoscopy-based study, which implies that CRP may be marking systemic factors that influence colorectal cancer risk or that the observational associations between CRP and colorectal cancer may be afflicted by biases. Further evidence from some Mendelian randomization studies have reported that the association between CRP concentration and risk of colorectal cancer may not be causal (free of biases) after using CRP genotypes as instruments of the blood concentrations (274, 275), although this evidence was not entirely consistent in other Mendelian randomization studies (276, 277). An empirical evaluation of the cancer epidemiology literature that our team conducted in 2012, identified a statistically significant excess of positive studies, suggesting potentially the presence of selective reporting biases, among articles that investigated the association between biomarkers of inflammation and cancer risk (182). More studies and individual-level data pooled analysis thereof are warranted to elucidate the potential association of plasma IL-6 with colonic inflammation and colorectal cancer risk.

Several factors should be considered in the interpretation of our findings.

The strengths of our study include its prospective design and highly complete follow-up rate, that IL-6 was measured pre-diagnostically and that almost all colorectal cancer cases were pathologically confirmed. Our study also has potential limitations. A single measurement of IL-6 does not necessarily represent an average concentration over time for this biomarker and this might have caused regression dilution bias. However, IL-6 concentrations have been shown to be generally stable over time (278). Moreover, plasma IL-6 might not be well correlated with tissue-specific inflammation that is most relevant for colorectal carcinogenesis. In addition, it is always possible that inadequate control for potential confounders may influence findings of

epidemiological studies, but we have measured and adjusted for many potential confounders in the current study.

4.5 CONCLUSIONS

In summary, our findings provide support for a modest positive association between circulating IL-6 concentration and colon cancer risk. More work is needed to determine whether IL-6 is a valid marker of colorectal inflammation and whether such inflammation contributes and how to colon and rectal cancer risk.

Chapter 5

Discussion

5.1 SUMMARY OF FINDINGS

This thesis aimed to investigate potential associations between hypertension, T2DM and inflammation with cancer incidence and mortality. We examined these associations in three separate studies. Two of the studies were conducted within two cohorts: EPIC (115) and CLUE II (240). The third study was an umbrella review of the evidence on the association of T2DM and the risk of developing cancer with an additional umbrella review of Mendelian randomization studies that assessed cancer incidence according to genetic instruments for T2DM, fasting insulin, glucose or glycated haemoglobin (HbA1C) levels.

In the first study presented in this thesis (chapter 2), we examined the association of SBP, DBP, MBP, hypertension and antihypertensive treatment with the development of incident cancer at all anatomical sites for. This study included 307,318 men and women, with an average follow-up of 13.7 (standard deviation 4.4) years and identified 39,298 incident cancers. We confirmed the expected positive association of SBP and DBP with renal cell carcinoma. We additionally found positive associations for oesophageal squamous cell carcinoma, and weaker associations for head and neck cancers, skin SCC, colon cancer, post menopausal breast cancer and uterine adenocarcinoma (AC), but not for oesophageal AC, lung SCC, lung AC or uterine endometrioid cancer. We observed weak inverse associations of SBP with cervical SCC and lymphomas. There were no consistent associations with cancers in other locations.

In the second study of this thesis (chapter 3), we evaluated the association of T2DM and the risk of developing cancer by performing an umbrella review of the observational evidence. Additionally, we extended the analysis to include evidence from Mendelian randomization studies. We found eligible observational meta-analyses that assessed associations between T2DM and cancer incidence in 18 cancer sites/sub-sites, cancer mortality in seven cancer sites, and cancer incidence or mortality in four cancer sites. When assessing study quality and strength of evidence, studies of six cancer sites did not have substantial heterogeneity and had strong or highly suggestive evidence of association with incident cancers - colorectal, hepatocellular,

gallbladder, pancreatic, breast and endometrial. In the umbrella review of Mendelian randomisation studies, we found four studies assessing the effect of genetically predicted T2DM and six studies assessing the effect of genetically predicted fasting insulin or fasting glucose upon site specific cancers. No association was found between genetically predicted T2DM or fasting glucose with any cancer, except for fasting glucose and squamous cell lung cancer, whereas genetically predicted fasting insulin was associated with an increased risk of breast, endometrial, pancreatic and renal cancer.

In the third study of this thesis (chapter 4), we examined the association between prediagnostic interleukin-6 (IL-6) concentrations and risk of colorectal cancer in a nested case-control study and a meta-analysis of prospective studies. Colorectal cancer cases (n=173) and matched controls (n=345) were identified between baseline in 1989 and 2000 from among participants in the CLUE II cohort of Washington County, Maryland. Participants in the highest third of plasma IL-6 concentration had a 2.48 times higher risk of colon cancer compared to participants in the bottom third (95% CI, 1.26-4.87; P-trend, 0.02) after multivariate adjustment. This association did not differ according to the stage of disease, age, sex, or by other potential modifying variables, and remained statistically significant after adjustment for C-reactive protein concentrations. No statistically significant association was observed for rectal cancer risk. The meta-analysis of six prospective studies yielded an increased but borderline statistically significant risk of colon cancer per one unit increase in naturally logarithm transformed IL-6 (summary RR, 1.22; 95% CI, 1.00-1.49; I^2 , 46%). An inverse association was noted for rectal cancer (RR, 0.69; 95% CI, 0.54-0.88; I^2 , 0%) but there was evidence for small-study effects bias (P, 0.02).

5.2 PUBLIC HEALTH IMPLICATIONS

Our findings provide insight into cancer burden providing a call for further research on cancer prevention and early detection in a time period where cancer incidence constantly increases at a global level. Diabetes, hypertension, obesity and cancer have a complex relationship, which is linked to several common factors such as diet, body fat distribution, physical activity, hyperglycemia, insulin and insulin-like growth factor signaling, adipokines, sex hormones, inflammation, and oxidative stress. The evidence provided by our studies has clinical and public health implications, particularly for the cancer sites where evidence is most robust. Hypertension, T2DM, inflammatory conditions and cancer have increased in prevalence over the past three decades and are expected to increase further. High BMI, a shared risk factor for all three conditions, has experienced similar trends. The global burden of cancer attributable to all diabetes is expected to increase 30% in women and 20% in men over the next two decades (165). Likewise, a total 481,000 or 3.6% of all new cancer cases worldwide in 2012 were attributable to excess BMI (279).

Secondary prevention measures are vital to reducing morbidity and mortality in patients with T2DM, hypertension and chronic inflammatory conditions. Population based strategies that target, the largest modifiable drivers of T2DM, hypertension, inflammation and cancer (poor diet, alcohol, tobacco and physical inactivity) and health promoting behaviours are the most effective and equitable approach and must be implemented without delay (232). Therefore, this should be an increasingly important clinical and public health priority, as rates of some leading cancers could be substantially reduced by lowering exposure to these risks.

5.3 DIRECTIONS OF FUTURE RESEARCH

There is evidence that inflammation, T2DM and hypertension affect cancer risk. Several of those associations can be causal but uncertainty still remains in many cases.

Moreover, more research is needed to dissect the biological mechanisms through which these factors lead to cancer.

Given that hypertension is a major modifiable risk factor and its control remains inadequate, our findings highlight the need and importance of current public health strategies aimed at preventing and effectively controlling hypertension to reduce the incidence of a number of diseases related to elevated BP including kidney cancer. In addition, more experimental studies are warranted to better delineate underlying biological mechanisms of this association. Molecular epidemiology studies may also help into better understanding the potential link between hypertension and cancer by incorporating multi-omics measurements.

Furthermore, documentation of exposure to lifestyle factors like T2DM is usually based on self-reports which are prone to measurement errors and biases. Therefore, future studies should improve the reliability of the exposures' measurements.

Finally, another idea for future research is to study the potential joint effects of inflammation, diabetic perturbations and hypertension on cancer risk, since there are common risk factors such as diet, body fat distribution, physical activity, hyperglycemia, insulin and insulin-like growth factor signaling, adipokines, sex hormones and oxidative stress. In the current dissertation, we investigated the independent effects on cancer, but several of the relevant pathophysiological pathways are interrelated, therefore it would be interesting to study their joint effect.

CHAPTER 6

CONCLUSIONS

From the current dissertation several important points arise. Firstly, we identified clear associations between inflammation, diabetes and several cancers. Therefore, there is still room for improvement in the area of cancer prevention and detection in order to reduce cancer incidence.

Secondly, there are some associations with hypertension and some cancers but in most cases, they were small in magnitude and weak associations can be explained by small biases.

Finally, further replication of the identified associations and research on the biological pathways mediating these associations is required to strengthen the public health messages and to potentially identify molecular targets for prevention and treatment of cancer.

ΠΕΡΙΛΗΨΗ ΣΤΑ ΕΛΛΗΝΙΚΑ

Ο καρκίνος είναι ένα σημαντικό πρόβλημα δημόσιας υγείας παγκοσμίως και είναι η δεύτερη αιτία θανάτου. Η τελευταία έκδοση της βάσης δεδομένων GLOBOCAN (Σεπτέμβριος 2018) προβλέπει 18 εκατομμύρια περιπτώσεις καρκίνου και 9.6 εκατ. θανάτους από καρκίνο για το 2018. Ο κύριος στόχος αυτής της εργασίας είναι η διερεύνηση πιθανών συσχετίσεων μεταξύ μεγάλων κατηγοριών πιθανών παραγόντων κινδύνου, δηλαδή αρτηριακή πίεση, σακχαρώδης διαβήτης τύπου 2 και φλεγμονή, και της επίπτωσης του καρκίνου. Τα συγκεκριμένα ερωτήματα διερευνήθηκαν μέσα από τρεις ξεχωριστές μελέτες:

Στην πρώτη μελέτη χρησιμοποιήθηκαν δεδομένα από την Ευρωπαϊκή Προοπτική Μελέτη Καρκίνου και Διατροφής (EPIC) και εξετάστηκε η συσχέτιση της αρτηριακής πίεσης με τον κίνδυνο εμφάνισης καρκίνου σε όλες τις ανατομικές περιοχές. Εκτιμήθηκαν οι λόγοι κινδύνου (HRs) χρησιμοποιώντας μοντέλα αναλογικού κινδύνου του Cox για τη συστολική αρτηριακή πίεση (ΣΑΠ), διαστολική αρτηριακή πίεση (ΔΑΠ), μέση αρτηριακή πίεση (ΜΑΠ), υπέρταση και αντιυπερτασική θεραπεία. Επιπλέον εξετάστηκε πιθανή παρουσία στατιστικών αλληλεπιδράσεων ανάλογα με την ηλικία, το φύλο, το δείκτη μάζας σώματος (ΔΜΣ), το κάπνισμα, την πρόσληψη οινοπνευματωδών ποτών και τη χρήση αντιυπερτασικής θεραπείας. Τέλος εκτελέστηκαν αναλύσεις ευαισθησίας, εξαιρώντας τα πρώτα δύο έτη της παρακολούθησης για να μειωθεί το ενδεχόμενο ανάστροφης αιτιότητας. Η μελέτη περιελάμβανε συνολικά 307.318 άνδρες και γυναίκες, με μέση παρακολούθηση 13.7 (τυπική απόκλιση 4.4) χρόνων και 39.298 περιστατικά καρκίνου. Επιβεβαιώσαμε την αναμενόμενη θετική συσχέτιση με τον καρκίνο του νεφρού: HR = 1.12 (1.08-1.17) ανά 10 mmHg υψηλότερης ΣΑΠ και HR = 1.23 (1.14-1.32) για την ΔΑΠ. Επιπλέον, διαπιστώσαμε θετικούς συσχετισμούς για τον καρκίνο πλακωδών κυττάρων του οισοφάγου: HR = 1.16 (1.07-1.26) (ΣΑΠ), HR = 1.31 (1.13-1.51) (ΔΑΠ), ασθενέστερους συσχετισμούς για καρκίνους κεφαλής και τραχήλου: HR = 1.08 (1.04-1.12) (ΣΑΠ), HR = 1.09 (1.01-1.17) (ΔΑΠ) και ομοίως για τον καρκίνο πλακωδών κυττάρων του δέρματος, τον καρκίνο του παχέος εντέρου, τον μετεμμηνοπαυσιακό καρκίνο του μαστού και το αδενοκαρκίνωμα της μήτρας. Παρατηρήσαμε αδύναμους αρνητικούς συσχετισμούς της ΣΑΠ με τον καρκίνο πλακωδών κυττάρων του τραχήλου της μήτρας : HR = 0.91 (0.82-1.00) και τα λεμφώματα: HR = 0.97 (0.93-1.00). Δεν βρέθηκαν συσχετίσεις με άλλους

καρκίνους. Τα αποτελέσματά μας είναι σε μεγάλο βαθμό συμβατά με δημοσιευμένες μελέτες και επιβεβαιώνουν ασθενείς συσχετισμούς αρτηριακής πίεσης με καρκίνους σε συγκεκριμένες θέσεις και μορφολογίες.

Στη δεύτερη μελέτη αξιολογήθηκε η ισχύς της βιβλιογραφίας αναφορικά με τη συσχέτιση του διαβήτη τύπου 2 (ΣΔτ2) με τον κίνδυνο ανάπτυξης και θανάτου από καρκίνο μέσω μιας ανασκόπησης ομπρέλας. Υπολογίστηκε η συνοπτική επίδραση και τα 95% διαστήματα εμπιστοσύνης με τη χρήση σταθμισμένων μεθόδων αντίστροφης διακύμανσης σταθερών και τυχαίων επιδράσεων. Επιπλέον αξιολογήθηκε η ετερογένεια της μελέτης με τη δοκιμασία Q του Cochran και τη μέτρηση I^2 της ασυνέπειας καθώς και η μεθοδολογική ποιότητα όλων των μετα-αναλύσεων που περιλαμβάνονταν με το εργαλείο AMSTAR, ένα ερωτηματολόγιο 11 σημείων στο οποίο αθροίζονται οι θετικές απαντήσεις για να επιτευχθεί συνολική βαθμολογία ποιότητας. Τέλος, πραγματοποιήθηκε μία πρόσθετη ανασκόπηση των μελετών Μεντελιανής τυχαιοποίησης που αξιολόγησαν κατά πόσο γενετικά προκαθορισμένη πιθανότητα εμφάνισης ΣΔτ2 και επιπέδων ινσουλίνης, γλυκόζης και γλυκοζυλιωμένης αιμοσφαιρίνης (HbA1C) συσχετίζονται με τον κίνδυνο εμφάνισης καρκίνου. Βρήκαμε σχετικές μετα-αναλύσεις μελετών παρατήρησης που αξιολόγησαν τις συσχετίσεις μεταξύ του ΣΔτ2 και της επίπτωσης 18 καρκίνων, τη θνησιμότητα από 7 καρκίνους και την εμφάνιση ή τη θνησιμότητα από 4 καρκίνους. Οι συνολικές εκτιμήσεις τυχαίων επιδράσεων ήταν στατιστικά σημαντικές με τιμή κριτηρίου $P < 0.05$ σε 23 μετα-αναλύσεις (79%). Κατά την αξιολόγηση της ποιότητας των διαθέσιμων τεκμηρίων, βρέθηκε ισχυρή ή εντόνως υποδηλωτική ένδειξη συσχέτισης του ΣΔτ2 με τον καρκίνο του παχέος εντέρου, ηπατοκυτταρικό καρκίνο, καρκίνο της χοληδόχου κύστεως, του παγκρέατος, του μαστού και του ενδομητρίου. Επίσης, βρήκαμε τέσσερις μελέτες Μεντελιανής τυχαιοποίησης που εξέτασαν την πιθανή αιτιώδη επίδραση του ΣΔτ2, και έξι μελέτες που εξέτασαν την πιθανή αιτιώδη επίδραση της ινσουλίνης νηστείας ή της γλυκόζης νηστείας με συγκεκριμένα είδη καρκίνου. Δεν βρέθηκε αιτιώδης επίδραση μεταξύ του ΣΔτ2 ή της γλυκόζης νηστείας και των καρκίνων, εκτός από τη γλυκόζη νηστείας και το πλακώδες καρκίνωμα του πνεύμονα, ενώ τα γενετικά προκαθορισμένα επίπεδα ινσουλίνης νηστείας βρέθηκε ότι σχετίζονταν αιτιακά με αυξημένο κίνδυνο καρκίνου του μαστού, του ενδομητρίου, του

παγκρέατος και του νεφρού. Συμπερασματικά λοιπόν, βρήκαμε ισχυρά τεκμήρια για τη συσχέτιση μεταξύ του ΣΔτ2 και διαφόρων καρκίνων.

Στην τρίτη μελέτη χρησιμοποιήθηκαν δεδομένα από την κοόρτη CLUE II και εξετάστηκε η πιθανή συσχέτιση μεταξύ της φλεγμονής και του καρκίνου του παχέος εντέρου, μέσω της αξιολόγησης των συγκεντρώσεων της ιντερλευκίνης-6 (IL-6). Συγκεκριμένα, υπολογίστηκαν οι σχετικοί λόγοι (ORs) και τα αντίστοιχα 95% διαστήματα εμπιστοσύνης (CIs) χρησιμοποιώντας μοντέλα λογιστικής παλινδρόμησης σε μια εμφωλεασμένη μελέτη ασθενή-μάρτυρα. Επιπλέον, αξιολογήθηκε η ισχύς της βιβλιογραφίας μέσω μιας μετα-ανάλυσης προοπτικών επιδημιολογικών μελετών για να συνοψίσουμε το σύνολο των τεκμηρίων της βιβλιογραφίας και να μελετήσουμε την ετερογένεια τους. Βρέθηκε πως οι συμμετέχοντες στο υψηλότερο τρίτο της συγκέντρωσης της IL-6 στο πλάσμα είχαν 2.48 φορές υψηλότερο κίνδυνο ανάπτυξης καρκίνου του παχέος εντέρου σε σύγκριση με τους συμμετέχοντες στο κατώτατο τρίτο (95% CI, 1.26-4.87, P, 0.02) μετά από πολυμεταβλητή ανάλυση. Αυτή η συσχέτιση δε διέφερε ανάλογα με το στάδιο της νόσου, την ηλικία, το φύλο ή άλλες πιθανές τροποποιητικές μεταβλητές και παρέμεινε στατιστικά σημαντική μετά την προσαρμογή για τις συγκεντρώσεις της C-αντιδρώσας πρωτεΐνης. Δεν παρατηρήθηκε στατιστικά σημαντική συσχέτιση για τον κίνδυνο καρκίνου του ορθού, αλλά μόνο του κόλου. Η μετα-ανάλυση έξι προοπτικών μελετών έδειξε αυξημένο αλλά οριακά στατιστικά σημαντικό κίνδυνο εμφάνισης καρκίνου του παχέος εντέρου ανά μονάδα αύξησης στο μετασχηματισμένο φυσικό λογάριθμο της IL-6 (περιληπτικό RR, 1.22, 95% CI, 1.00-1.49, I², 46%). Αρνητική συσχέτιση παρατηρήθηκε για τον καρκίνο του ορθού (RR, 0.69, 95% CI, 0.54-0.88, I², 0%), αλλά υπήρχαν ενδείξεις για συστηματικό σφάλμα δημοσίευσης (P, 0.02). Τα ευρήματα παρέχουν υποστήριξη για μέτρια θετική συσχέτιση μεταξύ των συγκεντρώσεων IL-6 και του κινδύνου καρκίνου του παχέος εντέρου. Χρειάζεται περισσότερη έρευνα για να καθοριστεί εάν η IL-6 είναι ένας έγκυρος δείκτης της φλεγμονής στο παχύ έντερο και πώς/εάν η φλεγμονή αυτή συμβάλλει στον κίνδυνο εμφάνισης καρκίνου του παχέος εντέρου.

SUMMARY IN ENGLISH

Cancer is a major public health problem worldwide and is the second leading cause of death. The latest version of the GLOBOCAN database (September 2018) predicts 18 million cancer cases and 9.6 million cancer deaths for 2018. The main objective of this work is to investigate possible associations between large categories of potential risk factors, namely hypertension, type 2 diabetes mellitus and inflammation, and the incidence of cancer. These questions were investigated through three separate studies:

The first study used data from the European Prospective Cancer and Nutrition Study (EPIC) and examined the association of blood pressure with the risk of cancer in all anatomical sites. Risk factors (HRs) were estimated using Cox proportional hazards models for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), hypertension and antihypertensive treatment in hypertensive subjects. In addition, statistical interactions were tested according to age, gender, body mass index (BMI), smoking, alcohol intake and use of hypertension therapy. Finally, sensitivity analyses were performed, excluding the first two years of follow-up. The study included 307,318 men and women, with an average follow-up of 13.7 (standard deviation 4.4) years and 39,298 incident cancers. We confirmed the expected positive association with renal cell carcinoma: HR=1.12 (1.08–1.17) per 10mm Hg higher SBP and HR=1.23(1.14–1.32) for DBP. We additionally found positive associations for esophageal squamous cell carcinoma (ESCC): HR=1.16 (1.07–1.26) (SBP), HR=1.31 (1.13–1.51) (DBP), weaker for head and neck cancers: HR=1.08 (1.04–1.12) (SBP), HR=1.09 (1.01–1.17) (DBP) and, similarly, for skin SCC, colon cancer, postmenopausal breast cancer and uterine adenocarcinoma (AC). We observed weak inverse associations of SBP with cervical SCC: HR=0.91 (0.82–1.00) and lymphomas: HR=0.97(0.93–1.00). There were no consistent associations with cancers in other locations. Our results are largely compatible with published studies and support weak associations of blood pressure with cancers in specific locations and morphologies.

The second study summarized and evaluated the validity of the literature regarding the association of type 2 diabetes (T2DM) with the risk of developing or dying from cancer using the umbrella review methodology. Summary effect and 95% confidence intervals were calculated using both fixed and random

effects inverse variants weighted methods. In addition, we assessed the heterogeneity between studies with the Cochran's Q test and the I^2 metric of inconsistency, as well as the methodological quality of all meta-analyses included in this study using the AMSTAR tool, an 11-item questionnaire summarizing the positive responses to achieve an overall quality score. Finally, an additional review of Mendelian randomization studies that evaluated whether genetically predicted probability of T2DM and levels of fasting insulin, glucose and glycosylated hemoglobin (HbA1C) was associated with risk of cancer. We found eligible observational meta-analyses that assessed associations between T2DM and cancer incidence in 18 cancer sites/sub-sites, cancer mortality in seven cancer sites, and cancer incidence or mortality in four cancer sites. The summary random effect estimates were significant at $P \leq 0.05$ in 23 meta-analyses (79%). When assessing study quality and evidence grade, studies of six cancer-sites did not have substantial heterogeneity and had strong or highly suggestive evidence of association with incident cancers, namely colorectal, hepatocellular, gallbladder, pancreatic, breast and endometrial cancer. Furthermore, we found four studies assessing the potential causal effect of T2DM and six studies assessing the potential causal effect of fasting insulin or fasting glucose upon site-specific cancers. No causal effect was found between genetically predicted T2DM or fasting glucose and cancers, except fasting glucose and squamous cell lung carcinoma, whereas genetically predicted fasting insulin was causally associated with an increased risk of breast, endometrial, pancreatic and renal cancers. In conclusion, we found strong evidence for the association between T2DM and various cancers.

In the third study, data from the CLUE II cohort were used and the possible association between inflammation and colorectal cancer was examined by evaluating the circulating concentrations of interleukin-6 (IL-6). Specifically, matched odds ratios and the corresponding 95 % confidence intervals (CIs) were estimated using conditional logistic regression models in a nested case-control study. In addition, the validity of the literature was evaluated through a meta-analysis of prospective epidemiological studies in order to summarize all bibliographic evidence and study its heterogeneity. Participants in the highest third of plasma IL-6 concentration had a 2.48 times higher risk of colon cancer compared to participants in the bottom third (95 % CI 1.26–4.87; p-trend 0.02) after multivariate adjustment. This association did not differ according to the stage of disease, age, sex, or other potential modifying variables and remained statistically significant after

adjustment for C-reactive protein concentrations. No statistically significant association was observed for rectal cancer risk. The meta-analysis of six prospective studies yielded an increased but borderline statistically significant risk of colon cancer per 1 unit increase in naturally logarithm transformed IL-6 (summary RR 1.22; 95 % CI 1.00–1.49; I^2 46 %). An inverse association was noted for rectal cancer (RR 0.69; 95 % CI 0.54–0.88; I^2 0 %), but there was evidence for small study effects (P 0.02). The findings provide support for a modest positive association between IL-6 concentrations and colon cancer risk. More work is needed to determine whether IL-6 is a valid marker of colorectal inflammation and whether such inflammation contributes to colon and rectal cancer risk.

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APPENDIX

A) Supplementary tables

Supplemental table 1: Definition of cancer locations at anatomical sites and morphological subtypes in EPIC

Cancer location Subtype	Topographical codes	Morphology (specific codes)	Rare morphologies (excluded codes)	Note
Head and Neck	C02, C03, C04, C05, C06, C09, C10, C11, C12, C13, C14.0, C30, C32	-	8800, 8850, 9120, 9220, 9591, 9673, 9680, 9690, 9691, 9734	89% (n=605) SCC
Mouth and oropharynx	C02, C03, C04, C05, C06, C09, C10,	-	as for Head & Neck	90% (n=297) SCC
Larynx	C32	-	as for Head & Neck	93% (n=221) SCC
Digestive system				
Esophagus	C15	-	8170, 8720, 9591	
Esophageal AC	C15	8140, 8144	-	
Esophageal SCC	C15	8070, 8071, 8072	-	
Stomach	C16	-	8560, 8800, 8891, 8936, 9590, 9591, 9595, 9663, 9670, 9676, 9680, 9699, 9702, 9711, 9715, 9823	
Gastric AC	C16	8140	-	
Colorectal	C18, C19, C20	-	8240, 8241, 8243, 8245, 8246, 8472, 8743, 8936, 9680, 9699	75% (n=3,489) code 8140
Colon	C18	-	as for Colorectal	72% (n=2,175) code 8140
Rectum and rectosigmoid junction	C19, C20	-	as for Colorectal	81% (n=1,314) code 8140
Liver	C22, C23, C24	-	9120, 9130, 9590, 9680	##
Hepatocellular Cancer	C22.0	8170, 8180	-	
Gallbladder and bile ducts	C22.1, C23, C24			
Pancreas	C25	-	8150, 8151, 8152, 8246, 9591	
Respiratory system				

Lung	C34	-	8710, 8800, 8801, 8990, 9050, 9120, 9133, 9591, 9680, 9699	
Lung AC	C34	8140, 8144, 8230, 8250, 8253, 8254, 8256, 8257, 8260, 8265, 8333, 8480, 8551	-	91% (n=1,027) code 8140
Lung SCC	C34	8070, 8071, 8072, 8083	-	
Lung SmallCC	C34	8041, 8045	-	
Lung (other morphology)	C34	any not excluded and not included above		***
Urinary system				
Kidney	C64	-	8800, 8830, 8890, 8964	
Renal pelvis and ureter	C65, C66	-		*
Bladder	C67	-	8800, 8801, 8980, 9590, 9671	#
Reproductive system				
Prostate (men)	C61	-		
Breast (women)	C50 (women)	-	8801, 8804, 8810, 8980, 8982, 9020, 9120, 9590, 9675, 9690, 9691	
Ovary (women)	C56, C48, C57.0	-	8890, 8980, 9680	
Corpus uteri (women)	C54 (women)	-	8890, 8930, 8931, 8933, 8935, 8950, 8951, 8980, 9100	**
Uterine AC	C54 (women)	8140	-	
Endometroid AC	C54 (women)	8380	-	
Cervix uteri (women)	C53	-	-	
Cervix SCC	C53	8070, 8071, 8072, 8076, 8083	-	###
Cervix AC	C53	8140	-	###
Cervix (other morphology)	C53	any not accounted for above	-	
Anogenital (not cervix)	C21, C51, C52, C60	-	-	
Anogenital SCC	C21, C51, C52, C60	8070, 8071, 8072, 8083	-	
Skin				
Skin (SCC)	C44	8070, 8071, 8072, 8083	-	
Melanoma (skin)	C44	8720 – 8780	-	
Nervous and endocrine system				
Brain and central nervous system	C70, C71, C72	-	8420, 8510, 9120, 9150, 9473, 9490, 9590, 9591, 9680, 9702, 9732	

Glioblastoma	C71	9440		
Thyroid	C73	-	8012, 8021, 8041, 8345, 8510, 8511, 9680	
Hematopoietic system				
Leukemia	C42	9700 – 9709, 9731 – 9989	-	
Multiple myeloma	C42	9731, 9732	-	
Lymphoma (all types)	C77	9590 – 9595, 9650 – 9761, 9820 – 9837, 9940 – 9945	-	
Non-Hodgkin Lymphomas	C77	9591, 9670 – 9719	-	
Other				
Other location AC	any not included above	8140		
Other location or morphology	any remaining, not accounted for above	any not accounted for above, including rare morphologies		

The order of the main anatomical sites, as in Figure 2, is according to the hazard ratio estimates for systolic blood pressure from the main adjusted analyses (specific locations and morphologies follow the relevant main anatomical site and other locations are listed last); All morphological codes had behavioural code 3 (xxxx/3) according to the International Classification of Diseases for Oncology (ICD-O) (<http://codes.iarc.fr/abouticdo.php>; Accessed: 24/01/2019); **AC** – adenocarcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; * renal pelvis and ureter cancers (n=112 cases) were 93% (n=104) with transitional-cell morphology (codes 8120/3 or 8130/3); ** corpus uteri cancers (n=1164) included 42% (n=488) AC (code 8140/3) and 47% (n=546) endometroid adenocarcinoma (code 8380/3); *** lung (other morphology) (n=1107) included: 50% (n=550) undifferentiated or unspecified (codes 8000/3, 8010/3 or 8020/3), 19% (n=207) non-small cell carcinoma (code 8046/3); # bladder cancers (n=1,192) comprised 89% (n=1,058) transitional-cell morphology (codes 8120/3 or 8130/3); ## liver cancers (n=653) comprised: 47% (n=307) cancers of the liver parenchyma (of which 62% (n=191) were with hepatocellular morphology), 11% (n=71) cancers of the intrahepatic bile ducts, 13% (n=86) cancers of the gallbladder, 29% (n=189) cancers of the extrahepatic bile ducts; ### cervical AC (n=37) and cervix (other morphology) (n=41) were considered only in the main analyses for continuous blood pressure variables, due to the small number of cases.

Supplemental table 2: Categories of blood pressure and adjustment variables in EPIC

Variable (units of measurement)	Categories used in models
hypertension (dichotomous)	SBP \geq 140 mmHg, or DBP \geq 90 mmHg at BP measurement visit, or self-reported hypertension
hypertension (American Society for Hypertension)	pre-hypertension (SBP 120–139 mmHg or DBP in 80–89 mmHg); hypertension stage I (SBP 140-159mmHg or DBP 90-99mmHg); hypertension stage II (SBP $>$ 160mmHg or DBP $>$ 100mmHg)
hypertension (European Society for Hypertension)	optimal (SBP $<$ 120mmHg and DBP $<$ 80mmHg); normal (SBP 120-129mmHg and DBP 80-84mmHg); high normal (SBP 130-139mmHg and/or DBP 85-89mmHg); grade I hypertension (SBP 140-159mmHg or DBP 90-99mmHg); grade II hypertension (SBP 160-179mmHg or DBP 100-109mmHg); grade III hypertension (SBP \geq 180mmHg or DBP \geq 110mmHg) and isolated systolic hypertension (elevated SBP with normal DBP)
mean blood pressure (MBP)	Cohort-wide quartiles (cut-points at: 88.8, 96.7, 106.0 mmHg)
sex	men, women
body mass index (kg/m ²)	cohort-wide quintiles (cut-points at: 22.3, 24.3, 26.2, 28.9 kg/m ²)
diabetes mellitus (self-reported)	yes, no, missing
educational attainment	none, primary school, technical/professional school, secondary school, longer education, missing
physical activity	inactive, moderately inactive, moderately active, active
smoking status	never, former, current smoker \leq 20 pack years, current smoker $>$ 20 pack years, missing
alcohol intake (g/day)	cohort-wide quintiles (cut-points at: 0.6, 3.5, 9.4, 20.6 g/day)
fruit consumption (g/day)	cohort-wide quintiles (cut-points at: 92, 155, 236, 345 g/day)
vegetable consumption (g/day)	cohort-wide quintiles (cut-points at: 93, 137, 193, 290 g/day)
red meat consumption (g/day)	cohort-wide quintiles (cut-points at: 16.5, 32.7, 50.9, 75.6 g/day)
age at first period (menarche) (years)*	$<$ 12 years, 12-15 years, $>$ 15 years, missing
age at first full-term pregnancy (years)*	\leq 21 years, 21-30 years, $>$ 30 years, missing
number of full-term pregnancies *	0, 1, 2, 3, \geq 4, missing
menopausal status *	pre-menopausal (self-reported or age at recruitment $<$ 46 years if missing), peri-menopausal or unknown, physiological postmenopausal (self-reported or age \geq 55 years if missing), surgical post-menopausal (self-reported)
age at menopause (years) *	$<$ 40 years, 40-46 years, 46-50 years, 50-56 years, $>$ 56 years, missing or not relevant
oral contraceptives use *	never, former, current, missing
hormone replacement therapy use *	never, former, current, missing

*reproductive variables used for adjustment in female cancers (breast, ovary, cervix and corpus uteri)

Supplemental table 3: EPIC cohort characteristics, cancer cases and blood pressure categories by country

	Total	Denmark	France	Germany	Greece	Italy	Netherlands	Spain	Sweden	UK
Cohort size: N	307318	54961	19195	33048	25854	43109	36517	6273	48184	40177
Age at recruitment, years: mean (SD)	52.5 (9.9)	56.7 (4.4)	52.8 (6.5)	50.3 (8.8)	53.1 (12.6)	50.5 (7.9)	49 (11.9)	50.3 (8.4)	52 (10.9)	54.6 (11.5)
Female: N (%)	194727 (63.4)	28691 (52.2)	19195 (100)	19342 (58.5)	15123 (58.5)	29659 (68.8)	26890 (73.6)	4231 (67.4)	26119 (54.2)	25477 (63.4)
Person years: mean (SD) #	13.7 (4.4)	14.8 (4.1)	9.8 (2.4)	9.6 (2.7)	10.8 (3.7)	14.1 (3.1)	14.4 (3.3)	14.6 (2.8)	16.4 (5)	14.7 (4)
Cancer cases: N										
Any malignant cancer	39298	11043	1256	2551	1266	4551	3767	604	8479	5781
Head and neck										
Head and neck (combined)	683	261	0	51	22	72	69	19	116	73
* Mouth and oropharynx	332	131	0	21	3	31	35	5	67	39
* Larynx	239	95	0	18	16	31	22	9	27	21
Digestive System										
Esophagus	387	133	1	17	4	11	42	4	67	108
* Esophageal AC	176	50	0	7	2	3	15	1	31	67
* Esophageal SCC	149	58	1	7	1	6	18	2	30	26
Stomach	738	169	4	58	62	129	61	15	150	90
* Gastric AC	403	98	1	11	9	52	29	5	123	75
Colorectal	4625	1317	96	267	126	562	510	89	921	737
* Colon	3003	804	63	165	82	417	328	68	592	484
* Rectum and rectosigmoid junction	1622	513	33	102	44	145	182	51	329	253
Liver and bile ducts	653	177	2	57	56	108	42	12	134	65
* HCC	191	48	0	19	14	38	7	1	41	23
* Gallbladder and bile ducts	346	89	2	31	22	48	33	7	74	40
Pancreas	990	325	16	70	44	102	96	13	203	121
Respiratory system										
Lung (combined)	3229	1257	1	193	175	293	338	37	548	387
* Lung AC	1130	485	1	69	33	107	109	8	220	98
* Lung SCC	613	246	0	31	20	46	65	8	108	89
* Lung SmallCC	379	198	0	32	16	21	62	5	2	43
* Lung (other morphology)	1107	328	0	61	106	119	102	16	218	157
Urinary system										
Kidney	758	185	1	96	29	122	70	11	138	106
Renal pelvis and ureter	112	41	0	3	1	8	10	1	29	19
Bladder	1192	260	2	80	56	134	65	32	403	160
Reproductive system										
Prostate	5848	1878	0	495	96	459	214	93	1817	769
Breast (female)	8154	1863	830	478	240	1174	1043	103	1301	1122
* Breast pre-menopausal	256	0	0	39	28	60	42	5	41	41
* Breast post-menopausal	4786	1451	388	263	142	534	582	38	715	673
Ovary	1007	224	55	51	44	129	132	11	175	186
Corpus uteri	1164	262	68	64	19	175	140	35	243	158
* Uterine AC	488	22	21	4	6	103	37	8	229	58
* Endometrioid AC	546	204	42	52	5	52	87	22	4	78
Cervix uteri	223	56	2	21	21	26	32	7	33	25
* Cervix SCC	145	44	0	14	7	16	22	6	23	13
* Cervix AC	37	8	1	2	2	6	5	0	8	5
* Cervix (other morphology)	41	4	1	5	12	4	5	1	2	7
Anogenital (not cervix)	244	66	4	25	12	24	19	0	56	38
* Anogenital SCC	173	45	3	15	5	12	17	0	49	27

Skin										
Skin SCC	1399	400	16	13	2	40	124	15	430	359
Melanoma (skin)	1617	444	80	107	22	143	171	15	379	256
Nervous and endocrine system										
Brain and CNS	591	160	1	45	19	91	58	13	105	99
* Glioblastoma	297	95	0	26	6	39	17	2	51	61
Thyroid	420	41	59	65	37	118	17	20	39	24
Hematopoietic system										
Leukemia	1308	315	0	88	41	170	143	24	305	222
* Multiple myeloma	475	110	0	35	14	69	39	3	131	74
Lymphoma (all types)	1058	329	0	39	24	99	65	10	276	216
* Non-Hodgkin lymphomas	882	287	0	31	18	86	59	10	108	183
Other										
Other location AC	406	109	0	15	4	47	54	2	118	57
Other location or other morphology	2492	771	18	153	110	315	252	23	493	357
Systolic Blood Pressure, N (%)										
< 120 mmHg	86141 (28.0)	8691 (15.8)	7918 (41.3)	10421 (31.5)	8151 (31.5)	12446 (28.9)	14872 (40.7)	2202 (35.1)	10478 (21.8)	10953 (27.3)
120-129 mmHg	66446 (21.6)	9787 (17.8)	4351 (22.7)	8117 (24.6)	5511 (21.3)	10206 (23.7)	8108 (22.02)	1414 (22.5)	10182 (21.1)	8770 (21.8)
130-139 mmHg	57482 (18.7)	10356 (18.8)	3412 (17.8)	6653 (20.1)	4180 (16.2)	8812 (20.4)	6074 (16.6)	1163 (18.5)	8935 (18.5)	7897 (19.7)
140-159 mmHg	68235 (22.2)	17674 (32.2)	2787 (14.5)	5894 (17.8)	5392 (20.9)	8746 (20.3)	5242 (14.4)	1124 (17.9)	12192 (25.3)	9184 (22.9)
160-179 mmHg	22656 (7.4)	6266 (11.4)	607 (3.2)	1607 (4.9)	2056 (8.0)	2334 (5.4)	1781 (4.9)	303 (4.8)	4953 (10.3)	2749 (6.8)
>= 180 mmHg	6358 (2.1)	2187 (4.0)	120 (0.6)	356 (1.1)	564 (2.2)	565 (1.3)	440 (1.2)	67 (1.1)	1435 (3.0)	624 (1.6)
SBP, mmHg: mean (SD)	131.5 (19.7)	139.6 (20.5)	125 (17.2)	129.2 (17.7)	129.8 (20.6)	129.5 (18.1)	126.2 (18.9)	128.2 (18.6)	134 (20)	131.2 (19.2)
Diastolic Blood Pressure, N (%)										
< 80 mmHg	132590 (43.1)	20292 (36.9)	12372 (64.5)	12577 (38.1)	10656 (41.2)	15892 (36.9)	21394 (58.6)	3192 (50.9)	17028 (35.3)	19187 (47.8)
80-84 mmHg	64872 (21.1)	11599 (21.1)	3031 (15.8)	6293 (19.0)	6189 (23.9)	11721 (27.2)	6246 (17.1)	1123 (17.9)	10667 (22.1)	8003 (19.9)
85-89 mmHg	41500 (13.5)	8863 (16.1)	1901 (9.9)	5522 (16.7)	2738 (10.6)	5779 (13.4)	4081 (11.2)	818 (13.0)	6853 (14.2)	4945 (12.3)
90-99 mmHg	51196 (16.7)	10521 (19.1)	1544 (8.0)	6362 (19.3)	4784 (18.5)	7440 (17.3)	3685 (10.1)	828 (13.2)	10117 (21.0)	5915 (14.7)
100-109 mmHg	13896 (4.5)	2955 (5.4)	269 (1.4)	1874 (5.7)	1204 (4.7)	1822 (4.2)	916 (2.5)	222 (3.5)	2952 (6.1)	1682 (4.2)
>= 110 mmHg	3264 (1.1)	731 (1.3)	78 (0.4)	420 (1.3)	283 (1.1)	455 (1.1)	195 (0.5)	90 (1.4)	567 (1.2)	445 (1.1)
DBP, mmHg: mean (SD)	81.1 (10.9)	83.1 (10.6)	76.7 (10)	83.5 (10.6)	80.5 (10.6)	81.7 (10.1)	77.8 (10.7)	80.3 (11.7)	82.2 (10.9)	80.1 (11.5)
Mean Blood Pressure, N (%)										
50.0-88.3 mmHg	76991 (25.1)	8532 (15.5)	7505 (39.1)	7052 (21.3)	7108 (27.5)	9839 (22.8)	13546 (37.1)	1879 (30.0)	10381 (21.5)	11149 (27.7)
88.5-96.6 mmHg	77727 (25.3)	11503 (20.9)	5146 (26.8)	8266 (25.0)	7003 (27.1)	12659 (29.4)	9409 (25.8)	1525 (24.3)	12282 (25.5)	9934 (24.7)
96.8-105.5 mmHg	76327 (24.8)	15558 (28.3)	4230 (22.0)	9455 (28.6)	5777 (22.3)	11080 (25.7)	7862 (21.5)	1594 (25.4)	11192 (23.2)	9579 (23.8)
105.6-216.6 mmHg	76273 (24.8)	19368 (35.2)	2314 (12.1)	8275 (25.0)	5966 (23.1)	9531 (22.1)	5700 (15.6)	1275 (20.3)	14329 (29.7)	9515 (23.7)
MBP, mmHg: mean (SD)	97.9 (12.9)	101.9 (12.9)	92.8 (11.4)	98.7 (12.2)	96.9 (12.8)	97.7 (11.9)	94 (12.5)	96.2 (13.1)	99.5 (13)	97.2 (13.3)

Hypertension (yes/no), N (%)										
No hypertension	174179 (56.7)	25551 (46.5)	13495 (70.3)	17799 (53.9)	14383 (55.6)	26131 (60.6)	23286 (63.8)	3740 (59.6)	25183 (52.3)	24611 (61.3)
Hypertension	133139 (43.3)	29410 (53.5)	5700 (29.7)	15249 (46.1)	11471 (44.4)	16978 (39.4)	13231 (36.2)	2533 (40.4)	23001 (47.7)	15566 (38.7)
Treatment of hypertension (yes/no), N (%)										
Untreated hypertension	73714 (66.6)	18458 (73.3)	3980 (74.2)	7681 (50.5)	6179 (54.3)	11495 (68.5)	8603 (67.9)	1661 (66.0)	12992 (68.6)	2665 (100.0)
Treated hypertension	37017 (33.4)	6733 (26.7)	1382 (25.8)	7525 (49.5)	5204 (45.7)	5292 (31.5)	4070 (32.1)	854 (34.0)	5957 (31.4)	0 (0.0)

EPIC - European Prospective Investigation into Cancer and Nutrition; **N** - number of individuals; (%) - percentage from total number per country; **SD** - standard deviation; **DBP** – diastolic blood pressure; **SBP** – systolic blood pressure; **MBP (Mean Blood Pressure)**: calculated as $(1/3)*SBP+(2/3)*DBP$; **#** - person years of follow-up in the study from the date of blood pressure measurement; **Hypertension**: defined as $SBP \geq 140$ mmHg, or $DBP \geq 90$ mmHg, or self-reported; **Treatment of hypertension**: summary of self-reported antihypertensive treatment (yes/no) for individuals with hypertension as defined above; The order of the main cancer locations corresponds to Figure 2 (by body system); * - specific cancer location or morphology (cancer morphologies and locations are defined in Supplementary Table 1); **AC** - adenocarcinoma; **SCC** - squamous cell carcinoma; **SmallCC** - small cell carcinoma; **HCC** - hepatocellular carcinoma.

Supplemental table 4: Baseline demographic, lifestyle and reproductive characteristics by blood pressure category in EPIC

Characteristics	Total	Systolic Blood Pressure					
		< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Cohort size: N	307318	86141	66446	57482	68235	22656	6358
Female: N (%)	194727 (63.4)	65461 (76.0)	40944 (61.6)	33415 (58.1)	38168 (55.9)	13066 (57.7)	3673 (57.8)
Age at recruitment, years: mean (SD)	52.5 (9.9)	47.3 (9.8)	50.9 (9.4)	53.6 (8.9)	56.8 (8.0)	59.5 (7.3)	60.5 (7.1)
Body Mass Index, kg/m ² : mean (SD)	25.8 (4.2)	24.1 (3.6)	25.5 (3.9)	26.3 (4.1)	27.0 (4.4)	27.6 (4.6)	27.9 (4.8)
Alcohol intake, g/day: mean (SD)	12.4 (17.1)	9.7 (13.5)	11.9 (15.9)	13.1 (17.6)	14.5 (19.5)	14.5 (20.3)	15.8 (22.3)
Fruit consumption, g/day: mean (SD)	230.6 (176.7)	237.9 (185.0)	233.0 (179.0)	229.4 (176.2)	225.0 (169.2)	220.2 (163.3)	214.6 (162.4)
Vegetable consumption, g/day: mean (SD)	200.9 (145.4)	209.0 (155.5)	201.4 (148.8)	197.2 (138.8)	197.1 (138.0)	193.6 (135.5)	188.2 (134.1)
Red meat consumption, g/day: mean (SD)	48.2 (36.3)	44.0 (34.6)	47.3 (36.0)	49.3 (36.2)	51.7 (37.6)	52.1 (37.3)	53.5 (37.5)
Diabetes: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Self-reported diabetes	8588 (2.8)	1034 (1.2)	1365 (2.1)	1582 (2.8)	2837 (4.2)	1317 (5.8)	453 (7.1)
Missing information	30147 (9.8)	5934 (6.9)	6280 (9.5)	6226 (10.8)	8421 (12.3)	2612 (11.5)	674 (10.6)
Smoking status: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Never smoker	141931 (46.2)	39958 (46.4)	30980 (46.6)	26660 (46.4)	31153 (45.7)	10419 (46.0)	2761 (43.4)
Former smoker	86314 (28.1)	21204 (24.6)	18180 (27.4)	16751 (29.1)	21025 (30.8)	7147 (31.5)	2007 (31.6)
Current smoker (≤ 20 pack-years)	32226 (10.5)	12765 (14.8)	7333 (11.0)	5130 (8.9)	5093 (7.5)	1457 (6.4)	448 (7.0)
Current smoker (> 20 pack-years)	34907 (11.4)	8959 (10.4)	7386 (11.1)	6629 (11.5)	8221 (12.0)	2787 (12.3)	925 (14.5)
Missing information	11940 (3.9)	3255 (3.8)	2567 (3.9)	2312 (4.0)	2743 (4.0)	846 (3.7)	217 (3.4)
Physical activity: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Inactive	67194 (21.9)	15201 (17.6)	13228 (19.9)	12770 (22.2)	17521 (25.7)	6542 (28.9)	1932 (30.4)
Moderately inactive	100295 (32.6)	28544 (33.1)	21835 (32.9)	18840 (32.8)	21753 (31.9)	7291 (32.2)	2032 (32.0)
Moderately active	70977 (23.1)	21409 (24.9)	15862 (23.9)	13326 (23.2)	14685 (21.5)	4467 (19.7)	1228 (19.3)
Active	62152 (20.2)	17801 (20.7)	14093 (21.2)	11555 (20.1)	13446 (19.7)	4123 (18.2)	1134 (17.8)
Missing information	6700 (2.2)	3186 (3.7)	1428 (2.1)	991 (1.7)	830 (1.2)	233 (1.0)	32 (0.5)
Education: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
None	9377 (3.1)	1661 (1.9)	1649 (2.5)	1786 (3.1)	2790 (4.1)	1164 (5.1)	327 (5.1)
Primary school completed	90254 (29.4)	18049 (21.0)	17950 (27.0)	17702 (30.8)	24700 (36.2)	9155 (40.4)	2698 (42.4)
Technical/professional school	77398 (25.2)	20712 (24.0)	16789 (25.3)	14704 (25.6)	17822 (26.1)	5759 (25.4)	1612 (25.4)
Secondary school	53830 (17.5)	19078 (22.1)	12696 (19.1)	9691 (16.9)	9148 (13.4)	2546 (11.2)	671 (10.6)

Longer education (incl. University degree)	67606 (22.0)	24418 (28.3)	15466 (23.3)	11838 (20.6)	11689 (17.1)	3335 (14.7)	860 (13.5)
Missing information	8853 (2.9)	2223 (2.6)	1896 (2.9)	1761 (3.1)	2086 (3.1)	697 (3.1)	190 (3.0)
Antihypertensive treatment: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
No treatment	227336 (74.0)	75558 (87.7)	53631 (80.7)	42212 (73.4)	42214 (61.9)	11150 (49.2)	2571 (40.4)
Treated	37017 (12.0)	2065 (2.4)	4241 (6.4)	6737 (11.7)	13884 (20.3)	7462 (32.9)	2628 (41.3)
Missing information	42965 (14.0)	8518 (9.9)	8574 (12.9)	8533 (14.8)	12137 (17.8)	4044 (17.8)	1159 (18.2)
Reproductive factors (women)							
Age at first menstrual period: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
< 12 years	27085 (13.9)	9595 (14.7)	5733 (14.0)	4716 (14.1)	5074 (13.3)	1514 (11.6)	453 (12.3)
≥ 12 and < 15 years	125828 (64.6)	42585 (65.1)	26680 (65.2)	21625 (64.7)	24337 (63.8)	8287 (63.4)	2314 (63.0)
≥ 15 years	32391 (16.6)	9329 (14.3)	6418 (15.7)	5762 (17.2)	7319 (19.2)	2794 (21.4)	769 (20.9)
Missing information	9423 (4.8)	3952 (6.0)	2113 (5.2)	1312 (3.9)	1438 (3.8)	471 (3.6)	137 (3.7)
Age at first full term pregnancy: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
≤ 21 years	36839 (18.9)	11093 (16.9)	7757 (18.9)	6509 (19.5)	7915 (20.7)	2769 (21.2)	796 (21.7)
> 21 and ≤ 30 years	106230 (54.6)	33698 (51.5)	22395 (54.7)	19006 (56.9)	21669 (56.8)	7421 (56.8)	2041 (55.6)
> 30 years	15709 (8.1)	5588 (8.5)	3297 (8.1)	2535 (7.6)	2964 (7.8)	1035 (7.9)	290 (7.9)
Missing information	35949 (18.5)	15082 (23.0)	7495 (18.3)	5365 (16.1)	5620 (14.7)	1841 (14.1)	546 (14.9)
Number of full-term pregnancies: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
None	25571 (13.1)	10307 (15.7)	5226 (12.8)	3944 (11.8)	4227 (11.1)	1438 (11.0)	429 (11.7)
One	28796 (14.8)	9326 (14.2)	6139 (15.0)	5018 (15.0)	5771 (15.1)	1977 (15.1)	565 (15.4)
Two	75357 (38.7)	24211 (37.0)	16178 (39.5)	13358 (40.0)	15223 (39.9)	5037 (38.6)	1350 (36.8)
Three	33031 (17.0)	9387 (14.3)	6941 (17.0)	6026 (18.0)	7340 (19.2)	2624 (20.1)	713 (19.4)
Four or more	14897 (7.7)	3448 (5.3)	2883 (7.0)	2861 (8.6)	3732 (9.8)	1484 (11.4)	489 (13.3)
Missing information	17075 (8.8)	8782 (13.4)	3577 (8.7)	2208 (6.6)	1875 (4.9)	506 (3.9)	127 (3.5)
Menopausal status: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Pre-menopausal	58190 (29.9)	32401 (49.5)	13167 (32.2)	7060 (21.1)	4551 (11.9)	825 (6.3)	186 (5.1)
Post-menopausal	96806 (49.7)	20155 (30.8)	18714 (45.7)	18853 (56.4)	26087 (68.3)	10027 (76.7)	2970 (80.9)
Peri-menopausal or unknown	33371 (17.1)	11425 (17.5)	7789 (19.0)	6270 (18.8)	5912 (15.5)	1607 (12.3)	368 (10.0)
Surgical post-menopausal	6360 (3.3)	1480 (2.3)	1274 (3.1)	1232 (3.7)	1618 (4.2)	607 (4.6)	149 (4.1)

Age at menopause: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
< 40 years	4301 (2.2)	950 (1.5)	853 (2.1)	821 (2.5)	1128 (3.0)	436 (3.3)	113 (3.1)
≥ 40 and ≤ 46 years	18912 (9.7)	4218 (6.4)	3594 (8.8)	3621 (10.8)	5030 (13.2)	1893 (14.5)	556 (15.1)
> 46 and ≤ 50 years	31996 (16.4)	6636 (10.1)	6298 (15.4)	6257 (18.7)	8493 (22.3)	3299 (25.2)	1013 (27.6)
> 50 and ≤ 56 years	29427 (15.1)	5220 (8.0)	5427 (13.3)	5940 (17.8)	8462 (22.2)	3415 (26.1)	963 (26.2)
> 56 years	1997 (1.0)	267 (0.4)	326 (0.8)	364 (1.1)	652 (1.7)	287 (2.2)	101 (2.7)
Missing information or not applicable	108094 (55.5)	48170 (73.6)	24446 (59.7)	16412 (49.1)	14403 (37.7)	3736 (28.6)	927 (25.2)
Oral contraceptive use: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Never	82568 (42.4)	20931 (32.0)	16050 (39.2)	15231 (45.6)	20282 (53.1)	7760 (59.4)	2314 (63.0)
Former	91622 (47.1)	34372 (52.5)	20156 (49.2)	15415 (46.1)	15725 (41.2)	4735 (36.2)	1219 (33.2)
Current	10050 (5.2)	5228 (8.0)	2345 (5.7)	1353 (4.0)	879 (2.3)	207 (1.6)	38 (1.0)
Missing information	10487 (5.4)	4930 (7.5)	2393 (5.8)	1416 (4.2)	1282 (3.4)	364 (2.8)	102 (2.8)
Hormone replacement therapy: N (%)	Total	< 120 mmHg	120-129 mmHg	130-139 mmHg	140-159 mmHg	160-179 mmHg	≥180 mmHg
Never	129049 (66.3)	46653 (71.3)	26815 (65.5)	21277 (63.7)	23675 (62.0)	8205 (62.8)	2424 (66.0)
Former	16259 (8.3)	4161 (6.4)	3354 (8.2)	3188 (9.5)	3917 (10.3)	1310 (10.0)	329 (9.0)
Current	30133 (15.5)	8768 (13.4)	6600 (16.1)	5701 (17.1)	6533 (17.1)	2014 (15.4)	517 (14.1)
Missing information	19286 (9.9)	5879 (9.0)	4175 (10.2)	3249 (9.7)	4043 (10.6)	1537 (11.8)	403 (11.0)
Diastolic Blood Pressure							
Characteristics	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥110 mmHg
Cohort size: N	307318	132590	64872	41500	51196	13896	3264
Female: N (%)	194727 (63.4)	96352 (72.7)	39059 (60.2)	23956 (57.7)	27199 (53.1)	6720 (48.4)	1441 (44.1)
Age at recruitment, years: mean (SD)	52.5 (9.9)	50.2 (10.5)	52.9 (9.6)	54.2 (8.7)	55.4 (8.4)	56.4 (8.0)	56.6 (7.9)
Body Mass Index, kg/m ² : mean (SD)	25.8 (4.2)	24.6 (3.8)	26.0 (4.1)	26.6 (4.2)	27.3 (4.4)	28.1 (4.7)	28.8 (5.1)
Alcohol intake, g/day: mean (SD)	12.4 (17.1)	10.4 (14.3)	12.7 (17.1)	13.6 (18.2)	14.8 (19.9)	16.2 (22.0)	17.2 (23.5)
Fruit consumption, g/day: mean (SD)	230.6 (176.7)	234.0 (178.4)	238.6 (184.6)	222.9 (170.7)	223.5 (169.3)	214.8 (166.0)	211.6 (163.5)
Vegetable consumption, g/day: mean (SD)	200.9 (145.4)	206.9 (149.3)	202.5 (146.6)	191.8 (138.5)	194.8 (140.7)	189.0 (138.7)	190.4 (138.4)
Red meat consumption, g/day: mean (SD)	48.2 (36.3)	46.1 (35.5)	48.3 (35.9)	50.1 (36.8)	50.6 (37.4)	51.9 (37.9)	53.9 (39.4)
Diabetes: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥110 mmHg
Self-reported diabetes	8588 (2.8)	2794 (2.1)	1897 (2.9)	1280 (3.1)	1920 (3.8)	539 (3.9)	158 (4.8)
Missing information	30147 (9.8)	11973 (9)	5761 (8.9)	4547 (11)	5692 (11.1)	1738 (12.5)	436 (13.4)
Smoking status: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥110 mmHg
Never smoker		62146 (46.9)	30071 (46.4)	19076 (46.0)	23182 (45.3)	6030 (43.4)	1426 (43.7)

	141931 (46.2)						
Former smoker	86314 (28.1)	34090 (25.7)	18378 (28.3)	12433 (30.0)	15817 (30.9)	4547 (32.7)	1049 (32.1)
Current smoker (\leq 20 pack-years)	32226 (10.5)	16753 (12.6)	6505 (10.0)	3576 (8.6)	4080 (8.0)	1066 (7.7)	246 (7.5)
Current smoker ($>$ 20 pack-years)	34907 (11.4)	14418 (10.9)	7493 (11.6)	4820 (11.6)	6068 (11.9)	1704 (12.3)	404 (12.4)
Missing information	11940 (3.9)	5183 (3.9)	2425 (3.7)	1595 (3.8)	2049 (4.0)	549 (4.0)	139 (4.3)
Physical activity: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	\geq110 mmHg
Inactive	67194 (21.9)	25354 (19.1)	14642 (22.6)	9415 (22.7)	12952 (25.3)	3859 (27.8)	972 (29.8)
Moderately inactive	100295 (32.6)	43034 (32.5)	21287 (32.8)	13573 (32.7)	16860 (32.9)	4489 (32.3)	1052 (32.2)
Moderately active	70977 (23.1)	32177 (24.3)	14749 (22.7)	9440 (22.7)	11100 (21.7)	2854 (20.5)	657 (20.1)
Active	62152 (20.2)	28031 (21.1)	13074 (20.2)	8365 (20.2)	9619 (18.8)	2519 (18.1)	544 (16.7)
Missing information	6700 (2.2)	3994 (3.0)	1120 (1.7)	707 (1.7)	665 (1.3)	175 (1.3)	39 (1.2)
Education: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	\geq110 mmHg
None	9377 (3.1)	3182 (2.4)	2255 (3.5)	1123 (2.7)	2100 (4.1)	560 (4.0)	157 (4.8)
Primary school completed	90254 (29.4)	31658 (23.9)	20359 (31.4)	13613 (32.8)	18220 (35.6)	5172 (37.2)	1232 (37.7)
Technical/professional school	77398 (25.2)	32758 (24.7)	15956 (24.6)	11061 (26.7)	13259 (25.9)	3588 (25.8)	776 (23.8)
Secondary school	53830 (17.5)	27531 (20.8)	11073 (17.1)	6263 (15.1)	6836 (13.4)	1719 (12.4)	408 (12.5)
Longer education (incl. University degree)	67606 (22.0)	33387 (25.2)	13330 (20.5)	8324 (20.1)	9457 (18.5)	2518 (18.1)	590 (18.1)
Missing information	8853 (2.9)	4074 (3.1)	1899 (2.9)	1116 (2.7)	1324 (2.6)	339 (2.4)	101 (3.1)
Antihypertensive treatment: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	\geq110 mmHg
No treatment	227336 (74.0)	110105 (83.0)	50113 (77.2)	28744 (69.3)	30577 (59.7)	6477 (46.6)	1320 (40.4)
Treated	37017 (12.0)	5988 (4.5)	6453 (9.9)	6278 (15.1)	12212 (23.9)	4847 (34.9)	1239 (38.0)
Missing information	42965 (14.0)	16497 (12.4)	8306 (12.8)	6478 (15.6)	8407 (16.4)	2572 (18.5)	705 (21.6)
Reproductive factors (women)							
Age at first menstrual period: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	\geq 110 mmHg
< 12 years	27085 (13.9)	13479 (14.0)	5358 (13.7)	3341 (13.9)	3709 (13.6)	973 (14.5)	225 (15.6)
\geq 12 and < 15 years	125828 (64.6)	62216 (64.6)	25302 (64.8)	15521 (64.8)	17646 (64.9)	4225 (62.9)	918 (63.7)
\geq 15 years	32391 (16.6)	15202 (15.8)	6700 (17.2)	4100 (17.1)	4843 (17.8)	1285 (19.1)	261 (18.1)
Missing information	9423 (4.8)	5455 (5.7)	1699 (4.3)	994 (4.1)	1001 (3.7)	237 (3.5)	37 (2.6)
Age at first full term pregnancy: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	\geq 110 mmHg
\leq 21 years	36839 (18.9)	16461 (17.1)	7737 (19.8)	4927 (20.6)	5914 (21.7)	1486 (22.1)	314 (21.8)
> 21 and \leq 30 years	106230 (54.6)	51245 (53.2)	21671 (55.5)	13514 (56.4)	15248 (56.1)	3752 (55.8)	800 (55.5)

> 30 years	15709 (8.1)	8160 (8.5)	3046 (7.8)	1798 (7.5)	2053 (7.5)	536 (8.0)	116 (8.0)
Missing information	35949 (18.5)	20486 (21.3)	6605 (16.9)	3717 (15.5)	3984 (14.6)	946 (14.1)	211 (14.6)
Number of full-term pregnancies: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
None	25571 (13.1)	14179 (14.7)	4822 (12.3)	2708 (11.3)	2966 (10.9)	733 (10.9)	163 (11.3)
One	28796 (14.8)	13454 (14.0)	5985 (15.3)	3708 (15.5)	4341 (16.0)	1089 (16.2)	219 (15.2)
Two	75357 (38.7)	36127 (37.5)	15607 (40.0)	9564 (39.9)	10861 (39.9)	2652 (39.5)	546 (37.9)
Three	33031 (17.0)	15360 (15.9)	6857 (17.6)	4320 (18.0)	5001 (18.4)	1213 (18.1)	280 (19.4)
Four or more	14897 (7.7)	6462 (6.7)	3007 (7.7)	2045 (8.5)	2540 (9.3)	674 (10.0)	169 (11.7)
Missing information	17075 (8.8)	10770 (11.2)	2781 (7.1)	1611 (6.7)	1490 (5.5)	359 (5.3)	64 (4.4)
Menopausal status: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
Pre-menopausal	58190 (29.9)	37077 (38.5)	10288 (26.3)	5117 (21.4)	4575 (16.8)	930 (13.8)	203 (14.1)
Post-menopausal	96806 (49.7)	40368 (41.9)	20574 (52.7)	13749 (57.4)	16786 (61.7)	4392 (65.4)	937 (65.0)
Peri-menopausal or unknown	33371 (17.1)	16206 (16.8)	6856 (17.6)	4236 (17.7)	4731 (17.4)	1107 (16.5)	235 (16.3)
Surgical post-menopausal	6360 (3.3)	2701 (2.8)	1341 (3.4)	854 (3.6)	1107 (4.1)	291 (4.3)	66 (4.6)
Age at menopause: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
< 40 years	4301 (2.2)	1857 (1.9)	952 (2.4)	543 (2.3)	728 (2.7)	178 (2.6)	43 (3.0)
≥ 40 and ≤ 46 years	18912 (9.7)	7770 (8.1)	4087 (10.5)	2617 (10.9)	3331 (12.2)	915 (13.6)	192 (13.3)
> 46 and ≤ 50 years	31996 (16.4)	12971 (13.5)	6878 (17.6)	4602 (19.2)	5723 (21.0)	1515 (22.5)	307 (21.3)
> 50 and ≤ 56 years	29427 (15.1)	11645 (12.1)	6290 (16.1)	4350 (18.2)	5449 (20.0)	1395 (20.8)	298 (20.7)
> 56 years	1997 (1.0)	740 (0.8)	438 (1.1)	296 (1.2)	377 (1.4)	112 (1.7)	34 (2.4)
Missing information or not applicable	108094 (55.5)	61369 (63.7)	20414 (52.3)	11548 (48.2)	11591 (42.6)	2605 (38.8)	567 (39.3)
Oral contraceptive use: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
Never	82568 (42.4)	35792 (37.1)	17637 (45.2)	10976 (45.8)	13796 (50.7)	3544 (52.7)	823 (57.1)
Former	91622 (47.1)	48163 (50.0)	17767 (45.5)	10943 (45.7)	11444 (42.1)	2758 (41.0)	547 (38.0)
Current	10050 (5.2)	5938 (6.2)	1853 (4.7)	1034 (4.3)	986 (3.6)	213 (3.2)	26 (1.8)
Missing information	10487 (5.4)	6459 (6.7)	1802 (4.6)	1003 (4.2)	973 (3.6)	205 (3.1)	45 (3.1)
Hormone replacement therapy: N (%)	Total	< 80 mmHg	80-84 mmHg	85-89 mmHg	90-99 mmHg	100-109 mmHg	≥ 110 mmHg
Never	129049 (66.3)	66219 (68.7)	25508 (65.3)	15027 (62.7)	17067 (62.7)	4232 (63.0)	996 (69.1)
Former	16259 (8.3)	7398 (7.7)	3453 (8.8)	2211 (9.2)	2451 (9.0)	621 (9.2)	125 (8.7)
Current	30133 (15.5)	14950 (15.5)	6120 (15.7)	3918 (16.4)	4049 (14.9)	919 (13.7)	177 (12.3)
Missing information	19286 (9.9)	7785 (8.1)	3978 (10.2)	2800 (11.7)	3632 (13.4)	948 (14.1)	143 (9.9)

N - number of individuals; (%) - percentage from total number in blood pressure category (for reproductive factors in women only); **SD** - standard deviation

< 120	7588	8611	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	7451	66446	1.014 (0.981-1.047)	0.988 (0.956-1.021)	0.985 (0.952-1.019)	0.985 (0.953-1.018)	1.013 (0.959-1.071)	1.010 (0.969-1.052)		0.999 (0.957-1.044)	0.982 (0.934-1.032)		1.018 (0.969-1.069)	0.993 (0.950-1.038)	
Any cancer	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Censoring Kidney cancer HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
130-139	7789	57482	1.070 (1.036-1.106)	1.031 (0.998-1.066)	1.021 (0.986-1.057)	1.026 (0.992-1.061)	1.031 (0.976-1.089)	1.078 (1.033-1.125)		1.030 (0.983-1.078)	1.039 (0.990-1.090)		1.050 (0.995-1.108)	1.046 (1.002-1.091)	
140-159	11003	68235	1.073 (1.041-1.107)	1.027 (0.995-1.060)	1.023 (0.990-1.058)	1.019 (0.987-1.053)	1.025 (0.973-1.080)	1.069 (1.025-1.114)	0.000001	1.019 (0.974-1.067)	1.041 (0.994-1.091)	0.08	1.025 (0.968-1.085)	1.042 (1.001-1.085)	0.024
160-179	4136	22656	1.105 (1.062-1.151)	1.057 (1.014-1.101)	1.046 (1.002-1.092)	1.044 (1.001-1.088)	1.044 (0.979-1.113)	1.106 (1.047-1.169)		1.080 (1.012-1.152)	1.058 (1.001-1.118)		1.134 (1.034-1.244)	1.057 (1.007-1.110)	
>= 180	1331	6358	1.243 (1.170-1.320)	1.175 (1.106-1.249)	1.164 (1.092-1.241)	1.158 (1.089-1.232)	1.177 (1.076-1.287)	1.219 (1.120-1.328)		1.189 (1.069-1.322)	1.182 (1.095-1.277)		1.320 (1.112-1.566)	1.172 (1.095-1.254)	
p-trend			2E-14	0.000003	0.00005	0.00007	0.012	0.0000009		0.004	0.00001		0.005	0.000008	
Diastolic Blood Pressure (mmHg)															
ESH classification															
< 80	14454	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	8211	64872	0.990 (0.963-1.018)	0.971 (0.945-0.999)	0.973 (0.946-1.002)	0.970 (0.943-0.997)	0.965 (0.924-1.007)	0.990 (0.955-1.027)		0.953 (0.916-0.993)	0.989 (0.952-1.028)		1.003 (0.955-1.053)	0.965 (0.933-0.998)	
85-89	5905	41500	1.038 (1.007-1.070)	1.009 (0.978-1.041)	1.014 (0.981-1.047)	1.009 (0.977-1.041)	0.993 (0.947-1.040)	1.035 (0.993-1.080)		1.044 (0.996-1.095)	0.994 (0.953-1.036)		1.023 (0.965-1.083)	1.009 (0.973-1.048)	
90-99	7786	51196	1.059 (1.029-1.089)	1.016 (0.986-1.046)	1.018 (0.988-1.050)	1.009 (0.979-1.039)	0.980 (0.939-1.023)	1.064 (1.022-1.108)	0.951	1.018 (0.972-1.066)	1.022 (0.983-1.061)	0.812	1.043 (0.986-1.103)	1.010 (0.976-1.045)	0.053
100-109	2344	13896	1.172 (1.121-1.224)	1.102 (1.054-1.153)	1.107 (1.056-1.160)	1.089 (1.041-1.140)	1.039 (0.977-1.106)	1.193 (1.117-1.275)		1.087 (1.002-1.179)	1.120 (1.061-1.183)		1.097 (0.998-1.207)	1.103 (1.049-1.161)	
>= 110	548	3264	1.198 (1.100-1.305)	1.108 (1.016-1.207)	1.127 (1.031-1.233)	1.087 (0.995-1.187)	1.078 (0.966-1.203)	1.136 (0.987-1.308)		1.269 (1.071-1.502)	1.079 (0.976-1.193)		1.364 (1.149-1.619)	1.039 (0.941-1.148)	
p-trend			9E-15	0.0001	0.00005	0.001	0.335	0.000001		0.006	0.0007		0.003	0.002	

(1/3SBP+2/3DBP)															
Cohort-specific quartiles															
50.0-88.3	7046	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	9002	77727	1.020 (0.988-1.053)	0.998 (0.966-1.030)	0.995 (0.962-1.029)	0.994 (0.963-1.027)	0.999 (0.945-1.055)	1.026 (0.986-1.067)		0.993 (0.952-1.036)	1.008 (0.959-1.059)		1.014 (0.966-1.066)	1.010 (0.968-1.053)	
Any cancer	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Censoring Kidney cancer HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
96.8-105.5	10476	76327	1.044 (1.012-1.077)	1.007 (0.976-1.040)	1.007 (0.974-1.041)	1.001 (0.969-1.034)	0.998 (0.945-1.053)	1.048 (1.006-1.091)	0.015	1.018 (0.975-1.063)	1.008 (0.960-1.057)	0.367	1.022 (0.969-1.077)	1.021 (0.981-1.064)	0.014
105.6-216.6	12774	76273	1.108 (1.074-1.143)	1.051 (1.018-1.085)	1.047 (1.012-1.082)	1.040 (1.007-1.074)	1.018 (0.966-1.074)	1.114 (1.068-1.161)		1.057 (1.010-1.107)	1.059 (1.010-1.110)		1.084 (1.023-1.148)	1.057 (1.016-1.101)	
p-trend			1E-12	0.0005	0.002	0.005	0.357	0.000002		0.01	0.003		0.011	0.001	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)															
Normotensive	18224	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	20374	133139	1.050 (1.028-1.072)	1.029 (1.007-1.051)	1.027 (1.004-1.050)	1.023 (1.001-1.045)	1.016 (0.984-1.049)	1.049 (1.019-1.080)	0.003	1.020 (0.988-1.053)	1.045 (1.016-1.075)	0.051	1.027 (0.987-1.069)	1.034 (1.008-1.061)	0.116

Any cancer	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	15120	23704		24429	14869		26864	5538	

Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.010 (1.001-1.020)	1.015 (1.008-1.022)	0.037	1.009 (1.002-1.016)	1.023 (1.014-1.032)	0.002	1.011 (1.004-1.019)	1.015 (1.001-1.029)	0.566
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.023 (1.007-1.040)	1.016 (1.003-1.029)	0.735	1.014 (1.002-1.027)	1.032 (1.016-1.049)	0.217	1.015 (1.002-1.028)	1.012 (0.985-1.039)	0.896
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.020 (1.005-1.034)	1.019 (1.008-1.031)	0.376	1.014 (1.003-1.025)	1.034 (1.020-1.048)	0.022	1.016 (1.005-1.028)	1.019 (0.996-1.043)	0.636
Any cancer	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.999 (0.948-1.052)	0.980 (0.939-1.022)		0.980 (0.941-1.020)	1.013 (0.958-1.072)		0.988 (0.952-1.024)	1.005 (0.854-1.183)	
130-139	1.042 (0.988-1.099)	1.025 (0.982-1.070)		1.021 (0.980-1.064)	1.063 (1.005-1.125)		1.021 (0.983-1.061)	1.079 (0.927-1.256)	
140-159	1.039 (0.987-1.094)	1.016 (0.975-1.059)	0.101	1.003 (0.964-1.044)	1.079 (1.023-1.139)	0.004	1.021 (0.983-1.060)	1.040 (0.899-1.202)	0.504
160-179	1.052 (0.985-1.125)	1.049 (0.995-1.106)		1.040 (0.987-1.095)	1.099 (1.028-1.176)		1.072 (1.017-1.131)	1.038 (0.893-1.207)	
>= 180	1.140 (1.029-1.264)	1.196 (1.108-1.290)		1.148 (1.060-1.244)	1.244 (1.131-1.369)		1.120 (1.022-1.227)	1.204 (1.021-1.421)	
p-trend	0.009	0.0003		0.01	0.000003		0.002	0.065	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.960 (0.918-1.004)	0.975 (0.941-1.011)		0.955 (0.922-0.989)	1.005 (0.960-1.052)		0.961 (0.931-0.993)	0.973 (0.883-1.073)	
85-89	1.039 (0.989-1.092)	0.987 (0.948-1.028)		0.990 (0.951-1.030)	1.047 (0.996-1.102)		1.030 (0.992-1.069)	0.900 (0.815-0.993)	
90-99	1.033 (0.986-1.083)	0.997 (0.961-1.036)	0.489	1.008 (0.971-1.046)	1.036 (0.988-1.086)	0.627	1.006 (0.969-1.043)	0.979 (0.897-1.069)	0.932
100-109	1.096 (1.017-1.180)	1.098 (1.038-1.162)		1.133 (1.069-1.200)	1.075 (1.001-1.153)		1.100 (1.031-1.173)	1.038 (0.937-1.151)	
>= 110	1.128 (0.978-1.301)	1.093 (0.980-1.219)		1.022 (0.908-1.151)	1.234 (1.088-1.400)		1.078 (0.938-1.238)	1.023 (0.872-1.200)	
p-trend	0.002	0.034		0.008	0.002		0.016	0.354	

Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.019 (0.974-1.067)	1.001 (0.964-1.039)		0.999 (0.964-1.035)	1.038 (0.987-1.091)		1.003 (0.971-1.036)	1.051 (0.908-1.216)	
140-159	1.037 (0.985-1.092)	1.013 (0.972-1.056)	0.114	1.001 (0.962-1.042)	1.077 (1.020-1.136)	0.006	1.019 (0.982-1.058)	1.037 (0.897-1.199)	0.986
>= 160	1.068 (1.003-1.137)	1.079 (1.028-1.134)		1.060 (1.010-1.113)	1.129 (1.060-1.203)		1.079 (1.027-1.134)	1.078 (0.930-1.250)	
p-trend	0.033	0.003		0.047	0.00005		0.007	0.32	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.992 (0.955-1.031)	0.980 (0.950-1.011)		0.969 (0.940-0.999)	1.022 (0.982-1.064)		0.987 (0.960-1.015)	0.936 (0.859-1.021)	
Any cancer	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
90-99	1.032 (0.985-1.082)	0.997 (0.961-1.035)	0.852	1.007 (0.971-1.046)	1.035 (0.988-1.085)	0.794	1.005 (0.969-1.043)	0.980 (0.898-1.070)	0.413
>= 100	1.101 (1.028-1.178)	1.097 (1.041-1.156)		1.112 (1.053-1.173)	1.103 (1.034-1.177)		1.095 (1.032-1.163)	1.037 (0.939-1.144)	
p-trend	0.012	0.029		0.011	0.006		0.089	0.142	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.001 (0.952-1.054)	0.997 (0.957-1.039)		1.010 (0.972-1.050)	0.979 (0.926-1.035)		0.997 (0.962-1.033)	0.977 (0.826-1.156)	
96.8-105.5	1.014 (0.964-1.067)	1.002 (0.962-1.044)	0.923	0.996 (0.958-1.036)	1.033 (0.978-1.091)	0.054	1.012 (0.976-1.049)	1.000 (0.856-1.167)	0.592
105.6-216.6	1.066 (1.012-1.123)	1.038 (0.996-1.082)		1.042 (1.001-1.085)	1.074 (1.017-1.134)		1.039 (0.999-1.080)	1.024 (0.880-1.191)	
p-trend	0.007	0.042		0.06	0.0003		0.033	0.329	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.026 (0.991-1.062)	1.024 (0.997-1.053)	0.294	1.020 (0.992-1.048)	1.049 (1.014-1.086)	0.06	1 (referent)	1.074 (1.038-1.111)	

Head and neck	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			683	683	609	476	207		303	380		242	441	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	683	30738	1.107 (1.065-1.150)	1.079 (1.037-1.124)	1.086 (1.040-1.133)	1.083 (1.031-1.138)	1.069 (0.995-1.148)	0.811	1.113 (1.049-1.182)	1.045 (0.990-1.104)	0.356	1.019 (0.941-1.103)	1.103 (1.053-1.157)	0.055
Head and neck	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	683	30738	1.160 (1.083-1.243)	1.090 (1.013-1.173)	1.120 (1.037-1.210)	1.068 (0.978-1.167)	1.148 (1.005-1.311)	0.129	1.093 (0.978-1.222)	1.073 (0.975-1.181)	0.876	0.980 (0.860-1.117)	1.146 (1.049-1.252)	0.028
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	683	30738	1.161 (1.095-1.231)	1.107 (1.040-1.178)	1.127 (1.055-1.203)	1.098 (1.018-1.184)	1.126 (1.007-1.259)	0.327	1.136 (1.034-1.247)	1.071 (0.986-1.163)	0.571	1.003 (0.893-1.126)	1.155 (1.072-1.244)	0.023
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	105	86141	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-129	125	66446	1.26 (0.97-1.64)	1.12 (0.86-1.46)	1.21 (0.92-1.60)	0.98 (0.70-1.36)	1.38 (0.89-2.14)		1.31 (0.92-1.87)	0.91 (0.61-1.35)		1.02 (0.71-1.48)	1.26 (0.86-1.86)	
130-139	132	57482	1.39 (1.07-1.80)	1.18 (0.91-1.54)	1.21 (0.91-1.61)	1.08 (0.78-1.50)	1.35 (0.85-2.14)		1.29 (0.89-1.88)	1.00 (0.68-1.46)		1.17 (0.79-1.72)	1.26 (0.86-1.84)	
140-159	205	68235	1.57 (1.22-2.01)	1.31 (1.02-1.69)	1.36 (1.04-1.78)	1.16 (0.85-1.59)	1.59 (1.03-2.47)	0.572	1.41 (0.98-2.03)	1.09 (0.76-1.57)	0.438	1.31 (0.89-1.93)	1.40 (0.98-2.00)	0.093

classification														
< 80	219	1325 90	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-89	243	1063 72	1.15 (0.96- 1.39)	1.06 (0.88- 1.28)	1.12 (0.92- 1.37)	1.05 (0.84- 1.32)	1.06 (0.76- 1.48)		0.96 (0.73- 1.25)	1.15 (0.88- 1.51)		0.85 (0.63- 1.16)	1.23 (0.96- 1.57)	
90-99	164	5119 6	1.50 (1.22- 1.84)	1.30 (1.05- 1.60)	1.41 (1.12- 1.76)	1.22 (0.95- 1.58)	1.50 (1.02- 2.21)	0.066	1.12 (0.80- 1.57)	1.41 (1.05- 1.87)	0.799	1.08 (0.75- 1.55)	1.46 (1.12- 1.91)	0.029
>= 100	57	1716 0	1.52 (1.13- 2.04)	1.23 (0.91- 1.66)	1.32 (0.96- 1.82)	1.15 (0.81- 1.64)	1.56 (0.87- 2.80)		1.64 (1.04- 2.58)	1.06 (0.71- 1.59)		0.79 (0.42- 1.47)	1.50 (1.05- 2.14)	
p-trend			0.0000 5	0.024	0.005	0.164	0.029		0.104	0.157		0.779	0.004	
Mean BP (mmHg) (1/3SBP+2/ 3DBP) Cohort- specific quartiles														
50.0-88.3	101	7699 1	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
88.5-96.6	148	7772 7	1.19 (0.92- 1.54)	1.08 (0.84- 1.40)	1.12 (0.86- 1.48)	1.08 (0.78- 1.50)	1.06 (0.70- 1.62)		1.32 (0.94- 1.85)	0.81 (0.54- 1.20)		0.83 (0.58- 1.19)	1.48 (1.01- 2.18)	
96.8-105.5	164	7632 7	1.16 (0.90- 1.50)	1.01 (0.78- 1.31)	1.03 (0.78- 1.35)	1.01 (0.73- 1.39)	0.98 (0.63- 1.52)	0.248	1.06 (0.73- 1.52)	0.86 (0.59- 1.24)	0.982	0.74 (0.50- 1.09)	1.40 (0.96- 2.04)	0.024
105.6-216.6	270	7627 3	1.70 (1.33- 2.16)	1.40 (1.09- 1.80)	1.51 (1.16- 1.97)	1.33 (0.97- 1.82)	1.55 (1.03- 2.36)		1.60 (1.12- 2.26)	1.11 (0.78- 1.59)		1.05 (0.71- 1.55)	1.88 (1.30- 2.70)	
Head and neck	Cas es	Coh ort	HR (crude)	HR (adjus ted)	Exclu ding first 2 years of follow- up HR (adjus ted)	Men HR (adjus ted)	Wome n HR (adjus ted)	Sex p- interac tion	BMI <= 25 mg/m² HR (adjus ted)	BMI > 25 mg/m² HR (adjus ted)	BMI p- interac tion	Age <= 53 yrs HR (adjus ted)	Age > 53 yrs HR (adjus ted)	Age p- interac tion
p-trend			0.0000 06	0.005	0.001	0.048	0.041		0.034	0.108		0.904	0.0007	
Hypertensi on (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self- reported)														
Normotensi ve	301	1741 79	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
Hypertensi ve	382	1331 39	1.27 (1.09- 1.49)	1.21 (1.03- 1.42)	1.22 (1.03- 1.45)	1.23 (1.01- 1.49)	1.17 (0.87- 1.56)	0.77	1.16 (0.91- 1.47)	1.22 (0.98- 1.51)	0.533	1.08 (0.82- 1.42)	1.29 (1.05- 1.58)	0.192

Head and neck	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p- interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p- interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p- interaction
Cases	125	550		310	373		480	106	
Cohort size	141931	160623		205214	102104		227336	37017	

< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
120-139	0.88 (0.51-1.50)	1.24 (0.95-1.62)		1.00 (0.73-1.37)	1.38 (0.96-1.99)		1.27 (0.98-1.64)	-	
140-159	1.17 (0.66-2.07)	1.35 (1.01-1.80)	0.996	1.01 (0.71-1.44)	1.73 (1.18-2.52)	0.03	1.38 (1.03-1.85)	-	-
>= 160	1.10 (0.55-2.20)	1.82 (1.32-2.52)		1.14 (0.74-1.76)	2.32 (1.53-3.51)		1.55 (1.07-2.25)	-	
p-trend	0.46	0.0004		0.608	0.00002		0.013	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.86 (0.55-1.33)	1.11 (0.90-1.38)		0.84 (0.64-1.10)	1.34 (1.03-1.76)		1.12 (0.91-1.39)	1.71 (0.70-4.16)	
90-99	1.04 (0.63-1.72)	1.35 (1.07-1.72)	0.776	1.00 (0.73-1.39)	1.66 (1.23-2.23)	0.087	1.18 (0.90-1.54)	2.41 (1.01-5.76)	0.392
>= 100	1.02 (0.50-2.11)	1.24 (0.89-1.74)		1.01 (0.62-1.62)	1.52 (1.02-2.28)		1.04 (0.67-1.63)	1.78 (0.69-4.57)	
p-trend	0.866	0.024		0.982	0.002		0.342	0.197	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	0.99 (0.56-1.77)	1.13 (0.84-1.51)		1.10 (0.79-1.54)	1.07 (0.72-1.60)		1.17 (0.89-1.56)	-	
96.8-105.5	0.77 (0.42-1.41)	1.08 (0.81-1.44)	0.775	0.86 (0.60-1.23)	1.20 (0.82-1.76)	0.016	1.12 (0.84-1.49)	-	-
105.6-216.6	1.16 (0.65-2.08)	1.48 (1.11-1.96)		1.06 (0.75-1.51)	1.78 (1.23-2.58)		1.36 (1.01-1.83)	-	
Head and neck	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.607	0.004		0.941	0.00009		0.064	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.12 (0.76-1.66)	1.22 (1.02-1.46)	0.848	1.02 (0.80-1.29)	1.42 (1.14-1.77)	0.08	1 (referent)	1.34 (1.05-1.71)	

Mouth and oropharynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			332	332	301	195	137		149	183		128	204	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	332	30738	1.095 (1.036-1.157)	1.070 (1.009-1.134)	1.082 (1.019-1.150)	1.036 (0.957-1.123)	1.107 (1.015-1.207)	0.06	1.146 (1.054-1.247)	1.008 (0.931-1.091)	0.166	0.913 (0.813-1.024)	1.138 (1.064-1.217)	0.002
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	332	30738	1.186 (1.076-1.308)	1.131 (1.019-1.255)	1.156 (1.037-1.288)	1.053 (0.917-1.211)	1.246 (1.069-1.452)	0.017	1.109 (0.945-1.302)	1.145 (1.000-1.310)	0.552	0.907 (0.756-1.089)	1.252 (1.110-1.413)	0.006
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	332	30738	1.164 (1.071-1.265)	1.119 (1.023-1.223)	1.141 (1.040-1.252)	1.054 (0.935-1.189)	1.205 (1.056-1.376)	0.022	1.171 (1.025-1.337)	1.077 (0.956-1.212)	0.707	0.892 (0.757-1.051)	1.236 (1.114-1.371)	0.002
Systolic Blood Pressure (mmHg) ESH classification														
< 120	54	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	64	66446	1.24 (0.86-1.79)	1.15 (0.80-1.66)	1.23 (0.83-1.81)	0.87 (0.54-1.41)	1.49 (0.84-2.64)		1.48 (0.90-2.46)	0.80 (0.47-1.36)		0.94 (0.58-1.53)	1.58 (0.86-2.89)	
130-139	66	57482	1.33 (0.92-1.92)	1.19 (0.82-1.73)	1.18 (0.79-1.76)	0.93 (0.58-1.50)	1.49 (0.82-2.71)		1.73 (1.02-2.91)	0.75 (0.44-1.27)		0.81 (0.47-1.39)	1.85 (1.03-3.32)	
140-159	92	68235	1.35 (0.95-1.92)	1.18 (0.82-1.70)	1.26 (0.86-1.84)	0.78 (0.48-1.25)	1.92 (1.09-3.36)	0.016	1.43 (0.83-2.46)	0.84 (0.51-1.36)	0.157	0.88 (0.52-1.50)	1.73 (0.98-3.04)	0.004
Mouth and oropharynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

160-179	39	22656	1.67 (1.08-2.58)	1.44 (0.92-2.25)	1.61 (1.01-2.56)	0.97 (0.54-1.75)	2.25 (1.15-4.43)		2.45 (1.26-4.77)	0.87 (0.48-1.56)		0.47 (0.16-1.38)	2.48 (1.34-4.58)	
>= 180	17	6358	2.52 (1.43-4.43)	2.09 (1.17-3.73)	2.18 (1.18-4.03)	1.83 (0.90-3.70)	2.12 (0.77-5.85)		4.70 (2.04-10.85)	1.01 (0.46-2.23)		0.51 (0.07-3.82)	3.58 (1.74-7.35)	
p-trend			0.003	0.04	0.023	0.669	0.011		0.003	0.984		0.229	0.0007	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	108	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	70	64872	1.16 (0.85-1.57)	1.10 (0.81-1.49)	1.14 (0.83-1.58)	0.95 (0.63-1.42)	1.28 (0.80-2.05)		1.00 (0.65-1.56)	1.19 (0.77-1.85)		0.78 (0.49-1.26)	1.46 (0.97-2.22)	
85-89	48	41500	1.12 (0.80-1.58)	1.04 (0.73-1.48)	1.08 (0.75-1.56)	0.93 (0.60-1.45)	1.15 (0.65-2.03)		1.24 (0.76-2.01)	0.92 (0.56-1.51)		0.49 (0.25-0.95)	1.63 (1.05-2.52)	
90-99	78	51196	1.47 (1.09-1.98)	1.30 (0.96-1.78)	1.40 (1.01-1.94)	1.04 (0.69-1.55)	1.76 (1.10-2.84)	0.004	0.98 (0.58-1.64)	1.51 (1.00-2.27)	0.576	0.90 (0.55-1.48)	1.74 (1.16-2.62)	0.007
100-109	23	13896	1.55 (0.98-2.44)	1.29 (0.81-2.05)	1.37 (0.84-2.24)	0.93 (0.50-1.73)	2.18 (1.08-4.42)		1.91 (0.96-3.79)	1.06 (0.56-1.99)		0.36 (0.11-1.18)	2.19 (1.27-3.77)	
>= 110	5	3264	1.49 (0.60-3.65)	1.21 (0.49-3.00)	1.42 (0.57-3.53)	0.91 (0.28-2.93)	2.14 (0.51-8.93)		no cases	1.64 (0.64-4.18)		1.08 (0.26-4.52)	1.37 (0.42-4.45)	
p-trend			0.007	0.11	0.046	0.973	0.007		0.42	0.157		0.168	0.003	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	54	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	130	123928	1.28 (0.93-1.77)	1.17 (0.84-1.62)	1.21 (0.85-1.71)	0.90 (0.59-1.37)	1.49 (0.89-2.50)		1.59 (1.01-2.49)	0.77 (0.48-1.23)		0.89 (0.57-1.37)	1.72 (0.99-2.97)	
140-159	92	68235	1.35 (0.95-1.92)	1.18 (0.82-1.69)	1.25 (0.86-1.84)	0.77 (0.48-1.24)	1.92 (1.09-3.35)	0.009	1.42 (0.82-2.43)	0.84 (0.51-1.36)	0.187	0.89 (0.52-1.51)	1.72 (0.97-3.02)	0.007
>= 160	56	29014	1.85 (1.25-2.76)	1.58 (1.05-2.39)	1.74 (1.13-2.68)	1.16 (0.68-1.98)	2.22 (1.17-4.23)		2.90 (1.59-5.27)	0.90 (0.52-1.57)		0.49 (0.18-1.28)	2.72 (1.51-4.89)	
p-trend			0.004	0.049	0.019	0.836	0.008		0.004	0.974		0.248	0.001	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	108	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Mouth and oropharynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					follow-up HR (adjusted)									
80-89	118	1063 72	1.14 (0.88- 1.49)	1.07 (0.82- 1.41)	1.12 (0.84- 1.48)	0.94 (0.66- 1.34)	1.23 (0.81- 1.87)		1.09 (0.75- 1.59)	1.07 (0.72- 1.59)		0.67 (0.44- 1.02)	1.53 (1.06- 2.21)	
90-99	78	5119 6	1.47 (1.09- 1.98)	1.30 (0.96- 1.78)	1.40 (1.01- 1.94)	1.04 (0.69- 1.55)	1.77 (1.10- 2.84)	0.003	0.98 (0.58- 1.64)	1.51 (1.00- 2.27)	0.527	0.91 (0.55- 1.49)	1.74 (1.16- 2.62)	0.007
>= 100	28	1716 0	1.54 (1.01- 2.34)	1.27 (0.82- 1.97)	1.38 (0.88- 2.18)	0.93 (0.52- 1.64)	2.18 (1.13- 4.21)		1.61 (0.81- 3.19)	1.17 (0.67- 2.07)		0.50 (0.19- 1.27)	2.03 (1.21- 3.41)	
p-trend			0.005	0.091	0.037	0.972	0.004		0.414	0.125		0.192	0.003	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
50.0-88.3	49	7699 1	1 (refer- ent)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)	
88.5-96.6	77	7772 7	1.29 (0.90- 1.86)	1.21 (0.84- 1.75)	1.27 (0.87- 1.87)	1.01 (0.62- 1.65)	1.38 (0.80- 2.39)		1.93 (1.18- 3.13)	0.62 (0.36- 1.08)		0.87 (0.55- 1.38)	2.32 (1.18- 4.54)	
96.8-105.5	71	7632 7	1.06 (0.73- 1.53)	0.96 (0.66- 1.41)	0.92 (0.61- 1.39)	0.80 (0.49- 1.32)	1.07 (0.59- 1.93)	0.013	1.20 (0.69- 2.08)	0.64 (0.38- 1.07)	0.749	0.38 (0.21- 0.69)	2.43 (1.26- 4.69)	0.0005
105.6-216.6	135	7627 3	1.80 (1.28- 2.54)	1.55 (1.08- 2.23)	1.71 (1.17- 2.49)	1.14 (0.71- 1.84)	2.17 (1.27- 3.73)		2.22 (1.32- 3.73)	0.97 (0.60- 1.56)		0.82 (0.48- 1.38)	3.44 (1.81- 6.53)	
p-trend			0.001	0.022	0.008	0.57	0.007		0.026	0.314		0.151	0.0000 8	
Hypertensio n (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self- reported)														
Normotensi ve	152	1741 79	1 (refer- ent)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)	
Hypertensiv e	180	1331 39	1.23 (0.98- 1.54)	1.15 (0.91- 1.45)	1.20 (0.94- 1.53)	1.04 (0.77- 1.41)	1.31 (0.91- 1.89)	0.076	1.07 (0.76- 1.51)	1.21 (0.89- 1.66)	0.319	0.97 (0.66- 1.41)	1.28 (0.95- 1.72)	0.242

Mouth and oropharynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p- interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p- interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p- interaction
Cases	88	241		154	178		247	42	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.045 (0.930- 1.175)	1.075 (1.004- 1.151)	0.647	1.033 (0.945- 1.129)	1.103 (1.020- 1.193)	0.305	1.062 (0.987- 1.142)	1.138 (0.975- 1.328)	0.218
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.073 (0.872- 1.321)	1.145 (1.013- 1.293)	0.9	1.025 (0.875- 1.201)	1.224 (1.064- 1.408)	0.181	1.154 (1.016- 1.310)	1.141 (0.837- 1.555)	0.924

Mouth and oropharynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.072 (0.897-1.282)	1.129 (1.018-1.252)	0.864	1.038 (0.906-1.189)	1.190 (1.056-1.341)	0.201	1.125 (1.007-1.256)	1.197 (0.925-1.548)	0.448
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-129	1.02 (0.50-2.10)	1.21 (0.79-1.87)		1.03 (0.61-1.71)	1.29 (0.75-2.21)		1.36 (0.91-2.04)	-	
130-139	0.75 (0.34-1.67)	1.39 (0.90-2.14)		1.28 (0.77-2.13)	1.11 (0.63-1.93)		1.45 (0.96-2.20)	-	
140-159	1.31 (0.66-2.61)	1.12 (0.72-1.73)	0.441	1.06 (0.63-1.78)	1.31 (0.78-2.21)	0.45	1.43 (0.94-2.16)	-	-
160-179	1.35 (0.58-3.14)	1.43 (0.84-2.44)		1.43 (0.75-2.72)	1.48 (0.79-2.78)		1.92 (1.13-3.28)	-	
>= 180	1.17 (0.32-4.34)	2.56 (1.34-4.91)		1.21 (0.41-3.55)	2.88 (1.39-5.97)		0.93 (0.28-3.05)	-	
p-trend	0.358	0.078		0.398	0.039		0.072	-	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
80-84	1.04 (0.58-1.87)	1.09 (0.76-1.57)		0.86 (0.56-1.34)	1.45 (0.93-2.25)		1.00 (0.71-1.42)	-	
85-89	0.89 (0.44-1.77)	1.10 (0.73-1.65)		0.73 (0.43-1.25)	1.41 (0.87-2.28)		1.24 (0.85-1.82)	-	
90-99	0.98 (0.52-1.83)	1.42 (1.00-2.03)	0.954	0.99 (0.62-1.56)	1.73 (1.12-2.66)	0.147	1.37 (0.96-1.97)	-	-
100-109	0.76 (0.26-2.24)	1.42 (0.83-2.42)		0.97 (0.45-2.06)	1.70 (0.92-3.13)		1.13 (0.58-2.21)	-	
>= 110	3.10 (1.05-9.18)	0.34 (0.05-2.47)		1.02 (0.25-4.24)	1.48 (0.45-4.85)		0.53 (0.07-3.83)	-	
p-trend	0.717	0.132		0.841	0.022		0.159	-	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-139	0.90 (0.47-1.72)	1.30 (0.88-1.91)		1.14 (0.73-1.78)	1.20 (0.73-1.95)		1.40 (0.98-2.02)	-	
140-159	1.33 (0.67-2.65)	1.11 (0.72-1.71)	0.278	1.05 (0.63-1.76)	1.31 (0.78-2.21)	0.411	1.42 (0.94-2.16)	-	-
>= 160	1.33 (0.59-2.99)	1.67 (1.03-2.72)		1.37 (0.74-2.51)	1.81 (1.02-3.21)		1.72 (1.02-2.88)	-	

p-trend	0.241	0.141		0.473	0.04		0.053	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
Mouth and oropharynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
80-89	0.98 (0.58-1.64)	1.09 (0.80-1.50)		0.81 (0.55-1.19)	1.43 (0.97-2.12)		1.10 (0.81-1.48)	-	
90-99	0.98 (0.52-1.83)	1.42 (1.00-2.03)	0.969	0.99 (0.62-1.57)	1.73 (1.12-2.66)	0.161	1.37 (0.95-1.97)	-	-
>= 100	1.23 (0.54-2.80)	1.22 (0.72-2.05)		0.98 (0.49-1.96)	1.66 (0.94-2.95)		1.02 (0.54-1.94)	-	
p-trend	0.77	0.106		0.906	0.018		0.237	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	1.42 (0.71-2.84)	1.15 (0.75-1.78)		1.47 (0.90-2.39)	0.93 (0.53-1.63)		1.36 (0.91-2.02)	-	
96.8-105.5	0.79 (0.36-1.72)	1.01 (0.65-1.57)	0.911	0.93 (0.55-1.59)	0.96 (0.56-1.65)	0.132	1.16 (0.76-1.76)	-	-
105.6-216.6	1.39 (0.68-2.85)	1.61 (1.06-2.45)		1.33 (0.79-2.24)	1.69 (1.01-2.81)		1.78 (1.18-2.70)	-	
p-trend	0.635	0.021		0.69	0.006		0.015	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.14 (0.71-1.81)	1.13 (0.86-1.48)	0.433	1.05 (0.75-1.48)	1.26 (0.92-1.74)	0.528	1 (referent)	0.96 (0.66-1.39)	

Larynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			239	239	207	201	38		101	138		67	172	
Cohort size			30731	30731	30185	11259	19472		14632	16099		15330	15401	
			8	8	7	1	7		6	2		3	5	

< 80	73	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	49	6487 2	1.18 (0.82-1.71)	1.09 (0.75-1.57)	1.16 (0.78-1.73)	1.09 (0.73-1.64)	1.13 (0.47-2.71)		0.76 (0.42-1.38)	1.37 (0.84-2.23)		0.83 (0.40-1.70)	1.20 (0.78-1.85)	
85-89	31	4150 0	1.05 (0.69-1.61)	0.92 (0.60-1.42)	1.02 (0.65-1.62)	0.97 (0.61-1.54)	0.63 (0.18-2.20)		0.81 (0.41-1.60)	0.98 (0.56-1.73)		1.27 (0.62-2.62)	0.81 (0.47-1.37)	
90-99	65	5119 6	1.77 (1.26-2.49)	1.48 (1.04-2.10)	1.67 (1.14-2.43)	1.45 (0.98-2.13)	1.72 (0.72-4.11)	0.781	1.66 (0.99-2.76)	1.36 (0.84-2.20)	0.186	1.25 (0.61-2.55)	1.55 (1.03-2.34)	0.944
100-109	17	1389 6	1.70 (0.99-2.89)	1.33 (0.77-2.29)	1.47 (0.82-2.65)	1.37 (0.77-2.44)	0.80 (0.10-6.23)		1.56 (0.65-3.75)	1.23 (0.61-2.47)		2.43 (0.95-6.23)	1.05 (0.54-2.07)	
Larynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
>= 110	4	3264	1.67 (0.61-4.58)	1.24 (0.45-3.45)	0.78 (0.19-3.24)	1.04 (0.32-3.36)	3.62 (0.45-29.04)		2.54 (0.60-10.68)	0.79 (0.19-3.33)		no cases	1.59 (0.56-4.48)	
p-trend			0.001	0.063	0.037	0.102	0.379		0.039	0.584		0.206	0.157	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	34	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	85	1239 28	1.37 (0.92-2.06)	1.10 (0.73-1.65)	1.21 (0.77-1.89)	1.06 (0.66-1.69)	1.22 (0.52-2.87)		1.03 (0.58-1.82)	1.16 (0.64-2.13)		1.28 (0.67-2.44)	1.00 (0.59-1.69)	
140-159	73	6823 5	1.72 (1.12-2.65)	1.35 (0.88-2.10)	1.46 (0.91-2.35)	1.31 (0.80-2.15)	1.64 (0.63-4.26)	0.265	1.59 (0.87-2.94)	1.17 (0.62-2.20)	0.545	2.04 (0.97-4.32)	1.12 (0.65-1.93)	0.634
>= 160	47	2901 4	2.47 (1.54-3.95)	1.97 (1.21-3.19)	2.12 (1.25-3.60)	2.10 (1.23-3.59)	0.89 (0.22-3.59)		2.37 (1.17-4.80)	1.69 (0.86-3.33)		2.75 (1.00-7.57)	1.68 (0.95-2.99)	
p-trend			0.0008	0.002	0.003	0.002	0.712		0.007	0.124		0.019	0.031	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	73	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	80	1063 72	1.13 (0.82-1.56)	1.02 (0.74-1.41)	1.10 (0.78-1.57)	1.04 (0.73-1.49)	0.93 (0.42-2.05)		0.78 (0.48-1.29)	1.19 (0.77-1.86)		1.00 (0.56-1.80)	1.03 (0.70-1.52)	
90-99	65	5119 6	1.77 (1.26-2.49)	1.48 (1.04-2.10)	1.67 (1.14-2.43)	1.45 (0.99-2.13)	1.72 (0.72-4.11)	0.776	1.66 (0.99-2.76)	1.36 (0.84-2.20)	0.289	1.25 (0.61-2.54)	1.55 (1.03-2.34)	0.832
>= 100	21	1716 0	1.69 (1.03-2.76)	1.31 (0.79-2.17)	1.34 (0.76-2.34)	1.31 (0.76-2.24)	1.32 (0.29-5.96)		1.72 (0.79-3.76)	1.13 (0.59-2.19)		1.96 (0.76-5.01)	1.16 (0.64-2.12)	
p-trend			0.0008	0.043	0.024	0.075	0.332		0.048	0.394		0.227	0.104	

Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	33	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	51	7772 7	1.26 (0.81-1.95)	1.06 (0.68-1.66)	1.13 (0.70-1.84)	1.16 (0.70-1.94)	0.73 (0.27-1.96)		0.95 (0.52-1.75)	1.28 (0.65-2.53)		0.95 (0.46-1.95)	1.15 (0.65-2.04)	
96.8-105.5	58	7632 7	1.23 (0.79-1.90)	1.00 (0.64-1.56)	1.10 (0.68-1.78)	1.02 (0.61-1.70)	1.07 (0.42-2.69)	0.767	0.83 (0.44-1.56)	1.16 (0.60-2.24)	0.608	1.11 (0.53-2.29)	0.98 (0.56-1.73)	0.961
105.6-216.6	97	7627 3	1.82 (1.20-2.74)	1.39 (0.91-2.14)	1.55 (0.97-2.48)	1.47 (0.90-2.39)	1.19 (0.46-3.06)		1.58 (0.89-2.82)	1.34 (0.70-2.54)		1.57 (0.74-3.32)	1.36 (0.80-2.33)	
p-trend			0.003	0.087	0.042	0.102	0.569		0.118	0.462		0.206	0.221	
Larynx	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	97	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	142	1331 39	1.42 (1.08-1.85)	1.37 (1.04-1.80)	1.37 (1.02-1.83)	1.37 (1.01-1.85)	1.38 (0.70-2.72)	0.873	1.61 (1.07-2.43)	1.15 (0.80-1.66)	0.308	1.37 (0.82-2.29)	1.36 (0.98-1.89)	0.717

Larynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	16	218		102	137		149	50	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.045 (0.781-1.398)	1.135 (1.059-1.217)	0.677	1.043 (0.935-1.164)	1.160 (1.065-1.264)	0.166	1.047 (0.953-1.152)	1.197 (1.036-1.383)	0.088
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.003 (0.593-1.698)	1.127 (0.992-1.280)	0.903	1.076 (0.888-1.303)	1.133 (0.963-1.334)	0.774	0.980 (0.828-1.161)	1.253 (0.939-1.672)	0.09

Mean Blood Pressure (1/3SBP+2/3DBP)	1.037 (0.661-1.628)	1.170 (1.051-1.303)	0.775	1.070 (0.907-1.263)	1.196 (1.045-1.369)	0.371	1.026 (0.887-1.188)	1.309 (1.030-1.665)	0.05
continuous (per 10mmHg increase)									
Systolic Blood Pressure (mmHg)									
ESH classification									
< 120	two cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	-	1.09 (0.67-1.78)		0.82 (0.44-1.54)	1.45 (0.72-2.91)		1.05 (0.63-1.75)	-	
130-139	-	1.13 (0.69-1.84)		0.99 (0.53-1.85)	1.28 (0.63-2.58)		0.95 (0.56-1.63)	-	
140-159	-	1.46 (0.92-2.31)	-	0.88 (0.47-1.64)	1.95 (1.02-3.73)	0.074	1.17 (0.70-1.95)	-	-
160-179	-	1.97 (1.15-3.38)		1.22 (0.55-2.69)	2.42 (1.16-5.05)		1.10 (0.52-2.29)	-	
>= 180	-	2.93 (1.49-5.77)		1.42 (0.46-4.39)	4.39 (1.86-10.38)		2.29 (0.91-5.78)	-	
p-trend	-	0.0006		0.606	0.0005		0.303	-	
Larynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-84	0.49 (0.09-2.67)	1.16 (0.79-1.70)		1.32 (0.78-2.22)	0.94 (0.55-1.58)		1.19 (0.78-1.81)	-	
85-89	0.38 (0.04-3.53)	1.00 (0.64-1.55)		0.73 (0.36-1.50)	1.03 (0.60-1.78)		0.95 (0.57-1.59)	-	
90-99	1.74 (0.47-6.46)	1.45 (1.00-2.10)	0.605	1.39 (0.80-2.41)	1.51 (0.95-2.40)	0.665	0.96 (0.58-1.56)	-	-
100-109	0.91 (0.09-8.72)	1.39 (0.79-2.46)		1.34 (0.55-3.29)	1.34 (0.67-2.69)		1.19 (0.53-2.67)	-	
>= 110	no cases	1.35 (0.48-3.75)		1.60 (0.38-6.79)	1.09 (0.26-4.61)		0.67 (0.09-4.90)	-	
p-trend	0.544	0.076		0.369	0.093		0.829	-	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	two cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	-	1.11 (0.72-1.71)		0.90 (0.52-1.55)	1.36 (0.72-2.56)		1.00 (0.64-1.58)	-	
140-159	-	1.45 (0.91-2.30)	-	0.87 (0.47-1.63)	1.94 (1.02-3.71)	0.069	1.17 (0.70-1.95)	-	-
>= 160	-	2.18 (1.32-3.62)		1.25 (0.60-2.60)	2.84 (1.42-5.68)		1.34 (0.70-2.58)	-	

p-trend	-	0.0006		0.69	0.0005		0.306	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-89	0.45 (0.10-2.02)	1.09 (0.78-1.53)		1.07 (0.67-1.74)	0.98 (0.63-1.53)		1.10 (0.75-1.59)	-	
90-99	1.75 (0.47-6.51)	1.45 (1.00-2.10)	0.622	1.40 (0.81-2.42)	1.51 (0.95-2.40)	0.885	0.96 (0.59-1.57)	-	-
>= 100	0.73 (0.08-7.05)	1.39 (0.82-2.34)		1.41 (0.63-3.14)	1.29 (0.67-2.49)		1.09 (0.51-2.34)	-	
p-trend	0.556	0.052		0.212	0.104		0.951	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	three cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	-	1.21 (0.75-1.93)		0.79 (0.43-1.47)	1.37 (0.71-2.67)		1.12 (0.69-1.84)	-	
96.8-105.5	-	1.08 (0.67-1.74)	-	0.86 (0.47-1.58)	1.16 (0.60-2.25)	0.44	0.99 (0.60-1.65)	-	-
105.6-216.6	-	1.52 (0.97-2.40)		1.06 (0.58-1.93)	1.73 (0.92-3.26)		1.00 (0.59-1.70)	-	
Larynx	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	-	0.068		0.672	0.085		0.831	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.46 (0.47-4.57)	1.38 (1.03-1.84)	0.765	1.01 (0.67-1.54)	1.67 (1.15-2.44)	0.087	1 (referent)	2.29 (1.55-3.38)	

Esophagus	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			387	387	344	257	130		153	234		110	277	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood	387	30738	1.122 (1.067)	1.087 (1.030-1.146)	1.088 (1.028-1.151)	1.101 (1.031-1.177)	1.060 (0.970-1.160)	0.757	1.048 (0.961-1.142)	1.108 (1.036-1.184)	0.489	1.139 (1.022-1.271)	1.069 (1.005-1.136)	0.086

Pressure continuous (per 10mmHg increase)			- 1.180)											
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	387	3073 18	1.233 (1.128- 1.349)	1.147 (1.043- 1.261)	1.162 (1.052- 1.284)	1.160 (1.033- 1.302)	1.118 (0.947- 1.320)	0.626	1.093 (0.936- 1.277)	1.179 (1.048- 1.326)	0.711	1.172 (0.976- 1.406)	1.132 (1.013- 1.265)	0.305
Mean Blood Pressure (1/3SBP+2/ 3DBP) continuous (per 10mmHg increase)	387	3073 18	1.207 (1.119- 1.303)	1.139 (1.051- 1.235)	1.148 (1.053- 1.250)	1.157 (1.047- 1.278)	1.104 (0.961- 1.268)	0.672	1.081 (0.949- 1.233)	1.171 (1.059- 1.296)	0.564	1.190 (1.014- 1.395)	1.118 (1.018- 1.228)	0.16
Systolic Blood Pressure (mmHg) ESH classificatio n														
< 120	56	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	57	6644 6	0.99 (0.68- 1.43)	0.89 (0.61- 1.29)	0.89 (0.60- 1.31)	0.88 (0.54- 1.44)	0.87 (0.48- 1.57)		0.64 (0.38- 1.08)	1.26 (0.71- 2.23)		0.73 (0.38- 1.38)	0.95 (0.59- 1.50)	
130-139	81	5748 2	1.39 (0.98- 1.96)	1.17 (0.82- 1.67)	1.19 (0.82- 1.72)	1.13 (0.71- 1.79)	1.23 (0.71- 2.13)		0.77 (0.46- 1.28)	1.70 (0.99- 2.92)		1.18 (0.65- 2.14)	1.12 (0.72- 1.74)	
140-159	116	6823 5	1.37 (0.98- 1.91)	1.11 (0.79- 1.57)	1.14 (0.80- 1.63)	1.11 (0.71- 1.72)	1.12 (0.66- 1.92)	0.643	0.98 (0.62- 1.56)	1.39 (0.82- 2.37)	0.621	1.17 (0.64- 2.13)	1.05 (0.69- 1.59)	0.062
Esophagus	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow- up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p- interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p- interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p- interaction
160-179	54	2265 6	1.78 (1.20- 2.64)	1.43 (0.96- 2.14)	1.37 (0.89- 2.11)	1.57 (0.95- 2.61)	1.11 (0.56- 2.22)		1.29 (0.71- 2.36)	1.79 (1.00- 3.23)		1.95 (0.92- 4.15)	1.27 (0.78- 2.04)	
>= 180	23	6358	2.70 (1.63- 4.46)	2.10 (1.26- 3.52)	2.14 (1.24- 3.70)	2.27 (1.21- 4.27)	1.71 (0.67- 4.32)		1.27 (0.49- 3.34)	2.96 (1.50- 5.84)		3.52 (1.27- 9.79)	1.83 (1.00- 3.33)	
p-trend			0.0003	0.005	0.009	0.006	0.309		0.253	0.008		0.015	0.083	
Diastolic Blood Pressure (mmHg) ESH classificatio n														
< 80	113	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

3DBP)														
Cohort-specific quartiles														
50.0-88.3	51	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	79	7772 7	1.21 (0.85-1.72)	1.10 (0.77-1.57)	1.16 (0.79-1.69)	1.08 (0.67-1.75)	1.10 (0.64-1.89)		0.75 (0.46-1.22)	1.61 (0.91-2.85)		1.03 (0.56-1.88)	1.11 (0.71-1.72)	
96.8-105.5	95	7632 7	1.24 (0.88-1.75)	1.05 (0.74-1.50)	1.09 (0.75-1.59)	0.97 (0.61-1.56)	1.21 (0.71-2.05)	0.48	0.93 (0.58-1.49)	1.29 (0.74-2.27)	0.801	0.93 (0.49-1.75)	1.06 (0.69-1.63)	0.213
105.6-216.6	162	7627 3	1.80 (1.30-2.50)	1.43 (1.02-2.01)	1.49 (1.04-2.14)	1.52 (0.97-2.38)	1.20 (0.70-2.06)		1.17 (0.74-1.86)	1.84 (1.08-3.15)		1.59 (0.87-2.92)	1.34 (0.89-2.02)	
p-trend			0.000 1	0.022	0.021	0.02	0.467		0.299	0.039		0.108	0.116	
Hypertension (SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or self-reported)														
Normotensive	160	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	227	1331 39	1.32 (1.07-1.63)	1.20 (0.97-1.49)	1.20 (0.96-1.51)	1.22 (0.94-1.60)	1.17 (0.81-1.70)	0.994	1.18 (0.85-1.65)	1.22 (0.92-1.61)	0.918	1.23 (0.82-1.83)	1.17 (0.91-1.51)	0.42

Esophagus	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	82	298		202	185		233	37	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.111 (0.989-1.249)	1.085 (1.021-1.153)	0.552	1.016 (0.940-1.098)	1.161 (1.079-1.249)	0.012	1.123 (1.046-1.206)	1.184 (1.009-1.389)	0.56
Esophagus	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.185 (0.964-1.458)	1.135 (1.019-1.265)	0.944	0.968 (0.844-1.109)	1.360 (1.195-1.547)	0.0006	1.241 (1.092-1.411)	1.099 (0.793-1.524)	0.366
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.178 (0.987-1.406)	1.132 (1.032-1.241)	0.786	0.996 (0.886-1.119)	1.304 (1.167-1.459)	0.001	1.218 (1.092-1.359)	1.221 (0.933-1.597)	0.913

< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.21 (0.71-2.07)	1.19 (0.89-1.60)		0.98 (0.71-1.36)	1.64 (1.08-2.48)		1.36 (0.99-1.88)	0.85 (0.25-2.90)	
90-99	1.30 (0.69-2.47)	1.51 (1.09-2.09)	0.898	1.00 (0.68-1.49)	2.30 (1.48-3.57)	0.002	1.64 (1.13-2.40)	1.52 (0.48-4.80)	0.719
>= 100	1.99 (0.91-4.39)	1.38 (0.88-2.15)		0.84 (0.45-1.56)	2.63 (1.54-4.50)		1.95 (1.14-3.34)	1.36 (0.38-4.88)	
p-trend	0.116	0.021		0.734	0.00003		0.002	0.337	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	0.80 (0.38-1.67)	1.20 (0.79-1.81)		1.20 (0.78-1.86)	0.94 (0.51-1.74)		1.04 (0.67-1.62)	-	
96.8-105.5	0.93 (0.46-1.89)	1.08 (0.72-1.64)	0.637	1.00 (0.64-1.57)	1.16 (0.65-2.06)	0.003	1.17 (0.76-1.81)	-	-
105.6-216.6	1.15 (0.58-2.28)	1.54 (1.03-2.29)		1.02 (0.65-1.60)	2.02 (1.17-3.47)		1.63 (1.06-2.51)	-	
p-trend	0.471	0.025		0.757	0.0002		0.01	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.38 (0.85-2.23)	1.16 (0.91-1.49)	0.436	1.05 (0.78-1.40)	1.43 (1.04-1.97)	0.176	1 (referent)	0.84 (0.57-1.23)	

Esophageal AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			176	176	160	139	37		52	124		47	129	
Cohort size			30738	307318	301857	112597	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	176	30738	1.112 (1.031-1.200)	1.040 (0.958-1.128)	1.014 (0.929-1.107)	1.062 (0.969-1.164)	0.956 (0.799-1.144)	0.641	0.925 (0.788-1.085)	1.096 (0.998-1.204)	0.238	1.006 (0.839-1.207)	1.043 (0.952-1.144)	0.815
Esophageal AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first	Men HR (adjusted)	Women	Sex p-interaction	BMI <= 25 mg/m ²	BMI > 25 mg/m ²	BMI p-interaction	Age <= 53 yrs	Age > 53 yrs	Age p-interaction

					2 years of follow- up HR (adju- sted)		HR (adju- sted)		HR (adju- sted)	HR (adju- sted)		HR (adju- sted)	HR (adju- sted)	
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	176	3073 18	1.251 (1.098- 1.426)	1.078 (0.936- 1.241)	1.059 (0.912- 1.229)	1.080 (0.922- 1.266)	1.036 (0.755- 1.421)	0.963	1.002 (0.769- 1.304)	1.132 (0.960- 1.333)	0.71	0.987 (0.739- 1.318)	1.100 (0.936- 1.293)	0.899
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	176	3073 18	1.208 (1.079- 1.352)	1.069 (0.946- 1.207)	1.040 (0.913- 1.184)	1.087 (0.947- 1.246)	0.982 (0.748- 1.289)	0.83	0.947 (0.752- 1.192)	1.139 (0.989- 1.311)	0.413	0.997 (0.769- 1.293)	1.082 (0.942- 1.243)	0.971
Systolic Blood Pressure (mmHg) ESH classification														
< 120	26	8614 1	1 (refer- ent)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)	
120-129	22	6644 6	0.83 (0.47- 1.46)	0.64 (0.36- 1.14)	0.64 (0.36- 1.16)	0.66 (0.35- 1.27)	0.52 (0.15- 1.81)		0.51 (0.22- 1.22)	0.81 (0.37- 1.80)		0.56 (0.21- 1.48)	0.67 (0.32- 1.37)	
130-139	35	5748 2	1.28 (0.76- 2.15)	0.89 (0.53- 1.50)	0.91 (0.54- 1.56)	0.79 (0.43- 1.46)	1.17 (0.43- 3.20)		0.49 (0.20- 1.20)	1.31 (0.64- 2.67)		0.83 (0.34- 2.05)	0.86 (0.45- 1.65)	
140-159	57	6823 5	1.41 (0.87- 2.30)	0.91 (0.55- 1.50)	0.89 (0.54- 1.49)	0.93 (0.53- 1.64)	0.78 (0.28- 2.21)	0.828	0.60 (0.27- 1.32)	1.29 (0.65- 2.55)	0.308	1.02 (0.43- 2.44)	0.83 (0.45- 1.53)	0.545
160-179	26	2265 6	1.76 (0.99- 3.13)	1.09 (0.61- 1.96)	0.92 (0.49- 1.72)	1.13 (0.58- 2.21)	0.88 (0.25- 3.05)		1.01 (0.38- 2.65)	1.43 (0.66- 3.10)		1.13 (0.33- 3.86)	1.03 (0.52- 2.04)	
>= 180	10	6358	2.41 (1.12- 5.15)	1.43 (0.66- 3.10)	1.29 (0.56- 2.98)	1.63 (0.70- 3.79)	0.67 (0.08- 5.87)		0.49 (0.06- 3.85)	2.29 (0.91- 5.75)		1.22 (0.15- 10.10)	1.42 (0.60- 3.34)	
p-trend			0.002	0.212	0.522	0.153	0.925		0.615	0.043		0.531	0.344	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	49	1325 90	1 (refer- ent)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)		1 (refere- nt)	1 (refere- nt)	
80-84	36	6487 2	1.35 (0.88- 2.09)	1.12 (0.73- 1.74)	1.23 (0.78- 1.93)	1.13 (0.69- 1.86)	1.01 (0.40- 2.57)		0.98 (0.45- 2.10)	1.23 (0.72- 2.11)		0.98 (0.42- 2.31)	1.17 (0.70- 1.94)	
85-89	34	4150 0	1.79 (1.15- 2.78)	1.36 (0.87- 2.13)	1.45 (0.91- 2.31)	1.29 (0.78- 2.16)	1.51 (0.59- 3.88)		1.87 (0.91- 3.85)	1.23 (0.70- 2.16)		1.60 (0.69- 3.72)	1.27 (0.75- 2.16)	
90-99	37	5119 6	1.53 (0.99- 2.37)	1.06 (0.68- 1.66)	1.08 (0.68- 1.73)	0.98 (0.59- 1.62)	1.34 (0.53- 3.37)	0.652	0.88 (0.37- 2.10)	1.18 (0.70- 1.99)	0.699	1.16 (0.49- 2.74)	1.02 (0.61- 1.71)	0.626
100-109	18	1389 6	2.62 (1.52- 4.53)	1.68 (0.96- 2.94)	1.51 (0.81- 2.81)	1.72 (0.94- 3.18)	1.38 (0.30- 6.27)		0.89 (0.21- 3.86)	2.06 (1.10- 3.86)		1.47 (0.45- 4.77)	1.68 (0.89- 3.17)	

Esophageal AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
≥ 110	2	3264	1.18 (0.29-4.88)	0.66 (0.16-2.74)	0.77 (0.18-3.21)	0.72 (0.17-3.02)	no cases		no cases	0.86 (0.20-3.64)		no cases	0.86 (0.20-3.63)	
p-trend			0.002	0.353	0.487	0.504	0.548		0.997	0.19		0.665	0.46	
Systolic Blood Pressure (mmHg) ASH classification														
< 120	26	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	57	1239 28	1.05 (0.65-1.68)	0.77 (0.48-1.24)	0.78 (0.48-1.27)	0.73 (0.42-1.27)	0.85 (0.34-2.17)		0.50 (0.24-1.04)	1.08 (0.55-2.11)		0.69 (0.31-1.52)	0.77 (0.43-1.41)	
140-159	57	6823 5	1.40 (0.86-2.27)	0.90 (0.55-1.48)	0.88 (0.53-1.47)	0.92 (0.52-1.63)	0.76 (0.27-2.16)	0.685	0.60 (0.27-1.32)	1.27 (0.64-2.52)	0.472	1.01 (0.42-2.40)	0.83 (0.45-1.52)	0.581
≥ 160	36	2901 4	1.87 (1.09-3.22)	1.15 (0.66-2.00)	0.98 (0.54-1.76)	1.23 (0.66-2.31)	0.81 (0.25-2.67)		0.89 (0.35-2.27)	1.60 (0.76-3.33)		1.12 (0.35-3.56)	1.11 (0.58-2.12)	
p-trend			0.007	0.326	0.779	0.197	0.69		0.738	0.111		0.654	0.452	
Diastolic Blood Pressure (mmHg) ASH classification														
< 80	49	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	70	1063 72	1.53 (1.06-2.22)	1.23 (0.84-1.78)	1.32 (0.90-1.95)	1.20 (0.78-1.84)	1.21 (0.56-2.63)		1.32 (0.72-2.44)	1.23 (0.77-1.97)		1.23 (0.60-2.51)	1.22 (0.78-1.89)	
90-99	37	5119 6	1.53 (0.99-2.36)	1.06 (0.68-1.65)	1.08 (0.68-1.72)	0.98 (0.59-1.62)	1.34 (0.53-3.36)	0.753	0.87 (0.37-2.09)	1.18 (0.70-1.99)	0.442	1.15 (0.49-2.71)	1.02 (0.61-1.71)	0.735
≥ 100	20	1716 0	2.33 (1.38-3.95)	1.45 (0.85-2.49)	1.34 (0.74-2.43)	1.49 (0.83-2.68)	1.09 (0.24-4.99)		0.72 (0.17-3.11)	1.78 (0.97-3.27)		1.15 (0.35-3.71)	1.50 (0.81-2.76)	
p-trend			0.002	0.338	0.494	0.442	0.631		0.752	0.121		0.773	0.4	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles														
50.0-88.3	20	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	40	7772 7	1.61 (0.93-2.76)	1.27 (0.74-2.19)	1.28 (0.73-2.23)	1.31 (0.69-2.46)	1.02 (0.35-2.97)		0.86 (0.39-1.91)	1.77 (0.80-3.92)		1.09 (0.44-2.68)	1.33 (0.67-2.64)	

96.8-105.5	39	7632 7	1.33 (0.77- 2.29)	0.91 (0.52- 1.59)	0.91 (0.51- 1.61)	0.79 (0.41- 1.53)	1.26 (0.45- 3.49)	0.98	0.64 (0.27- 1.52)	1.28 (0.58- 2.82)	0.745	0.72 (0.26- 1.94)	0.97 (0.49- 1.91)	0.593
105.6-216.6	77	7627 3	2.19 (1.31- 3.65)	1.32 (0.78- 2.23)	1.26 (0.73- 2.18)	1.38 (0.75- 2.54)	0.94 (0.32- 2.73)		1.00 (0.46- 2.19)	1.82 (0.85- 3.86)		1.29 (0.50- 3.28)	1.31 (0.69- 2.49)	
p-trend			0.003	0.415	0.595	0.382	0.953		0.931	0.226		0.694	0.561	
Esophageal AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	70	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	106	1331 39	1.38 (1.01- 1.89)	1.11 (0.80- 1.52)	1.01 (0.73- 1.41)	1.15 (0.80- 1.66)	0.97 (0.48- 1.96)	0.868	1.03 (0.58- 1.82)	1.18 (0.81- 1.74)	0.865	1.22 (0.66- 2.25)	1.04 (0.71- 1.51)	0.361

Esophageal AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	45	128		105	71		94	12	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.061 (0.901- 1.249)	1.037 (0.943- 1.141)	0.61	1.007 (0.903- 1.122)	1.080 (0.955- 1.223)	0.238	1.051 (0.935- 1.181)	1.400 (1.029- 1.905)	0.162
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.128 (0.851- 1.496)	1.059 (0.898- 1.249)	0.737	1.009 (0.838- 1.214)	1.171 (0.942- 1.457)	0.284	1.093 (0.888- 1.346)	1.383 (0.730- 2.622)	0.542
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.110 (0.869- 1.417)	1.057 (0.917- 1.219)	0.65	1.009 (0.860- 1.185)	1.148 (0.951- 1.386)	0.224	1.087 (0.909- 1.300)	1.663 (0.960- 2.882)	0.248
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	

120-129	0.55 (0.17-1.76)	0.63 (0.32-1.23)		0.53 (0.26-1.12)	0.85 (0.33-2.18)		0.49 (0.24-1.02)	-	
130-139	1.01 (0.37-2.78)	0.83 (0.45-1.54)		1.03 (0.55-1.92)	0.63 (0.24-1.67)		0.68 (0.35-1.34)	-	
140-159	0.77 (0.28-2.11)	0.94 (0.53-1.68)	0.763	0.88 (0.48-1.64)	0.97 (0.42-2.27)	0.232	0.81 (0.43-1.52)	-	-
160-179	1.59 (0.54-4.70)	0.91 (0.45-1.86)		0.97 (0.45-2.09)	1.27 (0.49-3.27)		0.95 (0.42-2.13)	-	
>= 180	0.63 (0.07-5.46)	1.70 (0.73-3.96)		0.84 (0.24-2.96)	2.08 (0.70-6.22)		1.53 (0.53-4.40)	-	
Esophageal AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.49	0.254		0.698	0.149		0.426	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
80-84	1.43 (0.62-3.28)	1.06 (0.63-1.77)		0.94 (0.54-1.64)	1.49 (0.72-3.09)		1.38 (0.79-2.42)	-	
85-89	1.32 (0.53-3.32)	1.34 (0.79-2.26)		1.14 (0.64-2.04)	1.85 (0.89-3.84)		1.68 (0.93-3.03)	-	
90-99	1.12 (0.46-2.77)	1.04 (0.62-1.75)	0.99	0.99 (0.57-1.72)	1.21 (0.57-2.58)	0.473	0.86 (0.43-1.71)	-	-
100-109	2.15 (0.73-6.35)	1.55 (0.80-3.00)		1.56 (0.75-3.23)	1.92 (0.78-4.76)		2.06 (0.90-4.72)	-	
>= 110	no cases	0.84 (0.20-3.56)		no cases	1.74 (0.38-8.03)		1.01 (0.13-7.63)	-	
p-trend	0.634	0.444		0.793	0.302		0.525	-	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
120-139	0.78 (0.31-1.98)	0.73 (0.42-1.28)		0.79 (0.44-1.40)	0.73 (0.31-1.70)		0.59 (0.32-1.06)	-	
140-159	0.75 (0.27-2.07)	0.93 (0.52-1.66)	0.614	0.87 (0.47-1.60)	0.97 (0.42-2.27)	0.139	0.79 (0.42-1.50)	-	-
>= 160	1.37 (0.47-3.97)	1.08 (0.56-2.07)		0.92 (0.44-1.90)	1.47 (0.60-3.60)		1.05 (0.50-2.22)	-	
p-trend	0.49	0.424		0.987	0.128		0.571	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	

80-89	1.38 (0.66-2.91)	1.18 (0.76-1.83)		1.03 (0.64-1.64)	1.65 (0.87-3.13)		1.50 (0.91-2.46)	-	
90-99	1.12 (0.46-2.77)	1.04 (0.62-1.75)	0.862	0.99 (0.57-1.72)	1.21 (0.57-2.57)	0.509	0.86 (0.43-1.71)	-	-
>= 100	1.68 (0.57-4.96)	1.39 (0.74-2.61)		1.22 (0.59-2.52)	1.88 (0.80-4.40)		1.84 (0.83-4.08)	-	
p-trend	0.488	0.472		0.747	0.329		0.509	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
88.5-96.6	1.91 (0.60-6.09)	1.21 (0.64-2.27)		1.31 (0.68-2.52)	1.17 (0.44-3.11)		1.09 (0.55-2.18)	-	
Esophageal AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
96.8-105.5	1.69 (0.53-5.40)	0.77 (0.40-1.48)	0.897	0.95 (0.48-1.86)	0.84 (0.32-2.25)	0.344	0.94 (0.47-1.89)	-	-
105.6-216.6	1.63 (0.51-5.15)	1.31 (0.72-2.40)		1.18 (0.62-2.26)	1.48 (0.60-3.68)		1.17 (0.58-2.36)	-	
p-trend	0.672	0.434		0.904	0.28		0.71	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.20 (0.62-2.31)	1.06 (0.73-1.55)	0.575	1.10 (0.73-1.67)	1.11 (0.66-1.87)	0.814	1 (referent)	0.58 (0.30-1.12)	

Esophageal SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			149	149	124	76	73		80	69		39	110	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	149	30738	1.155 (1.067-1.250)	1.161 (1.071-1.258)	1.207 (1.107-1.315)	1.201 (1.072-1.346)	1.127 (1.005-1.263)	0.892	1.128 (1.011-1.259)	1.159 (1.031-1.303)	0.805	1.235 (1.040-1.466)	1.140 (1.039-1.249)	0.127

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	149	3073 18	1.282 (1.110-1.481)	1.306 (1.126-1.515)	1.417 (1.211-1.657)	1.424 (1.161-1.747)	1.211 (0.974-1.505)	0.426	1.290 (1.047-1.590)	1.272 (1.031-1.569)	0.681	1.417 (1.050-1.912)	1.265 (1.065-1.503)	0.214
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	149	3073 18	1.258 (1.114-1.420)	1.276 (1.127-1.445)	1.366 (1.197-1.560)	1.368 (1.149-1.629)	1.202 (1.005-1.438)	0.602	1.238 (1.043-1.471)	1.259 (1.053-1.506)	0.938	1.387 (1.074-1.791)	1.240 (1.074-1.431)	0.152
Systolic Blood Pressure (mmHg) ESH classification														
< 120	21	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Esophageal SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
120-129	21	6644 6	0.92 (0.50-1.69)	0.97 (0.53-1.79)	0.94 (0.47-1.87)	0.74 (0.29-1.89)	1.14 (0.51-2.56)		0.59 (0.26-1.34)	1.69 (0.59-4.84)		0.47 (0.14-1.59)	1.23 (0.59-2.54)	
130-139	25	5748 2	1.08 (0.60-1.94)	1.14 (0.63-2.07)	1.12 (0.57-2.18)	0.97 (0.40-2.36)	1.29 (0.58-2.87)		0.99 (0.48-2.05)	1.29 (0.44-3.77)		0.89 (0.31-2.53)	1.23 (0.59-2.54)	
140-159	52	6823 5	1.54 (0.91-2.60)	1.64 (0.96-2.80)	1.85 (1.02-3.34)	1.51 (0.68-3.36)	1.72 (0.83-3.56)	0.736	1.56 (0.82-2.96)	1.65 (0.61-4.48)	0.863	1.33 (0.51-3.48)	1.74 (0.90-3.34)	0.134
160-179	21	2265 6	1.74 (0.93-3.25)	1.87 (0.98-3.56)	2.08 (1.03-4.22)	2.37 (0.97-5.81)	1.24 (0.47-3.30)		1.48 (0.62-3.51)	2.21 (0.75-6.51)		2.46 (0.78-7.76)	1.72 (0.79-3.75)	
>= 180	9	6358	2.64 (1.18-5.90)	2.81 (1.24-6.39)	3.73 (1.58-8.80)	2.98 (0.93-9.51)	2.61 (0.80-8.52)		1.75 (0.49-6.27)	3.59 (1.05-12.27)		3.74 (0.72-19.57)	2.71 (1.04-7.06)	
p-trend			0.003	0.002	0.0003	0.004	0.121		0.036	0.062		0.029	0.023	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	44	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	29	6487 2	1.14 (0.71-1.83)	1.18 (0.73-1.89)	1.31 (0.77-2.22)	1.16 (0.56-2.38)	1.22 (0.64-2.31)		1.51 (0.82-2.78)	0.74 (0.34-1.60)		1.15 (0.45-2.95)	1.17 (0.67-2.04)	
85-89	19	4150 0	1.05 (0.61-1.80)	1.12 (0.65-1.94)	1.19 (0.64-2.21)	0.95 (0.40-2.22)	1.35 (0.66-2.75)		1.23 (0.59-2.58)	0.84 (0.38-1.87)		0.84 (0.26-2.71)	1.19 (0.64-2.21)	

50.0-88.3	19	7699 1	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	27	7772 7	1.04 (0.58-1.88)	1.10 (0.61-1.99)	1.27 (0.65-2.50)	0.79 (0.30-2.10)	1.31 (0.62-2.76)		0.89 (0.41-1.91)	1.20 (0.45-3.19)		0.92 (0.31-2.73)	1.14 (0.56-2.33)	
96.8-105.5	37	7632 7	1.21 (0.69-2.11)	1.30 (0.74-2.30)	1.50 (0.78-2.88)	1.17 (0.48-2.89)	1.41 (0.68-2.95)	0.292	1.54 (0.77-3.06)	0.81 (0.31-2.16)	0.586	0.81 (0.26-2.51)	1.43 (0.74-2.79)	0.312
105.6-216.6	66	7627 3	1.84 (1.09-3.10)	2.00 (1.16-3.44)	2.53 (1.36-4.71)	2.37 (1.02-5.53)	1.57 (0.76-3.26)		1.82 (0.92-3.62)	1.70 (0.70-4.14)		2.09 (0.76-5.72)	1.91 (1.00-3.64)	
p-trend			0.005	0.003	0.0006	0.002	0.234		0.025	0.131		0.083	0.02	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	59	1741 79	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Hypertensive	90	1331 39	1.40 (1.00-1.96)	1.47 (1.04-2.09)	1.75 (1.19-2.57)	1.63 (0.99-2.69)	1.35 (0.83-2.21)	0.982	1.55 (0.98-2.44)	1.27 (0.76-2.13)	0.467	1.50 (0.77-2.93)	1.43 (0.95-2.15)	0.499

Esophageal SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	31	117		63	86		102	16	
Cohort size	141931	160623		205214	102104		227336	37017	
Esophageal SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.117 (0.927-1.346)	1.174 (1.073-1.284)	0.505	1.005 (0.877-1.152)	1.270 (1.150-1.402)	0.012	1.191 (1.076-1.318)	1.227 (0.970-1.552)	0.424
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.221 (0.871-1.711)	1.325 (1.121-1.566)	0.243	0.984 (0.770-1.258)	1.587 (1.315-1.916)	0.001	1.403 (1.166-1.688)	1.452 (0.926-2.277)	0.983
Mean Blood Pressure (1/3SBP+2/3DBP) continuous	1.197 (0.901-1.590)	1.296 (1.127-1.490)	0.322	0.996 (0.808-1.227)	1.498 (1.283-1.749)	0.002	1.354 (1.157-1.584)	1.413 (0.976-2.046)	0.627

ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
80-89	1.27 (0.54-2.99)	1.16 (0.71-1.88)		1.01 (0.57-1.77)	1.46 (0.77-2.77)		1.09 (0.66-1.81)	-	
90-99	1.74 (0.65-4.70)	2.07 (1.25-3.42)	0.301	0.84 (0.40-1.77)	3.63 (1.95-6.75)	0.0004	2.32 (1.37-3.94)	-	-
>= 100	1.65 (0.35-7.73)	1.87 (0.93-3.73)		0.53 (0.12-2.29)	3.60 (1.65-7.85)		2.32 (1.04-5.17)	-	
p-trend	0.275	0.005		0.426	0.000007		0.001	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	0.32 (0.08-1.21)	1.55 (0.75-3.21)		1.30 (0.62-2.72)	0.86 (0.32-2.33)		1.11 (0.57-2.17)	-	
96.8-105.5	0.77 (0.28-2.14)	1.68 (0.82-3.42)	0.186	1.05 (0.48-2.28)	1.67 (0.70-4.00)	0.001	1.22 (0.62-2.37)	-	-
105.6-216.6	1.06 (0.40-2.83)	2.59 (1.30-5.13)		1.00 (0.45-2.20)	3.32 (1.45-7.59)		2.36 (1.25-4.45)	-	
p-trend	0.511	0.003		0.791	0.00004		0.003	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.62 (0.75-3.50)	1.43 (0.97-2.12)	0.989	0.89 (0.52-1.50)	2.19 (1.36-3.55)	0.021	1 (referent)	0.86 (0.48-1.53)	

Stomach	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			738	738	674	424	314		296	442		164	574	
Cohort size			307318	307318	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure	738	307318	1.028 (0.990-1.069)	1.005 (0.965-1.046)	1.004 (0.962-1.047)	0.993 (0.940-1.049)	1.020 (0.960-1.083)	0.815	1.030 (0.967-1.097)	0.995 (0.944-1.048)	0.384	1.027 (0.932-1.132)	1.000 (0.957-1.046)	0.456
continuous (per 10mmHg increase)														
Mean Diastolic Blood	738	307318	1.107 (1.033)	1.055 (0.982-1.134)	1.069 (0.992-1.152)	1.013 (0.921-1.114)	1.118 (1.003-1.247)	0.241	1.050 (0.936-1.177)	1.070 (0.977-1.171)	0.736	1.058 (0.902-1.239)	1.055 (0.974-1.143)	0.782

Pressure continuous (per 10mmHg increase)			- 1.186)											
Mean Blood Pressure (1/3SBP+2/ 3DBP) continuous (per 10mmHg increase)	738	3073 18	1.074 (1.012 - 1.138)	1.030 (0.969- 1.096)	1.036 (0.972- 1.105)	1.001 (0.922- 1.088)	1.072 (0.977- 1.176)	0.45	1.048 (0.951- 1.154)	1.030 (0.952- 1.114)	0.803	1.049 (0.912- 1.207)	1.027 (0.958- 1.099)	0.588
Systolic Blood Pressure (mmHg) ESH classificatio n														
< 120	122	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-129	143	6644 6	1.10 (0.86- 1.41)	1.01 (0.79- 1.29)	0.99 (0.76- 1.28)	1.06 (0.75- 1.49)	0.94 (0.65- 1.35)		0.93 (0.66- 1.32)	1.08 (0.76- 1.53)		0.97 (0.63- 1.49)	1.03 (0.76- 1.39)	
130-139	148	5748 2	1.10 (0.86- 1.40)	0.96 (0.75- 1.23)	0.94 (0.72- 1.22)	0.96 (0.68- 1.36)	0.96 (0.67- 1.39)		0.87 (0.60- 1.26)	1.05 (0.74- 1.48)		0.98 (0.62- 1.57)	0.96 (0.71- 1.30)	
140-159	205	6823 5	1.04 (0.82- 1.31)	0.89 (0.70- 1.13)	0.91 (0.70- 1.17)	0.81 (0.58- 1.14)	1.04 (0.73- 1.47)	0.61	0.97 (0.68- 1.38)	0.88 (0.63- 1.24)	0.207	0.81 (0.49- 1.35)	0.90 (0.68- 1.20)	0.468
160-179	89	2265 6	1.20 (0.90- 1.60)	1.02 (0.76- 1.37)	1.03 (0.76- 1.40)	0.92 (0.62- 1.38)	1.15 (0.74- 1.78)		1.18 (0.74- 1.86)	0.99 (0.67- 1.47)		1.09 (0.52- 2.31)	1.01 (0.73- 1.41)	
>= 180	31	6358	1.49 (0.99- 2.23)	1.25 (0.83- 1.90)	1.17 (0.75- 1.82)	1.31 (0.77- 2.24)	1.16 (0.60- 2.26)		1.91 (1.03- 3.54)	1.04 (0.60- 1.81)		3.23 (1.32- 7.86)	1.10 (0.69- 1.75)	
p-trend			0.209	0.996	0.93	0.507	0.44		0.257	0.51		0.644	0.822	
Diastolic Blood Pressure (mmHg) ESH classificatio n														
< 80	243	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
Stomach	Cas es	Coh ort	HR (crud e)	HR (adju sted)	Exclu ding first 2 years of follow- up HR (adju sted)	Men HR (adju sted)	Wome n HR (adju sted)	Sex p- interac tion	BMI <= 25 mg/m ² HR (adju sted)	BMI > 25 mg/m ² HR (adju sted)	BMI p- interac tion	Age <= 53 yrs HR (adju sted)	Age > 53 yrs HR (adju sted)	Age p- interac tion
80-84	147	6487 2	0.95 (0.77- 1.17)	0.89 (0.72- 1.10)	0.88 (0.70- 1.10)	0.83 (0.62- 1.09)	0.98 (0.72- 1.34)		0.85 (0.62- 1.17)	0.94 (0.71- 1.25)		0.99 (0.65- 1.50)	0.87 (0.68- 1.11)	
85-89	112	4150 0	1.08 (0.86- 1.35)	1.00 (0.79- 1.25)	1.03 (0.81- 1.30)	0.96 (0.72- 1.30)	1.02 (0.71- 1.46)		1.06 (0.74- 1.50)	0.99 (0.73- 1.34)		0.73 (0.43- 1.27)	1.07 (0.83- 1.38)	
90-99	172	5119 6	1.22 (1.00- 1.49)	1.09 (0.89- 1.34)	1.16 (0.93- 1.43)	0.96 (0.73- 1.26)	1.28 (0.94- 1.76)	0.257	1.09 (0.78- 1.52)	1.13 (0.86- 1.47)	0.997	1.00 (0.63- 1.60)	1.12 (0.89- 1.40)	0.708

100-109	46	1389 6	1.17 (0.85- 1.61)	1.01 (0.73- 1.39)	1.02 (0.73- 1.44)	0.73 (0.47- 1.14)	1.61 (1.00- 2.59)		0.69 (0.34- 1.42)	1.17 (0.80- 1.70)		1.12 (0.54- 2.33)	0.98 (0.68- 1.42)	
>= 110	18	3264	2.02 (1.25- 3.26)	1.67 (1.03- 2.72)	1.74 (1.06- 2.88)	1.85 (1.07- 3.19)	1.05 (0.33- 3.34)		3.46 (1.68- 7.15)	1.20 (0.62- 2.30)		3.27 (1.37- 7.79)	1.34 (0.74- 2.43)	
p-trend			0.004	0.138	0.052	0.77	0.048		0.297	0.195		0.423	0.208	
Systolic Blood Pressure (mmHg)														
ASH classificatio n														
< 120	122	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-139	291	1239 28	1.10 (0.89- 1.37)	0.98 (0.79- 1.22)	0.96 (0.76- 1.21)	1.01 (0.74- 1.37)	0.95 (0.69- 1.30)		0.90 (0.66- 1.23)	1.06 (0.77- 1.46)		0.97 (0.66- 1.42)	0.99 (0.76- 1.30)	
140-159	205	6823 5	1.04 (0.82- 1.31)	0.89 (0.70- 1.13)	0.91 (0.71- 1.17)	0.81 (0.58- 1.14)	1.04 (0.73- 1.47)	0.602	0.97 (0.68- 1.38)	0.88 (0.63- 1.24)	0.195	0.81 (0.48- 1.34)	0.90 (0.68- 1.20)	0.576
>= 160	120	2901 4	1.26 (0.96- 1.65)	1.07 (0.81- 1.41)	1.07 (0.80- 1.42)	1.01 (0.69- 1.47)	1.15 (0.77- 1.73)		1.33 (0.88- 2.01)	1.01 (0.69- 1.46)		1.48 (0.79- 2.76)	1.03 (0.75- 1.42)	
p-trend			0.215	0.96	0.836	0.531	0.429		0.245	0.53		0.74	0.917	
Diastolic Blood Pressure (mmHg)														
ASH classificatio n														
< 80	243	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-89	259	1063 72	1.00 (0.84- 1.19)	0.93 (0.78- 1.12)	0.94 (0.78- 1.13)	0.88 (0.69- 1.13)	1.00 (0.76- 1.30)		0.92 (0.71- 1.21)	0.97 (0.76- 1.23)		0.89 (0.61- 1.30)	0.95 (0.78- 1.17)	
90-99	172	5119 6	1.22 (1.00- 1.49)	1.09 (0.89- 1.34)	1.16 (0.93- 1.43)	0.96 (0.73- 1.26)	1.28 (0.94- 1.76)	0.141	1.09 (0.78- 1.52)	1.13 (0.86- 1.47)	0.691	1.01 (0.63- 1.60)	1.11 (0.89- 1.40)	0.543
>= 100	64	1716 0	1.33 (1.01- 1.76)	1.13 (0.85- 1.51)	1.16 (0.86- 1.56)	0.94 (0.65- 1.36)	1.51 (0.96- 2.37)		1.15 (0.68- 1.95)	1.17 (0.83- 1.65)		1.53 (0.84- 2.79)	1.05 (0.76- 1.46)	
p-trend			0.012	0.258	0.133	0.829	0.041		0.59	0.213		0.378	0.41	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
Stomach	Cas es	Coh ort	HR (crud e)	HR (adjus ted)	Exclu ding first 2 years of follow- up HR (adjus ted)	Men HR (adjus ted)	Wome n HR (adjus ted)	Sex p- interac tion	BMI <= 25 mg/m² HR (adjus ted)	BMI > 25 mg/m² HR (adjus ted)	BMI p- interac tion	Age <= 53 yrs HR (adjus ted)	Age > 53 yrs HR (adjus ted)	Age p- interac tion
50.0-88.3	115	7699 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	

88.5-96.6	160	7772 7	0.99 (0.78- 1.27)	0.92 (0.72- 1.17)	0.84 (0.65- 1.09)	0.98 (0.70- 1.38)	0.82 (0.58- 1.18)		0.80 (0.57- 1.12)	1.04 (0.73- 1.49)		1.10 (0.71- 1.70)	0.85 (0.64- 1.15)	
96.8-105.5	190	7632 7	1.00 (0.79- 1.26)	0.88 (0.69- 1.13)	0.87 (0.68- 1.12)	0.80 (0.57- 1.13)	1.01 (0.72- 1.43)	0.174	0.96 (0.69- 1.35)	0.87 (0.61- 1.24)	0.482	0.77 (0.47- 1.27)	0.90 (0.68- 1.20)	0.875
105.6-216.6	273	7627 3	1.21 (0.96- 1.52)	1.03 (0.81- 1.30)	1.02 (0.80- 1.30)	0.91 (0.65- 1.27)	1.22 (0.87- 1.71)		1.12 (0.80- 1.57)	1.03 (0.73- 1.44)		1.17 (0.72- 1.91)	0.99 (0.75- 1.30)	
p-trend			0.056	0.592	0.44	0.464	0.098		0.291	0.95		0.864	0.593	
Hypertension (SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or self-reported)														
Normotensive	337	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	401	1331 39	1.00 (0.86- 1.17)	0.94 (0.80- 1.10)	0.98 (0.83- 1.15)	0.84 (0.68- 1.02)	1.11 (0.87- 1.41)	0.165	1.02 (0.80- 1.29)	0.92 (0.75- 1.12)	0.578	0.97 (0.69- 1.36)	0.93 (0.78- 1.11)	0.517

Stomach	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	263	464		441	297		502	122	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.025 (0.958- 1.096)	0.987 (0.938- 1.039)	0.204	1.005 (0.954- 1.059)	1.004 (0.942- 1.069)	0.633	0.997 (0.946- 1.052)	1.058 (0.964- 1.162)	0.427
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.067 (0.944- 1.207)	1.036 (0.947- 1.134)	0.326	1.054 (0.961- 1.157)	1.050 (0.937- 1.176)	0.806	1.040 (0.947- 1.142)	1.212 (1.023- 1.436)	0.156
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.053 (0.948- 1.170)	1.008 (0.932- 1.089)	0.227	1.031 (0.951- 1.116)	1.027 (0.932- 1.132)	0.914	1.018 (0.938- 1.104)	1.157 (0.998- 1.343)	0.207
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.83 (0.54- 1.27)	1.13 (0.84- 1.54)		1.04 (0.77- 1.42)	0.95 (0.63- 1.43)		1.05 (0.80-1.38)	0.81 (0.30-2.22)	
Stomach	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
130-139	0.93 (0.61- 1.42)	1.01 (0.74- 1.38)		0.88 (0.64- 1.22)	1.07 (0.72- 1.60)		1.05 (0.79-1.39)	0.70 (0.27-1.80)	

140-159	0.87 (0.58-1.30)	0.92 (0.68-1.25)	0.278	0.99 (0.73-1.34)	0.76 (0.51-1.13)	0.687	0.93 (0.70-1.24)	0.79 (0.33-1.91)	0.823
160-179	1.07 (0.66-1.72)	0.95 (0.64-1.39)		0.95 (0.64-1.40)	1.10 (0.70-1.74)		1.11 (0.76-1.62)	0.77 (0.31-1.93)	
>= 180	1.16 (0.58-2.32)	1.28 (0.76-2.16)		1.24 (0.72-2.15)	1.25 (0.66-2.35)		1.26 (0.68-2.33)	1.26 (0.47-3.38)	
p-trend	0.66	0.619		0.971	0.965		0.92	0.535	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.90 (0.64-1.28)	0.91 (0.70-1.18)		0.88 (0.67-1.15)	0.91 (0.66-1.28)		0.86 (0.68-1.10)	1.25 (0.63-2.50)	
85-89	0.94 (0.63-1.39)	1.01 (0.76-1.35)		1.08 (0.81-1.44)	0.88 (0.60-1.27)		0.99 (0.75-1.30)	1.13 (0.55-2.31)	
90-99	1.10 (0.78-1.56)	1.05 (0.81-1.36)	0.462	1.11 (0.85-1.45)	1.06 (0.77-1.47)	0.853	1.09 (0.84-1.40)	1.34 (0.71-2.51)	0.178
100-109	1.10 (0.65-1.87)	0.89 (0.58-1.37)		0.92 (0.59-1.44)	1.10 (0.68-1.77)		0.95 (0.60-1.53)	1.54 (0.75-3.16)	
>= 110	1.29 (0.52-3.22)	1.90 (1.06-3.37)		1.64 (0.85-3.13)	1.67 (0.80-3.49)		1.41 (0.62-3.20)	3.33 (1.46-7.59)	
p-trend	0.404	0.385		0.279	0.351		0.446	0.027	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.88 (0.61-1.28)	1.07 (0.81-1.41)		0.97 (0.73-1.27)	1.01 (0.71-1.45)		1.05 (0.82-1.34)	0.74 (0.30-1.81)	
140-159	0.86 (0.57-1.30)	0.92 (0.68-1.25)	0.329	1.00 (0.74-1.35)	0.76 (0.51-1.13)	0.829	0.93 (0.70-1.24)	0.79 (0.33-1.91)	0.983
>= 160	1.08 (0.68-1.70)	1.02 (0.72-1.46)		1.02 (0.71-1.46)	1.13 (0.73-1.74)		1.14 (0.80-1.62)	0.89 (0.37-2.18)	
p-trend	0.722	0.671		0.842	0.862		0.892	0.671	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.92 (0.68-1.24)	0.95 (0.76-1.19)		0.96 (0.76-1.21)	0.90 (0.67-1.20)		0.91 (0.74-1.12)	1.19 (0.64-2.22)	
90-99	1.10 (0.78-1.56)	1.05 (0.81-1.36)	0.365	1.11 (0.85-1.44)	1.06 (0.77-1.47)	0.96	1.09 (0.84-1.40)	1.33 (0.71-2.51)	0.188
>= 100	1.14 (0.70-1.84)	1.08 (0.75-1.56)		1.06 (0.72-1.56)	1.21 (0.79-1.85)		1.03 (0.67-1.57)	1.91 (0.98-3.72)	
p-trend	0.448	0.604		0.515	0.362		0.659	0.038	
Stomach	Never smokers	Ever smokers	Smoking p-interaction	Alcohol <= 12g	Alcohol > 12g	Alcohol p-interaction	No antihypertensive	Antihypertensive treatment	Treatment

	HR (adjusted)	HR (adjusted)		HR (adjusted)	HR (adjusted)		treatment HR (adjusted)	HR (adjusted)	p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.97 (0.63-1.49)	0.91 (0.67-1.23)		1.01 (0.74-1.37)	0.77 (0.51-1.15)		1.03 (0.79-1.36)	0.34 (0.12-0.98)	
96.8-105.5	0.96 (0.63-1.47)	0.87 (0.65-1.17)	0.192	0.98 (0.72-1.34)	0.74 (0.50-1.09)	0.664	0.97 (0.74-1.29)	0.56 (0.24-1.31)	0.715
105.6-216.6	1.14 (0.75-1.73)	0.96 (0.72-1.29)		1.12 (0.83-1.52)	0.88 (0.60-1.28)		1.07 (0.80-1.42)	0.68 (0.31-1.51)	
p-trend	0.407	0.896		0.432	0.871		0.76	0.461	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.90 (0.69-1.17)	0.94 (0.78-1.14)	0.776	1.02 (0.83-1.25)	0.83 (0.65-1.06)	0.354	1 (referent)	1.06 (0.84-1.35)	

Gastic AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			403	403	375	254	149		171	232		88	315	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	403	30738	1.038 (0.986-1.094)	1.008 (0.955-1.065)	1.017 (0.962-1.076)	1.021 (0.952-1.095)	0.989 (0.906-1.080)	0.821	0.989 (0.909-1.076)	1.034 (0.963-1.109)	0.436	1.025 (0.899-1.167)	1.005 (0.946-1.067)	0.48
Mean Diastolic Blood Pressure continuous (per	403	30738	1.128 (1.028-1.236)	1.054 (0.957-1.161)	1.095 (0.991-1.209)	1.002 (0.885-1.133)	1.154 (0.987-1.350)	0.101	1.002 (0.861-1.166)	1.118 (0.988-1.264)	0.264	1.052 (0.848-1.305)	1.054 (0.946-1.175)	0.698

10mmHg increase)														
Gastic AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	403	30738	1.091 (1.008-1.180)	1.032 (0.950-1.122)	1.059 (0.973-1.154)	1.017 (0.914-1.131)	1.062 (0.929-1.214)	0.432	0.992 (0.872-1.129)	1.084 (0.974-1.205)	0.298	1.045 (0.864-1.263)	1.030 (0.939-1.129)	0.562
Systolic Blood Pressure (mmHg) ESH classification														
< 120	64	86141	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-129	74	66446	1.02 (0.73-1.43)	0.91 (0.65-1.27)	0.93 (0.65-1.32)	0.74 (0.47-1.16)	1.17 (0.70-1.97)		0.93 (0.59-1.45)	0.93 (0.55-1.56)		0.85 (0.47-1.54)	0.94 (0.62-1.42)	
130-139	84	57482	1.09 (0.78-1.53)	0.92 (0.66-1.29)	0.94 (0.66-1.33)	0.90 (0.59-1.38)	0.86 (0.49-1.50)		0.80 (0.49-1.30)	1.09 (0.67-1.78)		0.79 (0.41-1.51)	0.97 (0.65-1.45)	
140-159	108	68235	0.93 (0.67-1.28)	0.76 (0.54-1.05)	0.79 (0.56-1.12)	0.63 (0.41-0.97)	0.99 (0.59-1.66)	0.911	0.79 (0.50-1.26)	0.81 (0.50-1.32)	0.663	0.69 (0.35-1.35)	0.78 (0.53-1.15)	0.639
160-179	53	22656	1.19 (0.81-1.75)	0.96 (0.65-1.43)	1.03 (0.69-1.54)	0.90 (0.55-1.47)	1.01 (0.53-1.92)		0.92 (0.50-1.69)	1.09 (0.64-1.87)		0.66 (0.22-1.97)	1.02 (0.66-1.59)	
>= 180	20	6358	1.60 (0.95-2.70)	1.28 (0.76-2.17)	1.34 (0.78-2.32)	1.40 (0.74-2.63)	0.95 (0.35-2.55)		1.44 (0.62-3.34)	1.32 (0.65-2.65)		3.50 (1.26-9.74)	1.08 (0.58-2.00)	
p-trend			0.346	0.81	0.896	0.943	0.773		0.762	0.777		0.949	0.793	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	136	132590	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
80-84	72	64872	0.83 (0.62-1.10)	0.76 (0.57-1.01)	0.80 (0.59-1.09)	0.61 (0.41-0.89)	1.04 (0.67-1.63)		0.59 (0.37-0.93)	0.96 (0.65-1.43)		0.95 (0.54-1.69)	0.71 (0.50-0.99)	
85-89	62	41500	1.03 (0.76-1.40)	0.91 (0.67-1.24)	0.99 (0.72-1.36)	0.86 (0.59-1.26)	0.98 (0.58-1.64)		0.95 (0.60-1.49)	0.95 (0.62-1.45)		0.75 (0.36-1.55)	0.95 (0.68-1.34)	
90-99	94	51196	1.15 (0.88-1.51)	0.98 (0.74-1.29)	1.08 (0.81-1.43)	0.91 (0.64-1.27)	1.06 (0.66-1.71)	0.234	0.98 (0.64-1.50)	1.10 (0.76-1.59)	0.413	0.93 (0.49-1.76)	0.99 (0.73-1.35)	0.795
100-109	27	13896	1.18 (0.78-1.80)	0.95 (0.62-1.45)	1.09 (0.71-1.68)	0.62 (0.35-1.10)	1.96 (1.05-3.66)		0.36 (0.11-1.15)	1.35 (0.83-2.21)		1.02 (0.38-2.71)	0.93 (0.58-1.50)	

>= 110	12	3264	2.38 (1.31-4.31)	1.84 (1.01-3.35)	2.10 (1.15-3.85)	1.88 (0.96-3.68)	1.42 (0.34-5.89)		2.95 (1.17-7.41)	1.60 (0.72-3.52)		2.64 (0.78-8.96)	1.67 (0.83-3.33)	
p-trend			0.023	0.398	0.097	0.864	0.211		0.969	0.161		0.786	0.421	
Gastic AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	64	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	158	123928	1.06 (0.79-1.42)	0.91 (0.68-1.23)	0.93 (0.68-1.27)	0.82 (0.56-1.21)	1.02 (0.64-1.63)		0.87 (0.58-1.30)	1.02 (0.64-1.61)		0.82 (0.49-1.40)	0.95 (0.66-1.38)	
140-159	108	68235	0.92 (0.67-1.28)	0.76 (0.54-1.05)	0.79 (0.56-1.12)	0.63 (0.41-0.96)	1.00 (0.60-1.68)	0.601	0.79 (0.50-1.27)	0.81 (0.50-1.31)	0.818	0.68 (0.35-1.35)	0.78 (0.53-1.15)	0.768
>= 160	73	29014	1.28 (0.89-1.83)	1.03 (0.72-1.49)	1.10 (0.75-1.60)	0.99 (0.63-1.58)	1.01 (0.55-1.85)		1.03 (0.59-1.79)	1.14 (0.68-1.90)		1.19 (0.52-2.72)	1.03 (0.68-1.58)	
p-trend			0.416	0.757	0.93	0.684	0.991		0.824	0.925		0.81	0.807	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	136	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	134	106372	0.91 (0.71-1.16)	0.82 (0.64-1.05)	0.88 (0.68-1.14)	0.71 (0.52-0.98)	1.02 (0.69-1.50)		0.73 (0.51-1.04)	0.96 (0.68-1.35)		0.87 (0.52-1.46)	0.81 (0.61-1.07)	
90-99	94	51196	1.16 (0.88-1.51)	0.98 (0.74-1.29)	1.07 (0.81-1.43)	0.90 (0.64-1.27)	1.06 (0.66-1.71)	0.093	0.98 (0.64-1.50)	1.10 (0.76-1.59)	0.161	0.93 (0.50-1.76)	0.99 (0.73-1.34)	0.633
>= 100	39	17160	1.40 (0.98-2.01)	1.11 (0.77-1.61)	1.28 (0.87-1.86)	0.85 (0.53-1.37)	1.87 (1.03-3.37)		0.79 (0.38-1.67)	1.40 (0.89-2.20)		1.33 (0.58-3.01)	1.07 (0.70-1.62)	
p-trend			0.061	0.656	0.206	0.635	0.146		0.528	0.146		0.754	0.733	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	64	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	86	77727	0.93 (0.67-1.29)	0.83 (0.60-1.15)	0.76 (0.53-1.07)	0.73 (0.48-1.12)	0.95 (0.57-1.59)		0.74 (0.48-1.16)	1.00 (0.60-1.67)		0.99 (0.54-1.81)	0.78 (0.52-1.15)	

96.8-105.5	97	7632 7	0.88 (0.64- 1.22)	0.74 (0.54- 1.03)	0.77 (0.55- 1.07)	0.65 (0.42- 0.99)	0.88 (0.53- 1.48)	0.313	0.78 (0.50- 1.22)	0.81 (0.49- 1.34)	0.729	0.73 (0.37- 1.44)	0.73 (0.50- 1.07)	0.774
105.6-216.6	156	7627 3	1.15 (0.85- 1.56)	0.92 (0.67- 1.25)	0.94 (0.68- 1.30)	0.79 (0.53- 1.19)	1.11 (0.68- 1.84)		0.92 (0.59- 1.43)	1.04 (0.65- 1.67)		1.00 (0.51- 1.95)	0.88 (0.62- 1.27)	
p-trend			0.231	0.829	0.783	0.527	0.633		0.87	0.779		0.811	0.895	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	193	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Gastic AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertensive	210	1331 39	0.91 (0.74- 1.12)	0.83 (0.67- 1.02)	0.87 (0.70- 1.08)	0.81 (0.62- 1.05)	0.87 (0.61- 1.23)	0.538	0.85 (0.62- 1.17)	0.84 (0.64- 1.11)	0.995	0.72 (0.45- 1.15)	0.85 (0.67- 1.08)	0.957

Gastic AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	134	261		237	166		264	53	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.040 (0.945- 1.144)	0.988 (0.923- 1.057)	0.192	1.013 (0.943- 1.089)	1.003 (0.921- 1.091)	0.821	1.014 (0.944- 1.090)	1.217 (1.059- 1.398)	0.035
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.107 (0.932- 1.313)	1.026 (0.910- 1.156)	0.166	1.076 (0.948- 1.221)	1.024 (0.879- 1.192)	0.632	1.042 (0.915- 1.186)	1.654 (1.272- 2.152)	0.005
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.084 (0.936- 1.256)	1.003 (0.905- 1.111)	0.146	1.047 (0.940- 1.167)	1.014 (0.890- 1.154)	0.876	1.032 (0.923- 1.154)	1.522 (1.214- 1.907)	0.005
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	

120-129	0.84 (0.46-1.54)	0.97 (0.64-1.47)		0.95 (0.62-1.46)	0.82 (0.48-1.43)		0.99 (0.67-1.46)	-	
130-139	0.83 (0.45-1.52)	1.02 (0.68-1.54)		0.91 (0.58-1.41)	0.92 (0.54-1.56)		1.01 (0.68-1.51)	-	
140-159	0.80 (0.45-1.43)	0.75 (0.50-1.14)	0.387	0.92 (0.61-1.40)	0.56 (0.32-0.95)	0.972	0.86 (0.57-1.28)	-	-
160-179	1.01 (0.51-1.98)	0.92 (0.56-1.51)		0.86 (0.51-1.48)	1.04 (0.58-1.86)		1.10 (0.66-1.83)	-	
>= 180	1.12 (0.43-2.93)	1.32 (0.69-2.54)		1.39 (0.69-2.81)	1.15 (0.51-2.57)		1.73 (0.85-3.53)	-	
p-trend	0.923	0.629		0.993	0.713		0.754	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
Gastic AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
80-84	0.75 (0.45-1.25)	0.80 (0.56-1.15)		0.65 (0.44-0.96)	0.92 (0.59-1.43)		0.72 (0.51-1.02)	-	
85-89	1.01 (0.60-1.69)	0.87 (0.59-1.28)		1.00 (0.68-1.47)	0.81 (0.49-1.35)		0.97 (0.67-1.39)	-	
90-99	0.93 (0.57-1.52)	0.99 (0.70-1.39)	0.39	1.02 (0.71-1.45)	0.94 (0.60-1.45)	0.733	0.93 (0.65-1.33)	-	-
100-109	1.02 (0.50-2.09)	0.88 (0.51-1.52)		0.85 (0.47-1.55)	1.08 (0.58-2.00)		0.97 (0.53-1.80)	-	
>= 110	1.92 (0.67-5.47)	1.93 (0.92-4.03)		1.95 (0.89-4.28)	1.72 (0.67-4.40)		1.65 (0.60-4.53)	-	
p-trend	0.581	0.624		0.404	0.74		0.804	-	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
120-139	0.83 (0.49-1.43)	0.99 (0.69-1.44)		0.93 (0.63-1.36)	0.88 (0.54-1.41)		1.00 (0.71-1.41)	-	
140-159	0.80 (0.45-1.43)	0.75 (0.50-1.13)	0.325	0.92 (0.61-1.40)	0.55 (0.32-0.95)	0.921	0.85 (0.57-1.27)	-	-
>= 160	1.03 (0.54-1.97)	1.01 (0.64-1.59)		0.98 (0.60-1.59)	1.06 (0.60-1.84)		1.22 (0.76-1.95)	-	
p-trend	0.879	0.518		0.928	0.7		0.818	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	

80-89	0.86 (0.56-1.31)	0.83 (0.61-1.13)		0.79 (0.58-1.09)	0.88 (0.59-1.29)		0.82 (0.61-1.09)	-	
90-99	0.93 (0.57-1.51)	0.99 (0.70-1.39)	0.437	1.01 (0.71-1.45)	0.94 (0.60-1.45)	0.964	0.93 (0.65-1.32)	-	-
>= 100	1.18 (0.62-2.22)	1.07 (0.67-1.71)		1.06 (0.64-1.75)	1.20 (0.69-2.09)		1.08 (0.62-1.86)	-	
p-trend	0.797	0.809		0.796	0.695		0.861	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
88.5-96.6	1.18 (0.63-2.21)	0.75 (0.50-1.11)		0.88 (0.58-1.34)	0.74 (0.43-1.25)		0.94 (0.65-1.37)	-	
96.8-105.5	0.98 (0.52-1.84)	0.71 (0.48-1.05)	0.131	0.80 (0.52-1.22)	0.66 (0.39-1.11)	0.445	0.84 (0.57-1.23)	-	-
105.6-216.6	1.25 (0.67-2.31)	0.81 (0.56-1.18)		1.06 (0.70-1.58)	0.73 (0.44-1.21)		0.99 (0.67-1.47)	-	
p-trend	0.558	0.463		0.635	0.355		0.907	-	
Gastic AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.76 (0.52-1.09)	0.84 (0.65-1.09)	0.895	0.88 (0.67-1.16)	0.76 (0.55-1.05)	0.681	1 (referent)	1.05 (0.75-1.47)	

Colorectal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			4625	4625	4265	2180	2445		1846	2779		1140	3485	
Cohort size			307318	307318	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per	4625	307318	1.033 (1.018-1.049)	1.011 (0.995-1.027)	1.009 (0.993-1.027)	1.030 (1.006-1.055)	0.995 (0.973-1.017)	0.014	0.984 (0.959-1.010)	1.035 (1.015-1.056)	0.02	0.991 (0.955-1.029)	1.016 (0.998-1.034)	0.386

10mmHg increase)														
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	4625	307318	1.092 (1.063-1.123)	1.043 (1.013-1.073)	1.044 (1.013-1.075)	1.053 (1.010-1.098)	1.032 (0.992-1.075)	0.233	1.011 (0.965-1.059)	1.077 (1.039-1.117)	0.029	1.023 (0.963-1.086)	1.048 (1.014-1.083)	0.623
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	4625	307318	1.070 (1.046-1.096)	1.029 (1.004-1.055)	1.029 (1.003-1.055)	1.049 (1.012-1.088)	1.011 (0.978-1.046)	0.05	0.993 (0.954-1.033)	1.066 (1.033-1.099)	0.014	1.006 (0.953-1.061)	1.036 (1.007-1.065)	0.494
Systolic Blood Pressure (mmHg) ESH classification														
< 120	812	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	835	66446	1.00 (0.90-1.10)	0.93 (0.84-1.03)	0.92 (0.83-1.02)	0.98 (0.84-1.15)	0.91 (0.81-1.04)		1.00 (0.88-1.14)	0.89 (0.76-1.03)		0.89 (0.75-1.05)	0.96 (0.84-1.08)	
130-139	896	57482	1.04 (0.94-1.15)	0.94 (0.85-1.04)	0.95 (0.86-1.06)	1.02 (0.87-1.19)	0.90 (0.79-1.02)		0.87 (0.75-1.00)	1.03 (0.90-1.19)		0.92 (0.77-1.10)	0.96 (0.85-1.08)	
140-159	1378	68235	1.10 (1.01-1.21)	0.97 (0.88-1.07)	0.97 (0.88-1.07)	0.99 (0.85-1.15)	0.98 (0.87-1.11)	0.045	0.84 (0.73-0.97)	1.11 (0.97-1.26)	0.002	0.92 (0.76-1.10)	0.99 (0.89-1.11)	0.62
Colorectal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
160-179	520	22656	1.12 (1.00-1.26)	0.97 (0.86-1.09)	0.98 (0.86-1.10)	1.10 (0.92-1.31)	0.87 (0.74-1.03)		0.85 (0.70-1.04)	1.10 (0.94-1.29)		1.03 (0.77-1.37)	0.98 (0.85-1.12)	
>= 180	184	6358	1.37 (1.16-1.62)	1.17 (0.99-1.39)	1.14 (0.95-1.36)	1.34 (1.05-1.70)	1.04 (0.82-1.32)		1.22 (0.91-1.64)	1.26 (1.02-1.55)		1.10 (0.64-1.89)	1.20 (1.00-1.43)	
p-trend			0.0001	0.384	0.434	0.08	0.646		0.048	0.0005		0.797	0.257	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	1597	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	942	64872	1.00 (0.92-1.09)	0.95 (0.87-1.03)	0.95 (0.87-1.03)	0.94 (0.83-1.06)	0.95 (0.85-1.06)		0.93 (0.83-1.06)	0.98 (0.88-1.10)		0.94 (0.80-1.10)	0.95 (0.87-1.05)	

< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.90 (0.77- 1.06)	0.95 (0.83- 1.08)		0.94 (0.83- 1.06)	0.92 (0.78- 1.09)		0.97 (0.87-1.08)	0.66 (0.40-1.07)	
130-139	0.87 (0.74- 1.02)	0.98 (0.86- 1.11)		0.95 (0.84- 1.07)	0.94 (0.80- 1.12)		0.96 (0.86-1.08)	0.95 (0.62-1.46)	
140-159	0.97 (0.84- 1.13)	0.97 (0.85- 1.09)	0.459	0.92 (0.81- 1.03)	1.07 (0.92- 1.25)	0.063	1.00 (0.90-1.12)	0.86 (0.57-1.29)	0.202
160-179	0.91 (0.75- 1.09)	1.00 (0.86- 1.16)		0.91 (0.79- 1.06)	1.08 (0.89- 1.31)		0.94 (0.80-1.10)	0.90 (0.59-1.37)	
>= 180	1.06 (0.80- 1.40)	1.24 (1.01- 1.54)		1.07 (0.86- 1.33)	1.36 (1.05- 1.77)		1.26 (0.99-1.61)	0.97 (0.61-1.54)	
p-trend	0.978	0.332		0.441	0.013		0.664	0.41	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.89 (0.78- 1.01)	0.98 (0.88- 1.09)		0.94 (0.85- 1.04)	0.97 (0.84- 1.11)		0.98 (0.89-1.07)	1.04 (0.78-1.38)	
85-89	1.00 (0.86- 1.15)	1.04 (0.92- 1.16)		0.98 (0.88- 1.10)	1.07 (0.92- 1.24)		1.09 (0.97-1.21)	0.99 (0.74-1.32)	
90-99	1.09 (0.96- 1.25)	0.98 (0.88- 1.10)	0.965	0.98 (0.88- 1.09)	1.13 (0.99- 1.30)	0.114	1.04 (0.93-1.15)	1.08 (0.83-1.40)	0.336
100-109	1.14 (0.93- 1.40)	1.16 (0.99- 1.36)		1.24 (1.05- 1.45)	1.05 (0.86- 1.29)		1.07 (0.88-1.29)	1.22 (0.90-1.64)	
>= 110	1.19 (0.80- 1.75)	1.51 (1.15- 1.97)		1.09 (0.79- 1.50)	1.77 (1.31- 2.40)		1.84 (1.36-2.51)	1.44 (0.94-2.20)	
p-trend	0.037	0.066		0.199	0.005		0.028	0.078	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.89 (0.77- 1.02)	0.96 (0.86- 1.08)		0.94 (0.85- 1.05)	0.93 (0.80- 1.08)		0.97 (0.88-1.06)	0.84 (0.56-1.28)	
140-159	0.98 (0.84- 1.13)	0.96 (0.85- 1.09)	0.56	0.92 (0.81- 1.03)	1.07 (0.92- 1.25)	0.065	1.00 (0.90-1.12)	0.86 (0.57-1.29)	0.363
>= 160	0.94 (0.79- 1.12)	1.05 (0.91- 1.21)		0.95 (0.82- 1.09)	1.14 (0.95- 1.37)		1.00 (0.86-1.15)	0.91 (0.60-1.38)	
p-trend	0.982	0.493		0.337	0.021		0.823	0.725	
Colorectal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.93 (0.83- 1.04)	1.00 (0.91- 1.10)		0.96 (0.88- 1.05)	1.01 (0.90- 1.14)		1.02 (0.94-1.11)	1.01 (0.78-1.31)	

90-99	1.09 (0.96-1.25)	0.98 (0.88-1.10)	0.871	0.98 (0.87-1.09)	1.13 (0.99-1.30)	0.237	1.04 (0.93-1.15)	1.08 (0.83-1.40)	0.221
>= 100	1.15 (0.95-1.39)	1.23 (1.06-1.42)		1.21 (1.04-1.40)	1.18 (0.99-1.42)		1.20 (1.01-1.41)	1.26 (0.95-1.67)	
p-trend	0.081	0.101		0.186	0.021		0.101	0.065	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.89 (0.76-1.04)	1.01 (0.89-1.14)		0.99 (0.88-1.11)	0.91 (0.77-1.08)		0.96 (0.87-1.08)	1.20 (0.72-1.99)	
96.8-105.5	0.90 (0.78-1.05)	0.99 (0.87-1.12)	0.954	0.95 (0.85-1.07)	0.96 (0.82-1.13)	0.114	1.00 (0.89-1.11)	1.00 (0.62-1.62)	0.383
105.6-216.6	1.03 (0.89-1.20)	1.03 (0.91-1.17)		1.00 (0.89-1.12)	1.10 (0.93-1.29)		1.03 (0.92-1.16)	1.14 (0.72-1.83)	
p-trend	0.297	0.649		0.916	0.042		0.43	0.583	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.01 (0.91-1.11)	1.00 (0.92-1.08)	0.932	0.96 (0.89-1.04)	1.08 (0.98-1.19)	0.103	1 (referent)	1.00 (0.91-1.10)	

Colon	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			3003	3003	2779	1304	1699		1190	1813		700	2303	
Cohort size			307318	307318	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure	3003	307318	1.032 (1.012-1.052)	1.011 (0.991-1.031)	1.008 (0.988-1.029)	1.030 (0.999-1.062)	0.998 (0.972-1.024)	0.061	0.986 (0.955-1.019)	1.035 (1.010-1.062)	0.101	0.994 (0.948-1.043)	1.015 (0.993-1.037)	0.654
continuous (per 10mmHg increase)														
Colon	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
Mean Diastolic Blood Pressure	3003	307318	1.103 (1.066-1.141)	1.060 (1.023-1.099)	1.058 (1.020-1.098)	1.080 (1.024-1.139)	1.044 (0.996-1.096)	0.103	1.040 (0.982-1.102)	1.088 (1.041-1.138)	0.163	1.022 (0.946-1.103)	1.071 (1.029-1.114)	0.462
continuous (per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/3DBP)	3003	307318	1.074 (1.044-1.106)	1.038 (1.007-1.070)	1.035 (1.002-1.068)	1.063 (1.015-1.113)	1.019 (0.979-1.061)	0.055	1.008 (0.960-1.059)	1.071 (1.031-1.113)	0.095	1.007 (0.941-1.079)	1.045 (1.010-1.081)	0.541
continuous (per 10mmHg increase)														
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	528	86141	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-129	534	66446	0.97 (0.86-1.09)	0.92 (0.81-1.04)	0.89 (0.79-1.01)	1.01 (0.82-1.24)	0.88 (0.76-1.03)		1.01 (0.86-1.19)	0.85 (0.71-1.02)		0.86 (0.70-1.06)	0.95 (0.81-1.10)	
130-139	579	57482	1.02 (0.90-1.15)	0.94 (0.83-1.06)	0.93 (0.82-1.05)	0.97 (0.79-1.19)	0.94 (0.80-1.09)		0.86 (0.71-1.03)	1.03 (0.86-1.22)		0.94 (0.75-1.17)	0.94 (0.81-1.09)	
140-159	896	68235	1.08 (0.97-1.21)	0.97 (0.86-1.09)	0.94 (0.84-1.06)	1.00 (0.82-1.21)	0.97 (0.84-1.13)	0.134	0.84 (0.71-1.00)	1.10 (0.93-1.29)	0.02	0.90 (0.71-1.14)	0.99 (0.86-1.14)	0.805
160-179	352	22656	1.13 (0.98-1.30)	0.99 (0.86-1.15)	0.99 (0.85-1.15)	1.14 (0.91-1.44)	0.89 (0.73-1.08)		0.90 (0.71-1.15)	1.11 (0.92-1.34)		1.14 (0.80-1.62)	0.99 (0.84-1.16)	
>= 180	114	6358	1.27 (1.03-1.57)	1.10 (0.89-1.35)	1.04 (0.83-1.30)	1.23 (0.89-1.69)	1.02 (0.76-1.36)		1.13 (0.78-1.65)	1.18 (0.91-1.54)		0.79 (0.35-1.80)	1.13 (0.90-1.42)	
p-trend			0.005	0.508	0.683	0.204	0.845		0.122	0.005		0.871	0.415	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	1034	132590	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
80-84	602	64872	0.98 (0.88-1.08)	0.94 (0.85-1.04)	0.92 (0.83-1.03)	0.94 (0.80-1.10)	0.94 (0.82-1.07)		0.94 (0.81-1.10)	0.96 (0.83-1.10)		0.85 (0.69-1.04)	0.97 (0.86-1.09)	
85-89	467	41500	1.10 (0.99-1.23)	1.03 (0.92-1.15)	1.02 (0.91-1.15)	0.93 (0.77-1.10)	1.12 (0.97-1.30)		0.94 (0.78-1.13)	1.13 (0.98-1.30)		1.01 (0.81-1.27)	1.04 (0.91-1.18)	
90-99	633	51196	1.15 (1.04-1.27)	1.05 (0.94-1.16)	1.03 (0.93-1.15)	1.02 (0.87-1.20)	1.05 (0.91-1.21)	0.478	0.93 (0.78-1.11)	1.15 (1.00-1.31)	0.072	0.82 (0.65-1.04)	1.11 (0.99-1.25)	0.271
100-109	209	13896	1.36 (1.17-1.58)	1.20 (1.02-1.39)	1.20 (1.02-1.40)	1.21 (0.98-1.50)	1.13 (0.90-1.43)		1.40 (1.07-1.83)	1.20 (0.99-1.45)		1.19 (0.84-1.68)	1.21 (1.02-1.43)	
Colon	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI p-interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p-interaction

					years of follow- up HR (adju- sted)				HR (adju- sted)	HR (adju- sted)		HR (adju- sted)		
>= 110	58	3264	1.68 (1.29- 2.19)	1.44 (1.10- 1.88)	1.42 (1.07- 1.87)	1.32 (0.92- 1.89)	1.57 (1.04- 2.37)		1.40 (0.77- 2.55)	1.56 (1.16- 2.11)		1.44 (0.78- 2.66)	1.44 (1.07- 1.94)	
p-trend			0.0000 002	0.005	0.011	0.066	0.042		0.477	0.0003		0.99	0.002	
Systolic Blood Pressure (mmHg)														
ASH classificatio n														
< 120	528	8614 1	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-139	111 3	1239 28	0.99 (0.89- 1.10)	0.93 (0.83- 1.03)	0.91 (0.81- 1.02)	0.99 (0.82- 1.19)	0.91 (0.79- 1.04)		0.94 (0.81- 1.09)	0.94 (0.81- 1.11)		0.89 (0.74- 1.07)	0.94 (0.82- 1.08)	
140-159	896	6823 5	1.08 (0.97- 1.21)	0.97 (0.86- 1.09)	0.94 (0.83- 1.06)	1.00 (0.82- 1.21)	0.97 (0.84- 1.12)	0.074	0.84 (0.71- 1.00)	1.09 (0.93- 1.29)	0.079	0.90 (0.71- 1.13)	0.99 (0.86- 1.14)	0.759
>= 160	466	2901 4	1.16 (1.01- 1.32)	1.01 (0.88- 1.16)	1.00 (0.87- 1.15)	1.16 (0.93- 1.45)	0.92 (0.76- 1.10)		0.96 (0.77- 1.19)	1.12 (0.93- 1.34)		1.08 (0.77- 1.50)	1.02 (0.87- 1.19)	
p-trend			0.008	0.579	0.771	0.145	0.617		0.238	0.021		0.79	0.457	
Diastolic Blood Pressure (mmHg)														
ASH classificatio n														
< 80	103 4	1325 90	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-89	106 9	1063 72	1.03 (0.94- 1.12)	0.98 (0.89- 1.07)	0.96 (0.88- 1.06)	0.93 (0.81- 1.07)	1.01 (0.90- 1.13)		0.94 (0.82- 1.07)	1.03 (0.92- 1.16)		0.91 (0.76- 1.08)	1.00 (0.90- 1.11)	
90-99	633	5119 6	1.15 (1.04- 1.27)	1.04 (0.94- 1.16)	1.03 (0.92- 1.15)	1.02 (0.87- 1.20)	1.05 (0.91- 1.21)	0.256	0.93 (0.78- 1.11)	1.15 (1.00- 1.31)	0.15	0.82 (0.64- 1.04)	1.11 (0.99- 1.25)	0.208
>= 100	267	1716 0	1.42 (1.24- 1.63)	1.24 (1.08- 1.43)	1.24 (1.07- 1.43)	1.23 (1.01- 1.50)	1.21 (0.98- 1.49)		1.40 (1.09- 1.80)	1.27 (1.07- 1.51)		1.23 (0.90- 1.69)	1.25 (1.07- 1.46)	
p-trend			0.0000 01	0.013	0.025	0.052	0.136		0.407	0.002		0.779	0.004	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
50.0-88.3	481	7699 1	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
88.5-96.6	659	7772 7	1.02 (0.91- 1.15)	0.98 (0.87- 1.10)	0.95 (0.84- 1.07)	1.15 (0.93- 1.42)	0.91 (0.78- 1.05)		0.96 (0.82- 1.13)	1.04 (0.87- 1.25)		0.94 (0.76- 1.15)	1.00 (0.86- 1.16)	
96.8-105.5	771	7632 7	1.01 (0.90- 1.14)	0.93 (0.83- 1.05)	0.92 (0.81- 1.04)	0.98 (0.80- 1.21)	0.94 (0.81- 1.08)	0.186	0.84 (0.71- 0.99)	1.08 (0.90- 1.29)	0.004	0.83 (0.66- 1.04)	0.97 (0.84- 1.12)	0.256

105.6-216.6	1092	76273	1.22 (1.09-1.37)	1.07 (0.96-1.21)	1.05 (0.93-1.18)	1.19 (0.97-1.47)	1.03 (0.89-1.19)		0.95 (0.80-1.12)	1.27 (1.07-1.50)		0.97 (0.76-1.22)	1.12 (0.97-1.28)	
Colon	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
p-trend			0.0001	0.148	0.243	0.143	0.5		0.276	0.0004		0.53	0.048	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	1347	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	1656	133139	1.10 (1.02-1.18)	1.02 (0.94-1.10)	1.00 (0.92-1.08)	1.02 (0.91-1.15)	1.01 (0.91-1.12)	0.466	0.87 (0.77-0.98)	1.17 (1.06-1.30)	0.0009	0.86 (0.73-1.02)	1.07 (0.98-1.16)	0.055

Colon	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	1228	1731		1912	1091		1978	457	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.995 (0.964-1.027)	1.024 (0.998-1.051)	0.2	0.993 (0.968-1.018)	1.044 (1.011-1.079)	0.065	1.003 (0.977-1.029)	1.030 (0.982-1.082)	0.1
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.056 (0.998-1.118)	1.069 (1.021-1.120)	0.605	1.037 (0.991-1.084)	1.105 (1.042-1.171)	0.055	1.061 (1.013-1.112)	1.077 (0.981-1.181)	0.529
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.023 (0.975-1.074)	1.052 (1.011-1.095)	0.342	1.012 (0.974-1.052)	1.086 (1.033-1.142)	0.042	1.032 (0.991-1.075)	1.065 (0.984-1.153)	0.201
Systolic Blood Pressure (mmHg) ESH classification < 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-129	0.88 (0.73-1.06)	0.95 (0.81-1.12)		0.86 (0.74-1.00)	1.05 (0.85-1.30)		0.98 (0.85-1.12)	0.45 (0.24-0.84)	
130-139	0.88 (0.73-1.06)	0.96 (0.82-1.13)		0.92 (0.80-1.07)	0.97 (0.78-1.21)		0.95 (0.82-1.10)	0.95 (0.58-1.58)	
140-159	0.93 (0.78-1.11)	1.01 (0.86-1.18)	0.333	0.89 (0.77-1.03)	1.14 (0.93-1.40)	0.157	1.02 (0.89-1.17)	0.81 (0.50-1.32)	0.179
160-179	0.88 (0.70-1.10)	1.07 (0.88-1.30)		0.91 (0.76-1.09)	1.18 (0.92-1.51)		0.95 (0.78-1.16)	0.89 (0.54-1.46)	
Colon	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
>= 180	1.02 (0.73-1.43)	1.18 (0.89-1.55)		1.01 (0.77-1.32)	1.30 (0.92-1.84)		1.15 (0.84-1.57)	0.84 (0.48-1.47)	
p-trend	0.716	0.206		0.561	0.055		0.778	0.364	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.85 (0.72-1.00)	0.99 (0.86-1.13)		0.96 (0.85-1.09)	0.89 (0.74-1.06)		0.95 (0.84-1.08)	0.97 (0.69-1.38)	
85-89	0.98 (0.82-1.17)	1.11 (0.96-1.28)		1.04 (0.90-1.19)	1.03 (0.85-1.24)		1.10 (0.96-1.26)	1.00 (0.71-1.41)	
90-99	1.06 (0.90-1.25)	1.04 (0.90-1.19)	0.806	1.02 (0.89-1.16)	1.09 (0.92-1.30)	0.268	1.06 (0.93-1.22)	1.04 (0.77-1.43)	0.564
100-109	1.19 (0.93-1.51)	1.22 (1.00-1.49)		1.23 (1.01-1.50)	1.14 (0.89-1.47)		1.15 (0.92-1.45)	1.17 (0.82-1.68)	
>= 110	1.27 (0.81-2.00)	1.62 (1.16-2.27)		1.28 (0.88-1.85)	1.66 (1.12-2.45)		1.69 (1.13-2.52)	1.53 (0.93-2.53)	
p-trend	0.07	0.016		0.082	0.018		0.025	0.129	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.88 (0.74-1.03)	0.96 (0.83-1.10)		0.89 (0.79-1.02)	1.01 (0.83-1.23)		0.97 (0.86-1.09)	0.77 (0.47-1.27)	
140-159	0.93 (0.78-1.11)	1.01 (0.86-1.18)	0.298	0.89 (0.77-1.03)	1.14 (0.93-1.40)	0.083	1.02 (0.89-1.17)	0.81 (0.50-1.31)	0.374
>= 160	0.91 (0.73-1.12)	1.09 (0.91-1.31)		0.92 (0.78-1.09)	1.21 (0.96-1.53)		0.99 (0.83-1.19)	0.87 (0.53-1.42)	
p-trend	0.631	0.215		0.387	0.034		0.789	0.666	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

80-89	0.90 (0.79-1.04)	1.04 (0.92-1.16)		0.99 (0.89-1.11)	0.95 (0.81-1.10)		1.01 (0.91-1.12)	0.98 (0.73-1.34)	
90-99	1.06 (0.90-1.24)	1.03 (0.90-1.19)	0.796	1.02 (0.89-1.16)	1.09 (0.92-1.30)	0.381	1.06 (0.93-1.21)	1.04 (0.77-1.43)	0.49
>= 100	1.20 (0.96-1.50)	1.29 (1.08-1.55)		1.24 (1.03-1.48)	1.24 (0.99-1.55)		1.24 (1.01-1.52)	1.24 (0.88-1.74)	
p-trend	0.133	0.037		0.104	0.05		0.083	0.149	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Colon	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
88.5-96.6	0.86 (0.71-1.03)	1.07 (0.91-1.26)		0.98 (0.85-1.13)	0.98 (0.79-1.21)		1.00 (0.88-1.15)	0.93 (0.51-1.68)	
96.8-105.5	0.86 (0.72-1.03)	0.99 (0.84-1.16)	0.546	0.93 (0.80-1.07)	0.95 (0.77-1.17)	0.243	0.98 (0.86-1.13)	0.82 (0.47-1.42)	0.258
105.6-216.6	1.00 (0.84-1.20)	1.14 (0.98-1.34)		1.03 (0.90-1.19)	1.16 (0.94-1.42)		1.08 (0.93-1.24)	1.02 (0.60-1.73)	
p-trend	0.542	0.129		0.642	0.064		0.335	0.337	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.99 (0.87-1.12)	1.05 (0.95-1.16)	0.418	0.99 (0.90-1.09)	1.06 (0.93-1.21)	0.528	1 (referent)	1.00 (0.89-1.13)	

Rectum and rectosigmoid Junction	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1622	1622	1486	876	746		656	966		440	1182	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per	1622	30738	1.036 (1.010-1.063)	1.010 (0.983-1.038)	1.011 (0.983-1.040)	1.030 (0.992-1.069)	0.987 (0.949-1.028)	0.082	0.979 (0.936-1.023)	1.035 (1.000-1.071)	0.088	0.986 (0.929-1.047)	1.017 (0.986-1.048)	0.397

10mmHg increase)														
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1622	307318	1.073 (1.024-1.124)	1.010 (0.962-1.061)	1.016 (0.965-1.069)	1.013 (0.948-1.083)	1.005 (0.935-1.081)	0.855	0.957 (0.885-1.036)	1.055 (0.993-1.122)	0.074	1.024 (0.930-1.128)	1.004 (0.949-1.063)	0.805
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1622	307318	1.063 (1.022-1.106)	1.013 (0.971-1.056)	1.016 (0.973-1.062)	1.030 (0.973-1.090)	0.992 (0.933-1.056)	0.316	0.963 (0.900-1.030)	1.054 (1.001-1.111)	0.059	1.003 (0.920-1.093)	1.016 (0.968-1.065)	0.778
Systolic Blood Pressure (mmHg) ESH classification														
Rectum and rectosigmoid Junction	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
< 120	284	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	301	66446	1.05 (0.89-1.23)	0.95 (0.81-1.12)	0.97 (0.82-1.16)	0.95 (0.74-1.22)	0.98 (0.79-1.22)		0.98 (0.79-1.23)	0.95 (0.74-1.22)		0.93 (0.72-1.22)	0.97 (0.78-1.20)	
130-139	317	57482	1.09 (0.92-1.28)	0.95 (0.81-1.13)	1.00 (0.84-1.19)	1.10 (0.86-1.40)	0.81 (0.64-1.03)		0.89 (0.70-1.13)	1.04 (0.82-1.32)		0.90 (0.68-1.20)	0.99 (0.80-1.22)	
140-159	482	68235	1.14 (0.98-1.34)	0.98 (0.83-1.14)	1.01 (0.86-1.19)	0.99 (0.78-1.25)	0.99 (0.79-1.23)	0.139	0.84 (0.66-1.06)	1.12 (0.90-1.41)	0.047	0.94 (0.70-1.25)	1.00 (0.82-1.22)	0.609
160-179	168	22656	1.10 (0.90-1.34)	0.93 (0.76-1.14)	0.95 (0.76-1.17)	1.03 (0.77-1.37)	0.82 (0.60-1.12)		0.75 (0.53-1.07)	1.09 (0.83-1.42)		0.85 (0.52-1.39)	0.96 (0.75-1.21)	
>= 180	70	6358	1.57 (1.20-2.06)	1.32 (1.00-1.73)	1.33 (1.00-1.78)	1.51 (1.04-2.18)	1.11 (0.72-1.70)		1.39 (0.87-2.22)	1.41 (0.99-1.99)		1.56 (0.75-3.23)	1.32 (0.97-1.79)	
p-trend			0.011	0.594	0.468	0.229	0.584		0.21	0.041		0.819	0.438	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	563	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	340	64872	1.04 (0.91-1.19)	0.97 (0.85-1.11)	0.99 (0.86-1.14)	0.95 (0.78-1.15)	0.99 (0.81-1.21)		0.92 (0.75-1.13)	1.03 (0.86-1.25)		1.10 (0.85-1.42)	0.93 (0.79-1.09)	

specific quartiles														
50.0-88.3	267	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	349	7772 7	1.01 (0.86-1.19)	0.93 (0.79-1.09)	0.94 (0.79-1.11)	1.01 (0.79-1.30)	0.87 (0.70-1.08)		0.84 (0.68-1.05)	1.07 (0.83-1.38)		0.71 (0.54-0.94)	1.07 (0.87-1.31)	
96.8-105.5	461	7632 7	1.14 (0.98-1.33)	0.99 (0.85-1.16)	1.02 (0.86-1.20)	0.98 (0.77-1.25)	1.01 (0.82-1.26)	0.77	0.96 (0.78-1.20)	1.10 (0.87-1.40)	0.06	1.03 (0.79-1.35)	1.01 (0.82-1.23)	0.753
105.6-216.6	545	7627 3	1.15 (0.99-1.35)	0.96 (0.82-1.12)	0.97 (0.82-1.15)	0.99 (0.78-1.26)	0.92 (0.74-1.15)		0.78 (0.62-0.99)	1.17 (0.92-1.48)		0.91 (0.67-1.22)	1.00 (0.82-1.22)	
p-trend			0.022	0.865	0.957	0.905	0.842		0.132	0.15		0.828	0.738	
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)														
Normotensive	757	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	865	1331 39	1.05 (0.95-1.17)	0.97 (0.88-1.08)	0.98 (0.88-1.09)	0.94 (0.81-1.08)	1.01 (0.87-1.18)	0.734	0.89 (0.75-1.05)	1.06 (0.92-1.21)	0.101	1.03 (0.84-1.27)	0.95 (0.84-1.08)	0.476

Rectum and rectosigmoid Junction	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol \leq 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	577	1030		937	685		1103	221	
Cohort size	141931	160623		205214	102104		227336	37017	
Rectum and rectosigmoid Junction	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol \leq 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.011 (0.965-1.058)	1.005 (0.971-1.040)	0.86	0.991 (0.956-1.028)	1.039 (0.997-1.082)	0.183	1.005 (0.970-1.042)	1.031 (0.960-1.106)	0.38
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.029 (0.947-1.117)	0.993 (0.934-1.056)	0.975	0.984 (0.922-1.050)	1.056 (0.980-1.138)	0.171	1.016 (0.954-1.083)	1.048 (0.916-1.199)	0.486
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.022 (0.953-1.097)	1.000 (0.949-1.054)	0.914	0.986 (0.932-1.042)	1.058 (0.993-1.127)	0.145	1.012 (0.959-1.069)	1.051 (0.936-1.180)	0.374
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-129	0.96 (0.73-1.26)	0.94 (0.76-1.16)		1.10 (0.89-1.35)	0.75 (0.57-0.99)		0.95 (0.79-1.14)	1.16 (0.51-2.62)	
130-139	0.85 (0.64-1.12)	1.00 (0.81-1.23)		0.99 (0.80-1.23)	0.90 (0.70-1.17)		0.98 (0.81-1.19)	0.93 (0.43-2.05)	
140-159	1.08 (0.83-1.40)	0.90 (0.73-1.10)	0.984	0.96 (0.78-1.19)	0.98 (0.77-1.25)	0.215	0.97 (0.81-1.17)	0.98 (0.46-2.05)	0.766
160-179	0.97 (0.69-1.36)	0.88 (0.68-1.14)		0.92 (0.70-1.21)	0.93 (0.68-1.28)		0.90 (0.69-1.18)	0.92 (0.42-1.98)	
>= 180	1.13 (0.68-1.89)	1.35 (0.97-1.88)		1.21 (0.83-1.78)	1.44 (0.97-2.15)		1.48 (1.01-2.17)	1.28 (0.56-2.93)	
p-trend	0.564	0.943		0.601	0.109		0.74	0.888	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.96 (0.76-1.21)	0.96 (0.81-1.14)		0.90 (0.75-1.07)	1.11 (0.89-1.38)		1.02 (0.87-1.19)	1.20 (0.71-2.02)	
85-89	1.03 (0.80-1.33)	0.93 (0.76-1.12)		0.88 (0.72-1.08)	1.14 (0.90-1.44)		1.06 (0.89-1.27)	0.99 (0.58-1.69)	
90-99	1.17 (0.93-1.48)	0.90 (0.75-1.07)	0.903	0.90 (0.74-1.08)	1.21 (0.97-1.50)	0.195	0.99 (0.82-1.19)	1.16 (0.73-1.86)	0.41
100-109	1.02 (0.70-1.51)	1.07 (0.82-1.39)		1.25 (0.95-1.64)	0.89 (0.63-1.28)		0.93 (0.66-1.29)	1.32 (0.77-2.25)	
>= 110	1.00 (0.47-2.14)	1.33 (0.85-2.07)		0.72 (0.37-1.41)	1.97 (1.22-3.18)		2.12 (1.31-3.41)	1.28 (0.59-2.80)	
p-trend	0.302	0.918		0.811	0.115		0.496	0.363	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.90 (0.71-1.15)	0.97 (0.80-1.16)		1.05 (0.87-1.26)	0.83 (0.65-1.05)		0.96 (0.82-1.13)	1.02 (0.48-2.16)	
Rectum and rectosigmoid Junction	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
140-159	1.08 (0.83-1.40)	0.89 (0.73-1.09)	0.701	0.97 (0.78-1.19)	0.97 (0.76-1.24)	0.417	0.97 (0.80-1.16)	0.98 (0.46-2.05)	0.757
>= 160	1.01 (0.74-1.39)	0.98 (0.78-1.25)		0.99 (0.77-1.27)	1.04 (0.78-1.39)		1.01 (0.79-1.29)	1.01 (0.48-2.15)	
p-trend	0.464	0.611		0.653	0.288		0.994	0.997	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.99 (0.81-1.21)	0.95 (0.81-1.10)		0.89 (0.76-1.10)	1.12 (0.92-1.36)		1.03 (0.90-1.19)	1.09 (0.68-1.75)	
90-99	1.17 (0.93-1.48)	0.90 (0.75-1.07)	0.962	0.90 (0.74-1.08)	1.21 (0.97-1.50)	0.354	0.99 (0.82-1.18)	1.17 (0.73-1.87)	0.262

>= 100	1.02 (0.71-1.46)	1.12 (0.88-1.42)		1.15 (0.89-1.49)	1.09 (0.80-1.49)		1.12 (0.85-1.50)	1.32 (0.79-2.20)	
p-trend	0.374	0.981		0.988	0.204		0.67	0.251	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.96 (0.73-1.26)	0.91 (0.74-1.11)		1.01 (0.82-1.23)	0.82 (0.62-1.08)		0.90 (0.75-1.08)	2.21 (0.77-6.37)	
96.8-105.5	1.00 (0.77-1.31)	0.97 (0.80-1.19)	0.425	1.00 (0.82-1.22)	0.99 (0.76-1.27)	0.237	1.02 (0.85-1.22)	1.70 (0.61-4.77)	0.907
105.6-216.6	1.10 (0.84-1.44)	0.86 (0.70-1.05)		0.92 (0.75-1.13)	1.01 (0.78-1.31)		0.95 (0.79-1.15)	1.63 (0.59-4.49)	
p-trend	0.343	0.211		0.391	0.343		0.987	0.661	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.04 (0.87-1.24)	0.91 (0.80-1.04)	0.401	0.89 (0.78-1.02)	1.10 (0.94-1.30)	0.048	1 (referent)	1.00 (0.85-1.19)	

Liver	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			653	653	587	336	317		223	430		143	510	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Liver	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Mean Systolic Blood	653	30738	1.045 (1.004)	1.008 (0.967-1.052)	1.004 (0.960-1.050)	1.014 (0.955-1.076)	1.004 (0.945-1.066)	0.272	0.997 (0.927-1.073)	1.029 (0.978-1.083)	0.571	0.978 (0.882-1.085)	1.014 (0.968-1.061)	0.927

Pressure continuous (per 10mmHg increase)			- 1.088)											
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	653	3073 18	1.047 (0.972- 1.127)	0.975 (0.902- 1.054)	0.999 (0.921- 1.084)	0.971 (0.872- 1.080)	0.984 (0.879- 1.102)	0.822	1.007 (0.880- 1.153)	0.999 (0.910- 1.096)	0.99	0.920 (0.774- 1.094)	0.988 (0.906- 1.077)	0.77
Mean Blood Pressure (1/3SBP+2/ 3DBP) continuous (per 10mmHg increase)	653	3073 18	1.059 (0.995- 1.126)	0.995 (0.931- 1.062)	1.003 (0.935- 1.075)	0.996 (0.909- 1.091)	0.996 (0.905- 1.095)	0.493	1.001 (0.893- 1.122)	1.023 (0.945- 1.107)	0.769	0.943 (0.810- 1.098)	1.005 (0.934- 1.081)	0.813
Systolic Blood Pressure (mmHg) ESH classificatio n														
< 120	100	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-129	105	6644 6	0.96 (0.73- 1.26)	0.87 (0.66- 1.15)	0.89 (0.66- 1.19)	0.85 (0.56- 1.29)	0.89 (0.61- 1.30)		0.84 (0.55- 1.29)	0.90 (0.62- 1.30)		0.86 (0.54- 1.38)	0.87 (0.62- 1.23)	
130-139	138	5748 2	1.21 (0.93- 1.57)	1.04 (0.80- 1.36)	1.06 (0.80- 1.40)	1.00 (0.67- 1.49)	1.10 (0.76- 1.58)		1.33 (0.89- 1.98)	0.94 (0.66- 1.34)		0.90 (0.55- 1.48)	1.10 (0.79- 1.52)	
140-159	211	6823 5	1.24 (0.97- 1.59)	1.02 (0.79- 1.32)	1.00 (0.76- 1.30)	0.94 (0.64- 1.38)	1.12 (0.79- 1.59)	0.488	1.21 (0.81- 1.80)	0.99 (0.71- 1.38)	0.87	0.80 (0.48- 1.35)	1.08 (0.80- 1.47)	0.659
160-179	74	2265 6	1.15 (0.84- 1.57)	0.91 (0.66- 1.26)	0.86 (0.61- 1.22)	0.84 (0.53- 1.33)	1.00 (0.63- 1.56)		0.75 (0.40- 1.40)	1.01 (0.68- 1.50)		0.94 (0.44- 2.01)	0.94 (0.65- 1.35)	
>= 180	25	6358	1.33 (0.85- 2.09)	1.01 (0.64- 1.60)	1.08 (0.67- 1.73)	1.19 (0.66- 2.16)	0.76 (0.35- 1.63)		0.57 (0.17- 1.88)	1.19 (0.71- 2.01)		0.44 (0.06- 3.25)	1.11 (0.68- 1.81)	
p-trend			0.042	0.803	0.996	0.929	0.769		0.839	0.458		0.455	0.552	
Diastolic Blood Pressure (mmHg) ESH classificatio n														
< 80	211	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-84	155	6487 2	1.14 (0.92- 1.41)	1.06 (0.85- 1.30)	1.10 (0.88- 1.38)	1.27 (0.93- 1.73)	0.92 (0.68- 1.24)		1.09 (0.77- 1.53)	1.09 (0.83- 1.42)		0.82 (0.53- 1.27)	1.15 (0.90- 1.46)	
Liver	Cas es	Coh ort	HR (crude)	HR (adjusted)	Exclu ding first 2 years of follow- up	Men HR (adjusted)	Wome n HR (adjusted)	Sex p- interac tion	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p- interac tion	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p- interac tion

					HR (adjusted)									
85-89	103	41500	1.11 (0.87-1.41)	0.99 (0.78-1.26)	1.04 (0.81-1.34)	1.17 (0.83-1.65)	0.86 (0.60-1.22)		1.19 (0.80-1.77)	0.96 (0.71-1.30)		0.68 (0.39-1.18)	1.10 (0.84-1.44)	
90-99	130	51196	1.03 (0.83-1.29)	0.89 (0.70-1.11)	0.91 (0.71-1.16)	0.97 (0.70-1.35)	0.86 (0.62-1.19)	0.588	0.81 (0.52-1.24)	0.97 (0.74-1.28)	0.978	0.64 (0.38-1.07)	0.97 (0.75-1.25)	0.379
100-109	44	13896	1.27 (0.91-1.77)	1.02 (0.73-1.42)	1.12 (0.79-1.59)	1.08 (0.69-1.69)	1.00 (0.59-1.71)		1.27 (0.65-2.46)	1.06 (0.72-1.57)		0.83 (0.39-1.79)	1.08 (0.74-1.57)	
>= 110	10	3264	1.27 (0.67-2.40)	0.96 (0.51-1.83)	1.01 (0.51-1.98)	0.94 (0.41-2.17)	1.20 (0.44-3.26)		1.36 (0.33-5.55)	1.02 (0.50-2.10)		0.90 (0.22-3.75)	1.00 (0.49-2.05)	
p-trend			0.326	0.435	0.756	0.686	0.535		0.972	0.871		0.139	0.861	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	100	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	243	123928	1.08 (0.85-1.37)	0.96 (0.75-1.22)	0.97 (0.76-1.25)	0.93 (0.64-1.34)	0.99 (0.72-1.37)		1.06 (0.75-1.52)	0.92 (0.66-1.27)		0.88 (0.58-1.33)	0.99 (0.73-1.34)	
140-159	211	68235	1.23 (0.96-1.58)	1.01 (0.78-1.31)	0.99 (0.75-1.29)	0.93 (0.64-1.37)	1.11 (0.79-1.58)	0.57	1.20 (0.81-1.78)	0.99 (0.71-1.38)	0.573	0.80 (0.48-1.34)	1.08 (0.79-1.46)	0.802
>= 160	99	29014	1.18 (0.88-1.58)	0.93 (0.69-1.26)	0.91 (0.66-1.25)	0.91 (0.59-1.40)	0.93 (0.61-1.43)		0.70 (0.39-1.26)	1.05 (0.72-1.52)		0.84 (0.41-1.76)	0.97 (0.69-1.37)	
p-trend			0.124	0.855	0.62	0.753	0.951		0.678	0.526		0.455	0.916	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	211	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	258	106372	1.13 (0.94-1.36)	1.03 (0.85-1.24)	1.08 (0.88-1.31)	1.23 (0.93-1.62)	0.89 (0.69-1.16)		1.12 (0.83-1.52)	1.03 (0.81-1.31)		0.76 (0.52-1.13)	1.13 (0.91-1.40)	
90-99	130	51196	1.03 (0.83-1.29)	0.89 (0.71-1.11)	0.91 (0.71-1.16)	0.98 (0.70-1.35)	0.86 (0.62-1.19)	0.543	0.81 (0.52-1.24)	0.98 (0.74-1.28)	0.889	0.64 (0.38-1.08)	0.97 (0.75-1.25)	0.396
>= 100	54	17160	1.27 (0.94-1.72)	1.01 (0.74-1.38)	1.10 (0.80-1.52)	1.06 (0.70-1.60)	1.04 (0.64-1.68)		1.28 (0.69-2.36)	1.06 (0.74-1.51)		0.85 (0.42-1.71)	1.07 (0.75-1.51)	
p-trend			0.257	0.548	0.906	0.824	0.584		0.965	0.96		0.174	0.968	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	84	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Liver	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI p-interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p-interaction

					years of follow-up HR (adjusted)				HR (adjusted)	HR (adjusted)		HR (adjusted)		
88.5-96.6	149	77727	1.23 (0.94-1.61)	1.13 (0.86-1.49)	1.26 (0.94-1.69)	1.29 (0.83-2.01)	1.09 (0.77-1.55)		1.18 (0.80-1.74)	1.14 (0.78-1.67)		1.43 (0.90-2.29)	1.01 (0.72-1.41)	
96.8-105.5	185	76327	1.28 (0.99-1.67)	1.11 (0.85-1.45)	1.17 (0.88-1.56)	1.28 (0.83-1.97)	1.04 (0.73-1.48)	0.379	1.15 (0.77-1.72)	1.15 (0.80-1.66)	0.848	0.79 (0.45-1.36)	1.19 (0.87-1.62)	0.396
105.6-216.6	235	76273	1.35 (1.04-1.74)	1.09 (0.83-1.42)	1.14 (0.86-1.52)	1.23 (0.80-1.87)	1.04 (0.73-1.49)		1.19 (0.79-1.80)	1.15 (0.80-1.64)		0.94 (0.54-1.63)	1.10 (0.81-1.51)	
p-trend			0.034	0.778	0.798	0.652	0.942		0.485	0.59		0.276	0.402	
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)														
Normotensive	263	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	390	133139	1.23 (1.05-1.45)	1.09 (0.92-1.29)	1.05 (0.88-1.26)	1.10 (0.87-1.39)	1.10 (0.86-1.39)	0.439	1.01 (0.77-1.33)	1.22 (0.99-1.51)	0.381	0.85 (0.59-1.22)	1.16 (0.96-1.41)	0.301

Liver	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol \leq 12g HR (adjusted)	Alcohol $>$ 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	239	409		411	242		429	129	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.037 (0.966-1.112)	0.994 (0.943-1.049)	0.596	0.989 (0.937-1.044)	1.042 (0.974-1.116)	0.13	1.016 (0.961-1.075)	0.952 (0.866-1.047)	0.298
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.001 (0.879-1.142)	0.955 (0.867-1.052)	0.894	0.921 (0.834-1.018)	1.065 (0.943-1.204)	0.124	0.943 (0.850-1.045)	0.888 (0.740-1.064)	0.904
Mean Blood Pressure (1/3SBP+2/3DBP) continuous	1.031 (0.923-1.151)	0.973 (0.896-1.057)	0.726	0.952 (0.875-1.037)	1.066 (0.960-1.184)	0.098	0.984 (0.901-1.075)	0.903 (0.773-1.055)	0.613

classification														
< 80	64	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	40	64872	0.95 (0.63-1.41)	0.81 (0.54-1.21)	0.77 (0.50-1.19)	0.77 (0.48-1.26)	0.86 (0.42-1.77)		1.08 (0.54-2.16)	0.75 (0.46-1.23)		0.34 (0.11-1.02)	0.96 (0.62-1.50)	
85-89	35	41500	1.21 (0.80-1.83)	0.96 (0.63-1.47)	1.00 (0.65-1.56)	0.84 (0.50-1.42)	1.23 (0.60-2.54)		1.66 (0.80-3.46)	0.87 (0.52-1.46)		1.09 (0.45-2.62)	0.95 (0.58-1.54)	
90-99	33	51196	0.82 (0.53-1.25)	0.59 (0.38-0.91)	0.57 (0.36-0.92)	0.55 (0.32-0.92)	0.71 (0.32-1.57)	0.33	0.41 (0.14-1.22)	0.71 (0.44-1.15)	0.852	0.72 (0.29-1.77)	0.55 (0.34-0.92)	0.492
100-109	15	13896	1.36 (0.77-2.40)	0.87 (0.49-1.56)	0.95 (0.52-1.72)	0.80 (0.41-1.57)	0.99 (0.29-3.38)		0.81 (0.19-3.55)	1.04 (0.55-1.97)		1.18 (0.37-3.75)	0.79 (0.40-1.56)	
>= 110	5	3264	2.07 (0.83-5.16)	1.21 (0.48-3.05)	1.34 (0.53-3.40)	0.84 (0.26-2.75)	3.07 (0.70-13.49)		1.94 (0.25-14.93)	1.26 (0.45-3.55)		no cases	1.54 (0.60-3.93)	
p-trend			0.523	0.199	0.357	0.121	0.925		0.527	0.741		0.847	0.155	
Hepatocellular	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	25	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	64	123928	1.10 (0.69-1.75)	0.84 (0.52-1.35)	0.79 (0.48-1.31)	0.71 (0.40-1.29)	1.08 (0.49-2.38)		1.09 (0.49-2.44)	0.70 (0.39-1.26)		0.72 (0.32-1.64)	0.86 (0.48-1.56)	
140-159	70	68235	1.54 (0.96-2.48)	1.03 (0.63-1.67)	0.95 (0.57-1.59)	0.95 (0.53-1.73)	1.14 (0.49-2.66)	0.541	1.54 (0.67-3.54)	0.89 (0.49-1.60)	0.843	0.82 (0.32-2.08)	1.09 (0.60-1.95)	0.766
>= 160	33	29014	1.49 (0.86-2.57)	0.93 (0.53-1.63)	0.93 (0.52-1.67)	0.91 (0.47-1.79)	0.92 (0.33-2.55)		0.47 (0.12-1.84)	1.05 (0.55-1.99)		0.60 (0.15-2.38)	1.00 (0.52-1.93)	
p-trend			0.039	0.755	0.777	0.631	0.937		0.832	0.36		0.562	0.569	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	64	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	75	106372	1.05 (0.75-1.48)	0.87 (0.62-1.23)	0.87 (0.60-1.25)	0.80 (0.53-1.22)	1.01 (0.56-1.84)		1.29 (0.71-2.32)	0.80 (0.53-1.22)		0.62 (0.29-1.35)	0.96 (0.65-1.41)	
90-99	33	51196	0.82 (0.53-1.25)	0.59 (0.38-0.91)	0.57 (0.36-0.91)	0.55 (0.32-0.92)	0.70 (0.32-1.56)	0.441	0.41 (0.14-1.21)	0.71 (0.44-1.15)	0.753	0.71 (0.29-1.75)	0.55 (0.34-0.92)	0.673
>= 100	20	17160	1.48 (0.89-2.47)	0.93 (0.55-1.58)	1.02 (0.60-1.74)	0.81 (0.44-1.50)	1.34 (0.49-3.67)		1.00 (0.29-3.44)	1.08 (0.61-1.93)		0.90 (0.28-2.87)	0.93 (0.52-1.68)	

p-trend			0.659	0.144	0.245	0.111	0.863		0.382	0.674		0.611	0.144	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	25	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	38	7772 7	1.00 (0.60-1.67)	0.84 (0.50-1.40)	0.77 (0.45-1.32)	0.89 (0.48-1.66)	0.65 (0.26-1.67)		1.25 (0.52-3.01)	0.64 (0.34-1.20)		1.25 (0.49-3.20)	0.69 (0.37-1.27)	
96.8-105.5	55	7632 7	1.21 (0.75-1.95)	0.89 (0.54-1.45)	0.83 (0.49-1.38)	0.68 (0.37-1.27)	1.31 (0.59-2.92)	0.413	1.38 (0.58-3.29)	0.72 (0.40-1.30)	0.362	0.65 (0.22-1.89)	0.91 (0.52-1.59)	0.988
105.6-216.6	74	7627 3	1.31 (0.82-2.10)	0.84 (0.51-1.36)	0.79 (0.47-1.31)	0.77 (0.42-1.39)	0.95 (0.41-2.21)		1.30 (0.54-3.16)	0.74 (0.42-1.31)		0.91 (0.32-2.56)	0.79 (0.45-1.37)	
p-trend			0.141	0.615	0.554	0.357	0.673		0.574	0.7		0.524	0.752	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	67	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hepatocellular	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertensive	124	1331 39	1.50 (1.10-2.05)	1.18 (0.86-1.63)	1.22 (0.87-1.71)	1.25 (0.85-1.85)	1.07 (0.62-1.85)	0.498	1.11 (0.63-1.93)	1.36 (0.93-2.00)	0.875	0.87 (0.45-1.69)	1.29 (0.89-1.85)	0.499

Hepatocellular	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	49	141		120	72		117	42	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.148 (0.993-1.326)	1.027 (0.938-1.123)	0.383	1.021 (0.926-1.127)	1.128 (0.997-1.275)	0.276	1.057 (0.951-1.175)	0.973 (0.825-1.147)	0.464
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.138 (0.856-1.512)	0.868 (0.733-1.029)	0.094	0.864 (0.719-1.037)	1.044 (0.827-1.317)	0.352	0.839 (0.686-1.027)	0.894 (0.649-1.233)	0.482

Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.194 (0.945-1.508)	0.955 (0.828-1.102)	0.157	0.947 (0.810-1.108)	1.126 (0.926-1.369)	0.27	0.962 (0.811-1.141)	0.924 (0.703-1.215)	0.991
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	three cases in referent		1 (referent)	two cases in referent	
120-129	0.45 (0.13-1.63)	0.98 (0.53-1.82)		0.69 (0.38-1.26)	-		0.75 (0.39-1.43)	-	
130-139	0.98 (0.34-2.80)	0.86 (0.46-1.61)		0.55 (0.29-1.03)	-		0.95 (0.51-1.77)	-	
140-159	1.17 (0.44-3.15)	1.01 (0.57-1.80)	0.352	0.68 (0.39-1.19)	-	-	1.09 (0.60-1.97)	-	-
160-179	0.98 (0.29-3.30)	0.81 (0.40-1.65)		0.54 (0.26-1.15)	-		1.06 (0.49-2.29)	-	
>= 180	2.39 (0.62-9.26)	1.10 (0.44-2.75)		1.05 (0.43-2.58)	-		0.93 (0.25-3.42)	-	
p-trend	0.146	0.891		0.421	-		0.502	-	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hepatocellular	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
80-84	1.64 (0.68-3.96)	0.65 (0.41-1.05)		1.03 (0.65-1.64)	0.38 (0.16-0.91)		0.70 (0.43-1.15)	0.63 (0.22-1.79)	
85-89	2.07 (0.84-5.14)	0.79 (0.48-1.30)		0.66 (0.36-1.21)	1.46 (0.78-2.76)		1.03 (0.62-1.70)	0.51 (0.17-1.55)	
90-99	1.67 (0.69-4.08)	0.43 (0.25-0.73)	0.052	0.50 (0.28-0.89)	0.75 (0.38-1.48)	0.354	0.53 (0.30-0.96)	0.41 (0.16-1.08)	0.439
100-109	1.00 (0.21-4.78)	0.84 (0.45-1.58)		0.91 (0.43-1.91)	0.87 (0.34-2.23)		0.41 (0.13-1.35)	0.66 (0.22-1.95)	
>= 110	3.94 (0.82-18.99)	0.81 (0.25-2.65)		1.17 (0.35-3.86)	1.36 (0.31-5.93)		0.68 (0.09-4.98)	1.03 (0.25-4.22)	
p-trend	0.265	0.053		0.08	0.76		0.052	0.515	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	three cases in referent		1 (referent)	two cases in referent	
120-139	0.73 (0.27-1.95)	0.92 (0.53-1.60)		0.62 (0.36-1.06)	-		0.85 (0.49-1.48)	-	

140-159	1.15 (0.43-3.07)	1.02 (0.57-1.80)	0.581	0.68 (0.39-1.20)	-	-	1.08 (0.60-1.95)	-	-
>= 160	1.24 (0.41-3.74)	0.88 (0.45-1.71)		0.66 (0.34-1.29)	-		1.02 (0.49-2.13)	-	
p-trend	0.315	0.885		0.417	-		0.611	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.82 (0.82-4.01)	0.71 (0.48-1.06)		0.88 (0.58-1.35)	0.85 (0.47-1.53)		0.83 (0.55-1.25)	0.57 (0.23-1.43)	
90-99	1.67 (0.69-4.07)	0.43 (0.25-0.73)	0.08	0.50 (0.28-0.89)	0.75 (0.38-1.48)	0.891	0.53 (0.30-0.95)	0.41 (0.16-1.09)	0.294
>= 100	1.58 (0.47-5.36)	0.83 (0.46-1.50)		0.97 (0.50-1.89)	0.94 (0.40-2.21)		0.46 (0.16-1.29)	0.74 (0.27-2.03)	
p-trend	0.383	0.042		0.164	0.637		0.018	0.551	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.53 (0.13-2.16)	0.96 (0.55-1.68)		0.74 (0.41-1.35)	1.26 (0.42-3.80)		1.02 (0.55-1.87)	0.17 (0.03-0.96)	
96.8-105.5	1.77 (0.58-5.43)	0.71 (0.40-1.26)	0.042	0.78 (0.44-1.37)	1.33 (0.47-3.78)	0.116	1.03 (0.57-1.89)	0.25 (0.08-0.80)	0.269
105.6-216.6	1.61 (0.52-4.99)	0.73 (0.42-1.27)		0.62 (0.35-1.11)	1.72 (0.62-4.78)		0.91 (0.49-1.71)	0.21 (0.07-0.62)	
p-trend	0.099	0.158		0.15	0.202		0.742	0.06	
Hepatocellular	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.62 (0.83-3.13)	1.08 (0.75-1.56)	0.385	1.09 (0.74-1.62)	1.46 (0.84-2.52)	0.489	1 (referent)	1.19 (0.78-1.83)	

Gallbladder and bile ducts	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			346	346	315	137	209		136	210		80	266	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	346	30738	1.001 (0.946-1.059)	0.989 (0.933-1.049)	0.975 (0.916-1.037)	0.991 (0.901-1.091)	0.991 (0.920-1.067)	0.847	0.956 (0.868-1.053)	1.021 (0.949-1.099)	0.367	0.961 (0.833-1.108)	0.994 (0.932-1.060)	0.807
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	346	30738	1.024 (0.925-1.134)	1.008 (0.906-1.121)	1.001 (0.895-1.120)	1.065 (0.907-1.251)	0.979 (0.851-1.126)	0.436	0.960 (0.806-1.143)	1.060 (0.930-1.209)	0.419	0.817 (0.644-1.037)	1.063 (0.944-1.196)	0.112
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	346	30738	1.012 (0.928-1.104)	0.995 (0.909-1.089)	0.981 (0.891-1.079)	1.026 (0.890-1.183)	0.983 (0.874-1.105)	0.582	0.947 (0.816-1.098)	1.046 (0.935-1.171)	0.354	0.875 (0.709-1.080)	1.024 (0.926-1.132)	0.303
Systolic Blood Pressure (mmHg) ESH classification														
< 120	56	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	58	66446	0.98 (0.67-1.41)	0.96 (0.66-1.39)	0.97 (0.66-1.43)	1.14 (0.57-2.29)	0.93 (0.59-1.45)		0.79 (0.47-1.34)	1.24 (0.71-2.17)		1.02 (0.56-1.84)	0.94 (0.58-1.53)	
130-139	83	57482	1.35 (0.95-1.91)	1.30 (0.91-1.85)	1.26 (0.87-1.82)	1.89 (0.99-3.57)	1.06 (0.68-1.66)		1.22 (0.75-2.00)	1.56 (0.92-2.65)		1.13 (0.61-2.12)	1.39 (0.90-2.17)	
140-159	105	68235	1.15 (0.82-1.62)	1.10 (0.77-1.56)	1.02 (0.71-1.48)	1.26 (0.66-2.41)	1.10 (0.72-1.69)	0.919	0.99 (0.59-1.63)	1.38 (0.82-2.32)	0.406	0.68 (0.32-1.44)	1.24 (0.81-1.90)	0.312
160-179	33	22656	0.93 (0.60-1.47)	0.88 (0.56-1.39)	0.81 (0.50-1.32)	0.83 (0.36-1.93)	0.97 (0.56-1.68)		0.65 (0.29-1.44)	1.19 (0.64-2.20)		0.72 (0.21-2.46)	0.96 (0.56-1.62)	
Gallbladder and bile ducts	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)										
>= 180	11	6358	1.07 (0.55-2.08)	0.99 (0.51-1.94)	0.95 (0.47-1.92)	1.58 (0.58-4.32)	0.74 (0.29-1.93)		0.31 (0.04-2.32)	1.58 (0.72-3.48)		no cases	1.15 (0.57-2.34)		
p-trend			0.71	0.995	0.652	0.989	0.943		0.528	0.425		0.279	0.613		
Diastolic Blood Pressure (mmHg)															
ESH classification															
< 80	119	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)		
80-84	79	64872	1.07 (0.80-1.43)	1.05 (0.79-1.41)	1.08 (0.80-1.46)	1.67 (1.01-2.75)	0.84 (0.58-1.22)		0.89 (0.56-1.40)	1.20 (0.82-1.77)		0.95 (0.55-1.63)	1.11 (0.78-1.56)		
85-89	53	41500	1.04 (0.75-1.44)	1.01 (0.73-1.41)	0.98 (0.69-1.39)	1.57 (0.91-2.70)	0.82 (0.53-1.26)		1.04 (0.62-1.75)	1.06 (0.69-1.64)		0.49 (0.21-1.11)	1.23 (0.85-1.79)		
90-99	72	51196	1.06 (0.78-1.43)	1.02 (0.75-1.39)	1.01 (0.73-1.40)	1.43 (0.85-2.41)	0.92 (0.62-1.36)	0.275	0.83 (0.48-1.42)	1.19 (0.81-1.76)	0.632	0.45 (0.20-0.99)	1.25 (0.88-1.76)		0.025
100-109	18	13896	0.96 (0.58-1.58)	0.91 (0.55-1.51)	0.89 (0.52-1.52)	1.32 (0.63-2.77)	0.76 (0.36-1.58)		1.03 (0.41-2.60)	0.97 (0.53-1.80)		0.20 (0.03-1.49)	1.17 (0.68-2.00)		
>= 110	5	3264	1.15 (0.47-2.81)	1.07 (0.43-2.65)	0.96 (0.35-2.62)	1.60 (0.48-5.34)	0.93 (0.23-3.80)		1.14 (0.16-8.26)	1.25 (0.45-3.48)		1.79 (0.42-7.71)	0.86 (0.27-2.74)		
p-trend			0.835	0.933	0.749	0.357	0.462		0.749	0.671		0.023	0.299		
Systolic Blood Pressure (mmHg)															
ASH classification															
< 120	56	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)		
120-139	141	123928	1.16 (0.84-1.59)	1.12 (0.81-1.55)	1.11 (0.80-1.55)	1.52 (0.83-2.80)	0.99 (0.67-1.46)		0.99 (0.64-1.52)	1.41 (0.86-2.31)		1.07 (0.63-1.80)	1.18 (0.78-1.78)		
140-159	105	68235	1.14 (0.81-1.61)	1.08 (0.76-1.54)	1.01 (0.70-1.46)	1.23 (0.64-2.36)	1.10 (0.72-1.68)	0.683	0.97 (0.59-1.61)	1.37 (0.81-2.30)	0.343	0.67 (0.32-1.43)	1.23 (0.80-1.88)		0.401
>= 160	44	29014	0.95 (0.63-1.45)	0.89 (0.58-1.37)	0.83 (0.53-1.31)	0.97 (0.45-2.08)	0.91 (0.54-1.54)		0.57 (0.26-1.23)	1.27 (0.71-2.27)		0.58 (0.17-2.00)	0.99 (0.60-1.62)		
p-trend			0.832	0.559	0.33	0.438	0.962		0.278	0.695		0.244	0.919		
Diastolic Blood Pressure (mmHg)															
ASH classification															
< 80	119	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)		
80-89	132	106372	1.06 (0.82-1.36)	1.04 (0.80-1.34)	1.04 (0.79-1.35)	1.63 (1.03-2.56)	0.83 (0.60-1.15)		0.95 (0.64-1.39)	1.14 (0.81-1.62)		0.77 (0.46-1.27)	1.16 (0.86-1.56)		
Gallbladder and bile ducts	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI p-interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p-interaction	

					years of follow-up HR (adjusted)				HR (adjusted)	HR (adjusted)		HR (adjusted)		
90-99	72	51196	1.06 (0.78-1.43)	1.03 (0.75-1.39)	1.01 (0.73-1.40)	1.43 (0.85-2.41)	0.92 (0.62-1.36)	0.238	0.83 (0.48-1.42)	1.20 (0.81-1.76)	0.543	0.45 (0.20-0.99)	1.25 (0.88-1.76)	0.041
>= 100	23	17160	0.99 (0.63-1.56)	0.94 (0.59-1.49)	0.90 (0.55-1.47)	1.38 (0.70-2.72)	0.79 (0.40-1.53)		1.05 (0.45-2.46)	1.03 (0.59-1.80)		0.50 (0.15-1.66)	1.11 (0.67-1.84)	
p-trend			0.833	0.941	0.821	0.323	0.432		0.664	0.614		0.037	0.341	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	47	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	85	77727	1.31 (0.92-1.88)	1.30 (0.90-1.86)	1.44 (0.98-2.11)	1.84 (0.83-4.07)	1.24 (0.82-1.88)		1.18 (0.73-1.89)	1.63 (0.91-2.95)		1.47 (0.82-2.61)	1.22 (0.77-1.95)	
96.8-105.5	93	76327	1.21 (0.85-1.74)	1.18 (0.82-1.70)	1.22 (0.83-1.80)	2.34 (1.09-5.03)	0.88 (0.56-1.38)	0.158	0.90 (0.54-1.51)	1.66 (0.94-2.95)	0.342	0.77 (0.38-1.56)	1.34 (0.86-2.10)	0.101
105.6-216.6	121	76273	1.31 (0.92-1.86)	1.25 (0.87-1.81)	1.24 (0.84-1.83)	2.10 (0.98-4.53)	1.10 (0.71-1.69)		1.05 (0.63-1.77)	1.72 (0.97-3.02)		0.75 (0.35-1.60)	1.42 (0.91-2.21)	
p-trend			0.267	0.432	0.706	0.103	0.91		0.869	0.145		0.185	0.114	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	150	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	196	133139	1.11 (0.89-1.39)	1.07 (0.85-1.35)	1.01 (0.80-1.28)	1.21 (0.84-1.74)	1.01 (0.76-1.36)	0.391	0.81 (0.56-1.16)	1.36 (1.00-1.84)	0.053	0.68 (0.41-1.12)	1.22 (0.93-1.58)	0.079

Gallbladder and bile ducts	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	151	192		228	118		237	60	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure	1.004 (0.918-1.098)	0.981 (0.906-1.061)	0.7	0.986 (0.917-1.061)	0.994 (0.900-1.098)	0.665	1.011 (0.938-1.090)	0.927 (0.806-1.067)	0.361

classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	1.10 (0.68-1.76)	1.19 (0.76-1.85)		1.13 (0.77-1.67)	1.12 (0.63-1.98)		0.88 (0.62-1.24)	-	
140-159	1.03 (0.61-1.76)	1.17 (0.73-1.88)	0.785	1.14 (0.74-1.75)	0.99 (0.54-1.82)	0.763	1.01 (0.68-1.50)	-	-
>= 160	1.07 (0.57-1.99)	0.82 (0.45-1.48)		0.94 (0.56-1.59)	0.79 (0.38-1.66)		0.85 (0.50-1.45)	-	
Gallbladder and bile ducts	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.949	0.52		0.873	0.41		0.847	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.02 (0.70-1.50)	1.04 (0.74-1.48)		1.06 (0.78-1.44)	1.00 (0.63-1.58)		0.85 (0.63-1.15)	1.56 (0.63-3.89)	
90-99	0.89 (0.55-1.44)	1.10 (0.74-1.66)	0.722	0.87 (0.59-1.29)	1.34 (0.81-2.22)	0.395	0.97 (0.66-1.42)	1.37 (0.54-3.49)	0.757
>= 100	1.07 (0.55-2.09)	0.85 (0.45-1.60)		0.82 (0.45-1.50)	1.15 (0.55-2.40)		1.01 (0.53-1.91)	0.95 (0.32-2.88)	
p-trend	0.862	0.963		0.409	0.339		0.829	0.667	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	1.21 (0.72-2.05)	1.37 (0.83-2.27)		1.29 (0.83-1.98)	1.34 (0.68-2.62)		1.18 (0.81-1.74)	-	
96.8-105.5	0.99 (0.58-1.70)	1.35 (0.82-2.23)	0.334	1.16 (0.75-1.81)	1.23 (0.63-2.39)	0.909	0.94 (0.62-1.41)	-	-
105.6-216.6	1.13 (0.66-1.93)	1.35 (0.82-2.23)		1.24 (0.80-1.92)	1.30 (0.67-2.50)		1.16 (0.77-1.76)	-	
p-trend	0.888	0.383		0.551	0.616		0.796	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.09 (0.77-1.54)	1.05 (0.78-1.43)	0.78	1.16 (0.88-1.54)	0.92 (0.63-1.36)	0.427	1 (referent)	1.02 (0.72-1.43)	

Pancreas	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			990	990	921	452	538		428	562		240	750	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	990	30738	1.025 (0.992-1.060)	1.013 (0.979-1.049)	1.012 (0.976-1.049)	1.012 (0.960-1.067)	1.010 (0.965-1.057)	0.797	1.068 (1.015-1.124)	0.980 (0.937-1.026)	0.01	0.990 (0.913-1.073)	1.017 (0.979-1.056)	0.738
Pancreas	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	990	30738	1.035 (0.975-1.099)	1.014 (0.952-1.080)	1.012 (0.949-1.080)	1.014 (0.924-1.113)	1.007 (0.924-1.097)	0.93	1.079 (0.981-1.187)	0.984 (0.907-1.069)	0.149	0.942 (0.825-1.076)	1.034 (0.963-1.111)	0.371
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	990	30738	1.037 (0.985-1.091)	1.017 (0.965-1.073)	1.015 (0.961-1.073)	1.016 (0.938-1.101)	1.011 (0.941-1.087)	0.849	1.092 (1.009-1.183)	0.977 (0.911-1.048)	0.032	0.962 (0.856-1.082)	1.030 (0.971-1.094)	0.487
Systolic Blood Pressure (mmHg) ESH classification														
< 120	176	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	184	66446	1.01 (0.82-1.24)	0.98 (0.79-1.21)	0.98 (0.79-1.22)	0.88 (0.63-1.24)	1.02 (0.78-1.34)		1.06 (0.78-1.43)	0.87 (0.65-1.17)		1.14 (0.81-1.61)	0.89 (0.68-1.16)	
130-139	182	57482	0.97 (0.79-1.20)	0.93 (0.75-1.15)	0.97 (0.78-1.21)	0.91 (0.66-1.27)	0.89 (0.67-1.18)		1.25 (0.93-1.70)	0.70 (0.52-0.94)		1.04 (0.71-1.52)	0.87 (0.67-1.13)	
140-159	289	68235	1.06 (0.87-1.29)	1.00 (0.82-1.22)	1.01 (0.82-1.24)	0.89 (0.65-1.22)	1.06 (0.81-1.38)	0.649	1.23 (0.92-1.66)	0.81 (0.62-1.07)	0.008	0.73 (0.48-1.13)	1.03 (0.81-1.31)	0.439

classification														
< 80	346	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	356	1063 72	1.02 (0.88-1.19)	1.00 (0.86-1.16)	1.01 (0.86-1.18)	1.08 (0.85-1.37)	0.93 (0.76-1.14)		1.04 (0.83-1.30)	0.98 (0.79-1.21)		0.92 (0.68-1.24)	1.03 (0.86-1.23)	
90-99	213	5119 6	1.15 (0.97-1.37)	1.10 (0.92-1.32)	1.12 (0.93-1.34)	1.16 (0.89-1.51)	1.05 (0.82-1.34)	0.646	1.18 (0.89-1.56)	1.08 (0.85-1.36)	0.419	0.88 (0.59-1.31)	1.17 (0.96-1.44)	0.407
>= 100	75	1716 0	1.19 (0.92-1.53)	1.12 (0.86-1.45)	1.09 (0.83-1.49)	1.02 (0.70-1.49)	1.27 (0.88-1.82)		1.35 (0.87-2.10)	1.05 (0.76-1.45)		0.99 (0.55-1.77)	1.16 (0.87-1.55)	
p-trend			0.068	0.23	0.277	0.518	0.349		0.128	0.536		0.649	0.116	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	156	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	223	7772 7	1.08 (0.87-1.32)	1.05 (0.85-1.29)	1.11 (0.90-1.38)	1.12 (0.79-1.59)	1.00 (0.77-1.30)		1.17 (0.87-1.55)	0.91 (0.67-1.23)		1.43 (1.01-2.03)	0.88 (0.68-1.14)	
96.8-105.5	267	7632 7	1.09 (0.89-1.34)	1.06 (0.86-1.30)	1.09 (0.88-1.35)	1.11 (0.79-1.57)	1.00 (0.77-1.30)	0.919	1.39 (1.05-1.85)	0.80 (0.60-1.07)	0.036	0.91 (0.61-1.36)	1.06 (0.83-1.35)	0.296
105.6-216.6	344	7627 3	1.20 (0.98-1.46)	1.13 (0.92-1.39)	1.14 (0.92-1.41)	1.17 (0.83-1.65)	1.09 (0.84-1.41)		1.39 (1.03-1.86)	0.93 (0.70-1.23)		1.04 (0.68-1.59)	1.10 (0.87-1.40)	
p-trend			0.064	0.243	0.322	0.413	0.518		0.016	0.748		0.52	0.104	
Pancreas	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	437	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	553	1331 39	1.14 (1.00-1.30)	1.11 (0.97-1.27)	1.11 (0.97-1.28)	1.13 (0.92-1.38)	1.08 (0.90-1.30)	0.973	1.23 (1.01-1.50)	1.04 (0.87-1.24)	0.164	0.88 (0.66-1.16)	1.19 (1.02-1.38)	0.107

Pancreas	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	365	612		599	391		682	152	
Cohort size	141931	160623		205214	102104		227336	37017	

Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.018 (0.962-1.078)	1.004 (0.961-1.049)	0.818	1.002 (0.958-1.048)	1.030 (0.977-1.087)	0.175	1.002 (0.958-1.047)	0.994 (0.912-1.084)	0.401
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.068 (0.964-1.184)	0.965 (0.890-1.046)	0.464	1.014 (0.935-1.099)	1.019 (0.922-1.126)	0.697	1.005 (0.928-1.089)	0.925 (0.784-1.091)	0.233
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.048 (0.959-1.144)	0.986 (0.921-1.055)	0.596	1.008 (0.941-1.080)	1.034 (0.950-1.124)	0.354	1.004 (0.937-1.075)	0.957 (0.831-1.103)	0.254
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.21 (0.85-1.70)	0.84 (0.64-1.10)		1.10 (0.85-1.43)	0.79 (0.55-1.13)		0.96 (0.76-1.21)	1.41 (0.51-3.88)	
130-139	0.96 (0.66-1.38)	0.92 (0.71-1.21)		0.99 (0.76-1.30)	0.84 (0.59-1.19)		0.86 (0.67-1.10)	1.18 (0.45-3.13)	
140-159	1.08 (0.77-1.53)	0.96 (0.74-1.23)	0.659	1.03 (0.80-1.34)	0.94 (0.68-1.30)	0.354	0.94 (0.75-1.19)	1.23 (0.49-3.12)	0.634
160-179	1.38 (0.92-2.07)	1.07 (0.78-1.46)		1.25 (0.91-1.72)	1.12 (0.76-1.65)		1.11 (0.81-1.51)	1.27 (0.49-3.32)	
Pancreas	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
>= 180	1.22 (0.64-2.32)	0.72 (0.42-1.24)		0.85 (0.48-1.50)	1.01 (0.57-1.80)		0.89 (0.50-1.58)	1.24 (0.43-3.63)	
p-trend	0.357	0.858		0.684	0.362		0.974	0.907	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.07 (0.81-1.43)	1.05 (0.85-1.31)		1.09 (0.87-1.35)	1.05 (0.79-1.39)		1.00 (0.82-1.22)	1.25 (0.73-2.14)	
85-89	0.96 (0.69-1.35)	0.87 (0.67-1.12)		0.85 (0.65-1.11)	0.98 (0.72-1.35)		0.92 (0.73-1.17)	0.67 (0.36-1.26)	
90-99	1.33 (0.99-1.78)	0.96 (0.76-1.21)	0.56	1.12 (0.89-1.41)	1.09 (0.82-1.45)	0.929	0.98 (0.78-1.23)	1.00 (0.60-1.66)	0.28
100-109	1.10 (0.67-1.81)	1.11 (0.79-1.56)		1.28 (0.90-1.83)	0.99 (0.64-1.55)		1.22 (0.84-1.78)	0.84 (0.44-1.60)	
>= 110	1.04 (0.38-2.84)	0.70 (0.31-1.58)		0.76 (0.31-1.87)	1.19 (0.55-2.58)		0.55 (0.18-1.73)	0.61 (0.18-2.07)	
p-trend	0.18	0.627		0.466	0.683		0.909	0.318	

Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.08 (0.79-1.48)	0.88 (0.70-1.12)		1.05 (0.83-1.32)	0.81 (0.60-1.11)		0.91 (0.74-1.12)	1.27 (0.50-3.24)	
140-159	1.09 (0.77-1.54)	0.96 (0.74-1.23)	0.452	1.04 (0.80-1.34)	0.94 (0.68-1.30)	0.453	0.95 (0.75-1.20)	1.24 (0.49-3.13)	0.601
>= 160	1.36 (0.92-2.01)	0.99 (0.73-1.33)		1.17 (0.86-1.59)	1.09 (0.75-1.58)		1.07 (0.80-1.44)	1.27 (0.49-3.27)	
p-trend	0.157	0.81		0.402	0.32		0.718	0.812	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.03 (0.80-1.33)	0.98 (0.81-1.18)		0.99 (0.82-1.20)	1.02 (0.80-1.31)		0.97 (0.81-1.16)	0.97 (0.59-1.59)	
90-99	1.33 (1.00-1.78)	0.96 (0.76-1.21)	0.682	1.12 (0.89-1.41)	1.09 (0.82-1.46)	0.829	0.98 (0.78-1.23)	1.01 (0.61-1.68)	0.452
>= 100	1.09 (0.69-1.73)	1.03 (0.75-1.43)		1.19 (0.85-1.67)	1.03 (0.69-1.55)		1.11 (0.77-1.59)	0.81 (0.44-1.50)	
p-trend	0.147	0.959		0.221	0.648		0.88	0.603	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.14 (0.81-1.61)	1.01 (0.77-1.31)		1.12 (0.87-1.44)	0.95 (0.66-1.37)		1.09 (0.87-1.38)	1.23 (0.49-3.07)	
96.8-105.5	1.12 (0.79-1.58)	1.02 (0.79-1.33)	0.842	1.01 (0.78-1.31)	1.14 (0.81-1.60)	0.65	1.04 (0.82-1.32)	0.95 (0.40-2.27)	0.162
105.6-216.6	1.24 (0.88-1.74)	1.05 (0.81-1.36)		1.18 (0.91-1.52)	1.08 (0.76-1.52)		1.09 (0.86-1.40)	0.92 (0.39-2.15)	
Pancreas	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.265	0.7		0.334	0.457		0.617	0.403	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.12 (0.90-1.40)	1.07 (0.91-1.27)	0.873	1.10 (0.93-1.31)	1.12 (0.90-1.38)	0.591	1 (referent)	0.98 (0.80-1.21)	

Lung	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			3229	3229	2993	1714	1515		1586	1643		766	2463	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	3229	30738	1.017 (0.999-1.036)	1.031 (1.012-1.050)	1.028 (1.008-1.048)	1.021 (0.995-1.048)	1.042 (1.015-1.070)	0.341	1.032 (1.005-1.059)	1.022 (0.996-1.049)	0.782	1.031 (0.987-1.076)	1.032 (1.011-1.054)	0.721
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	3229	30738	0.976 (0.943-1.009)	1.000 (0.967-1.035)	0.998 (0.963-1.035)	0.976 (0.931-1.023)	1.036 (0.985-1.090)	0.149	1.017 (0.967-1.068)	0.971 (0.926-1.018)	0.183	1.033 (0.960-1.111)	0.993 (0.955-1.033)	0.7
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	3229	30738	1.002 (0.974-1.031)	1.025 (0.996-1.055)	1.021 (0.991-1.053)	1.004 (0.964-1.046)	1.052 (1.009-1.096)	0.174	1.034 (0.992-1.077)	1.004 (0.964-1.045)	0.371	1.039 (0.975-1.107)	1.024 (0.991-1.057)	0.963
Systolic Blood Pressure (mmHg) ESH classification														
< 120	576	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	571	66446	0.94 (0.84-1.06)	0.98 (0.87-1.10)	0.93 (0.83-1.05)	0.96 (0.80-1.14)	1.00 (0.85-1.17)		0.98 (0.84-1.15)	0.93 (0.77-1.12)		0.88 (0.72-1.08)	1.04 (0.90-1.21)	
130-139	624	57482	0.99 (0.88-1.11)	1.04 (0.93-1.17)	1.01 (0.90-1.14)	0.96 (0.80-1.13)	1.14 (0.97-1.35)		1.04 (0.89-1.22)	0.99 (0.83-1.18)		0.99 (0.80-1.22)	1.09 (0.95-1.26)	
Lung	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
140-159	947	68235	0.99 (0.89-1.10)	1.07 (0.95-1.19)	1.06 (0.94-1.18)	1.02 (0.87-1.20)	1.10 (0.95-1.29)	0.38	1.09 (0.94-1.27)	0.99 (0.84-1.18)	0.833	1.01 (0.81-1.25)	1.11 (0.97-1.27)	0.562

160-179	385	22656	1.08 (0.94-1.24)	1.19 (1.04-1.37)	1.13 (0.98-1.31)	1.08 (0.89-1.32)	1.34 (1.10-1.63)		1.22 (1.00-1.48)	1.10 (0.90-1.34)		1.19 (0.85-1.66)	1.24 (1.06-1.45)	
>= 180	126	6358	1.19 (0.98-1.45)	1.26 (1.03-1.54)	1.22 (0.99-1.50)	1.22 (0.93-1.61)	1.33 (0.99-1.79)		1.23 (0.89-1.69)	1.21 (0.92-1.58)		1.67 (0.95-2.96)	1.28 (1.03-1.60)	
p-trend			0.079	0.002	0.006	0.114	0.002		0.026	0.088		0.207	0.002	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	1243	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	642	64872	0.85 (0.77-0.94)	0.90 (0.81-0.99)	0.90 (0.81-0.99)	0.90 (0.79-1.03)	0.87 (0.76-1.01)		0.86 (0.75-0.98)	0.91 (0.79-1.05)		1.10 (0.91-1.33)	0.84 (0.75-0.94)	
85-89	502	41500	0.95 (0.86-1.06)	1.02 (0.91-1.13)	1.04 (0.94-1.16)	0.95 (0.82-1.10)	1.11 (0.95-1.29)		1.05 (0.90-1.22)	0.96 (0.83-1.12)		1.09 (0.87-1.36)	0.99 (0.88-1.12)	
90-99	605	51196	0.88 (0.79-0.97)	0.93 (0.84-1.03)	0.93 (0.83-1.03)	0.87 (0.76-1.00)	1.03 (0.88-1.20)	0.059	1.00 (0.86-1.16)	0.86 (0.75-0.99)	0.576	1.06 (0.85-1.32)	0.90 (0.80-1.01)	0.746
100-109	196	13896	1.01 (0.87-1.17)	1.05 (0.90-1.23)	1.06 (0.90-1.25)	0.93 (0.75-1.13)	1.31 (1.03-1.66)		0.86 (0.65-1.13)	1.12 (0.93-1.36)		1.15 (0.80-1.66)	1.03 (0.87-1.22)	
>= 110	41	3264	0.93 (0.68-1.28)	0.97 (0.71-1.32)	0.97 (0.70-1.35)	0.96 (0.66-1.40)	0.92 (0.51-1.68)		1.18 (0.69-2.01)	0.85 (0.58-1.26)		0.93 (0.41-2.10)	0.97 (0.69-1.36)	
p-trend			0.177	0.907	0.959	0.154	0.101		0.999	0.526		0.477	0.678	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	576	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1195	12398	0.96 (0.87-1.07)	1.01 (0.91-1.12)	0.97 (0.87-1.08)	0.96 (0.82-1.12)	1.06 (0.93-1.22)		1.01 (0.88-1.15)	0.96 (0.82-1.13)		0.93 (0.78-1.10)	1.07 (0.94-1.21)	
140-159	947	68235	0.99 (0.89-1.10)	1.06 (0.95-1.19)	1.05 (0.94-1.18)	1.02 (0.87-1.20)	1.10 (0.94-1.28)	0.448	1.09 (0.94-1.26)	0.99 (0.84-1.17)	0.753	1.00 (0.81-1.25)	1.11 (0.97-1.27)	0.465
>= 160	511	29014	1.10 (0.97-1.25)	1.21 (1.06-1.37)	1.15 (1.01-1.32)	1.11 (0.92-1.34)	1.33 (1.11-1.60)		1.22 (1.01-1.46)	1.12 (0.93-1.35)		1.27 (0.93-1.71)	1.25 (1.08-1.45)	
p-trend			0.112	0.003	0.013	0.114	0.005		0.029	0.117		0.311	0.003	
Diastolic Blood Pressure (mmHg)														
ASH classification														
Lung	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
< 80	1243	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1144	106372	0.89 (0.82-0.97)	0.94 (0.87-1.03)	0.96 (0.88-1.04)	0.92 (0.82-1.04)	0.96 (0.86-1.08)		0.93 (0.83-1.04)	0.93 (0.83-1.05)		1.10 (0.93-1.30)	0.90 (0.82-0.99)	
90-99	605	51196	0.88 (0.79-0.97)	0.93 (0.84-1.03)	0.93 (0.83-1.03)	0.87 (0.76-1.00)	1.03 (0.88-1.19)	0.101	1.00 (0.86-1.16)	0.86 (0.75-0.99)	0.941	1.06 (0.85-1.32)	0.90 (0.80-1.01)	0.533
>= 100	237	17160	0.99 (0.86-1.14)	1.04 (0.90-1.20)	1.04 (0.90-1.21)	0.93 (0.77-1.12)	1.24 (0.99-1.56)		0.91 (0.71-1.17)	1.07 (0.89-1.28)		1.11 (0.79-1.57)	1.01 (0.87-1.19)	
p-trend			0.088	0.603	0.61	0.113	0.236		0.507	0.572		0.41	0.356	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	558	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	733	77727	0.97 (0.86-1.08)	1.02 (0.91-1.14)	0.97 (0.86-1.09)	1.03 (0.86-1.22)	1.02 (0.88-1.19)		1.00 (0.87-1.16)	0.99 (0.83-1.19)		0.97 (0.79-1.19)	1.05 (0.92-1.21)	
96.8-105.5	852	76327	0.92 (0.83-1.03)	1.00 (0.90-1.12)	0.99 (0.88-1.11)	1.05 (0.89-1.24)	0.96 (0.82-1.12)	0.192	1.03 (0.89-1.19)	0.92 (0.78-1.10)	0.204	1.05 (0.85-1.30)	1.00 (0.88-1.14)	0.982
105.6-216.6	1086	76273	0.97 (0.88-1.08)	1.07 (0.96-1.19)	1.04 (0.93-1.16)	1.00 (0.85-1.18)	1.19 (1.02-1.38)		1.12 (0.96-1.29)	0.97 (0.82-1.14)		1.10 (0.88-1.38)	1.08 (0.94-1.22)	
p-trend			0.612	0.24	0.353	0.895	0.048		0.129	0.62		0.311	0.36	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	1522	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	1707	133139	0.96 (0.90-1.03)	1.04 (0.97-1.12)	1.03 (0.96-1.12)	1.01 (0.91-1.12)	1.08 (0.97-1.21)	0.618	1.04 (0.94-1.16)	1.02 (0.92-1.13)	0.882	1.07 (0.91-1.25)	1.04 (0.95-1.13)	0.901

Lung	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
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Cases	280	2922		1862	1367		2225	409	
Cohort size	141931	160623		205214	102104		227336	37017	
Lung	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.051 (0.986-1.120)	1.026 (1.006-1.046)	0.758	1.021 (0.996-1.047)	1.042 (1.013-1.071)	0.177	1.034 (1.010-1.059)	1.084 (1.032-1.140)	0.32
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.003 (0.890-1.130)	0.987 (0.952-1.023)	0.912	0.973 (0.929-1.018)	1.033 (0.980-1.088)	0.148	1.012 (0.969-1.058)	0.981 (0.888-1.083)	0.462
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.042 (0.943-1.152)	1.014 (0.984-1.046)	0.915	1.004 (0.966-1.043)	1.050 (1.005-1.096)	0.128	1.033 (0.996-1.073)	1.066 (0.981-1.159)	0.836
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.21 (0.80-1.81)	0.94 (0.83-1.07)		0.97 (0.84-1.12)	0.98 (0.81-1.20)		0.96 (0.84-1.10)	0.93 (0.52-1.67)	
130-139	1.36 (0.91-2.04)	1.01 (0.89-1.14)		1.02 (0.88-1.18)	1.07 (0.88-1.30)		1.06 (0.93-1.21)	0.80 (0.46-1.39)	
140-159	1.11 (0.74-1.66)	1.04 (0.93-1.17)	0.847	1.02 (0.88-1.18)	1.12 (0.94-1.34)	0.143	1.06 (0.93-1.21)	1.00 (0.60-1.65)	0.289
160-179	1.48 (0.92-2.38)	1.13 (0.98-1.31)		1.11 (0.92-1.33)	1.30 (1.05-1.61)		1.25 (1.05-1.48)	1.22 (0.73-2.05)	
>= 180	1.68 (0.86-3.29)	1.22 (0.99-1.51)		1.25 (0.95-1.65)	1.30 (0.96-1.75)		1.24 (0.93-1.66)	1.55 (0.88-2.71)	
p-trend	0.176	0.011		0.123	0.004		0.01	0.006	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.97 (0.70-1.34)	0.88 (0.79-0.97)		0.88 (0.78-1.00)	0.92 (0.79-1.08)		0.87 (0.78-0.98)	0.81 (0.56-1.15)	
85-89	0.96 (0.66-1.38)	0.99 (0.89-1.11)		0.94 (0.82-1.09)	1.11 (0.94-1.30)		1.02 (0.90-1.16)	1.02 (0.73-1.43)	
90-99	0.87 (0.61-1.24)	0.91 (0.82-1.02)	0.784	0.92 (0.80-1.05)	0.96 (0.82-1.12)	0.262	0.96 (0.85-1.09)	0.85 (0.62-1.17)	0.725
100-109	1.53 (0.96-2.45)	0.97 (0.82-1.15)		0.97 (0.78-1.21)	1.16 (0.93-1.45)		1.14 (0.92-1.41)	0.97 (0.67-1.40)	

>= 110	0.91 (0.29-2.91)	0.95 (0.68-1.31)		0.85 (0.54-1.35)	1.07 (0.69-1.66)		0.76 (0.45-1.30)	0.97 (0.54-1.76)	
p-trend	0.734	0.376		0.298	0.377		0.806	0.918	
Systolic Blood Pressure (mmHg)									
ASH classification									
Lung	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.28 (0.89-1.84)	0.97 (0.87-1.08)		0.99 (0.87-1.13)	1.03 (0.87-1.22)		1.01 (0.90-1.13)	0.85 (0.51-1.43)	
140-159	1.11 (0.74-1.65)	1.04 (0.92-1.17)	0.881	1.02 (0.88-1.17)	1.12 (0.94-1.34)	0.133	1.06 (0.93-1.20)	1.00 (0.60-1.65)	0.266
>= 160	1.51 (0.97-2.37)	1.15 (1.00-1.32)		1.14 (0.96-1.35)	1.30 (1.06-1.59)		1.24 (1.05-1.46)	1.31 (0.78-2.17)	
p-trend	0.214	0.019		0.164	0.004		0.016	0.006	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.97 (0.73-1.28)	0.92 (0.85-1.01)		0.90 (0.81-1.01)	1.00 (0.88-1.14)		0.93 (0.84-1.03)	0.91 (0.67-1.24)	
90-99	0.87 (0.61-1.24)	0.91 (0.82-1.01)	0.562	0.91 (0.80-1.05)	0.96 (0.82-1.12)	0.317	0.96 (0.85-1.09)	0.85 (0.62-1.16)	0.698
>= 100	1.42 (0.91-2.23)	0.97 (0.83-1.12)		0.95 (0.78-1.17)	1.14 (0.93-1.41)		1.08 (0.88-1.31)	0.96 (0.67-1.37)	
p-trend	0.587	0.184		0.216	0.593		0.856	0.726	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.17 (0.80-1.72)	0.99 (0.88-1.12)		1.03 (0.90-1.19)	0.98 (0.81-1.19)		1.03 (0.91-1.17)	0.74 (0.42-1.30)	
96.8-105.5	1.02 (0.69-1.51)	0.98 (0.87-1.10)	0.844	0.96 (0.83-1.10)	1.06 (0.88-1.27)	0.113	1.02 (0.90-1.16)	0.82 (0.50-1.34)	0.893
105.6-216.6	1.14 (0.77-1.68)	1.03 (0.92-1.16)		1.01 (0.88-1.16)	1.14 (0.95-1.37)		1.11 (0.97-1.27)	0.91 (0.57-1.46)	
p-trend	0.724	0.567		0.846	0.053		0.15	0.552	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.00 (0.77-1.28)	1.01 (0.94-1.10)	0.71	1.01 (0.92-1.12)	1.07 (0.96-1.20)	0.321	1 (referent)	0.98 (0.87-1.10)	

ESH classification														
Lung AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
< 80	464	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	221	64872	0.77 (0.66-0.91)	0.83 (0.71-0.98)	0.85 (0.72-1.00)	0.84 (0.66-1.07)	0.80 (0.64-1.00)		0.84 (0.68-1.05)	0.78 (0.61-1.00)		1.18 (0.89-1.57)	0.72 (0.59-0.88)	
85-89	176	41500	0.88 (0.74-1.05)	0.99 (0.83-1.18)	0.99 (0.82-1.19)	0.84 (0.65-1.10)	1.12 (0.88-1.42)		1.09 (0.85-1.39)	0.83 (0.64-1.08)		0.84 (0.57-1.23)	1.03 (0.84-1.26)	
90-99	190	51196	0.74 (0.62-0.87)	0.84 (0.70-1.00)	0.83 (0.69-0.99)	0.76 (0.59-0.98)	0.91 (0.71-1.16)	0.331	0.87 (0.67-1.11)	0.75 (0.58-0.95)	0.205	0.81 (0.55-1.18)	0.84 (0.69-1.03)	0.319
100-109	64	13896	0.89 (0.68-1.16)	1.01 (0.78-1.33)	1.05 (0.80-1.38)	0.91 (0.63-1.32)	1.12 (0.75-1.67)		0.98 (0.64-1.51)	0.92 (0.65-1.30)		0.94 (0.50-1.77)	1.02 (0.76-1.38)	
>= 110	15	3264	0.94 (0.56-1.57)	1.08 (0.65-1.82)	1.10 (0.64-1.89)	0.96 (0.49-1.89)	1.30 (0.57-2.93)		1.91 (0.94-3.89)	0.63 (0.29-1.34)		1.61 (0.59-4.42)	0.96 (0.52-1.76)	
p-trend			0.012	0.43	0.457	0.151	0.758		0.996	0.073		0.393	0.707	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	229	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	410	123928	0.83 (0.70-0.98)	0.91 (0.77-1.08)	0.88 (0.74-1.05)	0.77 (0.59-1.00)	1.03 (0.83-1.27)		0.95 (0.77-1.17)	0.80 (0.61-1.05)		0.85 (0.65-1.12)	0.97 (0.79-1.20)	
140-159	318	68235	0.85 (0.71-1.01)	0.99 (0.82-1.19)	0.97 (0.80-1.17)	0.85 (0.64-1.12)	1.08 (0.85-1.38)	0.279	0.96 (0.76-1.23)	0.88 (0.67-1.17)	0.121	0.89 (0.62-1.26)	1.06 (0.85-1.32)	0.31
>= 160	173	29014	0.97 (0.79-1.20)	1.17 (0.94-1.45)	1.16 (0.93-1.45)	0.95 (0.69-1.32)	1.36 (1.02-1.81)		1.48 (1.12-1.97)	0.82 (0.59-1.14)		1.26 (0.78-2.03)	1.21 (0.94-1.55)	
p-trend			0.826	0.118	0.138	0.809	0.051		0.041	0.59		0.849	0.077	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	464	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	397	106372	0.82 (0.71-0.94)	0.89 (0.78-1.03)	0.90 (0.78-1.04)	0.84 (0.68-1.04)	0.92 (0.77-1.11)		0.93 (0.78-1.12)	0.81 (0.65-0.99)		1.05 (0.81-1.36)	0.85 (0.72-1.00)	
90-99	190	51196	0.74 (0.62-0.87)	0.84 (0.70-1.00)	0.82 (0.69-0.99)	0.76 (0.59-0.98)	0.91 (0.71-1.16)	0.56	0.86 (0.67-1.11)	0.75 (0.58-0.95)	0.334	0.81 (0.56-1.19)	0.84 (0.69-1.03)	0.709
>= 100	79	17160	0.90 (0.71-1.14)	1.02 (0.80-1.31)	1.06 (0.82-1.36)	0.92 (0.66-1.29)	1.14 (0.79-1.65)		1.12 (0.77-1.63)	0.86 (0.62-1.19)		1.07 (0.62-1.85)	1.01 (0.76-1.33)	

p-trend			0.005	0.247	0.296	0.148	0.816		0.62	0.07		0.652	0.308	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Lung AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	223	7699 1	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	265	7772 7	0.87 (0.72-1.04)	0.95 (0.79-1.13)	0.92 (0.76-1.11)	0.96 (0.72-1.30)	0.92 (0.73-1.16)		1.01 (0.80-1.27)	0.78 (0.58-1.05)		0.95 (0.70-1.29)	0.96 (0.76-1.20)	
96.8-105.5	276	7632 7	0.75 (0.63-0.90)	0.86 (0.72-1.04)	0.86 (0.71-1.04)	0.84 (0.63-1.13)	0.87 (0.68-1.10)	0.278	0.91 (0.72-1.16)	0.70 (0.53-0.93)	0.075	0.74 (0.53-1.05)	0.92 (0.74-1.15)	0.341
105.6-216.6	366	7627 3	0.84 (0.70-0.99)	1.00 (0.83-1.20)	0.98 (0.81-1.18)	0.89 (0.66-1.19)	1.11 (0.88-1.40)		1.15 (0.91-1.45)	0.74 (0.56-0.97)		1.01 (0.71-1.43)	1.02 (0.82-1.27)	
p-trend			0.036	0.948	0.906	0.334	0.449		0.399	0.065		0.636	0.761	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	557	1741 79	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Hypertensive	573	1331 39	0.92 (0.82-1.04)	1.04 (0.91-1.17)	1.03 (0.90-1.17)	0.96 (0.80-1.15)	1.10 (0.93-1.30)	0.336	1.04 (0.88-1.23)	0.97 (0.81-1.16)	0.731	0.95 (0.74-1.22)	1.07 (0.93-1.24)	0.277

Lung AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	149	973		658	472		830	138	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.977 (0.892-1.070)	1.026 (0.991-1.061)	0.289	1.006 (0.964-1.049)	1.043 (0.994-1.093)	0.188	1.025 (0.986-1.066)	1.106 (1.015-1.204)	0.282
Mean Diastolic Blood	0.892 (0.754-1.056)	0.986 (0.926-1.051)	0.182	0.950 (0.878-1.027)	1.019 (0.931-1.116)	0.176	0.978 (0.909-1.052)	1.021 (0.861-1.211)	0.91

Pressure continuous (per 10mmHg increase)									
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	0.929 (0.806-1.072)	1.014 (0.962-1.070)	0.194	0.981 (0.918-1.047)	1.044 (0.969-1.126)	0.148	1.010 (0.949-1.074)	1.107 (0.960-1.276)	0.48
Lung AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.16 (0.69-1.95)	0.86 (0.70-1.06)		0.94 (0.74-1.19)	0.83 (0.60-1.15)		0.85 (0.69-1.05)	1.77 (0.57-5.47)	
130-139	1.24 (0.74-2.10)	0.87 (0.70-1.07)		0.92 (0.72-1.18)	0.93 (0.68-1.28)		0.90 (0.73-1.12)	1.52 (0.51-4.53)	
140-159	0.96 (0.57-1.64)	0.98 (0.80-1.19)	0.301	0.93 (0.74-1.18)	1.07 (0.80-1.44)	0.147	1.00 (0.81-1.23)	1.50 (0.53-4.25)	0.435
160-179	0.76 (0.36-1.59)	1.16 (0.91-1.48)		0.93 (0.68-1.29)	1.38 (0.98-1.95)		1.20 (0.91-1.59)	1.85 (0.63-5.37)	
>= 180	1.45 (0.57-3.65)	1.23 (0.86-1.77)		1.52 (0.99-2.34)	1.01 (0.59-1.74)		1.23 (0.76-1.97)	2.77 (0.90-8.47)	
p-trend	0.704	0.109		0.727	0.051		0.156	0.082	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.90 (0.59-1.39)	0.81 (0.68-0.97)		0.83 (0.67-1.02)	0.85 (0.65-1.10)		0.83 (0.69-1.00)	0.82 (0.43-1.55)	
85-89	1.19 (0.75-1.87)	0.93 (0.77-1.13)		0.85 (0.66-1.08)	1.15 (0.88-1.49)		0.89 (0.72-1.10)	1.21 (0.68-2.16)	
90-99	0.63 (0.37-1.08)	0.85 (0.70-1.02)	0.244	0.85 (0.68-1.08)	0.83 (0.63-1.08)	0.476	0.87 (0.70-1.07)	0.85 (0.49-1.48)	0.817
100-109	0.63 (0.25-1.60)	1.05 (0.79-1.39)		0.98 (0.67-1.42)	1.07 (0.73-1.57)		0.96 (0.66-1.40)	1.15 (0.61-2.17)	
>= 110	1.11 (0.27-4.58)	1.07 (0.61-1.86)		1.16 (0.57-2.36)	1.05 (0.49-2.25)		1.24 (0.61-2.52)	0.91 (0.30-2.72)	
p-trend	0.225	0.531		0.353	0.844		0.359	0.899	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.20 (0.76-1.90)	0.86 (0.72-1.03)		0.93 (0.76-1.15)	0.88 (0.66-1.17)		0.87 (0.73-1.05)	1.61 (0.56-4.62)	

140-159	0.96 (0.57-1.63)	0.98 (0.80-1.19)	0.198	0.93 (0.74-1.18)	1.07 (0.80-1.44)	0.102	1.00 (0.81-1.23)	1.50 (0.53-4.24)	0.559
>= 160	0.90 (0.47-1.74)	1.18 (0.94-1.48)		1.06 (0.80-1.41)	1.29 (0.92-1.79)		1.21 (0.93-1.57)	2.08 (0.73-5.96)	
p-trend	0.522	0.087		0.834	0.035		0.159	0.117	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Lung AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
80-89	1.02 (0.71-1.47)	0.86 (0.74-1.00)		0.84 (0.70-1.00)	0.97 (0.78-1.21)		0.85 (0.73-1.00)	1.02 (0.60-1.74)	
90-99	0.63 (0.37-1.08)	0.85 (0.70-1.02)	0.175	0.85 (0.68-1.08)	0.83 (0.63-1.08)	0.629	0.87 (0.70-1.07)	0.85 (0.49-1.47)	0.894
>= 100	0.72 (0.32-1.60)	1.05 (0.81-1.36)		1.01 (0.72-1.42)	1.06 (0.74-1.52)		1.01 (0.72-1.41)	1.10 (0.59-2.03)	
p-trend	0.128	0.373		0.309	0.542		0.255	0.95	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.10 (0.68-1.79)	0.92 (0.75-1.11)		0.95 (0.76-1.19)	0.92 (0.67-1.26)		0.95 (0.78-1.16)	0.62 (0.22-1.75)	
96.8-105.5	0.91 (0.55-1.51)	0.84 (0.69-1.03)	0.26	0.83 (0.66-1.04)	0.91 (0.67-1.24)	0.149	0.83 (0.68-1.03)	1.02 (0.42-2.46)	0.887
105.6-216.6	0.84 (0.50-1.41)	1.00 (0.83-1.22)		0.93 (0.74-1.17)	1.09 (0.81-1.46)		1.03 (0.84-1.28)	0.93 (0.40-2.19)	
p-trend	0.335	0.934		0.384	0.374		0.972	0.678	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.89 (0.63-1.26)	1.04 (0.91-1.18)	0.349	1.02 (0.87-1.20)	1.05 (0.87-1.27)	0.59	1 (referent)	0.92 (0.75-1.13)	

Lung SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			613	613	569	405	208		282	331		116	497	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	613	30738	0.995 (0.954-1.037)	0.990 (0.948-1.033)	0.985 (0.941-1.030)	0.990 (0.938-1.045)	0.988 (0.920-1.062)	0.887	0.969 (0.909-1.033)	1.004 (0.947-1.065)	0.433	1.009 (0.901-1.130)	0.988 (0.942-1.035)	0.663
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	613	30738	0.981 (0.909-1.059)	0.965 (0.892-1.045)	0.967 (0.891-1.049)	0.931 (0.845-1.025)	1.037 (0.905-1.188)	0.269	0.990 (0.881-1.113)	0.942 (0.848-1.047)	0.618	1.027 (0.851-1.239)	0.955 (0.876-1.042)	0.504
Lung SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	613	30738	0.987 (0.926-1.053)	0.975 (0.912-1.043)	0.972 (0.907-1.042)	0.958 (0.882-1.041)	1.007 (0.900-1.126)	0.589	0.971 (0.880-1.071)	0.975 (0.891-1.066)	0.901	1.020 (0.865-1.204)	0.969 (0.901-1.042)	0.553
Systolic Blood Pressure (mmHg) ESH classification														
< 120	105	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	117	66446	1.02 (0.78-1.34)	1.00 (0.77-1.31)	0.92 (0.69-1.21)	1.07 (0.76-1.52)	0.90 (0.58-1.39)		0.89 (0.62-1.27)	1.15 (0.76-1.74)		1.13 (0.67-1.90)	0.96 (0.70-1.31)	
130-139	111	57482	0.91 (0.69-1.19)	0.87 (0.66-1.15)	0.85 (0.64-1.13)	0.78 (0.54-1.12)	1.12 (0.73-1.72)		0.84 (0.58-1.23)	0.93 (0.61-1.41)		0.84 (0.45-1.55)	0.86 (0.63-1.18)	
140-159	184	68235	0.94 (0.73-1.21)	0.91 (0.70-1.18)	0.89 (0.68-1.16)	0.89 (0.64-1.24)	0.97 (0.64-1.47)	0.83	1.00 (0.71-1.40)	0.87 (0.59-1.30)	0.476	1.31 (0.76-2.27)	0.83 (0.62-1.11)	0.256

classification														
< 80	234	1325 90	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
80-89	219	1063 72	0.91 (0.75-1.10)	0.92 (0.76-1.11)	0.96 (0.79-1.17)	0.91 (0.72-1.15)	0.95 (0.69-1.31)		0.94 (0.71-1.23)	0.90 (0.69-1.18)		0.89 (0.57-1.39)	0.92 (0.74-1.13)	
90-99	115	5119 6	0.87 (0.69-1.09)	0.84 (0.67-1.07)	0.88 (0.69-1.12)	0.82 (0.62-1.09)	0.87 (0.57-1.34)	0.311	1.04 (0.74-1.46)	0.73 (0.53-1.00)	0.996	1.33 (0.80-2.21)	0.76 (0.58-0.98)	0.285
>= 100	45	1716 0	0.97 (0.70-1.34)	0.89 (0.64-1.24)	0.90 (0.64-1.27)	0.75 (0.50-1.12)	1.38 (0.78-2.46)		0.59 (0.30-1.17)	0.98 (0.67-1.45)		0.82 (0.32-2.12)	0.90 (0.64-1.29)	
p-trend			0.379	0.191	0.319	0.085	0.815		0.408	0.276		0.675	0.111	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	100	7699 1	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	149	7772 7	1.08 (0.84-1.39)	1.08 (0.84-1.40)	1.00 (0.77-1.31)	1.08 (0.77-1.53)	1.12 (0.75-1.66)		1.03 (0.73-1.47)	1.10 (0.74-1.62)		1.01 (0.59-1.72)	1.11 (0.82-1.49)	
96.8-105.5	163	7632 7	0.93 (0.72-1.20)	0.93 (0.72-1.21)	0.90 (0.69-1.17)	0.95 (0.68-1.33)	0.93 (0.61-1.40)	0.516	1.11 (0.79-1.57)	0.78 (0.53-1.16)	0.288	1.17 (0.68-2.01)	0.88 (0.66-1.18)	0.309
105.6-216.6	201	7627 3	0.91 (0.71-1.17)	0.89 (0.68-1.15)	0.86 (0.66-1.12)	0.84 (0.60-1.17)	1.01 (0.67-1.52)		0.94 (0.66-1.35)	0.81 (0.55-1.18)		1.02 (0.57-1.84)	0.86 (0.65-1.15)	
p-trend			0.218	0.145	0.16	0.108	0.794		0.832	0.06		0.809	0.087	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	286	1741 79	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Lung SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Hypertensive	327	1331 39	0.92 (0.78-1.09)	0.95 (0.80-1.13)	0.95 (0.80-1.14)	0.92 (0.75-1.13)	1.02 (0.76-1.36)	0.781	1.00 (0.78-1.27)	0.91 (0.73-1.14)	0.666	1.44 (0.98-2.11)	0.86 (0.72-1.04)	0.015

Lung SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	17	593		339	274		397	74	
Cohort size	141931	160623		205214	102104		227336	37017	

Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.089 (0.831-1.426)	0.985 (0.942-1.029)	0.699	0.956 (0.901-1.016)	1.023 (0.960-1.089)	0.116	0.954 (0.900-1.011)	1.136 (1.011-1.277)	0.006
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.361 (0.852-2.175)	0.945 (0.872-1.024)	0.232	0.860 (0.772-0.959)	1.094 (0.975-1.227)	0.011	0.961 (0.866-1.066)	1.025 (0.804-1.306)	0.294
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.243 (0.827-1.868)	0.961 (0.898-1.029)	0.384	0.898 (0.819-0.985)	1.062 (0.964-1.171)	0.026	0.945 (0.864-1.033)	1.141 (0.934-1.394)	0.038
Systolic Blood Pressure (mmHg) ESH classification									
< 120	two cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	-	0.98 (0.74-1.28)		0.84 (0.59-1.18)	1.32 (0.85-2.05)		1.05 (0.78-1.41)	-	
130-139	-	0.85 (0.64-1.13)		0.84 (0.59-1.19)	0.93 (0.58-1.47)		0.81 (0.58-1.12)	-	
140-159	-	0.90 (0.69-1.16)	-	0.82 (0.59-1.14)	1.06 (0.69-1.60)	0.136	0.90 (0.66-1.23)	-	-
160-179	-	0.94 (0.68-1.30)		0.83 (0.54-1.27)	1.32 (0.81-2.14)		0.88 (0.57-1.34)	-	
>= 180	-	0.81 (0.49-1.34)		0.41 (0.16-1.02)	1.34 (0.70-2.56)		0.52 (0.21-1.30)	-	
p-trend	-	0.381		0.129	0.549		0.156	-	
Diastolic Blood Pressure (mmHg) ESH classification									
Lung SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
< 80	three cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	-	0.89 (0.71-1.12)		0.77 (0.57-1.03)	1.27 (0.90-1.79)		0.97 (0.75-1.26)	0.64 (0.26-1.60)	
85-89	-	0.86 (0.67-1.11)		0.83 (0.60-1.14)	1.02 (0.69-1.51)		0.96 (0.70-1.29)	0.71 (0.30-1.71)	
90-99	-	0.80 (0.63-1.02)	-	0.56 (0.40-0.79)	1.32 (0.94-1.86)	0.002	0.90 (0.67-1.22)	0.71 (0.33-1.53)	0.28
100-109	-	0.78 (0.53-1.13)		0.60 (0.35-1.05)	1.34 (0.82-2.18)		0.90 (0.52-1.54)	0.80 (0.33-1.95)	
>= 110	-	0.91 (0.46-1.78)		0.50 (0.16-1.59)	1.72 (0.74-4.00)		0.24 (0.03-1.76)	1.17 (0.35-3.90)	

p-trend	-	0.059		0.0006	0.106		0.272	0.948	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	two cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	-	0.91 (0.72-1.16)		0.84 (0.62-1.14)	1.11 (0.75-1.66)		0.93 (0.71-1.22)	-	
140-159	-	0.90 (0.69-1.17)	-	0.82 (0.59-1.14)	1.07 (0.70-1.62)	0.079	0.91 (0.67-1.24)	-	-
>= 160	-	0.91 (0.67-1.24)		0.74 (0.49-1.11)	1.34 (0.85-2.12)		0.82 (0.54-1.23)	-	
p-trend	-	0.583		0.162	0.28		0.353	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	three cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	-	0.88 (0.73-1.07)		0.79 (0.62-1.01)	1.16 (0.86-1.58)		0.96 (0.77-1.21)	0.68 (0.31-1.47)	
90-99	-	0.80 (0.63-1.02)	-	0.56 (0.40-0.78)	1.33 (0.94-1.87)	0.0007	0.90 (0.67-1.22)	0.71 (0.33-1.53)	0.344
>= 100	-	0.80 (0.57-1.13)		0.58 (0.35-0.97)	1.41 (0.90-2.21)		0.77 (0.46-1.30)	0.87 (0.38-2.01)	
p-trend	-	0.057		0.0004	0.064		0.304	0.988	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	two cases in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	-	1.06 (0.81-1.37)		1.02 (0.74-1.41)	1.18 (0.76-1.82)		1.08 (0.80-1.46)	-	
96.8-105.5	-	0.91 (0.70-1.18)	-	0.85 (0.61-1.18)	1.06 (0.69-1.62)	0.167	1.02 (0.75-1.37)	-	-
105.6-216.6	-	0.84 (0.65-1.09)		0.73 (0.52-1.02)	1.12 (0.73-1.70)		0.83 (0.60-1.14)	-	
p-trend	-	0.07		0.025	0.837		0.177	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Lung SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.59 (0.54-4.68)	0.91 (0.77-1.08)	0.412	0.85 (0.68-1.06)	1.08 (0.83-1.39)	0.148	1 (referent)	1.06 (0.79-1.40)	

Lung SmallCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			379	379	349	197	182		155	224		96	283	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	379	30738	1.050 (0.998-1.105)	1.043 (0.990-1.099)	1.027 (0.972-1.085)	1.043 (0.966-1.126)	1.038 (0.966-1.116)	0.376	1.046 (0.963-1.135)	1.041 (0.973-1.114)	0.819	1.082 (0.963-1.215)	1.036 (0.977-1.099)	0.593
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	379	30738	1.002 (0.910-1.102)	0.992 (0.898-1.095)	0.974 (0.878-1.080)	0.973 (0.846-1.118)	1.012 (0.877-1.167)	0.501	0.970 (0.829-1.136)	1.014 (0.894-1.151)	0.856	0.964 (0.784-1.185)	1.005 (0.898-1.125)	0.612
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	379	30738	1.041 (0.961-1.127)	1.031 (0.949-1.120)	1.009 (0.926-1.100)	1.019 (0.906-1.147)	1.038 (0.924-1.166)	0.38	1.023 (0.898-1.165)	1.040 (0.936-1.156)	0.976	1.042 (0.873-1.243)	1.032 (0.940-1.133)	0.951
Systolic Blood Pressure (mmHg) ESH classification														
< 120	70	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	61	66446	0.89 (0.63-1.26)	0.91 (0.64-1.29)	0.83 (0.58-1.19)	0.80 (0.47-1.36)	0.98 (0.61-1.55)		1.03 (0.64-1.68)	0.76 (0.46-1.26)		0.68 (0.37-1.24)	1.08 (0.70-1.67)	
130-139	74	57482	1.07 (0.77-1.49)	1.08 (0.77-1.51)	1.06 (0.75-1.50)	1.02 (0.62-1.68)	1.08 (0.68-1.72)		1.16 (0.71-1.88)	0.95 (0.59-1.52)		0.74 (0.40-1.39)	1.30 (0.85-1.97)	
140-159	119	68235	1.18 (0.87-1.61)	1.18 (0.86-1.62)	1.12 (0.81-1.54)	1.16 (0.72-1.85)	1.12 (0.73-1.73)	0.754	1.00 (0.61-1.63)	1.22 (0.80-1.87)	0.929	0.99 (0.55-1.79)	1.34 (0.91-1.98)	0.799
160-179	37	22656	1.05 (0.69-1.58)	1.03 (0.68-1.57)	0.82 (0.52-1.30)	0.96 (0.52-1.77)	1.05 (0.59-1.87)		1.33 (0.71-2.49)	0.86 (0.49-1.51)		0.83 (0.31-2.21)	1.18 (0.72-1.92)	
Lung SmallCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
>= 180	18	6358	1.67 (0.98-2.84)	1.56 (0.91-2.68)	1.50 (0.86-2.62)	1.85 (0.89-3.86)	1.21 (0.53-2.79)		1.50 (0.57-3.95)	1.52 (0.78-2.96)		3.42 (1.14-10.26)	1.53 (0.81-2.89)	
p-trend			0.073	0.122	0.336	0.145	0.555		0.439	0.171		0.519	0.137	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	154	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	68	64872	0.82 (0.61-1.09)	0.83 (0.62-1.12)	0.77 (0.56-1.04)	0.72 (0.48-1.09)	0.94 (0.63-1.42)		0.68 (0.43-1.07)	0.97 (0.66-1.43)		1.05 (0.61-1.81)	0.77 (0.55-1.08)	
85-89	62	41500	1.03 (0.77-1.38)	1.05 (0.78-1.42)	1.08 (0.79-1.46)	0.99 (0.66-1.49)	1.07 (0.68-1.68)		0.67 (0.39-1.17)	1.34 (0.92-1.95)		1.15 (0.63-2.12)	1.03 (0.73-1.46)	
90-99	67	51196	0.94 (0.70-1.25)	0.90 (0.67-1.22)	0.84 (0.61-1.15)	0.68 (0.45-1.04)	1.24 (0.82-1.88)	0.216	0.98 (0.62-1.56)	0.92 (0.62-1.36)	0.417	0.79 (0.40-1.55)	0.93 (0.67-1.31)	0.879
100-109	24	13896	1.21 (0.79-1.87)	1.17 (0.75-1.82)	1.08 (0.67-1.72)	1.21 (0.71-2.07)	0.90 (0.39-2.08)		0.65 (0.24-1.80)	1.54 (0.93-2.56)		1.74 (0.75-4.06)	1.02 (0.60-1.71)	
>= 110	4	3264	0.82 (0.30-2.21)	0.76 (0.28-2.08)	0.80 (0.29-2.17)	0.52 (0.13-2.15)	1.24 (0.30-5.12)		0.77 (0.11-5.58)	0.87 (0.27-2.77)		no cases	0.93 (0.34-2.55)	
p-trend			0.798	1	0.752	0.501	0.476		0.398	0.433		0.955	0.978	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	70	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	135	123928	0.98 (0.73-1.31)	0.99 (0.73-1.33)	0.94 (0.69-1.27)	0.91 (0.58-1.43)	1.02 (0.69-1.52)		1.09 (0.72-1.65)	0.86 (0.56-1.31)		0.70 (0.43-1.17)	1.19 (0.81-1.74)	
140-159	119	68235	1.18 (0.87-1.60)	1.17 (0.85-1.60)	1.10 (0.80-1.53)	1.15 (0.72-1.83)	1.12 (0.73-1.73)	0.615	1.00 (0.61-1.63)	1.21 (0.79-1.86)	0.926	0.98 (0.54-1.77)	1.33 (0.90-1.97)	0.769
>= 160	55	29014	1.18 (0.82-1.71)	1.15 (0.79-1.68)	0.98 (0.65-1.46)	1.15 (0.66-1.99)	1.08 (0.64-1.84)		1.36 (0.76-2.43)	1.02 (0.62-1.68)		1.23 (0.56-2.72)	1.26 (0.80-1.98)	
p-trend			0.162	0.245	0.7	0.305	0.64		0.481	0.337		0.681	0.242	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	154	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	130	106372	0.91 (0.72-1.15)	0.92 (0.73-1.17)	0.90 (0.70-1.15)	0.84 (0.60-1.18)	0.99 (0.70-1.40)		0.68 (0.46-1.00)	1.13 (0.82-1.56)		1.09 (0.69-1.74)	0.88 (0.66-1.16)	
Lung SmallCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ²	BMI > 25 mg/m ²	BMI p-interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p-interaction

					years of follow-up HR (adjusted)				HR (adjusted)	HR (adjusted)		HR (adjusted)		
90-99	67	51196	0.94 (0.70-1.25)	0.90 (0.67-1.22)	0.84 (0.61-1.15)	0.68 (0.44-1.04)	1.24 (0.81-1.88)	0.221	0.98 (0.62-1.56)	0.92 (0.62-1.36)	0.441	0.79 (0.40-1.55)	0.93 (0.67-1.30)	0.94
>= 100	28	17160	1.13 (0.75-1.70)	1.08 (0.71-1.64)	1.01 (0.65-1.57)	1.07 (0.64-1.79)	0.96 (0.46-2.01)		0.67 (0.27-1.67)	1.39 (0.86-2.26)		1.45 (0.62-3.37)	1.00 (0.62-1.61)	
p-trend			0.958	0.839	0.505	0.419	0.578		0.337	0.539		0.871	0.783	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	68	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	76	77727	0.91 (0.65-1.26)	0.93 (0.67-1.30)	0.84 (0.60-1.19)	1.01 (0.60-1.69)	0.84 (0.54-1.31)		0.84 (0.54-1.33)	1.07 (0.65-1.77)		0.83 (0.46-1.49)	1.00 (0.67-1.49)	
96.8-105.5	110	76327	1.07 (0.78-1.45)	1.10 (0.80-1.51)	1.04 (0.75-1.43)	1.25 (0.77-2.04)	0.94 (0.61-1.45)	0.394	0.93 (0.59-1.45)	1.30 (0.82-2.07)	0.553	1.11 (0.62-1.97)	1.12 (0.77-1.64)	0.95
105.6-216.6	125	76273	1.07 (0.79-1.45)	1.05 (0.76-1.45)	0.95 (0.69-1.32)	1.03 (0.63-1.70)	1.09 (0.72-1.66)		0.94 (0.59-1.50)	1.23 (0.77-1.95)		1.04 (0.56-1.95)	1.08 (0.74-1.58)	
p-trend			0.414	0.524	0.876	0.825	0.565		0.889	0.308		0.678	0.573	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	165	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	214	133139	1.22 (0.99-1.50)	1.25 (1.01-1.55)	1.15 (0.92-1.44)	1.30 (0.96-1.76)	1.20 (0.88-1.63)	0.834	1.09 (0.78-1.51)	1.41 (1.06-1.88)	0.371	1.15 (0.75-1.77)	1.30 (1.01-1.67)	0.568

Lung SmallCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases				203	176		249	56	
Cohort size				205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)				1.040 (0.967-1.118)	1.045 (0.968-1.127)	0.856	1.033 (0.965-1.106)	1.000 (0.869-1.150)	0.177

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)				0.985 (0.860-1.129)	0.999 (0.865-1.154)	0.922	1.015 (0.893-1.153)	0.852 (0.650-1.116)	0.16
Lung SmallCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)				1.025 (0.915-1.148)	1.036 (0.919-1.169)	0.884	1.034 (0.929-1.151)	0.924 (0.735-1.163)	0.13
Systolic Blood Pressure (mmHg) ESH classification									
< 120				1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129				0.87 (0.56-1.36)	0.94 (0.53-1.66)		0.91 (0.61-1.35)	-	
130-139				1.03 (0.66-1.60)	1.10 (0.64-1.88)		1.11 (0.75-1.64)	-	
140-159				1.00 (0.65-1.52)	1.35 (0.82-2.22)	0.877	1.04 (0.71-1.53)	-	-
160-179				1.05 (0.60-1.85)	1.06 (0.56-2.02)		1.09 (0.64-1.84)	-	
>= 180				1.62 (0.77-3.42)	1.53 (0.69-3.41)		1.27 (0.57-2.86)	-	
p-trend				0.41	0.182		0.486	-	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84				0.81 (0.54-1.20)	0.88 (0.57-1.35)		0.79 (0.56-1.13)	1.29 (0.53-3.16)	
85-89				0.93 (0.60-1.43)	1.19 (0.77-1.83)		0.99 (0.68-1.45)	1.80 (0.76-4.26)	
90-99				0.98 (0.65-1.46)	0.86 (0.55-1.34)	0.907	0.98 (0.67-1.43)	0.69 (0.27-1.73)	0.252
100-109				1.07 (0.55-2.09)	1.29 (0.71-2.36)		1.25 (0.68-2.30)	1.18 (0.42-3.37)	
>= 110				0.42 (0.06-3.02)	1.03 (0.32-3.33)		0.85 (0.21-3.47)	0.68 (0.08-5.59)	
p-trend				0.823	0.785		0.759	0.472	
Systolic Blood Pressure (mmHg) ASH classification									
< 120				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139				0.95 (0.65-1.38)	1.02 (0.63-1.66)		1.00 (0.71-1.41)	0.67 (0.21-2.14)	

140-159				0.99 (0.65-1.51)	1.34 (0.82-2.20)	0.897	1.03 (0.71-1.52)	0.91 (0.30-2.77)	0.217
>= 160				1.18 (0.71-1.95)	1.18 (0.65-2.11)		1.12 (0.69-1.82)	0.70 (0.21-2.27)	
p-trend				0.564	0.276		0.656	0.856	
Diastolic Blood Pressure (mmHg)									
ASH classification									
Lung SmallCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
< 80				1 (referent)	1 (referent)		1 (referent)	single case in referent	
80-89				0.86 (0.62-1.19)	1.01 (0.71-1.45)		0.87 (0.65-1.17)	-	
90-99				0.98 (0.65-1.46)	0.85 (0.55-1.33)	0.977	0.98 (0.67-1.43)	-	-
>= 100				0.94 (0.49-1.78)	1.23 (0.70-2.15)		1.17 (0.66-2.07)	-	
p-trend				0.761	0.934		0.909	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3				1 (referent)	1 (referent)		1 (referent)	three cases in referent	
88.5-96.6				0.99 (0.65-1.51)	0.82 (0.48-1.42)		0.97 (0.66-1.41)	-	
96.8-105.5				1.06 (0.70-1.59)	1.11 (0.67-1.83)	0.731	1.02 (0.70-1.49)	-	-
105.6-216.6				1.00 (0.65-1.52)	1.10 (0.67-1.81)		1.09 (0.74-1.61)	-	
p-trend				0.956	0.371		0.582	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	NA (NA-NA)	NA (NA-NA)	NA	1.19 (0.89-1.59)	1.35 (0.98-1.85)	0.689	1 (referent)	1.17 (0.83-1.63)	

Lung Other	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1107	1107	1023	595	512		547	560		253	854	
Cohort size			307318	307318	301857	112591	194727		146326	160992		153303	154015	

< 80	391	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	225	6487 2	0.92 (0.78-1.08)	0.97 (0.82-1.15)	0.98 (0.83-1.17)	1.00 (0.79-1.26)	0.95 (0.74-1.21)		0.92 (0.73-1.16)	1.02 (0.80-1.30)		1.14 (0.81-1.60)	0.93 (0.77-1.12)	
85-89	173	4150 0	1.04 (0.87-1.25)	1.13 (0.94-1.35)	1.15 (0.96-1.40)	1.15 (0.89-1.47)	1.12 (0.85-1.47)		1.17 (0.90-1.51)	1.08 (0.83-1.40)		1.54 (1.06-2.23)	1.03 (0.83-1.27)	
90-99	233	5119 6	1.02 (0.87-1.21)	1.12 (0.94-1.32)	1.11 (0.93-1.33)	1.09 (0.87-1.37)	1.17 (0.91-1.51)	0.446	1.14 (0.89-1.45)	1.09 (0.86-1.38)	0.87	1.37 (0.94-1.99)	1.06 (0.87-1.28)	0.29
100-109	72	1389 6	1.12 (0.87-1.44)	1.19 (0.92-1.54)	1.20 (0.91-1.57)	1.02 (0.72-1.45)	1.58 (1.08-2.33)		0.93 (0.59-1.48)	1.34 (0.97-1.85)		1.29 (0.68-2.47)	1.15 (0.87-1.53)	
>= 110	13	3264	0.90 (0.52-1.57)	0.95 (0.54-1.66)	0.95 (0.53-1.70)	1.12 (0.60-2.08)	0.51 (0.13-2.05)		0.98 (0.36-2.64)	0.94 (0.48-1.85)		1.06 (0.26-4.35)	0.92 (0.50-1.68)	
p-trend			0.438	0.094	0.105	0.434	0.065		0.36	0.194		0.061	0.333	
Lung Other	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	172	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	422	1239 28	1.14 (0.95-1.36)	1.19 (0.99-1.43)	1.17 (0.96-1.41)	1.25 (0.94-1.67)	1.16 (0.91-1.48)		1.14 (0.91-1.45)	1.20 (0.90-1.62)		1.08 (0.80-1.46)	1.28 (1.01-1.61)	
140-159	326	6823 5	1.14 (0.93-1.38)	1.23 (1.01-1.50)	1.26 (1.03-1.55)	1.31 (0.97-1.77)	1.19 (0.90-1.56)	0.913	1.33 (1.03-1.72)	1.14 (0.84-1.56)	0.738	1.01 (0.68-1.50)	1.35 (1.06-1.72)	0.378
>= 160	187	2901 4	1.31 (1.05-1.64)	1.45 (1.15-1.81)	1.39 (1.10-1.76)	1.43 (1.02-1.99)	1.56 (1.14-2.13)		1.25 (0.90-1.73)	1.55 (1.11-2.15)		1.25 (0.72-2.18)	1.57 (1.21-2.05)	
p-trend			0.03	0.002	0.005	0.051	0.012		0.055	0.021		0.606	0.001	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	391	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	398	1063 72	0.97 (0.84-1.11)	1.04 (0.90-1.20)	1.05 (0.91-1.22)	1.06 (0.86-1.30)	1.01 (0.82-1.24)		1.01 (0.83-1.23)	1.04 (0.84-1.29)		1.28 (0.96-1.72)	0.97 (0.82-1.14)	
90-99	233	5119 6	1.02 (0.87-1.21)	1.11 (0.94-1.32)	1.11 (0.93-1.33)	1.09 (0.86-1.37)	1.17 (0.91-1.51)	0.386	1.14 (0.89-1.45)	1.09 (0.86-1.38)	0.617	1.36 (0.94-1.98)	1.05 (0.87-1.28)	0.38
>= 100	85	1716 0	1.08 (0.85-1.37)	1.14 (0.90-1.46)	1.15 (0.89-1.48)	1.04 (0.75-1.43)	1.40 (0.96-2.04)		0.94 (0.61-1.44)	1.26 (0.93-1.71)		1.24 (0.68-2.27)	1.11 (0.85-1.45)	
p-trend			0.572	0.15	0.17	0.6	0.075		0.62	0.166		0.113	0.394	

Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	167	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	243	7772 7	1.05 (0.86-1.29)	1.12 (0.91-1.37)	1.07 (0.87-1.32)	1.05 (0.77-1.43)	1.20 (0.92-1.57)		1.04 (0.81-1.34)	1.19 (0.85-1.66)		1.04 (0.72-1.49)	1.15 (0.90-1.47)	
96.8-105.5	303	7632 7	1.09 (0.90-1.33)	1.20 (0.99-1.46)	1.21 (0.99-1.48)	1.29 (0.96-1.72)	1.12 (0.85-1.47)	0.831	1.18 (0.92-1.52)	1.22 (0.89-1.68)	0.923	1.43 (1.00-2.05)	1.15 (0.91-1.46)	0.638
105.6-216.6	394	7627 3	1.16 (0.96-1.41)	1.31 (1.08-1.59)	1.28 (1.05-1.57)	1.25 (0.93-1.67)	1.43 (1.09-1.87)		1.26 (0.97-1.63)	1.34 (0.98-1.83)		1.33 (0.89-1.97)	1.30 (1.04-1.64)	
p-trend			0.091	0.004	0.007	0.066	0.018		0.046	0.063		0.058	0.024	
Hypertension (SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or self-reported)														
Lung Other	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Normotensive	514	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	593	1331 39	0.95 (0.84-1.08)	1.04 (0.91-1.17)	1.05 (0.92-1.20)	1.04 (0.87-1.23)	1.05 (0.87-1.26)	0.756	1.06 (0.89-1.27)	1.01 (0.84-1.20)	0.824	1.03 (0.78-1.35)	1.04 (0.90-1.20)	0.985

Lung Other	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	110	986		662	445		749	141	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.129 (1.024-1.245)	1.049 (1.014-1.084)	0.196	1.063 (1.020-1.107)	1.050 (1.000-1.103)	0.967	1.088 (1.045-1.132)	1.071 (0.984-1.167)	0.615
Mean Diastolic Blood Pressure	1.067 (0.885-1.286)	1.027 (0.965-1.092)	0.556	1.054 (0.977-1.136)	1.024 (0.934-1.123)	0.516	1.083 (1.005-1.167)	0.980 (0.829-1.159)	0.239

continuous (per 10mmHg increase)									
Mean Blood Pressure (1/3SBP+2/3DBP)	1.140 (0.976-1.332)	1.052 (0.999-1.108)	0.303	1.076 (1.010-1.147)	1.053 (0.974-1.137)	0.711	1.113 (1.045-1.185)	1.054 (0.915-1.214)	0.392
continuous (per 10mmHg increase)									
Systolic Blood Pressure (mmHg)									
ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.14 (0.55-2.37)	1.06 (0.85-1.32)		1.14 (0.88-1.48)	0.99 (0.70-1.41)		1.09 (0.86-1.39)	0.48 (0.19-1.24)	
130-139	1.62 (0.81-3.21)	1.28 (1.03-1.59)		1.27 (0.98-1.65)	1.32 (0.95-1.85)		1.46 (1.16-1.85)	0.46 (0.19-1.09)	
140-159	1.43 (0.72-2.81)	1.21 (0.98-1.49)	0.263	1.28 (1.00-1.65)	1.14 (0.82-1.58)	0.896	1.27 (1.01-1.61)	0.67 (0.32-1.41)	0.944
160-179	2.33 (1.10-4.92)	1.34 (1.04-1.73)		1.54 (1.14-2.10)	1.30 (0.88-1.91)		1.65 (1.23-2.22)	0.80 (0.37-1.72)	
>= 180	2.01 (0.68-5.93)	1.47 (1.02-2.12)		1.48 (0.93-2.36)	1.53 (0.92-2.56)		1.84 (1.15-2.94)	1.11 (0.48-2.58)	
p-trend	0.032	0.006		0.004	0.076		0.0002	0.097	
Lung Other	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.85 (0.50-1.44)	0.98 (0.82-1.17)		1.04 (0.84-1.29)	0.86 (0.65-1.12)		0.91 (0.75-1.11)	0.71 (0.39-1.28)	
85-89	0.58 (0.29-1.18)	1.17 (0.97-1.42)		1.14 (0.90-1.46)	1.09 (0.82-1.45)		1.26 (1.01-1.56)	0.74 (0.40-1.37)	
90-99	1.01 (0.59-1.72)	1.09 (0.91-1.31)	0.398	1.22 (0.98-1.52)	0.96 (0.73-1.25)	0.28	1.12 (0.90-1.39)	0.97 (0.58-1.60)	0.419
100-109	2.05 (1.08-3.89)	1.03 (0.77-1.37)		1.22 (0.86-1.74)	1.14 (0.77-1.68)		1.50 (1.07-2.10)	0.82 (0.43-1.54)	
>= 110	0.72 (0.10-5.29)	0.95 (0.53-1.70)		0.98 (0.46-2.08)	0.81 (0.34-1.90)		0.54 (0.17-1.71)	0.99 (0.37-2.65)	
p-trend	0.306	0.316		0.073	0.729		0.037	0.845	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.38 (0.73-2.59)	1.17 (0.96-1.41)		1.20 (0.95-1.51)	1.16 (0.86-1.57)		1.26 (1.03-1.55)	0.47 (0.21-1.04)	
140-159	1.41 (0.72-2.78)	1.20 (0.97-1.48)	0.251	1.28 (0.99-1.65)	1.13 (0.82-1.56)	0.663	1.26 (0.99-1.59)	0.67 (0.32-1.41)	0.853

>= 160	2.22 (1.08-4.59)	1.36 (1.07-1.73)		1.52 (1.14-2.04)	1.34 (0.93-1.92)		1.66 (1.26-2.20)	0.88 (0.42-1.85)	
p-trend	0.039	0.018		0.005	0.189		0.002	0.113	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.74 (0.46-1.20)	1.06 (0.91-1.23)		1.08 (0.90-1.30)	0.95 (0.76-1.20)		1.04 (0.88-1.23)	0.72 (0.43-1.21)	
90-99	1.01 (0.59-1.72)	1.09 (0.91-1.31)	0.191	1.22 (0.98-1.52)	0.96 (0.73-1.25)	0.219	1.12 (0.90-1.38)	0.97 (0.58-1.60)	0.5
>= 100	1.82 (0.98-3.41)	1.01 (0.78-1.32)		1.17 (0.85-1.63)	1.07 (0.75-1.55)		1.33 (0.96-1.85)	0.85 (0.46-1.54)	
p-trend	0.155	0.536		0.089	0.926		0.1	0.927	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.27 (0.65-2.48)	1.08 (0.87-1.34)		1.17 (0.91-1.50)	1.01 (0.72-1.43)		1.14 (0.91-1.43)	0.64 (0.27-1.52)	
96.8-105.5	1.19 (0.61-2.31)	1.18 (0.96-1.45)	0.579	1.17 (0.92-1.50)	1.21 (0.87-1.68)	0.948	1.31 (1.05-1.65)	0.57 (0.26-1.24)	0.372
105.6-216.6	1.51 (0.79-2.89)	1.25 (1.01-1.53)		1.33 (1.04-1.70)	1.25 (0.91-1.74)		1.44 (1.14-1.82)	0.77 (0.37-1.59)	
p-trend	0.24	0.023		0.033	0.078		0.001	0.787	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Lung Other	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.10 (0.73-1.65)	1.00 (0.87-1.14)	0.589	1.06 (0.90-1.24)	1.00 (0.82-1.22)	0.754	1 (referent)	0.93 (0.76-1.15)	

Kidney	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			758	758	666	431	327		270	488		223	535	

< 80	214	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	157	64872	1.25 (1.02-1.55)	1.16 (0.94-1.43)	1.22 (0.97-1.52)	1.21 (0.91-1.62)	1.07 (0.78-1.47)		1.08 (0.78-1.50)	1.25 (0.94-1.65)		1.33 (0.90-1.95)	1.09 (0.85-1.40)	
85-89	109	41500	1.24 (0.98-1.57)	1.11 (0.88-1.41)	1.11 (0.86-1.43)	1.10 (0.80-1.52)	1.12 (0.79-1.59)		1.14 (0.78-1.66)	1.15 (0.85-1.56)		1.49 (0.97-2.28)	0.98 (0.74-1.30)	
90-99	185	51196	1.66 (1.36-2.03)	1.42 (1.16-1.75)	1.45 (1.16-1.81)	1.27 (0.95-1.69)	1.67 (1.23-2.26)	0.744	1.30 (0.91-1.86)	1.55 (1.20-2.02)	0.391	1.89 (1.28-2.79)	1.27 (0.99-1.62)	0.04
100-109	72	13896	2.32 (1.77-3.05)	1.90 (1.44-2.51)	1.84 (1.36-2.49)	1.83 (1.28-2.62)	1.96 (1.24-3.10)		2.13 (1.28-3.55)	2.00 (1.43-2.80)		2.67 (1.57-4.55)	1.66 (1.19-2.30)	
>= 110	21	3264	2.97 (1.89-4.66)	2.28 (1.45-3.61)	2.12 (1.28-3.51)	2.34 (1.36-4.02)	1.97 (0.80-4.88)		1.20 (0.29-4.90)	2.69 (1.64-4.41)		3.29 (1.40-7.76)	1.98 (1.15-3.39)	
p-trend			4E-13	0.000003	0.000006	0.0007	0.0001		0.015	0.000006		0.00001	0.001	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	96	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	288	123928	1.56 (1.24-1.98)	1.38 (1.08-1.74)	1.35 (1.05-1.74)	1.49 (1.04-2.12)	1.23 (0.88-1.71)		1.55 (1.10-2.17)	1.28 (0.92-1.79)		1.42 (0.98-2.05)	1.32 (0.97-1.81)	
140-159	238	68235	1.97 (1.54-2.52)	1.64 (1.27-2.12)	1.53 (1.17-2.00)	1.51 (1.04-2.19)	1.86 (1.31-2.64)	0.227	1.90 (1.30-2.78)	1.54 (1.10-2.18)	0.715	1.99 (1.30-3.04)	1.48 (1.07-2.04)	0.067
>= 160	136	29014	2.56 (1.94-3.38)	2.10 (1.58-2.79)	1.98 (1.47-2.68)	1.96 (1.30-2.95)	2.27 (1.52-3.40)		1.84 (1.12-3.02)	2.21 (1.53-3.20)		2.75 (1.60-4.73)	1.89 (1.34-2.67)	
p-trend			2E-12	0.0000009	0.000008	0.004	0.00003		0.002	0.000002		0.00004	0.0002	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	214	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Kidney	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-89	266	106372	1.25 (1.04-1.50)	1.14 (0.95-1.37)	1.17 (0.96-1.43)	1.17 (0.90-1.51)	1.09 (0.83-1.43)		1.10 (0.83-1.46)	1.20 (0.94-1.54)		1.39 (0.99-1.95)	1.04 (0.84-1.30)	
90-99	185	51196	1.66 (1.36-2.03)	1.42 (1.16-1.75)	1.45 (1.16-1.81)	1.27 (0.95-1.69)	1.67 (1.23-2.26)	0.866	1.30 (0.91-1.86)	1.55 (1.20-2.02)	0.375	1.89 (1.28-2.79)	1.27 (0.99-1.62)	0.054
>= 100	93	17160	2.45 (1.91-3.13)	1.98 (1.53-2.55)	1.90 (1.44-2.51)	1.94 (1.39-2.70)	1.96 (1.28-3.00)		1.98 (1.21-3.23)	2.14 (1.58-2.92)		2.79 (1.71-4.54)	1.72 (1.27-2.32)	
p-trend			1E-13	0.0000009	0.000001	0.0003	0.00009		0.011	0.000002		0.00001	0.0004	

Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	82	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	150	7772 7	1.43 (1.09-1.87)	1.30 (0.99-1.70)	1.33 (1.00-1.79)	1.36 (0.90-2.07)	1.25 (0.86-1.81)		1.38 (0.94-2.01)	1.26 (0.84-1.87)		1.19 (0.77-1.83)	1.36 (0.96-1.95)	
96.8-105.5	218	7632 7	1.82 (1.40-2.36)	1.57 (1.21-2.05)	1.62 (1.22-2.14)	1.70 (1.14-2.54)	1.43 (0.99-2.05)	0.506	1.85 (1.28-2.67)	1.45 (1.00-2.12)	0.777	1.51 (0.98-2.33)	1.60 (1.14-2.24)	0.121
105.6-216.6	308	7627 3	2.33 (1.81-3.00)	1.90 (1.46-2.47)	1.90 (1.43-2.52)	1.80 (1.20-2.68)	2.09 (1.47-2.97)		1.87 (1.26-2.76)	1.95 (1.35-2.81)		2.26 (1.46-3.49)	1.80 (1.29-2.51)	
p-trend			4E-13	0.0000 001	0.0000 01	0.002	0.0000 1		0.0005	0.0000 07		0.0000 6	0.0002	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	293	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	465	1331 39	1.56 (1.34-1.81)	1.41 (1.21-1.65)	1.38 (1.17-1.63)	1.14 (0.93-1.39)	1.87 (1.47-2.38)	0.007	1.49 (1.16-1.92)	1.42 (1.16-1.72)	0.753	1.74 (1.31-2.30)	1.28 (1.07-1.55)	0.055

Kidney	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	459		488	270		458	159	
Cohort size	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.126 (1.073-1.182)	0.528	1.119 (1.067-1.173)	1.127 (1.057-1.201)	0.878	1.107 (1.049-1.167)	1.060 (0.976-1.151)	0.296
Kidney	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.209 (1.107-1.321)	0.959	1.230 (1.131-1.339)	1.210 (1.078-1.359)	0.92	1.204 (1.096-1.322)	1.082 (0.925-1.266)	0.098
Mean Blood Pressure (1/3SBP+2/3DBP)	1.204 (1.117-1.297)	0.776	1.207 (1.123-1.298)	1.204 (1.091-1.328)	0.888	1.187 (1.095-1.288)	1.094 (0.957-1.250)	0.16

continuous (per 10mmHg increase)								
Systolic Blood Pressure (mmHg)								
ESH classification								
< 120	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	1.49 (1.04-2.12)		1.14 (0.83-1.58)	1.61 (0.99-2.63)		1.18 (0.87-1.59)	-	
130-139	1.68 (1.18-2.39)		1.43 (1.04-1.96)	1.64 (1.01-2.67)		1.25 (0.92-1.70)	-	
140-159	1.82 (1.29-2.56)	0.468	1.65 (1.22-2.23)	1.72 (1.07-2.77)	0.834	1.31 (0.97-1.78)	-	-
160-179	2.05 (1.37-3.07)		2.05 (1.43-2.94)	1.96 (1.13-3.41)		1.85 (1.25-2.72)	-	
>= 180	3.34 (2.04-5.48)		2.19 (1.29-3.72)	3.40 (1.77-6.54)		2.35 (1.30-4.25)	-	
p-trend	0.000004		0.000003	0.002		0.001	-	
Diastolic Blood Pressure (mmHg)								
ESH classification								
< 80	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.10 (0.84-1.44)		1.14 (0.88-1.48)	1.20 (0.83-1.72)		1.32 (1.03-1.69)	0.73 (0.41-1.31)	
85-89	1.03 (0.76-1.40)		1.14 (0.85-1.52)	1.06 (0.70-1.59)		1.21 (0.90-1.62)	0.69 (0.39-1.23)	
90-99	1.22 (0.93-1.60)	0.492	1.41 (1.09-1.82)	1.44 (1.01-2.04)	0.885	1.51 (1.15-1.98)	0.75 (0.46-1.23) 0.175	
100-109	1.92 (1.36-2.71)		2.16 (1.54-3.04)	1.55 (0.96-2.51)		1.57 (1.00-2.45)	1.06 (0.60-1.87)	
>= 110	1.95 (1.07-3.55)		2.23 (1.22-4.05)	2.47 (1.21-5.04)		2.16 (1.00-4.64)	1.49 (0.70-3.17)	
p-trend	0.001		0.00001	0.007		0.001	0.423	
Systolic Blood Pressure (mmHg)								
ASH classification								
< 120	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	1.58 (1.14-2.17)		1.28 (0.96-1.69)	1.62 (1.03-2.55)		1.21 (0.93-1.58)	-	
140-159	1.81 (1.28-2.54)	0.632	1.63 (1.21-2.21)	1.71 (1.07-2.75)	0.791	1.31 (0.96-1.77)	-	-
>= 160	2.31 (1.58-3.37)		2.06 (1.46-2.90)	2.27 (1.35-3.81)		1.93 (1.35-2.77)	-	
p-trend	0.00002		0.000007	0.004		0.001	-	
Diastolic Blood Pressure (mmHg)								
ASH classification								
< 80	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.07 (0.84-1.36)		1.14 (0.91-1.43)	1.14 (0.82-1.57)		1.28 (1.02-1.60)	0.71 (0.43-1.17)	
90-99	1.22 (0.93-1.60)	0.624	1.41 (1.09-1.82)	1.44 (1.01-2.04)	0.865	1.51 (1.15-1.98)	0.75 (0.46-1.24) 0.147	
Kidney	Ever smokers HR (adjusted)	Smoking p- interactio n	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p- interactio n	No antihypertensiv e treatment HR (adjusted)	Antihypertensi ve treatment HR (adjusted)	Treatment p- interactio n
>= 100	1.93 (1.40-2.66)		2.17 (1.58-2.98)	1.72 (1.11-2.66)		1.67 (1.12-2.50)	1.15 (0.68-1.95)	
p-trend	0.0003		0.000004	0.005		0.0007	0.383	

Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)		
88.5-96.6	1.51 (1.04-2.18)		1.19 (0.86-1.63)	1.69 (0.97-2.94)		1.42 (1.03-1.94)	0.65 (0.24-1.76)		
96.8-105.5	1.96 (1.37-2.80)	0.611	1.40 (1.03-1.91)	2.11 (1.24-3.60)	0.993	1.54 (1.12-2.10)	1.09 (0.46-2.60)	0.182	
105.6-216.6	2.09 (1.46-2.99)		1.86 (1.37-2.52)	2.18 (1.28-3.72)		1.81 (1.31-2.51)	0.96 (0.41-2.25)		
p-trend	0.00002		0.000007	0.005		0.0004	0.639		
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)		1 (referent)	1 (referent)		-	-		
Hypertensive	1.34 (1.09-1.63)	0.636	1.44 (1.19-1.75)	1.37 (1.05-1.78)	0.843	1 (referent)	1.43 (1.15-1.78)		

Renal pelvis and ureter	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			112	112	107	56	56		49	63		20	92	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	112	30738	1.043 (0.947-1.148)	1.049 (0.951-1.157)	1.049 (0.949-1.161)	0.995 (0.857-1.155)	1.100 (0.965-1.253)	0.281	0.889 (0.754-1.048)	1.166 (1.032-1.318)	0.011	0.968 (0.735-1.275)	1.060 (0.954-1.178)	0.483
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	112	30738	0.972 (0.812-1.165)	0.972 (0.807-1.173)	0.993 (0.820-1.202)	0.905 (0.691-1.184)	1.059 (0.818-1.371)	0.426	0.811 (0.603-1.089)	1.094 (0.860-1.391)	0.159	0.936 (0.592-1.480)	0.976 (0.795-1.199)	0.657
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	112	30738	1.021 (0.878-1.186)	1.027 (0.879-1.199)	1.036 (0.884-1.215)	0.949 (0.754-1.194)	1.111 (0.901-1.370)	0.301	0.825 (0.642-1.061)	1.184 (0.973-1.442)	0.034	0.945 (0.632-1.412)	1.039 (0.877-1.230)	0.53
Renal pelvis and ureter	Cases	Cohort			Excluding first	Men	Women	Sex	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI	Age <= 53 yrs	Age > 53 yrs	Age

			HR (crude)	HR (adjusted)	2 years of follow- up HR (adjusted)	HR (adjusted)	HR (adjusted)	p- interac- tion	HR (adjusted)	HR (adjusted)	p- interac- tion	HR (adjusted)	HR (adjusted)	p- interac- tion
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	22	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	20	6644 6	0.78 (0.43- 1.44)	0.79 (0.43- 1.46)	0.77 (0.41- 1.45)	0.33 (0.12- 0.89)	1.57 (0.69- 3.58)		0.57 (0.26- 1.24)	1.83 (0.57- 5.88)		1.20 (0.38- 3.81)	0.68 (0.33- 1.40)	
130-139	18	5748 2	0.65 (0.35- 1.23)	0.66 (0.35- 1.24)	0.60 (0.31- 1.17)	0.48 (0.20- 1.13)	0.87 (0.33- 2.26)		0.46 (0.20- 1.08)	1.47 (0.45- 4.78)		0.99 (0.27- 3.70)	0.58 (0.28- 1.21)	
140-159	29	6823 5	0.67 (0.38- 1.18)	0.67 (0.37- 1.21)	0.69 (0.38- 1.25)	0.52 (0.24- 1.13)	0.81 (0.33- 2.01)	0.306	0.34 (0.14- 0.80)	1.84 (0.61- 5.54)	0.005	0.68 (0.16- 2.91)	0.64 (0.33- 1.22)	0.38
160-179	16	2265 6	0.96 (0.49- 1.88)	1.00 (0.50- 2.00)	1.02 (0.51- 2.05)	0.77 (0.31- 1.94)	1.32 (0.47- 3.71)		0.40 (0.12- 1.42)	2.91 (0.91- 9.34)		0.86 (0.09- 7.85)	0.95 (0.45- 2.00)	
>= 180	7	6358	1.45 (0.60- 3.50)	1.42 (0.58- 3.47)	1.26 (0.49- 3.24)	0.27 (0.03- 2.14)	3.65 (1.22- 10.87)		1.05 (0.23- 4.75)	3.47 (0.89- 13.58)		no cases	1.41 (0.56- 3.54)	
p-trend			0.962	0.889	0.915	0.569	0.439		0.043	0.043		0.54	0.7	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	42	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	19	6487 2	0.75 (0.44- 1.30)	0.76 (0.44- 1.32)	0.70 (0.39- 1.25)	0.99 (0.46- 2.13)	0.55 (0.24- 1.28)		0.52 (0.22- 1.21)	1.12 (0.52- 2.40)		0.91 (0.27- 3.04)	0.71 (0.38- 1.33)	
85-89	16	4150 0	0.85 (0.48- 1.52)	0.86 (0.48- 1.54)	0.83 (0.45- 1.51)	1.04 (0.46- 2.34)	0.68 (0.28- 1.68)		0.47 (0.16- 1.34)	1.29 (0.60- 2.79)		1.40 (0.41- 4.77)	0.75 (0.38- 1.48)	
90-99	29	5119 6	1.19 (0.73- 1.93)	1.20 (0.73- 1.97)	1.22 (0.74- 2.02)	1.16 (0.56- 2.42)	1.36 (0.68- 2.71)	0.583	1.08 (0.52- 2.22)	1.43 (0.71- 2.91)	0.194	0.60 (0.12- 2.93)	1.27 (0.74- 2.17)	0.527
100-109	5	1389 6	0.72 (0.28- 1.82)	0.70 (0.27- 1.81)	0.72 (0.28- 1.85)	0.74 (0.21- 2.62)	0.69 (0.16- 2.97)		no cases	1.27 (0.45- 3.57)		1.31 (0.16- 11.08)	0.62 (0.22- 1.80)	
>= 110	1	3264	0.66 (0.09- 4.83)	0.67 (0.09- 4.89)	0.68 (0.09- 5.02)	no cases	1.84 (0.24- 13.92)		no cases	1.15 (0.15- 8.79)		no cases	0.77 (0.10- 5.68)	
p-trend			0.91	0.912	0.819	0.802	0.612		0.317	0.37		0.777	0.834	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	22	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-139	38	1239 28	0.72 (0.42- 1.22)	0.72 (0.42- 1.24)	0.69 (0.39- 1.20)	0.41 (0.19- 0.88)	1.22 (0.57- 2.64)		0.51 (0.26- 1.00)	1.64 (0.55- 4.86)		1.11 (0.39- 3.18)	0.63 (0.34- 1.17)	
Renal pelvis and ureter	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
140-159	29	6823 5	0.67 (0.38- 1.18)	0.68 (0.38- 1.22)	0.69 (0.38- 1.26)	0.52 (0.24- 1.12)	0.82 (0.33- 2.03)	0.285	0.34 (0.14- 0.80)	1.85 (0.61- 5.56)	0.004	0.68 (0.16- 2.93)	0.64 (0.33- 1.22)	0.424
>= 160	23	2901 4	1.07 (0.58- 1.99)	1.11 (0.59- 2.09)	1.08 (0.57- 2.08)	0.65 (0.26- 1.59)	1.89 (0.77- 4.66)		0.54 (0.19- 1.51)	3.06 (0.99- 9.49)		0.73 (0.08- 6.60)	1.06 (0.54- 2.11)	
p-trend			0.874	0.784	0.74	0.617	0.361		0.043	0.029		0.613	0.636	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	42	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	35	1063 72	0.80 (0.51- 1.25)	0.80 (0.51- 1.27)	0.75 (0.47- 1.21)	1.01 (0.52- 1.96)	0.60 (0.31- 1.19)		0.50 (0.24- 1.02)	1.20 (0.62- 2.30)		1.10 (0.41- 2.95)	0.73 (0.43- 1.23)	
90-99	29	5119 6	1.19 (0.73- 1.93)	1.20 (0.73- 1.97)	1.22 (0.74- 2.02)	1.16 (0.56- 2.42)	1.36 (0.68- 2.71)	0.667	1.08 (0.52- 2.22)	1.43 (0.71- 2.90)	0.178	0.60 (0.12- 2.90)	1.27 (0.74- 2.17)	0.511
>= 100	6	1716 0	0.71 (0.30- 1.67)	0.69 (0.29- 1.67)	0.71 (0.29- 1.71)	0.60 (0.17- 2.12)	0.87 (0.26- 2.95)		no cases	1.25 (0.48- 3.29)		0.98 (0.12- 8.22)	0.65 (0.25- 1.70)	
p-trend			0.97	0.964	0.963	0.779	0.759		0.259	0.412		0.711	0.943	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	18	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	28	7772 7	1.07 (0.59- 1.95)	1.09 (0.60- 1.98)	1.05 (0.56- 1.95)	1.83 (0.67- 5.02)	0.74 (0.33- 1.67)		0.93 (0.45- 1.93)	1.63 (0.52- 5.09)		1.25 (0.39- 4.05)	1.03 (0.51- 2.07)	
96.8-105.5	24	7632 7	0.74 (0.40- 1.37)	0.75 (0.40- 1.41)	0.74 (0.39- 1.42)	0.83 (0.28- 2.44)	0.77 (0.35- 1.72)	0.831	0.46 (0.19- 1.12)	1.48 (0.49- 4.49)	0.053	0.97 (0.26- 3.54)	0.70 (0.34- 1.45)	0.434
105.6-216.6	42	7627 3	1.03 (0.58- 1.81)	1.05 (0.58- 1.89)	1.04 (0.57- 1.92)	1.36 (0.49- 3.71)	0.98 (0.46- 2.10)		0.62 (0.27- 1.42)	2.01 (0.69- 5.85)		0.67 (0.15- 3.04)	1.07 (0.55- 2.08)	
p-trend			0.872	0.93	0.984	0.885	0.923		0.116	0.196		0.561	0.888	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	53	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-84	1.13 (0.44-2.95)	0.62 (0.31-1.24)		0.72 (0.34-1.50)	0.79 (0.34-1.82)		1.01 (0.52-1.94)	-	
85-89	0.95 (0.32-2.85)	0.83 (0.41-1.68)		0.78 (0.35-1.75)	0.88 (0.37-2.12)		0.70 (0.30-1.65)	-	
90-99	1.02 (0.38-2.74)	1.24 (0.69-2.23)	0.976	1.43 (0.76-2.70)	0.90 (0.40-2.02)	0.826	0.98 (0.47-2.06)	-	-
100-109	no cases	1.01 (0.38-2.67)		0.56 (0.13-2.39)	0.81 (0.23-2.90)		no cases	-	
>= 110	2.24 (0.27-18.39)	no cases		1.32 (0.17-9.92)	no cases		no cases	-	
p-trend	0.651	0.715		0.63	0.616		0.258	-	
Renal pelvis and ureter	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	single case in referent	1 (referent)		1 (referent)	1 (referent)		1 (referent)	no cases in referent	
120-139	-	0.54 (0.30-1.00)		0.68 (0.34-1.34)	0.76 (0.31-1.88)		0.72 (0.38-1.39)	-	
140-159	-	0.47 (0.23-0.93)	-	0.69 (0.33-1.47)	0.61 (0.23-1.60)	0.881	0.50 (0.22-1.10)	-	-
>= 160	-	1.00 (0.49-2.04)		1.28 (0.58-2.85)	0.89 (0.31-2.56)		0.65 (0.24-1.78)	-	
p-trend	-	0.872		0.572	0.756		0.165	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-89	1.06 (0.45-2.48)	0.71 (0.40-1.24)		0.74 (0.40-1.37)	0.83 (0.41-1.69)		0.89 (0.49-1.60)	-	
90-99	1.02 (0.38-2.75)	1.24 (0.69-2.22)	0.977	1.43 (0.76-2.69)	0.90 (0.40-2.02)	0.895	0.98 (0.47-2.07)	-	-
>= 100	0.39 (0.05-3.16)	0.83 (0.31-2.19)		0.69 (0.20-2.33)	0.66 (0.19-2.37)		no cases	-	
p-trend	0.587	0.812		0.75	0.595		0.299	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	two cases in referent	1 (referent)		1 (referent)	three cases in referent		1 (referent)	no cases in referent	
88.5-96.6	-	0.95 (0.49-1.85)		0.69 (0.32-1.46)	-		1.34 (0.65-2.76)	-	
96.8-105.5	-	0.52 (0.25-1.09)	-	0.64 (0.30-1.36)	-	-	0.59 (0.25-1.38)	-	-
105.6-216.6	-	0.85 (0.44-1.65)		0.93 (0.46-1.87)	-		0.77 (0.34-1.78)	-	
p-trend	-	0.444		0.98	-		0.186	-	

< 120	162	8614 1	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-129	205	6644 6	1.10 (0.89-1.36)	0.97 (0.79-1.19)	0.92 (0.74-1.14)	1.05 (0.80-1.36)	0.85 (0.60-1.22)		0.92 (0.69-1.24)	1.02 (0.75-1.39)		0.97 (0.66-1.42)	0.97 (0.75-1.24)	
130-139	245	5748 2	1.23 (1.01-1.51)	1.04 (0.85-1.28)	1.02 (0.83-1.26)	1.09 (0.84-1.41)	1.02 (0.72-1.45)		0.90 (0.66-1.21)	1.17 (0.87-1.57)		1.26 (0.86-1.84)	0.97 (0.76-1.24)	
140-159	391	6823 5	1.29 (1.06-1.56)	1.07 (0.88-1.31)	1.04 (0.85-1.27)	1.16 (0.91-1.49)	0.96 (0.69-1.35)	0.225	1.00 (0.75-1.32)	1.17 (0.88-1.54)	0.539	1.21 (0.81-1.80)	1.02 (0.81-1.29)	0.328
160-179	143	2265 6	1.20 (0.95-1.52)	1.00 (0.79-1.28)	0.95 (0.74-1.22)	1.14 (0.85-1.52)	0.77 (0.48-1.21)		0.95 (0.65-1.39)	1.08 (0.78-1.49)		1.30 (0.71-2.39)	0.95 (0.72-1.24)	
>= 180	46	6358	1.36 (0.97-1.91)	1.12 (0.80-1.58)	1.07 (0.75-1.53)	1.17 (0.78-1.76)	1.09 (0.58-2.06)		1.07 (0.59-1.92)	1.20 (0.78-1.86)		0.88 (0.21-3.65)	1.09 (0.76-1.57)	
p-trend			0.014	0.41	0.618	0.207	0.782		0.905	0.328		0.21	0.791	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	354	1325 90	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Bladder	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	264	6487 2	1.08 (0.92-1.27)	1.00 (0.85-1.18)	0.98 (0.82-1.16)	0.93 (0.76-1.14)	1.20 (0.91-1.58)		0.91 (0.71-1.17)	1.07 (0.86-1.33)		1.07 (0.75-1.51)	0.98 (0.81-1.17)	
85-89	180	4150 0	1.08 (0.90-1.29)	0.96 (0.80-1.15)	0.97 (0.81-1.18)	1.10 (0.89-1.35)	0.60 (0.40-0.91)		0.82 (0.61-1.12)	1.04 (0.82-1.32)		1.22 (0.83-1.81)	0.90 (0.73-1.11)	
90-99	281	5119 6	1.19 (1.01-1.40)	1.03 (0.87-1.21)	1.02 (0.86-1.21)	1.06 (0.87-1.29)	0.96 (0.70-1.32)	0.407	1.05 (0.81-1.36)	1.03 (0.84-1.28)	0.964	1.23 (0.85-1.78)	0.98 (0.81-1.18)	0.928
100-109	100	1389 6	1.50 (1.19-1.88)	1.20 (0.95-1.51)	1.19 (0.93-1.51)	1.14 (0.87-1.49)	1.53 (0.98-2.40)		1.17 (0.77-1.77)	1.25 (0.94-1.65)		0.98 (0.51-1.87)	1.22 (0.95-1.56)	
>= 110	13	3264	0.91 (0.52-1.59)	0.69 (0.39-1.20)	0.74 (0.42-1.29)	0.74 (0.41-1.33)	0.35 (0.05-2.52)		0.75 (0.24-2.36)	0.71 (0.37-1.34)		0.38 (0.05-2.76)	0.72 (0.40-1.30)	
p-trend			0.003	0.605	0.579	0.397	0.791		0.775	0.629		0.585	0.777	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	162	8614 1	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-139	450	1239 28	1.17 (0.97-1.40)	1.01 (0.84-1.21)	0.97 (0.80-1.17)	1.07 (0.84-1.35)	0.93 (0.69-1.27)		0.91 (0.71-1.18)	1.10 (0.84-1.45)		1.09 (0.78-1.52)	0.97 (0.78-1.21)	
140-159	391	6823 5	1.28 (1.06-1.55)	1.07 (0.88-1.30)	1.03 (0.84-1.26)	1.16 (0.91-1.48)	0.96 (0.69-1.34)	0.141	1.00 (0.75-1.32)	1.16 (0.88-1.54)	0.685	1.20 (0.81-1.78)	1.02 (0.81-1.28)	0.451

>= 160	189	2901 4	1.23 (0.98- 1.53)	1.03 (0.82- 1.29)	0.97 (0.77- 1.23)	1.14 (0.86- 1.51)	0.83 (0.55- 1.26)		0.97 (0.68- 1.39)	1.10 (0.81- 1.50)		1.21 (0.68- 2.17)	0.98 (0.76- 1.26)	
p-trend			0.037	0.596	0.902	0.241	0.489		0.898	0.548		0.356	0.905	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	354	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	444	1063 72	1.08 (0.93- 1.24)	0.98 (0.85- 1.13)	0.97 (0.84- 1.13)	1.00 (0.84- 1.19)	0.96 (0.74- 1.24)		0.88 (0.71- 1.09)	1.05 (0.87- 1.28)		1.13 (0.83- 1.53)	0.94 (0.80- 1.11)	
90-99	281	5119 6	1.19 (1.01- 1.40)	1.03 (0.87- 1.21)	1.02 (0.86- 1.21)	1.06 (0.87- 1.28)	0.96 (0.70- 1.33)	0.999	1.05 (0.81- 1.36)	1.03 (0.83- 1.28)	0.964	1.23 (0.85- 1.78)	0.98 (0.81- 1.18)	0.87
>= 100	113	1716 0	1.39 (1.12- 1.73)	1.10 (0.89- 1.38)	1.10 (0.88- 1.39)	1.06 (0.82- 1.37)	1.36 (0.87- 2.11)		1.10 (0.74- 1.65)	1.14 (0.87- 1.49)		0.86 (0.46- 1.61)	1.13 (0.89- 1.43)	
p-trend			0.001	0.408	0.455	0.513	0.498		0.653	0.448		0.675	0.497	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Bladder	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	162	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	254	7772 7	1.03 (0.84- 1.25)	0.92 (0.75- 1.13)	0.95 (0.77- 1.17)	0.94 (0.73- 1.21)	0.93 (0.67- 1.30)		0.88 (0.67- 1.16)	0.96 (0.71- 1.29)		0.83 (0.57- 1.20)	0.96 (0.76- 1.22)	
96.8-105.5	322	7632 7	1.09 (0.90- 1.32)	0.93 (0.76- 1.13)	0.94 (0.76- 1.15)	1.01 (0.79- 1.29)	0.82 (0.59- 1.15)	0.252	0.85 (0.64- 1.13)	0.99 (0.74- 1.31)	0.908	1.05 (0.72- 1.53)	0.90 (0.72- 1.14)	0.673
105.6-216.6	454	7627 3	1.21 (1.01- 1.46)	0.99 (0.81- 1.20)	1.00 (0.81- 1.22)	1.05 (0.82- 1.34)	0.92 (0.66- 1.29)		1.00 (0.76- 1.32)	1.00 (0.76- 1.31)		1.04 (0.69- 1.55)	0.97 (0.78- 1.22)	
p-trend			0.016	0.806	0.837	0.391	0.559		0.897	0.835		0.53	0.93	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	504	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	688	1331 39	1.08 (0.96- 1.22)	1.02 (0.91- 1.16)	1.02 (0.90- 1.15)	1.05 (0.91- 1.22)	0.97 (0.77- 1.22)	0.405	1.07 (0.88- 1.30)	1.00 (0.85- 1.17)	0.65	1.16 (0.89- 1.52)	0.99 (0.86- 1.14)	0.369

< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.93 (0.66-1.31)	1.03 (0.85-1.24)		1.03 (0.83-1.27)	0.95 (0.73-1.24)		0.97 (0.81-1.18)	1.07 (0.60-1.90)	
85-89	0.84 (0.57-1.25)	0.99 (0.81-1.22)		0.88 (0.69-1.13)	1.07 (0.81-1.41)		1.03 (0.83-1.27)	0.62 (0.32-1.18)	
90-99	0.82 (0.57-1.17)	1.08 (0.89-1.30)	0.171	0.95 (0.76-1.19)	1.12 (0.87-1.44)	0.29	1.03 (0.84-1.26)	0.96 (0.57-1.62)	0.969
100-109	1.06 (0.64-1.75)	1.22 (0.94-1.59)		1.27 (0.94-1.72)	1.13 (0.79-1.61)		1.12 (0.80-1.57)	1.19 (0.67-2.12)	
>= 110	no cases	0.87 (0.49-1.52)		0.48 (0.20-1.16)	0.96 (0.46-1.97)		0.53 (0.20-1.44)	0.73 (0.27-2.00)	
p-trend	0.222	0.304		0.816	0.297		0.774	0.778	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
120-139	1.25 (0.83-1.88)	0.96 (0.78-1.18)		0.99 (0.78-1.25)	1.05 (0.77-1.42)		0.99 (0.80-1.21)	-	
140-159	1.13 (0.73-1.75)	1.07 (0.86-1.33)	0.5	1.03 (0.80-1.33)	1.15 (0.84-1.57)	0.635	1.07 (0.86-1.34)	-	-
>= 160	0.98 (0.58-1.65)	1.02 (0.79-1.31)		1.01 (0.75-1.36)	1.06 (0.74-1.51)		1.02 (0.77-1.36)	-	
p-trend	0.646	0.483		0.805	0.585		0.588	-	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.89 (0.66-1.21)	1.01 (0.86-1.19)		0.97 (0.80-1.17)	1.00 (0.80-1.26)		1.00 (0.84-1.17)	0.84 (0.49-1.43)	
90-99	0.82 (0.57-1.18)	1.08 (0.89-1.30)	0.21	0.95 (0.77-1.19)	1.12 (0.87-1.44)	0.525	1.03 (0.84-1.26)	0.96 (0.57-1.63)	0.535
>= 100	0.87 (0.53-1.43)	1.16 (0.90-1.48)		1.12 (0.83-1.50)	1.10 (0.78-1.54)		1.02 (0.74-1.41)	1.12 (0.63-1.96)	
p-trend	0.345	0.213		0.779	0.365		0.79	0.374	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
88.5-96.6	0.98 (0.65-1.50)	0.92 (0.73-1.15)		0.93 (0.73-1.20)	0.90 (0.64-1.25)		0.89 (0.72-1.12)	-	
96.8-105.5	0.89 (0.59-1.36)	0.95 (0.76-1.18)	0.315	0.93 (0.72-1.19)	0.94 (0.68-1.30)	0.42	0.88 (0.70-1.09)	-	-
105.6-216.6	0.85 (0.56-1.29)	1.02 (0.82-1.27)		0.95 (0.74-1.22)	1.03 (0.75-1.41)		0.98 (0.78-1.23)	-	
p-trend	0.34	0.509		0.807	0.498		0.944	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	

Hypertensive	0.91 (0.70-1.19)	1.04 (0.91-1.20)	0.375	1.02 (0.87-1.20)	1.03 (0.86-1.24)	0.767	1 (referent)	0.97 (0.80-1.17)	
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Prostate	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			5848	5848	5616				2207	3641		1339	4509	
Cohort size			112591	112591	110306				41910	70681		54234	58357	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	5848	112591	0.985 (0.971-0.999)	0.993 (0.979-1.008)	0.991 (0.976-1.006)				1.003 (0.979-1.028)	0.985 (0.967-1.003)	0.64	0.980 (0.946-1.015)	0.997 (0.980-1.013)	0.346
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	5848	112591	1.000 (0.975-1.025)	1.012 (0.986-1.038)	1.011 (0.984-1.038)				1.014 (0.971-1.058)	1.005 (0.973-1.037)	0.813	0.986 (0.933-1.043)	1.020 (0.990-1.050)	0.247
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	5848	112591	0.988 (0.967-1.010)	1.001 (0.979-1.023)	0.998 (0.976-1.021)				1.009 (0.973-1.047)	0.991 (0.964-1.019)	0.71	0.979 (0.931-1.030)	1.007 (0.982-1.032)	0.278
Prostate	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg) ESH classification														
< 120	720	20680	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1113	25502	1.01 (0.92-1.11)	1.02 (0.93-1.13)	1.02 (0.92-1.12)				1.00 (0.88-1.15)	1.04 (0.91-1.19)		1.03 (0.88-1.20)	1.03 (0.92-1.16)	

130-139	122 6	2406 7	0.98 (0.90- 1.08)	1.01 (0.92- 1.11)	1.01 (0.91- 1.11)				0.99 (0.86- 1.13)	1.01 (0.88- 1.15)		0.91 (0.77- 1.08)	1.05 (0.94- 1.18)	
140-159	195 0	3006 7	0.99 (0.91- 1.08)	1.03 (0.94- 1.12)	1.02 (0.93- 1.11)				1.09 (0.95- 1.24)	0.98 (0.87- 1.12)	0.517	0.94 (0.79- 1.11)	1.06 (0.96- 1.19)	0.39
160-179	629	9590	0.86 (0.77- 0.96)	0.91 (0.81- 1.02)	0.89 (0.79- 1.00)				0.90 (0.75- 1.09)	0.89 (0.77- 1.03)		0.97 (0.74- 1.26)	0.92 (0.81- 1.05)	
>= 180	210	2685	1.01 (0.86- 1.18)	1.07 (0.91- 1.26)	1.06 (0.90- 1.24)				1.12 (0.84- 1.49)	1.03 (0.84- 1.25)		1.00 (0.61- 1.65)	1.10 (0.93- 1.31)	
p-trend			0.062	0.52	0.352				0.604	0.122		0.363	0.852	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	163 1	3623 8	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	124 4	2581 3	0.94 (0.87- 1.01)	0.95 (0.88- 1.02)	0.94 (0.88- 1.02)				0.91 (0.81- 1.02)	0.96 (0.87- 1.06)		0.84 (0.72- 0.98)	0.99 (0.91- 1.08)	
85-89	100 2	1754 4	0.98 (0.91- 1.06)	1.00 (0.92- 1.09)	1.00 (0.92- 1.08)				1.10 (0.97- 1.25)	0.94 (0.85- 1.04)		0.97 (0.83- 1.14)	1.02 (0.93- 1.12)	
90-99	138 9	2399 7	0.93 (0.87- 1.00)	0.96 (0.89- 1.03)	0.95 (0.88- 1.03)				0.94 (0.83- 1.07)	0.95 (0.86- 1.04)	0.448	0.85 (0.72- 1.00)	1.00 (0.92- 1.09)	0.44
100-109	455	7176	0.98 (0.88- 1.09)	1.01 (0.91- 1.13)	1.00 (0.90- 1.12)				1.06 (0.87- 1.29)	0.98 (0.86- 1.11)		1.10 (0.87- 1.38)	1.00 (0.89- 1.13)	
>= 110	127	1823	1.12 (0.94- 1.34)	1.16 (0.97- 1.40)	1.20 (1.00- 1.44)				1.45 (1.01- 2.06)	1.06 (0.86- 1.31)		1.05 (0.68- 1.62)	1.20 (0.98- 1.47)	
p-trend			0.663	0.668	0.731				0.413	0.684		0.748	0.481	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	720	20680	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	233 9	4956 9	1.00 (0.92- 1.09)	1.02 (0.93- 1.11)	1.01 (0.93- 1.10)				0.99 (0.88- 1.12)	1.02 (0.90- 1.16)		0.98 (0.84- 1.13)	1.04 (0.94- 1.16)	
140-159	195 0	3006 7	0.99 (0.91- 1.08)	1.03 (0.94- 1.12)	1.02 (0.93- 1.11)				1.09 (0.95- 1.24)	0.98 (0.87- 1.12)	0.541	0.94 (0.79- 1.12)	1.06 (0.95- 1.18)	0.806
Prostate	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
>= 160	839	12275	0.89 (0.81- 0.99)	0.94 (0.85- 1.05)	0.93 (0.83- 1.03)				0.95 (0.80- 1.12)	0.92 (0.80- 1.06)		0.98 (0.77- 1.26)	0.96 (0.85- 1.08)	
p-trend			0.034	0.34	0.199				0.733	0.079		0.626	0.444	

Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	1631	36238	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	2246	43357	0.96 (0.90-1.02)	0.97 (0.91-1.04)	0.97 (0.91-1.03)				0.99 (0.89-1.09)	0.95 (0.87-1.04)		0.89 (0.79-1.02)	1.00 (0.93-1.08)	
90-99	1389	23997	0.93 (0.87-1.00)	0.96 (0.89-1.03)	0.95 (0.88-1.03)				0.94 (0.83-1.07)	0.95 (0.86-1.04)	0.831	0.85 (0.72-0.99)	1.00 (0.92-1.09)	0.358
>= 100	582	8999	1.01 (0.92-1.11)	1.04 (0.95-1.15)	1.04 (0.94-1.15)				1.12 (0.94-1.34)	0.99 (0.88-1.12)		1.09 (0.88-1.34)	1.04 (0.93-1.16)	
p-trend			0.452	0.934	0.972				0.87	0.722		0.544	0.637	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	673	17721	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1233	28406	0.93 (0.85-1.02)	0.94 (0.85-1.03)	0.94 (0.85-1.03)				0.88 (0.77-1.01)	0.99 (0.86-1.14)		0.95 (0.80-1.12)	0.94 (0.84-1.06)	
96.8-105.5	1702	31346	0.95 (0.86-1.04)	0.97 (0.88-1.06)	0.97 (0.88-1.06)				0.96 (0.85-1.10)	0.97 (0.85-1.11)	0.608	0.87 (0.73-1.03)	1.01 (0.90-1.13)	0.174
105.6-216.6	2240	35118	0.92 (0.84-1.00)	0.96 (0.87-1.05)	0.95 (0.86-1.04)				0.96 (0.84-1.10)	0.95 (0.84-1.08)		0.91 (0.76-1.08)	0.98 (0.88-1.09)	
p-trend			0.133	0.681	0.525				0.833	0.289		0.205	0.765	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	2472	56915	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	3376	55676	0.98 (0.93-1.04)	1.01 (0.96-1.07)	1.00 (0.95-1.06)				1.07 (0.98-1.16)	0.97 (0.90-1.04)	0.263	0.95 (0.85-1.06)	1.03 (0.97-1.10)	0.167

Prostate	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	1937	3850		2902	2946		3862	844	

Cohort size	35854	74868		56044	56547		80227	13281	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.973 (0.948-0.999)	1.002 (0.984-1.020)	0.06	0.989 (0.969-1.011)	0.994 (0.974-1.015)	0.586	0.988 (0.969-1.008)	0.976 (0.940-1.014)	0.501
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.979 (0.935-1.025)	1.026 (0.994-1.059)	0.095	1.003 (0.967-1.041)	1.015 (0.979-1.053)	0.692	0.995 (0.962-1.030)	0.999 (0.930-1.072)	0.764
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	0.969 (0.931-1.009)	1.014 (0.987-1.042)	0.058	0.994 (0.963-1.026)	1.003 (0.972-1.035)	0.626	0.989 (0.960-1.019)	0.979 (0.920-1.040)	0.566
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.13 (0.96-1.33)	0.98 (0.87-1.10)		1.06 (0.93-1.21)	0.99 (0.86-1.14)		1.02 (0.92-1.13)	1.06 (0.65-1.72)	
130-139	1.11 (0.94-1.30)	0.97 (0.86-1.09)		1.03 (0.90-1.17)	0.98 (0.86-1.13)		0.98 (0.88-1.10)	1.14 (0.73-1.78)	
140-159	1.06 (0.90-1.24)	1.01 (0.91-1.13)	0.147	1.03 (0.91-1.17)	1.01 (0.89-1.15)	0.814	1.02 (0.91-1.13)	1.07 (0.69-1.64)	0.266
160-179	0.90 (0.74-1.11)	0.91 (0.79-1.04)		0.94 (0.80-1.10)	0.86 (0.73-1.01)		0.88 (0.76-1.02)	0.87 (0.56-1.36)	
>= 180	0.87 (0.64-1.20)	1.14 (0.95-1.37)		1.02 (0.81-1.30)	1.09 (0.88-1.35)		1.01 (0.80-1.29)	1.00 (0.62-1.62)	
p-trend	0.154	0.857		0.533	0.581		0.404	0.153	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.95 (0.84-1.08)	0.95 (0.86-1.04)		0.91 (0.82-1.02)	0.98 (0.88-1.09)		0.92 (0.84-1.00)	1.06 (0.78-1.43)	
85-89	1.08 (0.94-1.24)	0.96 (0.87-1.06)		0.96 (0.85-1.07)	1.04 (0.93-1.17)		0.97 (0.88-1.07)	0.94 (0.69-1.26)	
90-99	0.91 (0.79-1.03)	0.98 (0.89-1.07)	0.075	0.95 (0.86-1.06)	0.96 (0.86-1.06)	0.711	0.94 (0.85-1.03)	0.99 (0.76-1.29)	0.747
100-109	0.89 (0.74-1.09)	1.06 (0.94-1.21)		0.99 (0.84-1.15)	1.03 (0.89-1.19)		1.00 (0.86-1.16)	1.03 (0.77-1.38)	
>= 110	0.92 (0.65-1.31)	1.29 (1.04-1.60)		1.05 (0.80-1.37)	1.26 (0.98-1.62)		1.16 (0.87-1.55)	0.98 (0.66-1.46)	
p-trend	0.201	0.205		0.892	0.631		0.77	0.939	
Prostate	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment	Antihypertensive treatment	Treatment p-interaction

							HR (adjusted)	HR (adjusted)	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.12 (0.97-1.29)	0.97 (0.87-1.08)		1.04 (0.93-1.17)	0.99 (0.87-1.12)		1.00 (0.91-1.10)	1.11 (0.72-1.72)	
140-159	1.06 (0.90-1.24)	1.01 (0.91-1.13)	0.171	1.03 (0.91-1.17)	1.01 (0.89-1.15)	0.987	1.02 (0.92-1.13)	1.07 (0.69-1.64)	0.136
>= 160	0.90 (0.74-1.09)	0.96 (0.84-1.09)		0.96 (0.83-1.11)	0.91 (0.78-1.06)		0.91 (0.79-1.04)	0.90 (0.58-1.40)	
p-trend	0.128	0.873		0.497	0.345		0.371	0.054	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.01 (0.90-1.13)	0.95 (0.88-1.03)		0.93 (0.85-1.02)	1.01 (0.92-1.11)		0.94 (0.87-1.01)	0.99 (0.76-1.30)	
90-99	0.90 (0.79-1.03)	0.98 (0.89-1.07)	0.037	0.95 (0.86-1.06)	0.96 (0.86-1.06)	0.764	0.94 (0.85-1.03)	0.99 (0.76-1.29)	0.913
>= 100	0.90 (0.75-1.07)	1.11 (0.98-1.25)		1.00 (0.87-1.15)	1.07 (0.93-1.23)		1.02 (0.89-1.18)	1.02 (0.77-1.35)	
p-trend	0.081	0.246		0.739	0.852		0.532	0.844	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.03 (0.87-1.21)	0.91 (0.81-1.02)		0.98 (0.86-1.11)	0.89 (0.77-1.03)		0.92 (0.83-1.02)	0.83 (0.49-1.41)	
96.8-105.5	1.04 (0.88-1.21)	0.94 (0.84-1.05)	0.346	0.97 (0.86-1.10)	0.95 (0.83-1.09)	0.967	0.94 (0.85-1.04)	0.93 (0.57-1.50)	0.62
105.6-216.6	0.95 (0.81-1.12)	0.96 (0.86-1.07)		0.98 (0.86-1.11)	0.92 (0.80-1.05)		0.91 (0.82-1.02)	0.86 (0.54-1.38)	
p-trend	0.333	0.935		0.749	0.588		0.236	0.607	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.95 (0.86-1.05)	1.04 (0.97-1.11)	0.111	1.01 (0.93-1.09)	1.00 (0.93-1.09)	0.942	1 (referent)	1.08 (0.99-1.17)	

classification														
< 80	3764	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Breast	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	1637	39059	0.99 (0.94-1.05)	0.99 (0.93-1.05)	0.98 (0.92-1.05)				0.97 (0.89-1.05)	1.01 (0.92-1.10)		1.00 (0.91-1.09)	0.98 (0.90-1.06)	
85-89	1094	23956	1.05 (0.98-1.12)	1.03 (0.97-1.11)	1.05 (0.97-1.13)				1.11 (1.00-1.22)	0.98 (0.89-1.08)		1.01 (0.90-1.13)	1.05 (0.96-1.14)	
90-99	1253	27199	1.06 (1.00-1.14)	1.05 (0.98-1.12)	1.05 (0.98-1.13)				1.03 (0.93-1.15)	1.06 (0.97-1.16)	0.51	1.12 (1.00-1.25)	1.01 (0.93-1.10)	0.673
100-109	328	6720	1.14 (1.02-1.28)	1.13 (1.00-1.26)	1.14 (1.01-1.28)				1.15 (0.94-1.39)	1.12 (0.97-1.29)		1.04 (0.84-1.29)	1.16 (1.01-1.33)	
≥ 110	78	1441	1.32 (1.05-1.65)	1.30 (1.04-1.63)	1.41 (1.12-1.78)				1.46 (0.97-2.21)	1.25 (0.95-1.64)		1.56 (1.07-2.27)	1.19 (0.90-1.58)	
p-trend			0.001	0.008	0.004				0.038	0.058		0.035	0.072	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	2222	65461	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	3267	74359	1.11 (1.05-1.18)	1.10 (1.04-1.16)	1.09 (1.03-1.16)				1.14 (1.06-1.22)	1.06 (0.97-1.16)		1.13 (1.04-1.21)	1.08 (0.99-1.18)	
140-159	1836	38168	1.13 (1.05-1.20)	1.10 (1.03-1.18)	1.11 (1.03-1.19)				1.08 (0.98-1.18)	1.12 (1.01-1.23)	0.377	1.10 (0.98-1.22)	1.10 (1.00-1.20)	0.781
≥ 160	829	16739	1.18 (1.09-1.29)	1.16 (1.06-1.26)	1.16 (1.05-1.27)				1.23 (1.08-1.41)	1.11 (0.98-1.25)		1.19 (1.01-1.42)	1.13 (1.01-1.26)	
p-trend			0.00003	0.0008	0.0009				0.003	0.041		0.008	0.03	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	3764	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	2731	63015	1.02 (0.97-1.07)	1.00 (0.95-1.06)	1.01 (0.95-1.06)				1.02 (0.95-1.09)	1.00 (0.92-1.08)		1.00 (0.93-1.08)	1.01 (0.94-1.08)	
90-99	1253	27199	1.06 (1.00-1.14)	1.05 (0.98-1.12)	1.05 (0.98-1.13)				1.03 (0.93-1.15)	1.06 (0.97-1.16)	0.258	1.12 (1.00-1.25)	1.01 (0.93-1.10)	0.658

>= 100	406	8161	1.17 (1.05-1.30)	1.15 (1.04-1.28)	1.18 (1.06-1.32)				1.19 (1.00-1.42)	1.14 (1.00-1.30)		1.13 (0.94-1.36)	1.16 (1.02-1.32)	
p-trend			0.004	0.017	0.011				0.123	0.045		0.052	0.112	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Breast	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	2032	59270	1 (reference)	1 (reference)	1 (reference)				1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	2090	49321	1.10 (1.03-1.17)	1.09 (1.02-1.16)	1.09 (1.02-1.16)				1.11 (1.03-1.20)	1.07 (0.96-1.18)		1.11 (1.02-1.21)	1.07 (0.97-1.17)	
96.8-105.5	2044	44981	1.12 (1.05-1.20)	1.10 (1.03-1.18)	1.10 (1.03-1.18)				1.13 (1.03-1.23)	1.09 (0.98-1.20)	0.628	1.08 (0.98-1.19)	1.12 (1.02-1.22)	0.578
105.6-216.6	1988	41155	1.16 (1.09-1.24)	1.14 (1.06-1.22)	1.14 (1.06-1.23)				1.17 (1.07-1.29)	1.11 (1.00-1.23)		1.18 (1.06-1.31)	1.12 (1.02-1.23)	
p-trend			0.00001	0.0003	0.0006				0.0006	0.055		0.005	0.014	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	4645	117264	1 (reference)	1 (reference)	1 (reference)				1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Hypertensive	3509	77463	1.05 (1.00-1.10)	1.03 (0.98-1.08)	1.04 (0.99-1.09)				1.03 (0.97-1.11)	1.04 (0.97-1.11)	0.183	1.02 (0.94-1.10)	1.04 (0.98-1.11)	0.185

Breast	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	4222	3824		5770	2384		5997	1013	
Cohort size	106077	85755		149170	45557		147109	23736	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.016 (0.999-1.034)	1.034 (1.016-1.053)	0.431	1.024 (1.009-1.039)	1.034 (1.011-1.057)	0.992	1.031 (1.016-1.047)	1.010 (0.977-1.044)	0.227

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.027 (0.995-1.059)	1.037 (1.004-1.071)	0.847	1.035 (1.008-1.063)	1.027 (0.986-1.071)	0.273	1.031 (1.004-1.060)	1.038 (0.974-1.106)	0.796
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.026 (0.999-1.053)	1.045 (1.017-1.074)	0.767	1.036 (1.013-1.059)	1.040 (1.005-1.077)	0.543	1.040 (1.016-1.065)	1.027 (0.973-1.084)	0.471
Breast	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.09 (0.99-1.19)	1.06 (0.96-1.16)		1.07 (0.99-1.16)	1.07 (0.95-1.21)		1.07 (1.00-1.15)	0.91 (0.66-1.25)	
130-139	1.11 (1.01-1.22)	1.14 (1.03-1.26)		1.11 (1.02-1.20)	1.18 (1.04-1.34)		1.10 (1.02-1.19)	1.04 (0.77-1.39)	
140-159	1.10 (1.00-1.21)	1.08 (0.98-1.20)	0.695	1.09 (1.00-1.18)	1.15 (1.01-1.30)	0.855	1.09 (1.00-1.18)	0.98 (0.74-1.30)	0.567
160-179	1.08 (0.95-1.23)	1.16 (1.01-1.33)		1.13 (1.01-1.27)	1.11 (0.93-1.33)		1.23 (1.09-1.39)	0.91 (0.67-1.23)	
>= 180	1.19 (0.96-1.48)	1.40 (1.13-1.73)		1.28 (1.07-1.53)	1.34 (1.02-1.76)		1.11 (0.87-1.40)	1.29 (0.92-1.82)	
p-trend	0.059	0.002		0.004	0.013		0.002	0.409	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.94 (0.87-1.02)	1.03 (0.94-1.12)		0.98 (0.92-1.05)	0.99 (0.89-1.11)		0.98 (0.91-1.05)	0.89 (0.72-1.09)	
85-89	1.02 (0.93-1.12)	1.03 (0.93-1.14)		1.02 (0.93-1.10)	1.08 (0.96-1.23)		1.08 (0.99-1.17)	0.85 (0.68-1.05)	
90-99	1.04 (0.95-1.14)	1.05 (0.95-1.16)	0.645	1.09 (1.01-1.18)	0.95 (0.84-1.08)	0.152	1.05 (0.96-1.14)	0.95 (0.79-1.15)	0.818
100-109	1.12 (0.96-1.31)	1.12 (0.94-1.33)		1.11 (0.97-1.28)	1.17 (0.94-1.44)		1.16 (0.99-1.37)	1.21 (0.96-1.52)	
>= 110	1.28 (0.95-1.73)	1.35 (0.96-1.90)		1.31 (1.00-1.71)	1.30 (0.86-1.97)		1.31 (0.92-1.87)	1.14 (0.77-1.70)	
p-trend	0.055	0.074		0.008	0.402		0.02	0.145	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-139	1.10 (1.01-1.19)	1.09 (1.01-1.18)		1.09 (1.02-1.16)	1.12 (1.01-1.24)		1.09 (1.02-1.16)	0.98 (0.74-1.31)	
140-159	1.10 (1.00-1.21)	1.08 (0.98-1.19)	0.771	1.09 (1.00-1.18)	1.14 (1.01-1.29)	0.695	1.08 (1.00-1.18)	0.98 (0.74-1.30)	0.21
>= 160	1.10 (0.98-1.25)	1.21 (1.07-1.37)		1.16 (1.05-1.29)	1.15 (0.98-1.36)		1.21 (1.08-1.35)	1.00 (0.74-1.34)	
p-trend	0.081	0.008		0.007	0.041		0.001	0.949	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.97 (0.91-1.04)	1.03 (0.95-1.11)		0.99 (0.94-1.06)	1.03 (0.94-1.13)		1.01 (0.96-1.08)	0.87 (0.72-1.04)	
90-99	1.04 (0.95-1.14)	1.05 (0.95-1.16)	0.839	1.09 (1.00-1.18)	0.95 (0.84-1.08)	0.135	1.04 (0.96-1.14)	0.95 (0.79-1.15)	0.777
>= 100	1.15 (1.00-1.32)	1.16 (0.99-1.36)		1.15 (1.01-1.30)	1.19 (0.98-1.44)		1.18 (1.02-1.37)	1.19 (0.96-1.49)	
p-trend	0.122	0.075		0.014	0.523		0.063	0.077	
Breast	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.07 (0.98-1.16)	1.11 (1.02-1.22)		1.13 (1.04-1.21)	1.00 (0.89-1.13)		1.07 (1.00-1.15)	1.01 (0.72-1.42)	
96.8-105.5	1.04 (0.94-1.13)	1.17 (1.06-1.28)	0.521	1.11 (1.03-1.20)	1.09 (0.97-1.22)	0.672	1.09 (1.01-1.17)	1.07 (0.78-1.47)	0.596
105.6-216.6	1.10 (1.00-1.21)	1.17 (1.06-1.30)		1.14 (1.05-1.24)	1.13 (1.00-1.29)		1.13 (1.04-1.23)	1.08 (0.79-1.47)	
p-trend	0.12	0.0008		0.004	0.023		0.003	0.474	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.01 (0.94-1.08)	1.05 (0.98-1.12)	0.817	1.01 (0.95-1.07)	1.08 (0.99-1.18)	0.497	1 (referent)	1.03 (0.95-1.12)	

Breast Pre Menopausal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			256	256	196				199	57				
Cohort size			40846	40846	40429				27045	13801				
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	256	40846	1.036 (0.942-1.139)	1.068 (0.967-1.180)	1.096 (0.980-1.227)				1.064 (0.948-1.195)	1.098 (0.905-1.332)	0.982			
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	256	40846	1.017 (0.891-1.162)	1.056 (0.919-1.213)	1.090 (0.931-1.277)				1.119 (0.955-1.310)	0.905 (0.677-1.208)	0.151			
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	256	40846	1.031 (0.909-1.170)	1.074 (0.942-1.226)	1.113 (0.958-1.293)				1.111 (0.955-1.293)	0.999 (0.761-1.310)	0.36			
Breast Pre Menopausal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg) ESH classification														
< 120	171	25098	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)				
120-129	45	9105	0.78 (0.56-1.09)	0.81 (0.58-1.13)	0.84 (0.57-1.23)				0.93 (0.64-1.34)	0.49 (0.23-1.05)				
130-139	28	4158	1.21 (0.81-1.81)	1.31 (0.86-1.97)	1.32 (0.82-2.12)				1.35 (0.82-2.22)	1.17 (0.56-2.48)				
140-159	9	2113	0.86 (0.44-1.68)	0.94 (0.47-1.86)	1.15 (0.55-2.39)				1.31 (0.61-2.84)	0.47 (0.11-2.00)	0.341			

classification														
< 80	182	2736	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)				
80-89	56	10172	0.92 (0.68-1.25)	0.97 (0.71-1.32)	0.96 (0.67-1.37)				0.99 (0.69-1.43)	0.87 (0.48-1.58)				
90-99	14	2703	1.01 (0.58-1.75)	1.11 (0.63-1.95)	1.26 (0.68-2.32)				1.47 (0.77-2.83)	0.66 (0.23-1.91)	0.038			
>= 100	4	635	1.35 (0.50-3.64)	1.51 (0.55-4.13)	1.98 (0.72-5.48)				3.14 (1.14-8.63)	no cases				
p-trend			0.971	0.652	0.37				0.12	0.22				
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	142	22045	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)				
88.5-96.6	73	10950	1.15 (0.87-1.53)	1.19 (0.89-1.59)	1.22 (0.87-1.70)				1.00 (0.71-1.41)	1.92 (1.05-3.52)				
96.8-105.5	26	5433	0.95 (0.62-1.45)	1.03 (0.67-1.59)	1.03 (0.62-1.71)				1.17 (0.71-1.92)	0.84 (0.34-2.07)	0.298			
105.6-216.6	15	2418	1.42 (0.83-2.44)	1.62 (0.92-2.82)	2.06 (1.14-3.72)				2.17 (1.15-4.10)	1.14 (0.37-3.46)				
p-trend			0.38	0.169	0.073				0.085	0.928				
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	220	33368	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)				
Hypertensive	36	7478	0.84 (0.59-1.21)	0.91 (0.63-1.32)	0.97 (0.64-1.47)				1.02 (0.66-1.58)	0.74 (0.38-1.44)	0.496			

Breast Pre Menopausal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	126	125		201	55				
Cohort size	20361	19917		33542	7304				
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.062 (0.920-1.225)	1.049 (0.911-1.208)	0.935	1.121 (1.004-1.251)	0.879 (0.696-1.110)	0.042			

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.088 (0.893-1.325)	0.997 (0.817-1.216)	0.7	1.113 (0.952-1.300)	0.850 (0.625-1.156)	0.098			
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.091 (0.903-1.319)	1.027 (0.850-1.240)	0.775	1.141 (0.984-1.323)	0.840 (0.622-1.135)	0.053			
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)				
120-129	0.67 (0.41-1.10)	0.97 (0.61-1.54)		0.93 (0.65-1.35)	0.44 (0.18-1.06)				
130-139	1.28 (0.72-2.27)	1.15 (0.60-2.19)		1.38 (0.86-2.20)	1.26 (0.51-3.07)				
140-159	0.90 (0.36-2.26)	0.94 (0.34-2.61)	0.876	1.12 (0.54-2.33)	0.37 (0.05-2.77)	0.073			
160-179	1.70 (0.23-12.53)	1.71 (0.23-12.70)		2.50 (0.60-10.35)	no cases				
>= 180	8.79 (1.16-66.39)	no cases		5.87 (0.80-42.80)	no cases				
p-trend	0.65	0.843		0.152	0.271				
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)				
80-84	0.80 (0.48-1.32)	1.02 (0.61-1.70)		0.99 (0.67-1.47)	0.79 (0.36-1.74)				
85-89	0.95 (0.46-1.99)	0.92 (0.42-2.03)		1.11 (0.63-1.94)	0.51 (0.12-2.18)				
90-99	0.72 (0.28-1.82)	1.53 (0.75-3.14)	0.569	1.04 (0.54-2.02)	1.30 (0.43-3.98)	0.766			
100-109	1.63 (0.39-6.80)	1.01 (0.14-7.35)		1.14 (0.28-4.67)	2.42 (0.31-19.06)				
>= 110	4.35 (0.58-32.48)	no cases		3.45 (0.47-25.41)	no cases				
p-trend	0.905	0.549		0.592	1				
Breast Pre Menopausal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)				

120-139	0.83 (0.55-1.25)	1.02 (0.67-1.53)		1.05 (0.77-1.44)	0.65 (0.33-1.27)				
140-159	0.88 (0.35-2.23)	0.93 (0.33-2.60)	0.827	1.11 (0.54-2.31)	0.36 (0.05-2.73)	0.036			
>= 160	2.81 (0.67-11.78)	1.39 (0.19-10.30)		3.06 (0.95-9.86)	no cases				
p-trend	0.816	0.928		0.326	0.099				
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)				
80-89	0.84 (0.54-1.31)	0.99 (0.63-1.56)		1.03 (0.73-1.45)	0.71 (0.34-1.47)				
90-99	0.72 (0.28-1.82)	1.54 (0.75-3.14)	0.503	1.04 (0.54-2.01)	1.31 (0.43-3.99)	0.855			
>= 100	2.05 (0.63-6.69)	0.83 (0.11-6.11)		1.46 (0.46-4.67)	2.00 (0.25-15.83)				
p-trend	0.772	0.534		0.672	0.95				
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)				
88.5-96.6	1.07 (0.70-1.63)	1.29 (0.86-1.95)		1.31 (0.94-1.81)	0.77 (0.39-1.50)				
96.8-105.5	1.01 (0.54-1.86)	0.90 (0.47-1.74)	0.868	1.20 (0.74-1.93)	0.57 (0.19-1.66)	0.109			
105.6-216.6	1.58 (0.73-3.43)	1.58 (0.70-3.56)		1.79 (0.96-3.35)	1.20 (0.34-4.18)				
p-trend	0.436	0.425		0.059	0.517				
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)				
Hypertensive	1.00 (0.60-1.67)	0.87 (0.51-1.49)	0.689	0.96 (0.64-1.44)	0.71 (0.29-1.75)	0.508			

classification														
< 80	1957	132590	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Breast Post Menopausal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	989	64872	1.00 (0.92-1.08)	0.98 (0.91-1.06)	0.98 (0.90-1.06)				0.97 (0.87-1.08)	1.01 (0.90-1.12)		0.99 (0.80-1.22)	0.98 (0.90-1.07)	
85-89	714	41500	1.07 (0.98-1.17)	1.05 (0.96-1.14)	1.05 (0.96-1.16)				1.12 (0.98-1.27)	1.01 (0.90-1.14)		0.97 (0.75-1.25)	1.06 (0.96-1.16)	
90-99	838	51196	1.06 (0.97-1.15)	1.04 (0.95-1.13)	1.04 (0.95-1.14)				1.00 (0.87-1.14)	1.07 (0.96-1.20)	0.555	1.27 (1.01-1.60)	1.01 (0.92-1.11)	0.572
100-109	240	13896	1.18 (1.03-1.36)	1.17 (1.02-1.34)	1.16 (1.00-1.34)				1.26 (1.00-1.58)	1.13 (0.95-1.34)		1.30 (0.86-1.98)	1.16 (1.00-1.34)	
≥ 110	48	3264	1.17 (0.88-1.56)	1.15 (0.86-1.54)	1.23 (0.91-1.66)				0.95 (0.51-1.78)	1.24 (0.90-1.72)		0.79 (0.25-2.47)	1.19 (0.88-1.60)	
p-trend			0.008	0.031	0.028				0.184	0.061		0.093	0.087	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	896	86141	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1873	123928	1.11 (1.02-1.20)	1.08 (1.00-1.17)	1.07 (0.98-1.17)				1.11 (1.00-1.23)	1.06 (0.93-1.21)		1.10 (0.91-1.33)	1.08 (0.99-1.18)	
140-159	1342	68235	1.14 (1.04-1.24)	1.10 (1.00-1.20)	1.10 (1.00-1.21)				1.07 (0.95-1.22)	1.12 (0.98-1.28)	0.473	1.18 (0.93-1.49)	1.09 (0.99-1.20)	0.607
≥ 160	675	29014	1.19 (1.07-1.32)	1.14 (1.03-1.27)	1.13 (1.01-1.27)				1.28 (1.09-1.50)	1.08 (0.93-1.26)		1.31 (0.93-1.84)	1.13 (1.01-1.26)	
p-trend			0.001	0.019	0.027				0.012	0.211		0.074	0.057	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	1957	132590	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1703	106372	1.03 (0.96-1.10)	1.01 (0.94-1.08)	1.01 (0.94-1.08)				1.02 (0.93-1.13)	1.01 (0.92-1.11)		0.98 (0.82-1.18)	1.01 (0.94-1.09)	
90-99	838	51196	1.06 (0.97-1.15)	1.04 (0.95-1.13)	1.04 (0.95-1.14)				1.00 (0.87-1.14)	1.07 (0.96-1.20)	0.402	1.27 (1.01-1.60)	1.01 (0.92-1.11)	0.487
≥ 100	288	17160	1.18 (1.04-1.34)	1.17 (1.03-1.32)	1.17 (1.02-1.34)				1.22 (0.98-1.51)	1.15 (0.98-1.35)		1.22 (0.82-1.81)	1.16 (1.01-1.33)	

p-trend			0.014	0.048	0.054				0.303	0.059		0.08	0.136	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Breast Post Menopausal	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	850	76991	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1141	77727	1.13 (1.03-1.23)	1.10 (1.01-1.21)	1.11 (1.01-1.22)				1.13 (1.01-1.27)	1.08 (0.94-1.25)		1.19 (0.96-1.48)	1.09 (0.98-1.20)	
96.8-105.5	1335	76327	1.17 (1.07-1.27)	1.13 (1.04-1.24)	1.13 (1.03-1.25)				1.11 (0.99-1.25)	1.16 (1.01-1.33)	0.957	1.15 (0.92-1.45)	1.13 (1.02-1.24)	0.302
105.6-216.6	1460	76273	1.19 (1.09-1.30)	1.16 (1.06-1.27)	1.16 (1.05-1.28)				1.20 (1.06-1.36)	1.15 (1.00-1.31)		1.41 (1.11-1.80)	1.13 (1.02-1.24)	
p-trend			0.0001	0.002	0.005				0.01	0.038		0.01	0.019	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	2269	49921	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	2517	53245	1.08 (1.02-1.15)	1.06 (1.00-1.13)	1.07 (1.00-1.14)				1.07 (0.98-1.16)	1.08 (0.99-1.17)	0.623	1.26 (1.06-1.48)	1.04 (0.97-1.11)	0.098

Breast Post Menopausal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	2547	2180		3345	1441		3273	783	
Cohort size	58521	43336		78695	24471		70455	17994	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.007 (0.986-1.029)	1.041 (1.019-1.064)	0.02	1.022 (1.003-1.040)	1.031 (1.003-1.059)	0.873	1.027 (1.007-1.047)	1.020 (0.983-1.058)	0.416

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.036 (0.996-1.077)	1.046 (1.003-1.091)	0.77	1.051 (1.016-1.088)	1.014 (0.962-1.068)	0.225	1.041 (1.004-1.080)	1.049 (0.976-1.127)	0.673
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.022 (0.989-1.057)	1.056 (1.020-1.094)	0.165	1.042 (1.012-1.072)	1.032 (0.988-1.078)	0.561	1.042 (1.010-1.074)	1.042 (0.980-1.107)	0.538
Breast Post Menopausal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.09 (0.96-1.24)	1.01 (0.88-1.16)		1.06 (0.94-1.18)	1.04 (0.88-1.23)		1.00 (0.91-1.12)	0.92 (0.61-1.37)	
130-139	1.10 (0.96-1.25)	1.11 (0.97-1.27)		1.10 (0.98-1.23)	1.15 (0.97-1.36)		1.05 (0.95-1.17)	1.15 (0.80-1.65)	
140-159	1.09 (0.96-1.23)	1.08 (0.95-1.23)	0.059	1.07 (0.96-1.20)	1.15 (0.98-1.35)	0.966	1.05 (0.95-1.17)	1.01 (0.71-1.43)	0.789
160-179	1.01 (0.86-1.19)	1.23 (1.04-1.45)		1.12 (0.98-1.29)	1.08 (0.87-1.34)		1.15 (1.00-1.33)	1.01 (0.70-1.46)	
>= 180	1.14 (0.89-1.45)	1.37 (1.07-1.74)		1.24 (1.01-1.53)	1.26 (0.93-1.73)		1.02 (0.78-1.34)	1.35 (0.90-2.02)	
p-trend	0.52	0.004		0.041	0.073		0.094	0.26	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.96 (0.86-1.07)	1.01 (0.90-1.13)		1.00 (0.91-1.09)	0.96 (0.83-1.10)		0.97 (0.88-1.06)	0.94 (0.74-1.18)	
85-89	1.08 (0.96-1.22)	1.00 (0.87-1.14)		1.04 (0.93-1.15)	1.07 (0.92-1.25)		1.09 (0.99-1.22)	0.87 (0.69-1.11)	
90-99	1.03 (0.92-1.16)	1.05 (0.92-1.19)	0.666	1.11 (1.00-1.23)	0.88 (0.75-1.03)	0.103	1.01 (0.90-1.12)	0.95 (0.77-1.18)	0.828
100-109	1.22 (1.01-1.46)	1.11 (0.90-1.38)		1.17 (0.99-1.38)	1.17 (0.91-1.51)		1.18 (0.97-1.44)	1.35 (1.04-1.75)	
>= 110	1.14 (0.78-1.68)	1.19 (0.77-1.84)		1.18 (0.83-1.67)	1.08 (0.64-1.82)		1.35 (0.88-2.09)	1.07 (0.67-1.73)	
p-trend	0.056	0.267		0.009	0.916		0.105	0.151	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-139	1.09 (0.97-1.23)	1.06 (0.94-1.19)		1.08 (0.98-1.19)	1.09 (0.94-1.26)		1.03 (0.94-1.13)	1.06 (0.74-1.50)	
140-159	1.09 (0.96-1.23)	1.07 (0.94-1.22)	0.065	1.07 (0.96-1.19)	1.15 (0.98-1.35)	0.848	1.05 (0.95-1.17)	1.00 (0.71-1.43)	0.399
>= 160	1.04 (0.89-1.21)	1.25 (1.08-1.46)		1.15 (1.01-1.30)	1.12 (0.92-1.36)		1.13 (0.98-1.29)	1.09 (0.76-1.56)	
p-trend	0.648	0.008		0.064	0.161		0.103	0.696	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.01 (0.92-1.11)	1.00 (0.91-1.11)		1.01 (0.93-1.10)	1.00 (0.89-1.13)		1.02 (0.94-1.10)	0.91 (0.74-1.11)	
90-99	1.03 (0.92-1.16)	1.05 (0.92-1.19)	0.843	1.11 (1.00-1.23)	0.88 (0.75-1.03)	0.084	1.00 (0.90-1.12)	0.95 (0.77-1.18)	0.703
>= 100	1.20 (1.02-1.42)	1.13 (0.93-1.37)		1.17 (1.00-1.36)	1.15 (0.91-1.46)		1.21 (1.00-1.45)	1.29 (1.01-1.66)	
Breast Post Menopausal	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.105	0.244		0.013	0.77		0.238	0.059	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.08 (0.95-1.23)	1.13 (0.99-1.29)		1.14 (1.02-1.27)	1.04 (0.88-1.22)		1.05 (0.95-1.16)	1.11 (0.74-1.68)	
96.8-105.5	1.07 (0.95-1.21)	1.20 (1.06-1.37)	0.1	1.16 (1.04-1.29)	1.08 (0.92-1.27)	0.814	1.09 (0.98-1.20)	1.20 (0.82-1.75)	0.688
105.6-216.6	1.09 (0.96-1.23)	1.24 (1.09-1.41)		1.17 (1.05-1.30)	1.14 (0.97-1.34)		1.12 (1.00-1.24)	1.20 (0.83-1.75)	
p-trend	0.306	0.001		0.011	0.094		0.039	0.315	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.03 (0.95-1.12)	1.09 (0.99-1.19)	0.351	1.04 (0.97-1.12)	1.12 (1.01-1.25)	0.419	1 (referent)	1.04 (0.95-1.15)	

Ovary	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1007	1007	893				512	495		355	652	
Cohort size			19477	19477	19151				104416	90311		99069	95658	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1007	194727	0.995 (0.962-1.029)	0.990 (0.956-1.025)	0.990 (0.954-1.027)				0.990 (0.942-1.042)	0.998 (0.951-1.047)	0.881	1.024 (0.958-1.094)	0.976 (0.937-1.018)	0.237
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1007	194727	0.998 (0.939-1.061)	0.997 (0.936-1.062)	0.988 (0.923-1.056)				1.057 (0.967-1.156)	0.955 (0.874-1.043)	0.086	1.087 (0.975-1.211)	0.954 (0.883-1.032)	0.085
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1007	194727	0.995 (0.945-1.048)	0.991 (0.939-1.046)	0.986 (0.931-1.044)				1.020 (0.945-1.100)	0.977 (0.906-1.052)	0.385	1.061 (0.965-1.167)	0.959 (0.899-1.024)	0.112
Ovary	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg) ESH classification														
< 120	262	65461	1 (reference)	1 (reference)	1 (reference)				1 (reference)	1 (reference)		1 (reference)	1 (reference)	
120-129	202	40944	1.00 (0.83-1.20)	1.00 (0.83-1.20)	0.99 (0.81-1.21)				1.08 (0.84-1.37)	0.90 (0.67-1.21)		1.06 (0.81-1.40)	0.94 (0.72-1.21)	
130-139	206	33415	1.12 (0.93-1.36)	1.11 (0.92-1.35)	1.08 (0.88-1.32)				1.25 (0.97-1.62)	0.98 (0.73-1.30)		1.03 (0.75-1.41)	1.11 (0.87-1.43)	
140-159	233	38168	0.97 (0.80-1.17)	0.95 (0.78-1.15)	0.95 (0.77-1.17)				1.05 (0.81-1.38)	0.86 (0.65-1.15)	0.911	1.01 (0.72-1.43)	0.90 (0.70-1.15)	0.188

classification														
< 80	441	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	371	63015	1.10 (0.96-1.27)	1.11 (0.96-1.27)	1.11 (0.95-1.29)				1.13 (0.92-1.38)	1.07 (0.88-1.32)		1.27 (1.00-1.61)	1.01 (0.85-1.21)	
90-99	154	27199	1.00 (0.83-1.21)	1.00 (0.83-1.21)	0.99 (0.80-1.21)				1.40 (1.07-1.83)	0.79 (0.60-1.03)	0.019	1.26 (0.89-1.78)	0.90 (0.71-1.13)	0.071
>= 100	41	8161	0.87 (0.63-1.21)	0.87 (0.63-1.21)	0.84 (0.59-1.20)				0.85 (0.47-1.53)	0.86 (0.58-1.28)		1.14 (0.61-2.12)	0.77 (0.53-1.14)	
p-trend			0.798	0.79	0.676				0.105	0.125		0.12	0.176	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	240	59270	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	258	49321	1.07 (0.90-1.28)	1.07 (0.90-1.28)	1.03 (0.85-1.25)				1.28 (1.02-1.61)	0.82 (0.61-1.09)		1.19 (0.91-1.56)	0.98 (0.77-1.24)	
96.8-105.5	259	44981	1.07 (0.89-1.28)	1.06 (0.88-1.28)	1.05 (0.86-1.27)				1.05 (0.81-1.36)	1.01 (0.77-1.32)	0.3	1.20 (0.89-1.62)	0.96 (0.76-1.22)	0.293
105.6-216.6	250	41155	1.01 (0.84-1.22)	1.00 (0.82-1.21)	0.99 (0.80-1.21)				1.19 (0.90-1.56)	0.85 (0.64-1.12)		1.11 (0.78-1.59)	0.92 (0.72-1.17)	
p-trend			0.951	0.94	0.911				0.423	0.555		0.398	0.46	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	554	117264	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	453	77463	0.98 (0.86-1.12)	0.97 (0.85-1.11)	1.00 (0.87-1.15)				1.06 (0.87-1.28)	0.93 (0.77-1.12)	0.335	1.27 (1.00-1.60)	0.86 (0.73-1.01)	0.01

Ovary	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	477		777	230		703	112	
Cohort size	85755		149170	45557		147109	23736	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.983 (0.934-1.035)	0.858	0.988 (0.949-1.028)	1.006 (0.934-1.083)	0.956	0.999 (0.955-1.045)	1.008 (0.914-1.113)	0.944

ASH classification								
< 80	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.17 (0.95-1.44)		1.12 (0.95-1.32)	1.09 (0.80-1.48)		1.06 (0.89-1.25)	1.78 (0.95-3.33)	
90-99	1.09 (0.83-1.44)	0.695	0.96 (0.77-1.20)	1.18 (0.80-1.73)	0.575	0.95 (0.74-1.22)	1.41 (0.73-2.73)	0.343
>= 100	0.68 (0.39-1.17)		0.91 (0.63-1.31)	0.77 (0.37-1.60)		0.74 (0.44-1.25)	1.65 (0.77-3.52)	
p-trend	0.903		0.763	0.824		0.515	0.511	
Mean BP (mmHg) (1/3SBP+2/3DBP)								
Cohort-specific quartiles								
50.0-88.3	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	1.11 (0.86-1.44)		1.12 (0.91-1.37)	0.96 (0.65-1.42)		1.15 (0.94-1.41)	-	
96.8-105.5	1.15 (0.88-1.50)	0.946	1.08 (0.87-1.33)	1.06 (0.72-1.57)	0.551	1.14 (0.92-1.42)	-	-
105.6-216.6	0.96 (0.72-1.29)		0.98 (0.78-1.22)	1.13 (0.75-1.70)		1.06 (0.83-1.35)	-	
p-trend	0.878		0.721	0.469		0.585	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)								
Normotensive	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.01 (0.83-1.23)	0.492	0.93 (0.80-1.09)	1.15 (0.87-1.53)	0.327	1 (referent)	0.87 (0.69-1.11)	

Corpus Uteri	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1164	1164	1042				462	702		387	777	
Cohort size			194727	194727	191551				104416	90311		99069	95658	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1164	194727	1.087 (1.055-1.120)	1.037 (1.005-1.070)	1.039 (1.005-1.074)				0.985 (0.934-1.039)	1.097 (1.056-1.140)	0.004	1.024 (0.963-1.088)	1.043 (1.005-1.082)	0.503
Corpus Uteri	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1164	194727	1.149 (1.087-1.214)	1.061 (1.002-1.125)	1.068 (1.005-1.136)				1.003 (0.912-1.104)	1.153 (1.074-1.238)	0.032	1.039 (0.937-1.152)	1.075 (1.002-1.153)	0.44
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1164	194727	1.140 (1.089-1.194)	1.059 (1.009-1.112)	1.064 (1.010-1.121)				0.990 (0.913-1.074)	1.153 (1.086-1.224)	0.006	1.037 (0.948-1.134)	1.071 (1.010-1.136)	0.417
Systolic Blood Pressure (mmHg) ESH classification														
< 120	240	65461	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	207	40944	1.08 (0.89-1.30)	0.98 (0.81-1.18)	0.97 (0.79-1.18)				1.01 (0.78-1.31)	1.05 (0.79-1.39)		0.99 (0.75-1.30)	0.99 (0.77-1.29)	
130-139	223	33415	1.28 (1.06-1.54)	1.08 (0.89-1.31)	1.06 (0.87-1.30)				1.09 (0.83-1.44)	1.25 (0.95-1.63)		1.05 (0.78-1.42)	1.11 (0.87-1.43)	
140-159	323	38168	1.46 (1.22-1.75)	1.16 (0.97-1.40)	1.17 (0.97-1.42)				1.01 (0.76-1.33)	1.49 (1.16-1.92)	0.012	1.22 (0.90-1.65)	1.16 (0.92-1.48)	0.646
160-179	128	13066	1.64 (1.31-2.06)	1.25 (0.99-1.58)	1.23 (0.96-1.58)				1.01 (0.67-1.55)	1.68 (1.24-2.27)		1.06 (0.63-1.79)	1.30 (0.98-1.72)	
>= 180	43	3673	1.97 (1.41-2.75)	1.42 (1.01-1.99)	1.43 (1.00-2.04)				1.02 (0.49-2.14)	2.01 (1.34-3.01)		1.69 (0.73-3.91)	1.41 (0.96-2.08)	
p-trend			0.00000 0004	0.006	0.008				0.858	0.0000 01		0.183	0.013	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	451	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	230	39059	1.06 (0.91-1.25)	0.97 (0.82-1.14)	0.95 (0.80-1.13)				1.07 (0.84-1.36)	0.96 (0.77-1.20)		1.21 (0.93-1.56)	0.85 (0.69-1.05)	
85-89	166	23956	1.17 (0.98-1.40)	1.02 (0.85-1.22)	1.01 (0.83-1.22)				0.83 (0.60-1.15)	1.22 (0.97-1.52)		0.82 (0.57-1.17)	1.10 (0.89-1.36)	
90-99	236	27199	1.43 (1.21-1.68)	1.18 (1.00-1.40)	1.19 (0.99-1.41)				1.18 (0.89-1.57)	1.34 (1.09-1.65)	0.052	1.06 (0.78-1.46)	1.23 (1.01-1.49)	0.292
100-109	71	6720	1.72 (1.34-2.22)	1.39 (1.07-1.80)	1.42 (1.08-1.86)				1.08 (0.61-1.90)	1.75 (1.30-2.36)		1.51 (0.93-2.46)	1.34 (0.99-1.82)	
Corpus Uteri	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					of follow -up HR (adju sted)									
>= 110	10	1441	1.19 (0.63- 2.23)	0.88 (0.47- 1.66)	1.01 (0.53- 1.89)				no cases	1.27 (0.67- 2.41)		1.09 (0.34- 3.44)	0.83 (0.39- 1.76)	
p-trend			0.0000 03	0.016	0.013				0.807	0.0000 3		0.537	0.012	
Systolic Blood Pressure (mmHg) ASH classificatio n														
< 120	240	6546 1	1 (referent)	1 (refere nt)	1 (refere nt)				1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-139	430	7435 9	1.17 (1.00- 1.38)	1.03 (0.87- 1.21)	1.01 (0.85- 1.20)				1.04 (0.83- 1.31)	1.15 (0.90- 1.46)		1.01 (0.80- 1.29)	1.06 (0.84- 1.32)	
140-159	323	3816 8	1.46 (1.22- 1.74)	1.16 (0.97- 1.39)	1.17 (0.96- 1.41)				1.01 (0.76- 1.33)	1.48 (1.15- 1.91)	0.016	1.21 (0.89- 1.64)	1.16 (0.92- 1.47)	0.63
>= 160	171	1673 9	1.70 (1.38- 2.10)	1.28 (1.03- 1.59)	1.27 (1.01- 1.60)				1.01 (0.69- 1.50)	1.74 (1.31- 2.31)		1.17 (0.73- 1.86)	1.32 (1.01- 1.72)	
p-trend			0.00000 003	0.011	0.015				0.957	0.0000 05		0.243	0.02	
Diastolic Blood Pressure (mmHg) ASH classificatio n														
< 80	451	9635 2	1 (referent)	1 (refere nt)	1 (refere nt)				1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-89	396	6301 5	1.11 (0.96- 1.27)	0.99 (0.86- 1.14)	0.98 (0.84- 1.13)				0.98 (0.79- 1.21)	1.07 (0.89- 1.29)		1.06 (0.84- 1.34)	0.96 (0.80- 1.14)	
90-99	236	2719 9	1.42 (1.21- 1.68)	1.18 (1.00- 1.40)	1.19 (0.99- 1.41)				1.18 (0.89- 1.57)	1.34 (1.09- 1.65)	0.12	1.07 (0.78- 1.47)	1.22 (1.00- 1.49)	0.687
>= 100	81	8161	1.63 (1.28- 2.08)	1.30 (1.02- 1.66)	1.34 (1.04- 1.74)				0.94 (0.53- 1.65)	1.66 (1.26- 2.19)		1.45 (0.91- 2.29)	1.25 (0.93- 1.67)	
p-trend			0.00000 03	0.014	0.012				0.556	0.0000 7		0.22	0.029	
Mean BP (mmHg) (1/3SBP+2/ 3DBP) Cohort- specific quartiles														
50.0-88.3	229	5927 0	1 (referent)	1 (refere nt)	1 (refere nt)				1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
88.5-96.6	252	4932 1	1.05 (0.88- 1.26)	0.95 (0.79- 1.14)	0.99 (0.82- 1.20)				0.95 (0.74- 1.21)	1.05 (0.80- 1.37)		1.07 (0.81- 1.41)	0.87 (0.68- 1.11)	
96.8-105.5	306	4498 1	1.24 (1.04- 1.48)	1.03 (0.86- 1.24)	1.06 (0.87- 1.28)				1.07 (0.83- 1.39)	1.17 (0.90- 1.51)	0.02	1.15 (0.86- 1.54)	0.97 (0.77- 1.22)	0.764
105.6-216.6	377	4115 5	1.52 (1.28- 1.81)	1.17 (0.98- 1.40)	1.20 (0.99- 1.45)				0.98 (0.73- 1.30)	1.53 (1.19- 1.97)		1.19 (0.87- 1.64)	1.13 (0.90- 1.41)	

classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.17 (0.90-1.50)	0.79 (0.59-1.06)		0.98 (0.79-1.22)	0.97 (0.64-1.46)		0.96 (0.78-1.19)	1.21 (0.53-2.74)	
130-139	1.21 (0.94-1.56)	0.94 (0.70-1.26)		1.06 (0.85-1.31)	1.19 (0.79-1.78)		1.01 (0.81-1.27)	1.29 (0.60-2.78)	
Corpus Uteri	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
140-159	1.23 (0.96-1.57)	1.15 (0.87-1.52)	0.02	1.05 (0.85-1.30)	1.61 (1.11-2.34)	0.465	1.17 (0.94-1.45)	1.05 (0.50-2.22)	0.686
160-179	1.56 (1.16-2.10)	0.81 (0.54-1.23)		1.21 (0.93-1.57)	1.40 (0.84-2.32)		0.93 (0.66-1.31)	1.45 (0.67-3.11)	
>= 180	1.77 (1.16-2.69)	0.95 (0.51-1.77)		1.42 (0.97-2.08)	1.37 (0.63-2.98)		1.47 (0.89-2.43)	1.36 (0.58-3.20)	
p-trend	0.002	0.611		0.072	0.012		0.21	0.403	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.93 (0.75-1.15)	1.01 (0.79-1.30)		0.90 (0.75-1.09)	1.24 (0.90-1.73)		0.93 (0.77-1.13)	0.81 (0.50-1.31)	
85-89	1.03 (0.82-1.31)	1.00 (0.74-1.34)		0.95 (0.77-1.17)	1.31 (0.90-1.90)		0.95 (0.75-1.19)	0.89 (0.55-1.43)	
90-99	1.33 (1.08-1.64)	0.90 (0.68-1.21)	0.044	1.18 (0.98-1.42)	1.18 (0.82-1.72)	0.615	1.05 (0.84-1.31)	1.04 (0.68-1.59)	0.535
100-109	1.36 (0.98-1.90)	1.39 (0.91-2.12)		1.21 (0.89-1.63)	2.18 (1.32-3.60)		1.36 (0.93-2.01)	1.14 (0.68-1.91)	
>= 110	0.97 (0.46-2.08)	0.72 (0.23-2.28)		0.76 (0.36-1.61)	1.44 (0.45-4.61)		0.77 (0.25-2.40)	0.96 (0.40-2.34)	
p-trend	0.006	0.92		0.118	0.024		0.462	0.38	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.19 (0.95-1.48)	0.86 (0.67-1.10)		1.02 (0.84-1.22)	1.07 (0.76-1.52)		0.98 (0.82-1.18)	1.26 (0.60-2.65)	
140-159	1.23 (0.96-1.57)	1.15 (0.87-1.51)	0.009	1.05 (0.85-1.29)	1.60 (1.10-2.32)	0.509	1.16 (0.93-1.44)	1.05 (0.50-2.21)	0.564
>= 160	1.60 (1.21-2.12)	0.84 (0.58-1.22)		1.25 (0.98-1.60)	1.38 (0.86-2.21)		1.03 (0.76-1.40)	1.42 (0.67-3.03)	
p-trend	0.002	0.904		0.098	0.022		0.34	0.366	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.97 (0.81-1.17)	1.01 (0.81-1.25)		0.92 (0.78-1.08)	1.27 (0.95-1.69)		0.94 (0.79-1.11)	0.85 (0.56-1.29)	
90-99	1.33 (1.08-1.64)	0.91 (0.68-1.21)	0.069	1.18 (0.98-1.42)	1.19 (0.82-1.72)	0.48	1.05 (0.84-1.31)	1.04 (0.68-1.59)	0.524

>= 100	1.29 (0.94-1.76)	1.27 (0.84-1.90)		1.13 (0.84-1.50)	2.05 (1.27-3.29)		1.27 (0.88-1.84)	1.10 (0.68-1.81)	
p-trend	0.008	0.778		0.127	0.015		0.439	0.374	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.10 (0.86-1.41)	0.79 (0.60-1.04)		0.93 (0.76-1.15)	1.03 (0.70-1.54)		0.88 (0.72-1.08)	1.27 (0.55-2.94)	
Corpus Uteri	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
96.8-105.5	1.10 (0.86-1.41)	0.96 (0.73-1.26)	0.008	0.94 (0.76-1.15)	1.44 (0.99-2.10)	0.505	1.02 (0.83-1.25)	1.07 (0.48-2.38)	0.634
105.6-216.6	1.38 (1.08-1.76)	0.90 (0.68-1.20)		1.11 (0.90-1.36)	1.43 (0.97-2.11)		1.03 (0.82-1.28)	1.26 (0.58-2.73)	
p-trend	0.007	0.826		0.233	0.025		0.547	0.569	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.21 (1.03-1.42)	1.08 (0.88-1.32)	0.115	1.11 (0.96-1.28)	1.35 (1.04-1.75)	0.488	1 (referent)	1.32 (1.09-1.58)	

Uterine AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			488	488	431				202	286		181	307	
Cohort size			19477	19477	19155				10441	90311		99069	95658	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	488	3073	1.116 (1.065-1.170)	1.065 (1.013-1.119)	1.069 (1.014-1.127)				1.012 (0.932-1.098)	1.135 (1.067-1.207)	0.063	1.069 (0.977-1.169)	1.065 (1.003-1.131)	0.892
Mean Diastolic Blood Pressure continuous	488	3073	1.215 (1.115-1.325)	1.112 (1.015-1.218)	1.133 (1.028-1.248)				1.040 (0.897-1.205)	1.232 (1.100-1.381)	0.125	1.103 (0.947-1.283)	1.127 (1.005-1.264)	0.592

(per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/3DBP)	488	3073 18	1.196 (1.112- 1.286)	1.106 (1.024- 1.195)	1.120 (1.032- 1.215)				1.028 (0.907- 1.166)	1.223 (1.111- 1.345)	0.063	1.102 (0.966- 1.258)	1.115 (1.013- 1.227)	0.675
continuous (per 10mmHg increase)														
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	91	8614 1	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Uterine AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
120-129	73	6644 6	0.95 (0.69- 1.30)	0.86 (0.63- 1.18)	0.88 (0.63- 1.23)				0.81 (0.53- 1.24)	1.00 (0.62- 1.61)		0.69 (0.44- 1.08)	1.10 (0.69- 1.76)	
130-139	97	5748 2	1.39 (1.03- 1.86)	1.18 (0.87- 1.59)	1.19 (0.86- 1.64)				1.28 (0.85- 1.93)	1.29 (0.82- 2.02)		1.28 (0.85- 1.95)	1.20 (0.77- 1.87)	
140-159	150	6823 5	1.65 (1.24- 2.18)	1.29 (0.96- 1.71)	1.37 (1.01- 1.86)				1.02 (0.66- 1.57)	1.77 (1.17- 2.70)	0.175	1.33 (0.86- 2.06)	1.36 (0.90- 2.07)	0.87
160-179	56	2265 6	1.67 (1.17- 2.39)	1.26 (0.87- 1.83)	1.25 (0.84- 1.86)				1.20 (0.65- 2.19)	1.66 (1.01- 2.74)		1.09 (0.50- 2.34)	1.37 (0.84- 2.21)	
≥ 180	21	6358	2.31 (1.40- 3.82)	1.66 (1.00- 2.77)	1.72 (1.01- 2.95)				1.33 (0.51- 3.49)	2.45 (1.30- 4.61)		2.54 (0.89- 7.23)	1.66 (0.89- 3.08)	
p-trend			0.000 002	0.007	0.007				0.35	0.0002		0.046	0.054	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	157	1325 90	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	103	6487 2	1.22 (0.94- 1.57)	1.11 (0.86- 1.43)	1.10 (0.83- 1.44)				1.03 (0.72- 1.48)	1.28 (0.89- 1.84)		1.45 (0.99- 2.11)	0.91 (0.65- 1.29)	
85-89	69	4150 0	1.25 (0.94- 1.67)	1.07 (0.80- 1.44)	1.12 (0.82- 1.53)				0.78 (0.47- 1.27)	1.46 (1.00- 2.13)		0.92 (0.54- 1.56)	1.17 (0.82- 1.67)	
90-99	123	5119 6	1.75 (1.37- 2.24)	1.42 (1.10- 1.83)	1.51 (1.16- 1.98)				1.23 (0.82- 1.84)	1.86 (1.33- 2.61)	0.063	1.45 (0.93- 2.25)	1.39 (1.01- 1.90)	0.807
100-109	33	1389 6	1.86 (1.27- 2.74)	1.45 (0.98- 2.14)	1.49 (0.98- 2.26)				0.93 (0.40- 2.16)	2.16 (1.36- 3.43)		1.81 (0.91- 3.61)	1.28 (0.79- 2.06)	

>= 110	3	3264	0.95 (0.30-3.00)	0.69 (0.22-2.17)	0.81 (0.26-2.57)				no cases	1.20 (0.37-3.84)		0.93 (0.13-6.79)	0.64 (0.16-2.63)	
p-trend			0.000008	0.016	0.005				0.885	0.00008		0.127	0.048	
Systolic Blood Pressure (mmHg) ASH classification														
< 120	91	86141	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	170	123928	1.15 (0.88-1.49)	1.01 (0.78-1.32)	1.02 (0.77-1.36)				1.01 (0.71-1.43)	1.14 (0.76-1.73)		0.93 (0.65-1.34)	1.15 (0.77-1.74)	
140-159	150	68235	1.63 (1.23-2.15)	1.27 (0.95-1.69)	1.35 (0.99-1.83)				1.00 (0.65-1.54)	1.76 (1.16-2.67)	0.157	1.30 (0.84-2.01)	1.36 (0.89-2.06)	0.775
>= 160	77	29014	1.77 (1.27-2.48)	1.32 (0.94-1.87)	1.32 (0.91-1.92)				1.20 (0.68-2.09)	1.81 (1.13-2.89)		1.31 (0.68-2.52)	1.42 (0.90-2.26)	
p-trend			0.00003	0.032	0.03				0.663	0.0007		0.22	0.075	
Uterine AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Diastolic Blood Pressure (mmHg) ASH classification														
< 80	157	132590	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	172	106372	1.23 (0.99-1.53)	1.09 (0.87-1.37)	1.11 (0.87-1.41)				0.94 (0.68-1.30)	1.35 (0.98-1.86)		1.26 (0.89-1.78)	1.02 (0.76-1.37)	
90-99	123	51196	1.75 (1.37-2.24)	1.42 (1.10-1.83)	1.51 (1.16-1.98)				1.23 (0.82-1.85)	1.86 (1.33-2.61)	0.088	1.46 (0.94-2.27)	1.38 (1.01-1.90)	0.774
>= 100	36	17160	1.73 (1.19-2.50)	1.33 (0.91-1.94)	1.38 (0.92-2.06)				0.82 (0.36-1.91)	2.00 (1.28-3.12)		1.68 (0.87-3.28)	1.18 (0.74-1.88)	
p-trend			0.000005	0.01	0.005				0.718	0.00007		0.04	0.083	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles														
50.0-88.3	80	76991	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	109	77727	1.22 (0.91-1.63)	1.10 (0.82-1.47)	1.12 (0.82-1.54)				1.06 (0.72-1.56)	1.26 (0.78-2.02)		1.05 (0.70-1.58)	1.17 (0.76-1.82)	

96.8-105.5	119	7632 7	1.33 (0.99- 1.78)	1.10 (0.81- 1.48)	1.13 (0.82- 1.56)				1.07 (0.71- 1.62)	1.32 (0.83- 2.10)	0.069	1.15 (0.75- 1.78)	1.12 (0.73- 1.72)	0.744
105.6-216.6	180	7627 3	1.87 (1.41- 2.48)	1.41 (1.05- 1.89)	1.50 (1.09- 2.06)				1.13 (0.73- 1.75)	2.02 (1.30- 3.14)		1.42 (0.90- 2.24)	1.45 (0.96- 2.20)	
p-trend			0.000 005	0.018	0.008				0.587	0.0002		0.131	0.052	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	214	1741 79	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	274	1331 39	1.45 (1.20- 1.75)	1.21 (0.99- 1.47)	1.23 (0.99- 1.51)				0.99 (0.73- 1.35)	1.58 (1.22- 2.06)	0.037	1.18 (0.85- 1.62)	1.26 (0.98- 1.62)	0.563

Uterine AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	298	184		395	93		316	93	
Cohort size	106077	85755		149170	45557		147109	23736	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.104 (1.037-1.175)	1.011 (0.929-1.100)	0.014	1.061 (1.005-1.122)	1.101 (0.979-1.237)	0.907	1.048 (0.980-1.121)	1.067 (0.955-1.192)	0.808
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.175 (1.046-1.320)	1.027 (0.884-1.194)	0.056	1.104 (0.998-1.221)	1.178 (0.951-1.460)	0.919	1.079 (0.956-1.219)	1.036 (0.823-1.306)	0.652
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.170 (1.061-1.290)	1.022 (0.898-1.162)	0.019	1.100 (1.010-1.198)	1.168 (0.974-1.401)	0.997	1.078 (0.971-1.197)	1.082 (0.895-1.308)	0.95

Systolic Blood Pressure (mmHg)									
ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	0.92 (0.61-1.41)	0.74 (0.46-1.20)		0.85 (0.60-1.21)	0.95 (0.48-1.91)		0.78 (0.54-1.11)	-	
130-139	1.21 (0.80-1.81)	1.15 (0.73-1.81)		1.19 (0.86-1.67)	1.14 (0.57-2.27)		1.18 (0.84-1.66)	-	
140-159	1.30 (0.88-1.92)	1.32 (0.85-2.05)	0.091	1.24 (0.90-1.72)	1.59 (0.84-3.02)	0.838	1.27 (0.90-1.79)	-	-
160-179	1.51 (0.95-2.41)	0.88 (0.45-1.72)		1.32 (0.88-1.97)	0.99 (0.37-2.67)		1.07 (0.65-1.78)	-	
>= 180	2.00 (1.08-3.70)	1.20 (0.45-3.18)		1.47 (0.82-2.63)	3.25 (1.10-9.62)		1.64 (0.79-3.43)	-	
p-trend	0.007	0.264		0.022	0.088		0.062	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.02 (0.72-1.44)	1.21 (0.82-1.79)		1.02 (0.77-1.36)	1.51 (0.87-2.62)		0.99 (0.74-1.34)	0.91 (0.38-2.19)	
85-89	1.12 (0.77-1.63)	1.07 (0.67-1.72)		1.05 (0.76-1.45)	1.20 (0.61-2.37)		1.03 (0.72-1.47)	1.13 (0.49-2.63)	
90-99	1.56 (1.13-2.15)	1.15 (0.75-1.77)	0.08	1.45 (1.10-1.92)	1.26 (0.66-2.40)	0.756	1.24 (0.89-1.73)	1.33 (0.62-2.89)	0.986
100-109	1.68 (1.04-2.69)	1.15 (0.56-2.36)		1.24 (0.79-1.95)	2.74 (1.24-6.08)		1.24 (0.68-2.29)	1.31 (0.54-3.16)	
>= 110	0.72 (0.18-2.98)	0.76 (0.10-5.53)		0.82 (0.26-2.60)	no cases		1.27 (0.31-5.21)	0.53 (0.07-4.31)	
p-trend	0.005	0.66		0.031	0.18		0.195	0.428	
Uterine AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	1.06 (0.74-1.52)	0.92 (0.62-1.37)		1.01 (0.75-1.36)	1.03 (0.57-1.88)		0.95 (0.71-1.28)	-	
140-159	1.29 (0.87-1.89)	1.29 (0.83-2.01)	0.065	1.22 (0.89-1.69)	1.57 (0.83-2.97)	0.919	1.24 (0.88-1.75)	-	-
>= 160	1.59 (1.02-2.47)	0.93 (0.51-1.70)		1.33 (0.91-1.94)	1.41 (0.61-3.25)		1.15 (0.72-1.82)	-	
p-trend	0.017	0.568		0.066	0.169		0.241	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

80-89	1.06 (0.79-1.43)	1.16 (0.82-1.64)		1.03 (0.80-1.33)	1.39 (0.84-2.30)		1.01 (0.77-1.31)	1.02 (0.47-2.21)	
90-99	1.55 (1.13-2.14)	1.15 (0.75-1.77)	0.104	1.45 (1.10-1.92)	1.26 (0.66-2.41)	0.955	1.24 (0.89-1.73)	1.32 (0.61-2.86)	0.981
>= 100	1.52 (0.96-2.41)	1.10 (0.55-2.18)		1.17 (0.76-1.81)	2.37 (1.07-5.27)		1.25 (0.70-2.21)	1.19 (0.50-2.82)	
p-trend	0.005	0.542		0.033	0.079		0.21	0.454	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	1.22 (0.81-1.83)	0.96 (0.62-1.49)		1.00 (0.72-1.40)	1.57 (0.78-3.14)		1.06 (0.76-1.47)	-	
96.8-105.5	1.10 (0.73-1.66)	1.10 (0.71-1.72)	0.046	1.01 (0.72-1.40)	1.64 (0.81-3.30)	0.916	1.05 (0.75-1.49)	-	-
105.6-216.6	1.68 (1.12-2.50)	1.09 (0.69-1.73)		1.33 (0.96-1.84)	1.88 (0.92-3.86)		1.32 (0.93-1.90)	-	
p-trend	0.008	0.578		0.049	0.11		0.146	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.37 (1.06-1.77)	1.02 (0.74-1.40)	0.046	1.20 (0.96-1.49)	1.35 (0.86-2.11)	0.902	1 (referent)	1.22 (0.92-1.61)	

Uterine Endometrioid AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			546	546	495				214	332		173	373	
Cohort size			194727	194727	191551				104416	90311		99069	95658	
Mean Systolic Blood Pressure continuous (per	546	30738	1.052 (1.007-1.099)	1.003 (0.958-1.050)	1.003 (0.956-1.053)				0.972 (0.900-1.050)	1.052 (0.994-1.113)	0.186	0.949 (0.863-1.043)	1.024 (0.971-1.080)	0.212

10mmHg increase)														
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	546	3073 18	1.092 (1.008- 1.183)	1.016 (0.934- 1.105)	1.006 (0.921- 1.099)				0.980 (0.852- 1.127)	1.090 (0.984- 1.208)	0.284	0.934 (0.799- 1.092)	1.054 (0.955- 1.164)	0.237
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	546	3073 18	1.085 (1.015- 1.160)	1.010 (0.940- 1.084)	1.005 (0.933- 1.084)				0.969 (0.861- 1.090)	1.085 (0.995- 1.184)	0.195	0.931 (0.811- 1.068)	1.045 (0.962- 1.136)	0.198
Systolic Blood Pressure (mmHg) ESH classification														
< 120	126	8614 1	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	108	6644 6	1.13 (0.87- 1.46)	1.03 (0.79- 1.33)	1.01 (0.77- 1.33)				1.14 (0.79- 1.65)	1.03 (0.71- 1.50)		1.30 (0.89- 1.92)	0.88 (0.62- 1.25)	
130-139	105	5748 2	1.21 (0.93- 1.58)	1.03 (0.78- 1.35)	1.01 (0.76- 1.34)				1.09 (0.72- 1.63)	1.13 (0.78- 1.63)		1.00 (0.63- 1.57)	1.04 (0.74- 1.46)	
140-159	140	6823 5	1.33 (1.03- 1.71)	1.06 (0.82- 1.38)	1.05 (0.80- 1.38)				0.98 (0.65- 1.48)	1.28 (0.90- 1.81)	0.247	0.96 (0.59- 1.56)	1.10 (0.80- 1.51)	0.229
160-179	51	2265 6	1.43 (1.02- 2.00)	1.10 (0.77- 1.55)	1.09 (0.76- 1.57)				0.95 (0.49- 1.84)	1.39 (0.90- 2.13)		0.82 (0.34- 1.94)	1.16 (0.78- 1.72)	
>= 180	16	6358	1.56 (0.92- 2.66)	1.13 (0.66- 1.94)	1.09 (0.62- 1.94)				0.97 (0.30- 3.16)	1.47 (0.79- 2.76)		0.59 (0.08- 4.30)	1.23 (0.69- 2.19)	
p-trend			0.006	0.516	0.6				0.843	0.041		0.5	0.191	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	244	1325 90	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Uterine Endometrioid AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	105	6487 2	0.99 (0.79- 1.25)	0.90 (0.71- 1.14)	0.90 (0.71- 1.15)				1.10 (0.78- 1.55)	0.84 (0.61- 1.15)		1.10 (0.75- 1.61)	0.81 (0.60- 1.09)	

85-89	74	4150 0	1.06 (0.82- 1.38)	0.93 (0.71- 1.22)	0.88 (0.67- 1.17)				0.82 (0.51- 1.35)	1.06 (0.77- 1.46)		0.68 (0.39- 1.17)	1.04 (0.76- 1.42)	
90-99	91	5119 6	1.23 (0.96- 1.57)	1.04 (0.81- 1.33)	0.99 (0.76- 1.29)				1.09 (0.69- 1.70)	1.14 (0.84- 1.54)	0.414	0.73 (0.43- 1.23)	1.18 (0.89- 1.58)	0.074
100-109	29	1389 6	1.59 (1.08- 2.35)	1.32 (0.89- 1.96)	1.32 (0.87- 2.00)				1.12 (0.45- 2.75)	1.57 (1.01- 2.44)		1.23 (0.56- 2.71)	1.36 (0.86- 2.14)	
>= 110	3	3264	0.72 (0.23- 2.25)	0.54 (0.17- 1.71)	0.61 (0.19- 1.92)				no cases	0.75 (0.24- 2.37)		no cases	0.74 (0.23- 2.34)	
p-trend			0.036	0.634	0.873				0.911	0.117		0.188	0.153	
Systolic Blood Pressure (mmHg)														
ASH classificatio n														
< 120	126	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)				1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-139	213	1239 28	1.17 (0.93- 1.46)	1.03 (0.82- 1.29)	1.01 (0.80- 1.28)				1.12 (0.81- 1.54)	1.08 (0.78- 1.50)		1.17 (0.83- 1.67)	0.96 (0.71- 1.30)	
140-159	140	6823 5	1.32 (1.03- 1.71)	1.06 (0.82- 1.38)	1.05 (0.80- 1.38)				0.98 (0.65- 1.48)	1.28 (0.90- 1.81)	0.275	0.97 (0.60- 1.58)	1.09 (0.79- 1.50)	0.391
>= 160	67	2901 4	1.45 (1.06- 1.99)	1.10 (0.80- 1.52)	1.09 (0.78- 1.53)				0.96 (0.53- 1.75)	1.40 (0.94- 2.10)		0.78 (0.35- 1.77)	1.17 (0.81- 1.69)	
p-trend			0.008	0.508	0.584				0.886	0.048		0.729	0.261	
Diastolic Blood Pressure (mmHg)														
ASH classificatio n														
< 80	244	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)				1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-89	179	1063 72	1.02 (0.84- 1.24)	0.91 (0.75- 1.12)	0.90 (0.73- 1.10)				1.00 (0.73- 1.36)	0.93 (0.72- 1.21)		0.94 (0.67- 1.33)	0.91 (0.71- 1.15)	
90-99	91	5119 6	1.23 (0.96- 1.57)	1.04 (0.81- 1.34)	0.99 (0.76- 1.29)				1.09 (0.70- 1.70)	1.14 (0.84- 1.54)	0.599	0.73 (0.43- 1.23)	1.18 (0.89- 1.57)	0.202
>= 100	32	1716 0	1.43 (0.99- 2.08)	1.17 (0.80- 1.70)	1.18 (0.79- 1.75)				0.94 (0.38- 2.32)	1.40 (0.92- 2.14)		0.99 (0.45- 2.17)	1.23 (0.80- 1.90)	
p-trend			0.032	0.581	0.768				0.867	0.145		0.409	0.227	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
Uterine Endometrioi d AC	Cas es	Coh ort	HR (crud e)	HR (adju sted)	Exclu ding first 2 years of follow- up	Men HR (adju sted)	Wome n HR (adju sted)	Sex p- interac tion	BMI <= 25 mg/m² HR (adju sted)	BMI > 25 mg/m² HR (adju sted)	BMI p- interac tion	Age <= 53 yrs HR (adju sted)	Age > 53 yrs HR (adju sted)	Age p- interac tion

					HR (adjusted)									
50.0-88.3	126	7699 1	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	115	7772 7	0.93 (0.72-1.20)	0.85 (0.66-1.10)	0.89 (0.68-1.17)				0.90 (0.63-1.30)	0.86 (0.60-1.25)		1.10 (0.74-1.63)	0.72 (0.51-1.01)	
96.8-105.5	155	7632 7	1.21 (0.95-1.54)	1.01 (0.79-1.29)	1.02 (0.78-1.32)				1.10 (0.77-1.59)	1.08 (0.77-1.52)	0.321	1.09 (0.71-1.66)	0.97 (0.71-1.32)	0.43
105.6-216.6	150	7627 3	1.25 (0.97-1.60)	0.97 (0.75-1.26)	0.95 (0.72-1.25)				0.87 (0.57-1.35)	1.18 (0.84-1.66)		0.82 (0.50-1.37)	0.99 (0.73-1.35)	
p-trend			0.021	0.787	0.963				0.857	0.114		0.594	0.447	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	269	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	277	1331 39	1.30 (1.09-1.55)	1.11 (0.92-1.33)	1.10 (0.91-1.33)	NA (NA-NA)	NA (NA-NA)	NA	0.93 (0.69-1.26)	1.36 (1.08-1.72)	0.062	0.98 (0.70-1.37)	1.18 (0.95-1.47)	0.373

Uterine Endometrioid AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	325	216		397	149		362	96	
Cohort size	106077	85755		149170	45557		147109	23736	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.019 (0.961-1.082)	0.969 (0.899-1.043)	0.098	0.985 (0.933-1.041)	1.046 (0.962-1.138)	0.574	0.995 (0.936-1.058)	0.973 (0.874-1.084)	0.978
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.024 (0.919-1.141)	0.977 (0.855-1.117)	0.316	0.994 (0.900-1.097)	1.081 (0.921-1.268)	0.94	1.005 (0.901-1.122)	0.994 (0.813-1.215)	0.857
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.027 (0.937-1.126)	0.964 (0.861-1.081)	0.154	0.985 (0.906-1.072)	1.075 (0.942-1.227)	0.737	0.999 (0.909-1.097)	0.974 (0.819-1.158)	0.918
Uterine Endometrioid AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment	Antihypertensive treatment	Treatment

							treatment HR (adjusted)	HR (adjusted)	p- interacti on
Systolic Blood Pressure (mmHg)									
ESH classificatio n									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.22 (0.86- 1.74)	0.87 (0.58- 1.30)		1.11 (0.82- 1.50)	0.80 (0.47- 1.38)		1.09 (0.81- 1.46)	0.79 (0.28- 2.22)	
130-139	1.26 (0.88- 1.80)	0.78 (0.50- 1.20)		1.02 (0.74- 1.39)	1.07 (0.63- 1.82)		0.94 (0.68- 1.30)	0.97 (0.39- 2.44)	
140-159	1.09 (0.76- 1.56)	1.11 (0.75- 1.64)	0.225	0.95 (0.70- 1.30)	1.43 (0.88- 2.31)	0.524	1.17 (0.86- 1.59)	0.70 (0.28- 1.74)	0.932
160-179	1.34 (0.86- 2.08)	0.75 (0.40- 1.37)		1.01 (0.66- 1.52)	1.36 (0.71- 2.59)		0.81 (0.47- 1.37)	0.98 (0.38- 2.52)	
>= 180	1.28 (0.64- 2.56)	0.91 (0.37- 2.20)		1.27 (0.69- 2.32)	0.75 (0.22- 2.53)		1.59 (0.76- 3.33)	0.64 (0.19- 2.09)	
p-trend	0.418	0.896		0.91	0.16		0.67	0.695	
Diastolic Blood Pressure (mmHg)									
ESH classificatio n									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.93 (0.69- 1.26)	0.84 (0.58- 1.22)		0.89 (0.68- 1.17)	0.96 (0.61- 1.50)		0.93 (0.71- 1.23)	0.70 (0.36- 1.35)	
85-89	0.86 (0.60- 1.22)	1.05 (0.70- 1.58)		0.81 (0.59- 1.12)	1.29 (0.80- 2.07)		0.86 (0.61- 1.21)	0.76 (0.39- 1.47)	
90-99	1.18 (0.86- 1.61)	0.79 (0.51- 1.22)	0.255	1.09 (0.82- 1.45)	0.94 (0.56- 1.58)	0.881	0.95 (0.68- 1.34)	0.86 (0.48- 1.54)	0.863
100-109	1.23 (0.73- 2.06)	1.27 (0.67- 2.43)		1.25 (0.79- 1.99)	1.55 (0.73- 3.30)		1.56 (0.90- 2.71)	0.93 (0.44- 1.98)	
>= 110	0.56 (0.14- 2.29)	0.47 (0.06- 3.39)		no cases	2.13 (0.65- 6.96)		0.53 (0.07- 3.81)	0.62 (0.14- 2.71)	
p-trend	0.512	0.659		0.992	0.306		0.983	0.844	
Systolic Blood Pressure (mmHg)									
ASH classificatio n									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.24 (0.91- 1.69)	0.83 (0.58- 1.18)		1.06 (0.82- 1.39)	0.93 (0.59- 1.46)		1.02 (0.79- 1.33)	0.91 (0.37- 2.22)	
140-159	1.09 (0.76- 1.56)	1.11 (0.76- 1.64)	0.216	0.95 (0.70- 1.30)	1.42 (0.88- 2.29)	0.577	1.17 (0.86- 1.60)	0.71 (0.29- 1.75)	0.928
>= 160	1.32 (0.87- 2.01)	0.79 (0.46- 1.36)		1.07 (0.73- 1.56)	1.19 (0.64- 2.21)		0.96 (0.61- 1.52)	0.89 (0.35- 2.26)	
p-trend	0.402	0.905		0.977	0.194		0.631	0.762	
Diastolic Blood Pressure (mmHg)									
ASH classificatio n									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.90 (0.69- 1.17)	0.92 (0.68- 1.26)		0.86 (0.68- 1.09)	1.09 (0.75- 1.58)		0.90 (0.71- 1.15)	0.73 (0.42- 1.27)	
90-99	1.18 (0.87- 1.61)	0.79 (0.50- 1.22)	0.189	1.09 (0.82- 1.45)	0.94 (0.56- 1.58)	0.904	0.95 (0.68- 1.34)	0.86 (0.48- 1.54)	0.904

Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	223	1947	0.986 (0.882-1.103)	0.980 (0.872-1.101)	1.015 (0.895-1.152)				1.074 (0.911-1.266)	0.889 (0.754-1.047)	0.225	1.093 (0.915-1.305)	0.897 (0.768-1.047)	0.099	
Cervix Uteri	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction	
Systolic Blood Pressure (mmHg) ESH classification															
< 120	68	65461	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)		
120-129	59	40944	1.40 (0.98-2.00)	1.39 (0.97-2.00)	1.21 (0.80-1.83)				1.20 (0.75-1.93)	1.70 (0.93-3.09)		1.26 (0.78-2.06)	1.46 (0.83-2.55)		
130-139	37	33415	1.09 (0.72-1.67)	1.10 (0.72-1.68)	1.17 (0.74-1.85)				0.83 (0.44-1.56)	1.44 (0.76-2.72)		1.66 (0.96-2.87)	0.71 (0.37-1.38)		
140-159	33	38168	0.80 (0.51-1.26)	0.80 (0.51-1.27)	0.91 (0.56-1.48)				0.50 (0.23-1.11)	1.05 (0.55-2.01)	0.478	0.72 (0.31-1.65)	0.74 (0.41-1.34)	0.151	
160-179	22	13066	1.50 (0.89-2.54)	1.49 (0.87-2.55)	1.59 (0.89-2.84)				3.01 (1.54-5.88)	0.80 (0.33-1.93)		2.23 (0.84-5.90)	1.18 (0.60-2.31)		
>= 180	4	3673	0.95 (0.34-2.69)	0.91 (0.32-2.60)	1.16 (0.40-3.32)				1.80 (0.41-7.81)	0.62 (0.14-2.79)		2.03 (0.27-15.36)	0.68 (0.20-2.34)		
p-trend			0.923	0.887	0.568				0.41	0.246		0.315	0.263		
Diastolic Blood Pressure (mmHg) ESH classification															
< 80	107	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)		
80-84	45	39059	1.01 (0.71-1.44)	1.00 (0.70-1.43)	0.92 (0.61-1.38)				0.99 (0.60-1.63)	0.98 (0.59-1.65)		1.26 (0.76-2.09)	0.80 (0.48-1.31)		
85-89	33	23956	1.21 (0.81-1.80)	1.21 (0.81-1.81)	1.42 (0.93-2.17)				1.25 (0.69-2.25)	1.19 (0.68-2.07)		1.97 (1.12-3.45)	0.76 (0.43-1.37)		
90-99	28	27199	0.89 (0.58-1.37)	0.87 (0.56-1.34)	0.90 (0.56-1.45)				0.78 (0.38-1.59)	0.91 (0.52-1.59)	0.545	1.04 (0.51-2.10)	0.72 (0.41-1.25)	0.123	
100-109	10	6720	1.30 (0.68-2.52)	1.28 (0.66-2.50)	1.41 (0.69-2.85)				2.08 (0.81-5.31)	0.93 (0.36-2.38)		1.51 (0.46-4.95)	1.07 (0.48-2.40)		
>= 110	0	1441													
p-trend			0.949	0.842	0.769				0.75	0.594		0.336	0.252		

Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	68	65461	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	96	74359	1.27 (0.92-1.76)	1.27 (0.91-1.78)	1.20 (0.83-1.73)				1.06 (0.69-1.64)	1.58 (0.91-2.74)		1.40 (0.91-2.15)	1.09 (0.64-1.84)	
Cervix Uteri	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
140-159	33	38168	0.81 (0.52-1.27)	0.82 (0.52-1.29)	0.91 (0.56-1.49)				0.51 (0.23-1.13)	1.06 (0.55-2.03)	0.306	0.70 (0.31-1.62)	0.75 (0.41-1.37)	0.371
>= 160	26	16739	1.41 (0.85-2.32)	1.39 (0.83-2.32)	1.50 (0.86-2.60)				2.84 (1.48-5.44)	0.77 (0.34-1.75)		2.15 (0.87-5.34)	1.08 (0.56-2.08)	
p-trend			0.672	0.697	0.427				0.15	0.295		0.366	0.709	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	107	96352	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	78	63015	1.08 (0.80-1.46)	1.08 (0.79-1.46)	1.10 (0.79-1.54)				1.07 (0.70-1.64)	1.06 (0.69-1.65)		1.49 (0.97-2.29)	0.78 (0.51-1.20)	
90-99	28	27199	0.89 (0.58-1.37)	0.87 (0.56-1.34)	0.90 (0.56-1.44)				0.77 (0.38-1.59)	0.91 (0.52-1.59)	0.533	1.02 (0.50-2.08)	0.72 (0.41-1.25)	0.182
>= 100	10	8161	1.07 (0.55-2.06)	1.03 (0.53-2.01)	1.13 (0.56-2.29)				1.76 (0.69-4.48)	0.73 (0.28-1.86)		1.19 (0.36-3.93)	0.87 (0.39-1.95)	
p-trend			0.916	0.804	0.986				0.762	0.543		0.451	0.297	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	67	59270	1 (referent)	1 (referent)	1 (referent)				1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	60	49321	1.09 (0.76-1.56)	1.09 (0.76-1.57)	1.06 (0.70-1.58)				1.03 (0.64-1.64)	1.14 (0.64-2.04)		1.37 (0.85-2.21)	0.80 (0.47-1.38)	
96.8-105.5	50	44981	0.99 (0.67-1.46)	0.98 (0.66-1.46)	1.13 (0.74-1.73)				0.83 (0.47-1.47)	1.07 (0.60-1.93)	0.512	1.45 (0.83-2.53)	0.64 (0.37-1.11)	0.098
105.6-216.6	46	41155	0.94 (0.62-1.42)	0.92 (0.60-1.41)	1.01 (0.64-1.61)				1.24 (0.69-2.21)	0.76 (0.41-1.41)		1.15 (0.57-2.32)	0.68 (0.40-1.16)	

p-trend			0.697	0.637	0.875				0.761	0.293		0.392	0.134	
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)														
Normotensive	136	117264	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	87	77463	0.92 (0.69-1.23)	0.91 (0.68-1.23)	0.96 (0.70-1.33)	NA (NA-NA)	NA (NA-NA)	NA	1.08 (0.71-1.64)	0.77 (0.52-1.16)	0.342	1.08 (0.69-1.70)	0.80 (0.54-1.17)	0.26

Cervix Uteri	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol \leq 12g HR (adjusted)	Alcohol $>$ 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	100	121		173	50		165	28	
Cohort size	106077	85755		149170	45557		147109	23736	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.992 (0.884-1.112)	0.977 (0.880-1.085)	0.542	0.995 (0.911-1.086)	0.934 (0.795-1.098)	0.657	0.997 (0.907-1.097)	0.861 (0.696-1.066)	0.495
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.960 (0.783-1.178)	0.993 (0.826-1.193)	0.778	0.959 (0.821-1.120)	1.006 (0.759-1.334)	0.528	1.001 (0.848-1.182)	0.824 (0.562-1.208)	0.578
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	0.974 (0.817-1.161)	0.979 (0.836-1.146)	0.637	0.976 (0.854-1.115)	0.952 (0.747-1.212)	0.91	0.999 (0.864-1.154)	0.800 (0.571-1.119)	0.484
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	1.12 (0.63-1.98)	1.71 (1.07-2.74)		1.40 (0.93-2.11)	1.35 (0.60-3.01)		1.38 (0.93-2.05)	-	
130-139	1.11 (0.60-2.07)	0.99 (0.54-1.84)		1.01 (0.61-1.66)	1.46 (0.61-3.47)		1.09 (0.67-1.77)	-	
140-159	0.68 (0.34-1.36)	0.94 (0.51-1.74)	0.713	0.77 (0.45-1.32)	0.85 (0.33-2.18)	0.79	0.57 (0.31-1.04)	-	-
160-179	1.24 (0.56-2.76)	1.68 (0.80-3.50)		1.66 (0.92-3.00)	0.90 (0.24-3.44)		1.69 (0.87-3.27)	-	

>= 180	1.17 (0.33-4.15)	0.50 (0.07-3.79)		0.92 (0.28-3.06)	0.74 (0.09-6.20)		1.63 (0.49-5.41)	-	
p-trend	0.827	0.951		0.988	0.621		0.873	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.93 (0.54-1.61)	1.08 (0.67-1.74)		0.88 (0.58-1.34)	1.41 (0.69-2.92)		1.10 (0.74-1.64)	0.55 (0.13-2.31)	
85-89	1.37 (0.78-2.42)	1.02 (0.56-1.86)		1.20 (0.76-1.90)	1.22 (0.50-2.97)		1.18 (0.72-1.93)	1.45 (0.47-4.48)	
90-99	0.63 (0.31-1.26)	1.05 (0.59-1.87)	0.599	0.82 (0.50-1.36)	0.98 (0.39-2.42)	0.554	0.89 (0.51-1.55)	0.75 (0.25-2.27)	0.534
100-109	1.66 (0.72-3.84)	0.81 (0.25-2.63)		1.12 (0.51-2.46)	1.43 (0.38-5.39)		1.69 (0.73-3.95)	0.47 (0.09-2.47)	
>= 110							no cases	no cases	
p-trend	0.809	0.81		0.658	0.969		0.795	0.343	
Cervix Uteri	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	1.11 (0.67-1.86)	1.43 (0.91-2.23)		1.24 (0.85-1.82)	1.39 (0.68-2.88)		1.27 (0.88-1.82)	-	
140-159	0.68 (0.34-1.36)	0.97 (0.53-1.81)	0.992	0.79 (0.46-1.35)	0.85 (0.33-2.17)	0.585	0.57 (0.31-1.06)	-	-
>= 160	1.23 (0.58-2.60)	1.47 (0.72-3.02)		1.54 (0.87-2.72)	0.85 (0.25-2.90)		1.71 (0.92-3.17)	-	
p-trend	0.896	0.52		0.525	0.6		0.76	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.10 (0.70-1.73)	1.06 (0.70-1.60)		1.00 (0.71-1.41)	1.34 (0.70-2.57)		1.13 (0.80-1.60)	0.99 (0.35-2.86)	
90-99	0.62 (0.31-1.25)	1.05 (0.59-1.87)	0.681	0.82 (0.50-1.35)	0.98 (0.39-2.42)	0.393	0.89 (0.51-1.54)	0.74 (0.24-2.25)	0.33
>= 100	1.33 (0.57-3.06)	0.68 (0.21-2.19)		0.90 (0.41-1.99)	1.17 (0.31-4.35)		1.41 (0.60-3.28)	0.36 (0.07-1.89)	
p-trend	0.729	0.856		0.532	0.827		0.73	0.198	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	

88.5-96.6	0.98 (0.55-1.75)	1.21 (0.76-1.93)		1.00 (0.66-1.50)	1.58 (0.71-3.52)		1.03 (0.69-1.55)	-	
96.8-105.5	1.10 (0.61-1.98)	0.85 (0.49-1.48)	0.563	0.86 (0.55-1.37)	1.43 (0.62-3.31)	0.892	1.03 (0.66-1.61)	-	-
105.6-216.6	0.87 (0.46-1.67)	0.96 (0.54-1.70)		0.97 (0.60-1.55)	0.70 (0.26-1.93)		0.88 (0.52-1.49)	-	
p-trend	0.773	0.651		0.751	0.506		0.742	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.80 (0.51-1.25)	0.96 (0.64-1.44)	0.989	0.92 (0.65-1.29)	0.84 (0.45-1.57)	0.803	1 (referent)	1.30 (0.78-2.16)	

Cervix SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			145	145	120				77	68		67	78	
Cohort size			19477	19477	19155				10441	90311		99069	95658	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	145	3073	0.909 (0.826-1.000)	0.910 (0.825-1.004)	0.937 (0.842-1.042)				1.008 (0.876-1.159)	0.812 (0.707-0.933)	0.641	0.974 (0.823-1.152)	0.875 (0.774-0.989)	0.63
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	145	3073	0.885 (0.750-1.045)	0.884 (0.744-1.049)	0.935 (0.776-1.127)				1.039 (0.819-1.317)	0.737 (0.574-0.945)	0.193	0.957 (0.738-1.241)	0.829 (0.659-1.043)	0.692
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per	145	3073	0.877 (0.760-1.011)	0.875 (0.754-1.015)	0.920 (0.783-1.081)				1.025 (0.834-1.260)	0.730 (0.589-0.904)	0.326	0.959 (0.758-1.215)	0.821 (0.677-0.994)	0.616

90 mmHg, or self-reported)														
Normotensive	94	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	51	133139	0.71 (0.50-1.02)	0.71 (0.49-1.03)	0.77 (0.51-1.15)	NA (NA-NA)	NA (NA-NA)	NA	0.85 (0.50-1.46)	0.58 (0.35-0.97)	0.863	0.59 (0.30-1.14)	0.76 (0.48-1.21)	0.403

Cervix SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)
Cases	55	90		117	28		109
Cohort size	106077	85755		149170	45557		147109
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.843 (0.714-0.996)	0.949 (0.840-1.073)	0.619	0.916 (0.821-1.023)	0.864 (0.693-1.078)	0.925	0.910 (0.804-1.029)
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.814 (0.612-1.082)	0.927 (0.747-1.151)	0.664	0.889 (0.734-1.075)	0.776 (0.517-1.165)	0.765	0.923 (0.750-1.136)
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	0.791 (0.616-1.015)	0.926 (0.769-1.115)	0.615	0.882 (0.747-1.041)	0.788 (0.559-1.112)	0.906	0.894 (0.744-1.074)
Systolic Blood Pressure (mmHg)							
ESH classification							
Cervix SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)
120-129	0.89 (0.42-1.87)	1.02 (0.58-1.80)		1.09 (0.66-1.78)	0.46 (0.14-1.45)		0.97 (0.60-1.59)
130-139	1.02 (0.47-2.20)	0.56 (0.26-1.20)		0.83 (0.46-1.49)	0.58 (0.18-1.85)		0.70 (0.38-1.30)
140-159	0.26 (0.09-0.76)	0.79 (0.41-1.53)	0.505	0.53 (0.27-1.01)	0.50 (0.16-1.54)	0.957	0.41 (0.19-0.85)
160-179	0.46 (0.14-1.54)	1.14 (0.49-2.65)		1.01 (0.48-2.13)	0.25 (0.03-2.12)		0.80 (0.32-2.01)
>= 180	0.39 (0.05-3.14)	0.46 (0.06-3.50)		0.30 (0.04-2.24)	0.54 (0.06-5.18)		1.13 (0.26-4.91)
p-trend	0.029	0.464		0.112	0.213		0.079

Diastolic Blood Pressure (mmHg)							
ESH classification							
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)
80-84	0.78 (0.38-1.61)	0.71 (0.39-1.29)		0.69 (0.41-1.17)	0.84 (0.31-2.29)		0.73 (0.43-1.24)
85-89	0.91 (0.41-2.00)	1.01 (0.53-1.93)		0.94 (0.53-1.66)	1.12 (0.37-3.34)		1.12 (0.63-2.01)
90-99	0.51 (0.20-1.29)	0.71 (0.35-1.44)	0.855	0.73 (0.40-1.33)	0.27 (0.05-1.37)	0.758	0.58 (0.27-1.25)
100-109	0.74 (0.17-3.24)	0.88 (0.27-2.89)		0.62 (0.19-2.00)	0.87 (0.15-4.96)		1.45 (0.52-4.09)
>= 110	no cases	no cases		no cases	no cases		no cases
p-trend	0.179	0.369		0.178	0.26		0.486
Systolic Blood Pressure (mmHg)							
ASH classification							
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)
120-139	0.95 (0.49-1.82)	0.83 (0.49-1.40)		0.98 (0.63-1.54)	0.51 (0.19-1.32)		0.87 (0.55-1.35)
140-159	0.26 (0.09-0.75)	0.81 (0.42-1.57)	0.312	0.54 (0.28-1.03)	0.50 (0.16-1.53)	0.713	0.41 (0.20-0.87)
>= 160	0.44 (0.15-1.34)	1.01 (0.45-2.29)		0.86 (0.42-1.79)	0.33 (0.06-1.74)		0.88 (0.39-2.01)
p-trend	0.021	0.793		0.238	0.151		0.137
Diastolic Blood Pressure (mmHg)							
ASH classification							
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)
80-89	0.83 (0.45-1.53)	0.82 (0.50-1.33)		0.79 (0.51-1.21)	0.94 (0.40-2.19)		0.86 (0.56-1.33)
90-99	0.51 (0.20-1.29)	0.71 (0.35-1.44)	0.888	0.72 (0.39-1.33)	0.27 (0.05-1.36)	0.668	0.58 (0.27-1.24)
>= 100	0.60 (0.14-2.61)	0.73 (0.22-2.40)		0.50 (0.15-1.63)	0.72 (0.13-4.03)		1.19 (0.42-3.35)
p-trend	0.16	0.279		0.115	0.247		0.36
Mean BP (mmHg) (1/3SBP+2/3DBP)							
Cohort-specific quartiles							
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)
88.5-96.6	0.81 (0.39-1.70)	0.95 (0.55-1.64)		0.91 (0.56-1.49)	0.73 (0.26-2.06)		0.79 (0.48-1.30)
96.8-105.5	0.81 (0.38-1.73)	0.70 (0.37-1.33)	0.591	0.75 (0.43-1.29)	0.74 (0.26-2.11)	0.742	0.85 (0.49-1.44)
105.6-216.6	0.35 (0.14-0.89)	0.81 (0.42-1.55)		0.69 (0.38-1.24)	0.25 (0.06-1.01)		0.57 (0.29-1.12)
p-trend	0.042	0.375		0.165	0.068		0.141
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)							
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-
Hypertensive	0.50 (0.27-0.93)	0.89 (0.56-1.41)	0.352	0.68 (0.45-1.04)	0.78 (0.34-1.78)	0.728	1 (referent)

Cervix AC	Cases	Total	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)
Cases			37	37	31
Total			194727	194727	191551
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	37	307318	0.968 (0.798-1.174)	0.962 (0.789-1.171)	1.003 (0.805-1.251)
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	37	307318	0.850 (0.606-1.192)	0.838 (0.592-1.187)	0.778 (0.525-1.152)
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	37	307318	0.900 (0.672-1.205)	0.889 (0.659-1.201)	0.883 (0.628-1.242)
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)					
Normotensive	23	174179	1 (referent)	1 (referent)	1 (referent)
Hypertensive	14	133139	1.17 (0.57-2.40)	1.23 (0.58-2.60)	1.40 (0.62-3.16)

Cervix Other	Cases	Total	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)
Cases			41	41	36
Total			194727	194727	191551
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	41	307318	1.278 (1.106-1.478)	1.276 (1.098-1.483)	1.270 (1.081-1.491)
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	41	307318	1.541 (1.187-2.001)	1.534 (1.169-2.012)	1.541 (1.155-2.056)
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	41	307318	1.489 (1.193-1.859)	1.489 (1.183-1.874)	1.486 (1.163-1.899)
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)					
Normotensive	19	174179	1 (referent)	1 (referent)	1 (referent)
Hypertensive	22	133139	1.88 (0.97-3.65)	1.82 (0.92-3.63)	1.62 (0.78-3.40)

classification														
< 80	93	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Anogenital (not cervix)	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow- up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p- interac- tion	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p- interac- tion	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p- interac- tion
80-84	56	6487 2	1.05 (0.75- 1.47)	1.05 (0.75- 1.47)	1.14 (0.80- 1.63)	0.81 (0.40- 1.67)	1.15 (0.78- 1.69)		0.79 (0.45- 1.36)	1.34 (0.86- 2.10)		1.01 (0.54- 1.89)	1.05 (0.70- 1.57)	
85-89	30	4150 0	0.81 (0.53- 1.23)	0.80 (0.52- 1.22)	0.85 (0.55- 1.32)	0.64 (0.27- 1.47)	0.87 (0.54- 1.42)		0.56 (0.25- 1.24)	1.06 (0.63- 1.77)		0.98 (0.46- 2.09)	0.73 (0.44- 1.20)	
90-99	50	5119 6	1.04 (0.73- 1.48)	1.02 (0.71- 1.47)	0.97 (0.66- 1.44)	0.97 (0.50- 1.89)	1.02 (0.66- 1.59)	0.664	1.12 (0.63- 2.01)	1.14 (0.71- 1.83)	0.236	1.64 (0.87- 3.07)	0.83 (0.53- 1.29)	0.006
100-109	11	1389 6	0.81 (0.43- 1.52)	0.80 (0.42- 1.52)	0.82 (0.42- 1.62)	0.45 (0.13- 1.57)	1.02 (0.49- 2.16)		no cases	1.27 (0.64- 2.51)		1.10 (0.33- 3.72)	0.71 (0.33- 1.50)	
>= 110	4	3264	1.38 (0.50- 3.77)	1.38 (0.50- 3.81)	1.55 (0.56- 4.29)	1.72 (0.49- 6.04)	0.66 (0.09- 4.78)		2.02 (0.28- 14.79)	1.56 (0.48- 5.08)		6.86 (2.30- 20.47)	no cases	
p-trend			0.805	0.758	0.701	0.801	0.818		0.43	0.559		0.035	0.083	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	54	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	91	1239 28	0.86 (0.61- 1.21)	0.86 (0.60- 1.21)	0.94 (0.64- 1.38)	0.94 (0.39- 2.23)	0.89 (0.60- 1.31)		0.68 (0.42- 1.12)	1.20 (0.70- 2.06)		0.68 (0.40- 1.15)	1.01 (0.62- 1.65)	
140-159	68	6823 5	0.92 (0.63- 1.34)	0.90 (0.61- 1.34)	0.99 (0.65- 1.50)	1.09 (0.44- 2.66)	0.90 (0.58- 1.41)	0.045	0.74 (0.41- 1.35)	1.29 (0.73- 2.27)	0.158	0.61 (0.29- 1.29)	1.06 (0.64- 1.76)	0.257
>= 160	31	2901 4	0.89 (0.55- 1.43)	0.85 (0.52- 1.39)	0.88 (0.52- 1.48)	1.50 (0.57- 3.98)	0.67 (0.36- 1.22)		0.67 (0.28- 1.60)	1.24 (0.65- 2.37)		2.06 (0.96- 4.44)	0.70 (0.37- 1.31)	
p-trend			0.733	0.631	0.747	0.273	0.267		0.264	0.506		0.564	0.351	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	93	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	86	1063 72	0.95 (0.71- 1.28)	0.95 (0.70- 1.28)	1.02 (0.74- 1.41)	0.74 (0.39- 1.39)	1.04 (0.74- 1.47)		0.71 (0.43- 1.15)	1.22 (0.81- 1.83)		1.00 (0.58- 1.71)	0.91 (0.63- 1.31)	
90-99	50	5119 6	1.04 (0.73- 1.48)	1.03 (0.71- 1.48)	0.98 (0.66- 1.45)	0.97 (0.50- 1.90)	1.03 (0.66- 1.59)	0.833	1.12 (0.63- 2.01)	1.15 (0.72- 1.84)	0.184	1.63 (0.87- 3.05)	0.83 (0.54- 1.30)	0.016
>= 100	15	1716 0	0.91 (0.52- 1.58)	0.90 (0.51- 1.59)	0.95 (0.53- 1.72)	0.72 (0.28- 1.87)	0.97 (0.48- 1.97)		0.26 (0.04- 1.91)	1.33 (0.71- 2.47)		2.10 (0.88- 5.00)	0.59 (0.28- 1.24)	

ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.21 (0.76-1.94)	0.76 (0.50-1.13)		1.04 (0.73-1.48)	0.75 (0.42-1.35)		1.20 (0.84-1.73)	1.02 (0.34-3.04)	
90-99	1.30 (0.74-2.25)	0.85 (0.52-1.39)	0.362	0.88 (0.55-1.40)	1.29 (0.71-2.35)	0.105	1.34 (0.84-2.12)	1.28 (0.44-3.79)	0.609
>= 100	0.99 (0.40-2.41)	0.82 (0.40-1.70)		0.68 (0.30-1.50)	1.27 (0.55-2.92)		1.60 (0.78-3.30)	0.92 (0.25-3.45)	
p-trend	0.587	0.444		0.366	0.327		0.111	0.901	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
Anogenital (not cervix)	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	0.68 (0.34-1.36)	0.63 (0.38-1.05)		0.65 (0.40-1.05)	0.65 (0.30-1.42)		0.62 (0.38-1.03)	-	
96.8-105.5	1.35 (0.74-2.46)	0.68 (0.42-1.13)	0.089	0.98 (0.63-1.53)	0.81 (0.39-1.66)	0.263	1.30 (0.83-2.02)	-	-
105.6-216.6	1.17 (0.62-2.19)	0.63 (0.38-1.06)		0.76 (0.47-1.23)	0.94 (0.46-1.89)		1.14 (0.70-1.85)	-	
p-trend	0.235	0.15		0.622	0.763		0.138	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.28 (0.84-1.96)	1.01 (0.70-1.45)	0.284	1.11 (0.80-1.55)	1.11 (0.68-1.79)	0.596	1 (referent)	0.85 (0.56-1.30)	

Anogenital (not cervix) SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			173	173	151	53	120		70	103		64	109	
Cohort size			30738	30738	30185	11259	19472		14632	16099		15330	15401	
Mean Systolic Blood Pressure	173	30738	1.029 (0.949-1.116)	1.019 (0.937-1.108)	1.000 (0.913-1.095)	1.106 (0.955-1.281)	0.987 (0.891-1.093)	0.072	0.980 (0.852-1.128)	1.067 (0.962-1.183)	0.183	1.068 (0.916-1.244)	1.001 (0.905-1.106)	0.419

continuous (per 10mmHg increase)														
Mean Diastolic Blood Pressure	173	3073 18	1.016 (0.879- 1.175)	0.998 (0.857- 1.161)	0.986 (0.837- 1.161)	1.035 (0.791- 1.353)	0.979 (0.814- 1.177)	0.415	0.938 (0.733- 1.201)	1.088 (0.899- 1.316)	0.268	1.224 (0.958- 1.565)	0.886 (0.731- 1.075)	0.035
continuous (per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/ 3DBP)	173	3073 18	1.030 (0.910- 1.166)	1.014 (0.891- 1.154)	0.993 (0.864- 1.142)	1.098 (0.876- 1.377)	0.980 (0.837- 1.146)	0.167	0.954 (0.772- 1.180)	1.096 (0.934- 1.287)	0.189	1.162 (0.935- 1.445)	0.946 (0.806- 1.111)	0.113
continuous (per 10mmHg increase)														
Systolic Blood Pressure (mmHg)														
ESH classificatio n														
Anogenital (not cervix) SCC	Cas es	Coh ort	HR (crud e)	HR (adjus ted)	Exclu ding first 2 years of follow- up HR (adjus ted)	Men HR (adjus ted)	Wome n HR (adjus ted)	Sex p- interac tion	BMI <= 25 mg/m ² HR (adjus ted)	BMI > 25 mg/m ² HR (adjus ted)	BMI p- interac tion	Age <= 53 yrs HR (adjus ted)	Age > 53 yrs HR (adjus ted)	Age p- interac tion
< 120	39	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-129	25	6644 6	0.67 (0.40- 1.11)	0.67 (0.40- 1.11)	0.76 (0.44- 1.31)	0.47 (0.15- 1.51)	0.77 (0.44- 1.36)		0.60 (0.29- 1.23)	0.84 (0.39- 1.79)		0.54 (0.26- 1.15)	0.80 (0.39- 1.64)	
130-139	37	5748 2	1.03 (0.65- 1.64)	1.01 (0.63- 1.62)	1.03 (0.61- 1.72)	0.83 (0.31- 2.23)	1.16 (0.67- 1.98)		1.05 (0.54- 2.03)	1.20 (0.59- 2.42)		0.92 (0.45- 1.87)	1.12 (0.58- 2.16)	
140-159	47	6823 5	0.95 (0.61- 1.50)	0.93 (0.58- 1.48)	0.97 (0.58- 1.61)	0.96 (0.38- 2.42)	0.96 (0.55- 1.66)	0.055	0.76 (0.36- 1.58)	1.26 (0.64- 2.48)	0.134	0.57 (0.24- 1.35)	1.12 (0.60- 2.09)	0.591
160-179	17	2265 6	0.97 (0.53- 1.77)	0.92 (0.50- 1.71)	0.93 (0.48- 1.82)	1.32 (0.45- 3.83)	0.72 (0.31- 1.64)		1.03 (0.37- 2.87)	1.12 (0.49- 2.57)		2.08 (0.82- 5.26)	0.71 (0.31- 1.63)	
>= 180	8	6358	1.64 (0.74- 3.63)	1.52 (0.68- 3.40)	1.31 (0.52- 3.28)	2.03 (0.55- 7.54)	1.23 (0.41- 3.65)		0.78 (0.10- 6.06)	2.31 (0.88- 6.04)		2.79 (0.62- 12.60)	1.44 (0.54- 3.84)	
p-trend			0.36	0.488	0.653	0.123	0.976		0.86	0.13		0.477	0.723	
Diastolic Blood Pressure (mmHg)														
ESH classificatio n														
< 80	65	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-84	37	6487 2	1.03 (0.68- 1.55)	1.01 (0.67- 1.53)	1.05 (0.68- 1.62)	0.58 (0.25- 1.36)	1.25 (0.78- 2.01)		1.04 (0.56- 1.92)	1.04 (0.59- 1.81)		0.97 (0.49- 1.96)	1.03 (0.62- 1.72)	

specific quartiles														
50.0-88.3	37	7699 1	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	29	7772 7	0.64 (0.39-1.05)	0.64 (0.39-1.04)	0.68 (0.40-1.16)	0.65 (0.22-1.90)	0.64 (0.37-1.14)		0.77 (0.39-1.53)	0.51 (0.25-1.06)		0.81 (0.41-1.63)	0.50 (0.25-1.02)	
96.8-105.5	49	7632 7	0.99 (0.63-1.54)	0.97 (0.61-1.52)	1.02 (0.63-1.67)	0.80 (0.29-2.17)	1.08 (0.65-1.81)	0.268	1.31 (0.69-2.48)	0.82 (0.43-1.55)	0.697	0.78 (0.36-1.68)	0.99 (0.55-1.77)	0.546
105.6-216.6	58	7627 3	1.03 (0.66-1.60)	0.99 (0.62-1.57)	0.89 (0.53-1.47)	1.13 (0.43-2.93)	0.93 (0.54-1.61)		1.08 (0.52-2.24)	0.96 (0.52-1.77)		1.38 (0.66-2.89)	0.82 (0.45-1.49)	
p-trend			0.385	0.515	0.903	0.375	0.745		0.511	0.417		0.45	0.809	
Hypertension (SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or self-reported)														
Normotensive	80	1741 79	1 (referent)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Hypertensive	93	1331 39	1.22 (0.89-1.68)	1.17 (0.85-1.62)	1.13 (0.80-1.60)	1.32 (0.73-2.41)	1.12 (0.76-1.65)	0.458	0.98 (0.58-1.65)	1.47 (0.95-2.26)	0.132	1.36 (0.80-2.32)	1.07 (0.71-1.60)	0.391

Anogenital (not cervix) SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol ≤ 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	66	106		115	58		115	23	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.070 (0.937-1.222)	0.977 (0.876-1.091)	0.133	1.000 (0.900-1.111)	1.052 (0.916-1.209)	0.35	1.093 (0.982-1.215)	1.041 (0.837-1.295)	0.976
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.161 (0.914-1.474)	0.890 (0.730-1.085)	0.039	0.897 (0.741-1.086)	1.205 (0.939-1.546)	0.073	1.164 (0.960-1.410)	0.941 (0.610-1.453)	0.599

Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.135 (0.925-1.392)	0.929 (0.784-1.099)	0.054	0.948 (0.806-1.116)	1.138 (0.921-1.405)	0.138	1.156 (0.980-1.362)	1.008 (0.701-1.450)	0.778
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-129	1.51 (0.57-4.04)	0.48 (0.26-0.90)		0.75 (0.40-1.40)	0.51 (0.21-1.24)		0.69 (0.38-1.26)	-	
130-139	2.48 (0.98-6.27)	0.66 (0.37-1.18)		1.47 (0.84-2.57)	0.41 (0.16-1.05)		1.05 (0.59-1.87)	-	
140-159	2.60 (1.04-6.50)	0.54 (0.30-0.98)	0.04	1.04 (0.57-1.87)	0.72 (0.33-1.55)	0.575	1.41 (0.81-2.45)	-	-
160-179	1.91 (0.62-5.94)	0.68 (0.31-1.46)		0.87 (0.38-1.97)	0.90 (0.35-2.31)		1.33 (0.60-2.97)	-	
>= 180	2.13 (0.41-11.02)	1.38 (0.54-3.50)		1.36 (0.45-4.14)	1.42 (0.43-4.68)		2.53 (0.84-7.62)	-	
p-trend	0.102	0.566		0.648	0.61		0.046	-	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-84	1.60 (0.81-3.15)	0.73 (0.42-1.25)		1.16 (0.72-1.87)	0.68 (0.29-1.56)		1.16 (0.71-1.91)	-	
85-89	1.56 (0.73-3.33)	0.44 (0.21-0.95)		0.89 (0.49-1.61)	0.59 (0.22-1.61)		0.98 (0.52-1.84)	-	
90-99	1.47 (0.71-3.05)	1.07 (0.64-1.80)	0.226	0.95 (0.55-1.65)	1.67 (0.85-3.29)	0.064	1.66 (0.98-2.80)	-	-
100-109	0.70 (0.16-3.10)	0.74 (0.28-1.90)		0.33 (0.08-1.38)	1.43 (0.51-3.99)		1.29 (0.45-3.67)	-	
>= 110	3.20 (0.72-14.26)	1.40 (0.33-5.90)		1.54 (0.37-6.49)	2.82 (0.63-12.60)		5.15 (1.55-17.12)	-	
p-trend	0.428	0.832		0.401	0.069		0.039	-	
Anogenital (not cervix) SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
120-139	1.96 (0.83-4.65)	0.56 (0.34-0.93)		1.07 (0.64-1.77)	0.46 (0.21-0.98)		0.85 (0.51-1.39)	-	
140-159	2.53 (1.01-6.31)	0.54 (0.30-0.96)	0.048	1.00 (0.55-1.80)	0.72 (0.33-1.55)	0.345	1.39 (0.80-2.40)	-	-
>= 160	1.89 (0.64-5.57)	0.82 (0.42-1.60)		0.93 (0.44-1.95)	1.02 (0.43-2.43)		1.52 (0.74-3.12)	-	

p-trend	0.203	0.364		0.817	0.559		0.105	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
80-89	1.58 (0.86-2.92)	0.61 (0.38-0.99)		1.05 (0.68-1.61)	0.64 (0.31-1.32)		1.10 (0.70-1.71)	-	
90-99	1.47 (0.71-3.05)	1.08 (0.64-1.80)	0.28	0.96 (0.55-1.65)	1.67 (0.85-3.28)	0.075	1.66 (0.98-2.80)	-	-
>= 100	1.15 (0.37-3.52)	0.86 (0.37-1.96)		0.54 (0.19-1.55)	1.66 (0.67-4.15)		1.90 (0.83-4.35)	-	
p-trend	0.486	0.906		0.434	0.077		0.038	-	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	single case in referent	
88.5-96.6	0.63 (0.23-1.72)	0.62 (0.35-1.10)		0.64 (0.36-1.16)	0.61 (0.24-1.52)		0.65 (0.36-1.18)	-	
96.8-105.5	2.12 (0.94-4.75)	0.55 (0.30-0.99)	0.03	1.11 (0.65-1.89)	0.69 (0.29-1.63)	0.393	1.39 (0.81-2.36)	-	-
105.6-216.6	1.50 (0.63-3.53)	0.79 (0.45-1.38)		0.88 (0.49-1.56)	1.15 (0.51-2.55)		1.43 (0.81-2.54)	-	
p-trend	0.097	0.494		0.869	0.382		0.047	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.36 (0.79-2.34)	1.07 (0.71-1.61)	0.146	1.12 (0.75-1.67)	1.26 (0.72-2.21)	0.65	1 (referent)	0.81 (0.48-1.35)	

Skin SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1399	1399	1346	729	670		697	702		219	1180	

Cohort size			30731 8	30731 8	30185 7	11259 1	19472 7		14632 6	16099 2		15330 3	15401 5	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1399	307318	1.000 (0.973-1.028)	1.007 (0.979-1.037)	1.003 (0.974-1.033)	1.005 (0.965-1.046)	1.012 (0.972-1.055)	0.768	1.005 (0.965-1.046)	1.007 (0.967-1.048)	0.898	1.053 (0.971-1.142)	1.002 (0.972-1.033)	0.606
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1399	307318	1.071 (1.019-1.126)	1.070 (1.016-1.127)	1.067 (1.011-1.125)	1.038 (0.966-1.115)	1.107 (1.027-1.194)	0.318	1.036 (0.962-1.116)	1.092 (1.016-1.173)	0.215	1.160 (1.015-1.326)	1.056 (0.998-1.117)	0.5
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1399	307318	1.033 (0.990-1.078)	1.039 (0.994-1.086)	1.034 (0.988-1.081)	1.022 (0.961-1.087)	1.059 (0.994-1.129)	0.713	1.021 (0.959-1.086)	1.049 (0.986-1.115)	0.438	1.119 (0.995-1.257)	1.028 (0.980-1.078)	0.501
Systolic Blood Pressure (mmHg) ESH classification														
< 120	203	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	249	66446	1.04 (0.86-1.25)	1.02 (0.85-1.23)	1.01 (0.84-1.23)	1.05 (0.78-1.40)	1.03 (0.80-1.33)		1.05 (0.83-1.32)	0.99 (0.72-1.35)		1.35 (0.93-1.95)	0.94 (0.75-1.16)	
130-139	253	57482	0.95 (0.78-1.14)	0.94 (0.77-1.13)	0.93 (0.76-1.13)	1.01 (0.76-1.34)	0.88 (0.68-1.15)		0.87 (0.68-1.12)	1.00 (0.74-1.36)		1.04 (0.68-1.59)	0.90 (0.72-1.11)	
140-159	437	68235	0.97 (0.82-1.16)	0.98 (0.82-1.17)	0.97 (0.81-1.16)	1.02 (0.78-1.34)	0.97 (0.76-1.23)	0.645	0.94 (0.74-1.19)	1.02 (0.76-1.36)	0.747	1.31 (0.87-1.98)	0.91 (0.75-1.12)	0.557
160-179	192	22656	0.99 (0.80-1.22)	1.02 (0.83-1.27)	0.96 (0.78-1.20)	0.99 (0.72-1.35)	1.11 (0.83-1.48)		0.99 (0.74-1.34)	1.04 (0.76-1.44)		1.51 (0.81-2.83)	0.94 (0.75-1.19)	
>= 180	65	6358	1.10 (0.82-1.47)	1.16 (0.86-1.55)	1.16 (0.86-1.56)	1.26 (0.84-1.89)	1.09 (0.70-1.68)		1.34 (0.88-2.03)	1.03 (0.67-1.59)		1.82 (0.56-5.93)	1.08 (0.79-1.47)	
p-trend			0.926	0.672	0.953	0.72	0.733		0.955	0.697		0.202	0.999	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	473	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Skin SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
80-84	275	6487 2	0.94 (0.81- 1.09)	0.94 (0.81- 1.09)	0.92 (0.79- 1.08)	0.95 (0.77- 1.17)	0.90 (0.73- 1.13)		0.90 (0.73- 1.11)	0.97 (0.78- 1.22)		1.01 (0.69- 1.47)	0.92 (0.78- 1.08)	
85-89	215	4150 0	1.04 (0.88- 1.22)	1.04 (0.89- 1.23)	1.04 (0.88- 1.22)	0.92 (0.73- 1.16)	1.18 (0.94- 1.49)		1.04 (0.83- 1.32)	1.04 (0.82- 1.32)		1.38 (0.92- 2.07)	0.99 (0.83- 1.19)	
90-99	297	5119 6	1.03 (0.89- 1.20)	1.03 (0.89- 1.20)	0.99 (0.84- 1.15)	0.92 (0.75- 1.14)	1.16 (0.93- 1.45)	0.086	1.05 (0.85- 1.31)	1.01 (0.81- 1.25)	0.475	1.30 (0.86- 1.95)	0.99 (0.84- 1.17)	0.277
100-109	116	1389 6	1.38 (1.12- 1.70)	1.37 (1.11- 1.69)	1.37 (1.11- 1.70)	1.19 (0.90- 1.58)	1.64 (1.19- 2.26)		1.14 (0.80- 1.63)	1.47 (1.12- 1.93)		2.35 (1.36- 4.05)	1.27 (1.01- 1.59)	
>= 110	23	3264	1.29 (0.85- 1.96)	1.26 (0.83- 1.93)	1.24 (0.81- 1.91)	1.16 (0.69- 1.94)	1.43 (0.67- 3.05)		1.43 (0.71- 2.90)	1.18 (0.69- 2.00)		0.68 (0.09- 4.96)	1.29 (0.83- 1.99)	
p-trend			0.016	0.021	0.053	0.651	0.003		0.261	0.061		0.013	0.127	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	203	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	502	1239 28	0.99 (0.84- 1.17)	0.98 (0.83- 1.16)	0.97 (0.82- 1.15)	1.03 (0.79- 1.33)	0.96 (0.77- 1.20)		0.96 (0.78- 1.19)	1.00 (0.75- 1.32)		1.22 (0.87- 1.70)	0.91 (0.75- 1.11)	
140-159	437	6823 5	0.98 (0.82- 1.16)	0.99 (0.82- 1.18)	0.97 (0.81- 1.16)	1.02 (0.78- 1.34)	0.97 (0.76- 1.24)	0.909	0.94 (0.75- 1.19)	1.02 (0.76- 1.36)	0.882	1.32 (0.87- 1.99)	0.91 (0.75- 1.12)	0.331
>= 160	257	2901 4	1.01 (0.83- 1.24)	1.06 (0.86- 1.29)	1.01 (0.82- 1.24)	1.05 (0.78- 1.46)	1.11 (0.84- 1.46)		1.07 (0.82- 1.41)	1.04 (0.76- 1.42)		1.58 (0.88- 2.82)	0.98 (0.78- 1.21)	
p-trend			0.939	0.545	0.881	0.803	0.469		0.765	0.7		0.09	0.973	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	473	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	490	1063 72	0.98 (0.86- 1.11)	0.98 (0.86- 1.12)	0.97 (0.85- 1.11)	0.94 (0.78- 1.13)	1.01 (0.84- 1.21)		0.96 (0.80- 1.14)	1.00 (0.83- 1.22)		1.15 (0.84- 1.58)	0.95 (0.82- 1.09)	
90-99	297	5119 6	1.03 (0.89- 1.20)	1.03 (0.88- 1.20)	0.99 (0.84- 1.15)	0.92 (0.75- 1.14)	1.16 (0.93- 1.45)	0.159	1.05 (0.85- 1.31)	1.01 (0.81- 1.25)	0.313	1.29 (0.86- 1.94)	0.99 (0.84- 1.17)	0.302
>= 100	139	1716 0	1.37 (1.13- 1.66)	1.35 (1.11- 1.65)	1.35 (1.10- 1.65)	1.19 (0.91- 1.54)	1.61 (1.19- 2.18)		1.19 (0.86- 1.64)	1.42 (1.10- 1.83)		2.06 (1.21- 3.51)	1.27 (1.03- 1.57)	
p-trend			0.018	0.025	0.061	0.533	0.007		0.392	0.044		0.017	0.139	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
Skin SCC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p- interaction	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI p- interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p- interaction

					years of follow-up HR (adjusted)				HR (adjusted)	HR (adjusted)		HR (adjusted)		
50.0-88.3	204	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	296	7772 7	1.01 (0.84-1.21)	1.00 (0.83-1.20)	1.01 (0.84-1.21)	0.99 (0.76-1.31)	0.99 (0.78-1.27)		1.07 (0.85-1.33)	0.90 (0.66-1.24)		1.36 (0.93-2.00)	0.92 (0.75-1.13)	
96.8-105.5	360	7632 7	0.96 (0.80-1.14)	0.95 (0.79-1.13)	0.95 (0.80-1.14)	0.89 (0.68-1.17)	1.00 (0.78-1.27)	0.372	0.85 (0.67-1.08)	1.03 (0.77-1.38)	0.307	1.29 (0.86-1.94)	0.87 (0.72-1.07)	0.323
105.6-216.6	539	7627 3	1.06 (0.90-1.26)	1.07 (0.90-1.28)	1.05 (0.88-1.25)	0.97 (0.75-1.26)	1.19 (0.94-1.51)		1.07 (0.85-1.34)	1.07 (0.81-1.42)		1.58 (1.03-2.42)	0.98 (0.81-1.19)	
p-trend			0.448	0.352	0.577	0.801	0.111		0.985	0.245		0.063	0.802	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	584	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	815	1331 39	1.04 (0.93-1.16)	1.09 (0.97-1.22)	1.06 (0.95-1.19)	1.03 (0.88-1.20)	1.16 (0.99-1.37)	0.558	1.03 (0.88-1.21)	1.13 (0.96-1.33)	0.406	1.45 (1.09-1.92)	1.03 (0.91-1.17)	0.079

Skin SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	556	816		865	534		834	221	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.028 (0.982-1.075)	0.991 (0.954-1.029)	0.091	1.012 (0.975-1.049)	0.996 (0.950-1.043)	0.577	1.007 (0.969-1.047)	0.966 (0.899-1.038)	0.175
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.075 (0.989-1.169)	1.063 (0.993-1.138)	0.368	1.096 (1.027-1.171)	1.021 (0.938-1.112)	0.228	1.037 (0.965-1.115)	1.033 (0.899-1.188)	0.914
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	1.058 (0.986-1.135)	1.022 (0.965-1.083)	0.166	1.055 (0.997-1.115)	1.007 (0.937-1.082)	0.336	1.023 (0.963-1.088)	0.984 (0.874-1.108)	0.493

Skin SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.91 (0.67-1.25)	1.10 (0.87-1.40)		1.08 (0.86-1.37)	0.91 (0.67-1.25)		1.12 (0.89-1.40)	1.28 (0.50-3.22)	
130-139	1.06 (0.78-1.44)	0.86 (0.67-1.11)		0.96 (0.75-1.22)	0.87 (0.64-1.19)		1.03 (0.82-1.31)	0.81 (0.32-2.02)	
140-159	1.07 (0.80-1.43)	0.92 (0.73-1.16)	0.062	0.99 (0.79-1.24)	0.95 (0.71-1.27)	0.568	0.96 (0.77-1.20)	1.16 (0.49-2.70)	0.264
160-179	1.14 (0.81-1.59)	0.94 (0.71-1.24)		1.08 (0.82-1.41)	0.91 (0.64-1.29)		1.06 (0.80-1.41)	1.05 (0.44-2.49)	
>= 180	1.20 (0.75-1.93)	1.11 (0.76-1.62)		1.28 (0.88-1.85)	0.93 (0.57-1.52)		1.32 (0.87-1.99)	0.74 (0.28-1.92)	
p-trend	0.199	0.507		0.585	0.831		0.945	0.419	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.09 (0.86-1.38)	0.86 (0.70-1.05)		0.93 (0.77-1.13)	0.92 (0.72-1.18)		0.91 (0.76-1.10)	1.23 (0.72-2.09)	
85-89	1.21 (0.93-1.57)	0.93 (0.75-1.16)		1.06 (0.86-1.31)	1.01 (0.77-1.31)		1.04 (0.84-1.28)	1.08 (0.63-1.84)	
90-99	1.13 (0.88-1.44)	0.96 (0.78-1.17)	0.328	1.08 (0.89-1.31)	0.94 (0.73-1.21)	0.154	1.04 (0.85-1.27)	0.98 (0.60-1.60)	0.815
100-109	1.27 (0.88-1.82)	1.46 (1.13-1.90)		1.49 (1.14-1.95)	1.18 (0.84-1.66)		1.24 (0.90-1.71)	1.39 (0.82-2.36)	
>= 110	1.56 (0.82-2.98)	1.05 (0.59-1.88)		1.58 (0.95-2.64)	0.84 (0.39-1.80)		0.96 (0.43-2.17)	0.84 (0.33-2.09)	
p-trend	0.093	0.137		0.007	0.816		0.298	0.833	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.99 (0.75-1.30)	0.98 (0.79-1.22)		1.02 (0.83-1.26)	0.89 (0.68-1.18)		1.08 (0.88-1.32)	0.98 (0.41-2.34)	
140-159	1.07 (0.80-1.42)	0.93 (0.74-1.17)	0.14	0.99 (0.79-1.24)	0.95 (0.71-1.27)	0.5	0.96 (0.77-1.21)	1.17 (0.50-2.73)	0.486
>= 160	1.14 (0.83-1.58)	0.99 (0.76-1.29)		1.13 (0.87-1.45)	0.92 (0.66-1.28)		1.12 (0.86-1.46)	0.97 (0.41-2.30)	
p-trend	0.286	0.794		0.453	0.876		0.843	0.797	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

80-89	1.14 (0.93-1.40)	0.89 (0.75-1.05)		0.98 (0.83-1.16)	0.96 (0.78-1.18)		0.96 (0.82-1.13)	1.15 (0.71-1.86)	
90-99	1.13 (0.88-1.44)	0.96 (0.78-1.17)	0.429	1.08 (0.89-1.31)	0.94 (0.73-1.21)	0.175	1.04 (0.85-1.27)	0.98 (0.60-1.60)	0.888
>= 100	1.32 (0.95-1.83)	1.39 (1.08-1.78)		1.50 (1.17-1.93)	1.12 (0.81-1.55)		1.20 (0.88-1.63)	1.29 (0.77-2.18)	
p-trend	0.122	0.112		0.01	0.816		0.398	0.539	
Skin SCC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.14 (0.84-1.55)	0.90 (0.72-1.14)		1.02 (0.82-1.28)	0.93 (0.69-1.26)		1.03 (0.83-1.27)	1.16 (0.42-3.17)	
96.8-105.5	1.16 (0.86-1.56)	0.84 (0.67-1.06)	0.028	0.99 (0.79-1.23)	0.86 (0.64-1.15)	0.441	0.98 (0.79-1.22)	1.05 (0.41-2.68)	0.717
105.6-216.6	1.29 (0.96-1.73)	0.93 (0.75-1.17)		1.12 (0.90-1.40)	0.96 (0.72-1.28)		1.03 (0.82-1.29)	1.19 (0.48-2.96)	
p-trend	0.086	0.68		0.259	0.897		0.893	0.591	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.21 (1.00-1.45)	1.01 (0.87-1.17)	0.076	1.08 (0.94-1.25)	1.08 (0.90-1.30)	0.933	1 (referent)	1.45 (1.22-1.72)	

Melanoma (skin)	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1617	1617	1452	699	918		775	842		641	976	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1617	30738	1.010 (0.983-1.038)	1.007 (0.979-1.036)	0.998 (0.968-1.028)	1.015 (0.972-1.060)	1.005 (0.969-1.043)	0.096	0.988 (0.947-1.030)	1.023 (0.986-1.062)	0.093	0.983 (0.933-1.035)	1.020 (0.986-1.055)	0.187
Mean Diastolic Blood Pressure	1617	30738	1.018 (0.971-1.068)	1.003 (0.954-1.055)	1.002 (0.951-1.056)	0.987 (0.914-1.065)	1.016 (0.951-1.085)	0.452	0.985 (0.914-1.060)	1.019 (0.953-1.089)	0.318	0.984 (0.906-1.068)	1.017 (0.955-1.083)	0.422

continuous (per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/ 3DBP)	161 7	3073 18	1.017 (0.976- 1.059)	1.007 (0.965- 1.051)	0.999 (0.955- 1.046)	1.005 (0.940- 1.073)	1.012 (0.956- 1.071)	0.203	0.983 (0.922- 1.048)	1.027 (0.970- 1.088)	0.153	0.979 (0.910- 1.054)	1.024 (0.971- 1.080)	0.261
continuous (per 10mmHg increase)														
Melanoma (skin)	Cas es	Coh ort	HR (crud e)	HR (adjus ted)	Exclu ding first 2 years of follow- up HR (adjus ted)	Men HR (adjus ted)	Wome n HR (adjus ted)	Sex p- interac tion	BMI <= 25 mg/m ² HR (adjus ted)	BMI > 25 mg/m ² HR (adjus ted)	BMI p- interac tion	Age <= 53 yrs HR (adjus ted)	Age > 53 yrs HR (adjus ted)	Age p- interac tion
Systolic Blood Pressure (mmHg)														
ESH classificatio n														
< 120	371	8614 1	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
120-129	311	6644 6	0.95 (0.82- 1.11)	0.93 (0.80- 1.08)	0.94 (0.80- 1.11)	0.94 (0.72- 1.23)	0.95 (0.78- 1.15)		1.01 (0.82- 1.23)	0.85 (0.66- 1.08)		0.96 (0.78- 1.19)	0.91 (0.72- 1.15)	
130-139	328	5748 2	1.08 (0.92- 1.26)	1.04 (0.89- 1.22)	1.01 (0.85- 1.19)	1.03 (0.80- 1.35)	1.09 (0.89- 1.33)		1.10 (0.88- 1.36)	0.99 (0.78- 1.25)		1.08 (0.86- 1.35)	1.05 (0.84- 1.31)	
140-159	406	6823 5	0.99 (0.85- 1.16)	0.96 (0.82- 1.13)	0.93 (0.79- 1.10)	1.01 (0.78- 1.31)	0.93 (0.76- 1.15)	0.144	0.99 (0.79- 1.23)	0.92 (0.73- 1.16)	0.409	0.87 (0.67- 1.12)	1.02 (0.83- 1.26)	0.142
160-179	157	2265 6	1.07 (0.87- 1.30)	1.04 (0.85- 1.28)	0.98 (0.79- 1.22)	1.08 (0.78- 1.48)	1.05 (0.79- 1.38)		1.07 (0.77- 1.48)	1.00 (0.76- 1.32)		0.80 (0.50- 1.29)	1.12 (0.88- 1.44)	
>= 180	44	6358	1.05 (0.76- 1.45)	1.03 (0.75- 1.43)	0.96 (0.68- 1.36)	0.91 (0.55- 1.50)	1.19 (0.77- 1.84)		0.79 (0.41- 1.50)	1.10 (0.74- 1.63)		1.12 (0.49- 2.54)	1.05 (0.72- 1.52)	
p-trend			0.505	0.688	0.683	0.694	0.757		0.971	0.602		0.441	0.242	
Diastolic Blood Pressure (mmHg)														
ESH classificatio n														
< 80	627	1325 90	1 (refer ent)	1 (refere nt)	1 (refere nt)	1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)		1 (refere nt)	1 (refere nt)	
80-84	345	6487 2	1.03 (0.90- 1.18)	1.02 (0.89- 1.16)	1.02 (0.89- 1.18)	1.01 (0.82- 1.25)	1.03 (0.87- 1.23)		0.99 (0.82- 1.20)	1.05 (0.86- 1.28)		0.95 (0.77- 1.17)	1.08 (0.90- 1.28)	
85-89	242	4150 0	1.09 (0.94- 1.27)	1.06 (0.91- 1.24)	1.04 (0.88- 1.22)	1.13 (0.90- 1.43)	1.00 (0.81- 1.23)		0.97 (0.77- 1.23)	1.14 (0.93- 1.40)		1.11 (0.87- 1.41)	1.06 (0.87- 1.29)	
90-99	299	5119 6	1.05 (0.91- 1.21)	1.02 (0.88- 1.18)	0.99 (0.85- 1.16)	1.04 (0.83- 1.29)	0.99 (0.81- 1.22)	0.759	1.05 (0.84- 1.32)	1.01 (0.83- 1.23)	0.856	0.95 (0.74- 1.22)	1.07 (0.89- 1.28)	0.162
100-109	91	1389 6	1.15 (0.92- 1.44)	1.10 (0.88- 1.39)	1.13 (0.89- 1.44)	0.87 (0.62- 1.22)	1.43 (1.05- 1.96)		1.20 (0.82- 1.77)	1.08 (0.81- 1.43)		0.68 (0.40- 1.13)	1.30 (1.00- 1.68)	

>= 110	13	3264	0.75 (0.43-1.31)	0.72 (0.41-1.25)	0.74 (0.42-1.32)	0.66 (0.32-1.35)	0.79 (0.32-1.91)		0.24 (0.03-1.74)	0.86 (0.48-1.54)		0.78 (0.29-2.10)	0.70 (0.36-1.36)	
p-trend			0.369	0.747	0.881	0.632	0.423		0.789	0.864		0.432	0.321	
Systolic Blood Pressure (mmHg) ASH classification														
< 120	371	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	639	1239 28	1.01 (0.89-1.16)	0.98 (0.86-1.12)	0.97 (0.85-1.12)	0.99 (0.78-1.25)	1.01 (0.85-1.19)		1.04 (0.88-1.24)	0.92 (0.74-1.14)		1.01 (0.84-1.21)	0.98 (0.80-1.20)	
Melanoma (skin)	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
140-159	406	6823 5	0.99 (0.85-1.15)	0.96 (0.82-1.12)	0.93 (0.79-1.09)	1.01 (0.78-1.31)	0.93 (0.75-1.14)	0.124	0.99 (0.79-1.23)	0.92 (0.73-1.15)	0.511	0.86 (0.67-1.12)	1.02 (0.83-1.26)	0.103
>= 160	201	2901 4	1.06 (0.88-1.28)	1.04 (0.85-1.25)	0.97 (0.79-1.19)	1.03 (0.76-1.40)	1.07 (0.83-1.38)		1.01 (0.74-1.37)	1.02 (0.78-1.32)		0.85 (0.56-1.30)	1.10 (0.87-1.40)	
p-trend			0.73	0.94	0.559	0.763	0.985		0.953	0.846		0.263	0.325	
Diastolic Blood Pressure (mmHg) ASH classification														
< 80	627	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	587	1063 72	1.06 (0.94-1.19)	1.03 (0.92-1.16)	1.03 (0.91-1.17)	1.06 (0.88-1.28)	1.02 (0.88-1.19)		0.98 (0.83-1.16)	1.09 (0.92-1.29)		1.01 (0.84-1.20)	1.07 (0.91-1.25)	
90-99	299	5119 6	1.05 (0.91-1.21)	1.02 (0.88-1.18)	0.99 (0.85-1.16)	1.03 (0.83-1.28)	0.99 (0.81-1.22)	0.958	1.05 (0.84-1.32)	1.01 (0.83-1.23)	0.968	0.95 (0.74-1.22)	1.07 (0.89-1.28)	0.069
>= 100	104	1716 0	1.08 (0.87-1.33)	1.03 (0.83-1.28)	1.06 (0.85-1.33)	0.83 (0.60-1.14)	1.33 (0.99-1.79)		1.06 (0.73-1.55)	1.03 (0.79-1.35)		0.69 (0.43-1.10)	1.19 (0.92-1.53)	
p-trend			0.366	0.74	0.792	0.47	0.287		0.687	0.938		0.257	0.208	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles														
50.0-88.3	337	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	382	7772 7	1.00 (0.87-1.17)	0.98 (0.84-1.14)	0.99 (0.85-1.16)	1.00 (0.77-1.31)	0.99 (0.83-1.20)		1.03 (0.85-1.24)	0.93 (0.73-1.20)		0.97 (0.79-1.20)	1.00 (0.81-1.25)	

96.8-105.5	422	7632 7	1.04 (0.90- 1.21)	1.01 (0.87- 1.17)	0.99 (0.84- 1.17)	1.00 (0.77- 1.30)	1.04 (0.86- 1.26)	0.216	1.00 (0.82- 1.24)	1.01 (0.80- 1.28)	0.306	1.05 (0.84- 1.32)	1.01 (0.81- 1.24)	0.5
105.6-216.6	476	7627 3	1.06 (0.91- 1.23)	1.02 (0.87- 1.19)	0.98 (0.83- 1.16)	1.02 (0.78- 1.33)	1.03 (0.84- 1.27)		0.98 (0.78- 1.23)	1.03 (0.82- 1.31)		0.95 (0.73- 1.23)	1.06 (0.86- 1.31)	
p-trend			0.397	0.706	0.857	0.879	0.653		0.853	0.478		0.926	0.505	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	846	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	771	1331 39	1.01 (0.91- 1.12)	1.00 (0.90- 1.12)	0.97 (0.87- 1.09)	0.98 (0.84- 1.15)	1.02 (0.88- 1.17)	0.461	0.99 (0.84- 1.15)	1.02 (0.88- 1.17)	0.6	0.97 (0.81- 1.16)	1.03 (0.90- 1.18)	0.543

Melanoma (skin)	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	731	865		1023	594		1136	197	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.017 (0.976-1.061)	0.999 (0.961-1.038)	0.175	1.008 (0.972-1.044)	1.007 (0.962-1.055)	0.687	1.001 (0.966-1.038)	1.003 (0.929-1.083)	0.89
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.007 (0.935-1.085)	1.000 (0.934-1.071)	0.596	1.015 (0.953-1.080)	0.985 (0.907-1.070)	0.585	1.019 (0.957-1.085)	0.915 (0.789-1.061)	0.107
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	1.017 (0.954-1.084)	0.999 (0.942-1.060)	0.319	1.013 (0.960-1.069)	0.998 (0.930-1.072)	0.609	1.011 (0.957-1.068)	0.960 (0.846-1.089)	0.325
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.80 (0.64-1.01)	1.06 (0.86-1.31)		0.87 (0.72-1.05)	1.05 (0.80-1.37)		0.90 (0.76-1.07)	1.70 (0.68-4.24)	

Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.91 (0.73-1.14)	1.04 (0.85-1.28)		0.93 (0.77-1.12)	1.07 (0.82-1.39)		0.98 (0.83-1.16)	1.84 (0.62-5.44)	
96.8-105.5	1.07 (0.85-1.33)	0.97 (0.78-1.20)	0.551	1.03 (0.85-1.24)	0.97 (0.74-1.27)	0.575	0.99 (0.83-1.19)	1.96 (0.70-5.53)	0.693
105.6-216.6	0.98 (0.78-1.24)	1.06 (0.85-1.31)		1.02 (0.84-1.24)	1.02 (0.78-1.34)		1.02 (0.85-1.24)	1.63 (0.58-4.55)	
p-trend	0.777	0.76		0.577	0.913		0.782	0.892	
Hypertension (SBP \geq 140 mmHg, or DBP \geq 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.06 (0.91-1.25)	0.97 (0.84-1.12)	0.214	1.01 (0.88-1.16)	1.00 (0.84-1.19)	0.796	1 (referent)	1.12 (0.94-1.34)	

Brain and CNS	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI \leq 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age \leq 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			591	591	522	291	300		246	345		210	381	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	591	30738	1.020 (0.976-1.066)	0.999 (0.954-1.047)	1.006 (0.958-1.057)	0.955 (0.890-1.024)	1.040 (0.978-1.107)	0.157	0.990 (0.918-1.066)	1.005 (0.948-1.066)	0.502	0.959 (0.875-1.050)	1.014 (0.961-1.071)	0.294
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	591	30738	1.019 (0.943-1.102)	0.973 (0.896-1.056)	0.968 (0.886-1.056)	0.909 (0.808-1.024)	1.043 (0.931-1.169)	0.188	1.080 (0.952-1.227)	0.910 (0.818-1.011)	0.14	0.957 (0.828-1.104)	0.980 (0.887-1.083)	0.821
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	591	30738	1.024 (0.958-1.095)	0.986 (0.919-1.058)	0.989 (0.917-1.066)	0.921 (0.829-1.022)	1.053 (0.956-1.159)	0.139	1.031 (0.924-1.152)	0.958 (0.875-1.049)	0.628	0.949 (0.834-1.080)	1.002 (0.921-1.090)	0.512

Normotensive	300	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	291	133139	1.03 (0.87-1.21)	0.97 (0.81-1.15)	0.99 (0.82-1.19)	0.91 (0.71-1.16)	1.04 (0.81-1.33)	0.673	1.16 (0.88-1.52)	0.85 (0.68-1.06)	0.175	0.81 (0.59-1.10)	1.05 (0.85-1.30)	0.219

Brain and CNS	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	238	345		347	244		399	71	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.004 (0.933-1.080)	1.000 (0.941-1.062)	0.82	1.018 (0.959-1.081)	0.976 (0.907-1.052)	0.169	1.002 (0.943-1.065)	0.962 (0.847-1.094)	0.892
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.004 (0.883-1.142)	0.959 (0.861-1.067)	0.509	1.009 (0.907-1.121)	0.931 (0.818-1.060)	0.256	0.945 (0.849-1.052)	0.922 (0.720-1.181)	0.556
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.005 (0.899-1.123)	0.979 (0.893-1.074)	0.626	1.018 (0.930-1.115)	0.948 (0.847-1.060)	0.179	0.973 (0.887-1.068)	0.929 (0.752-1.147)	0.68
Brain and CNS	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.85 (0.56-1.29)	0.94 (0.67-1.32)		0.83 (0.59-1.16)	0.99 (0.65-1.51)		0.85 (0.63-1.15)	0.70 (0.21-2.39)	
130-139	1.16 (0.78-1.73)	0.99 (0.70-1.40)		0.90 (0.64-1.27)	1.18 (0.79-1.79)		1.07 (0.79-1.44)	0.78 (0.25-2.41)	
140-159	0.94 (0.62-1.40)	0.99 (0.70-1.38)	0.829	0.98 (0.71-1.36)	0.89 (0.58-1.35)	0.246	0.98 (0.72-1.33)	0.44 (0.15-1.31)	0.817
160-179	0.99 (0.58-1.69)	0.91 (0.57-1.44)		0.92 (0.59-1.43)	0.99 (0.58-1.70)		0.92 (0.58-1.47)	0.45 (0.14-1.43)	
>= 180	0.80 (0.31-2.06)	0.92 (0.45-1.89)		1.06 (0.54-2.10)	0.58 (0.20-1.65)		0.46 (0.14-1.46)	0.89 (0.26-3.05)	
p-trend	0.964	0.83		0.855	0.466		0.802	0.381	

Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.17 (0.82-1.66)	1.00 (0.74-1.33)		1.13 (0.85-1.50)	0.94 (0.66-1.34)		0.98 (0.76-1.27)	1.66 (0.70-3.93)	
85-89	1.35 (0.93-1.98)	1.01 (0.72-1.40)		1.04 (0.74-1.45)	1.22 (0.85-1.76)		1.03 (0.76-1.39)	1.39 (0.58-3.33)	
90-99	1.03 (0.70-1.52)	1.00 (0.73-1.36)	0.501	1.17 (0.86-1.59)	0.80 (0.54-1.17)	0.181	0.79 (0.57-1.09)	1.17 (0.51-2.68)	0.687
100-109	1.13 (0.62-2.07)	0.72 (0.42-1.26)		0.97 (0.57-1.65)	0.80 (0.44-1.46)		1.03 (0.61-1.74)	0.64 (0.20-2.01)	
>= 110	0.34 (0.05-2.48)	0.61 (0.19-1.93)		0.75 (0.24-2.39)	0.26 (0.04-1.85)		no cases	1.73 (0.44-6.75)	
p-trend	0.925	0.42		0.733	0.207		0.187	0.49	
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.00 (0.70-1.42)	0.96 (0.71-1.30)		0.86 (0.65-1.15)	1.09 (0.75-1.57)		0.95 (0.73-1.23)	0.75 (0.25-2.22)	
140-159	0.92 (0.62-1.38)	0.98 (0.70-1.38)	0.986	0.98 (0.71-1.36)	0.88 (0.58-1.34)	0.229	0.97 (0.72-1.32)	0.43 (0.14-1.30)	0.679
>= 160	0.94 (0.57-1.56)	0.91 (0.59-1.39)		0.94 (0.63-1.42)	0.89 (0.53-1.50)		0.82 (0.53-1.29)	0.56 (0.18-1.68)	
p-trend	0.69	0.75		0.991	0.366		0.538	0.202	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.24 (0.92-1.68)	1.00 (0.78-1.29)		1.09 (0.85-1.40)	1.05 (0.78-1.43)		1.00 (0.80-1.25)	1.52 (0.69-3.35)	
90-99	1.03 (0.70-1.52)	1.00 (0.73-1.36)	0.511	1.17 (0.86-1.59)	0.80 (0.54-1.17)	0.114	0.79 (0.57-1.09)	1.17 (0.51-2.68)	0.584
>= 100	0.97 (0.54-1.74)	0.70 (0.42-1.17)		0.93 (0.57-1.53)	0.69 (0.39-1.24)		0.84 (0.50-1.43)	0.84 (0.30-2.31)	
p-trend	0.973	0.381		0.646	0.125		0.208	0.422	
Brain and CNS	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	0.81 (0.53-1.22)	0.78 (0.55-1.10)		0.79 (0.57-1.11)	0.74 (0.49-1.14)		0.79 (0.59-1.06)	-	
96.8-105.5	1.07 (0.72-1.58)	1.02 (0.74-1.41)	0.439	1.00 (0.73-1.37)	1.03 (0.69-1.53)	0.229	1.06 (0.80-1.41)	-	-

105.6-216.6	1.02 (0.68-1.53)	0.84 (0.60-1.18)		1.00 (0.72-1.39)	0.77 (0.51-1.17)		0.85 (0.62-1.18)	-	
p-trend	0.539	0.692		0.597	0.52		0.825	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.01 (0.76-1.33)	0.96 (0.76-1.20)	0.758	1.10 (0.88-1.38)	0.82 (0.63-1.07)	0.06	1 (referent)	1.03 (0.76-1.38)	

Glioblastoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			297	297	278	153	144		124	173		105	192	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	297	30738	0.999 (0.938 - 1.063)	0.971 (0.908-1.037)	0.978 (0.913-1.047)	0.900 (0.815-0.994)	1.030 (0.942-1.126)	0.027	0.941 (0.845-1.048)	0.999 (0.919-1.085)	0.271	0.914 (0.801-1.042)	0.993 (0.919-1.072)	0.23
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	297	30738	1.013 (0.908 - 1.130)	0.955 (0.851-1.073)	0.963 (0.855-1.086)	0.901 (0.765-1.060)	1.009 (0.854-1.191)	0.262	1.046 (0.875-1.252)	0.918 (0.790-1.066)	0.31	0.962 (0.786-1.177)	0.951 (0.826-1.096)	0.945
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	297	30738	1.005 (0.915 - 1.104)	0.956 (0.864-1.056)	0.965 (0.870-1.070)	0.878 (0.759-1.015)	1.028 (0.894-1.182)	0.079	0.979 (0.837-1.146)	0.958 (0.843-1.088)	0.988	0.922 (0.768-1.108)	0.971 (0.861-1.095)	0.602
Glioblastoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	66	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	60	6644 6	0.95 (0.67-1.36)	0.87 (0.61-1.25)	0.85 (0.59-1.23)	1.04 (0.62-1.72)	0.68 (0.41-1.15)		0.80 (0.48-1.31)	1.01 (0.60-1.69)		0.82 (0.48-1.40)	0.90 (0.56-1.45)	
130-139	62	5748 2	1.02 (0.71-1.45)	0.89 (0.62-1.28)	0.85 (0.58-1.24)	0.95 (0.56-1.60)	0.81 (0.48-1.35)		0.92 (0.55-1.54)	0.94 (0.56-1.59)		1.38 (0.82-2.31)	0.65 (0.39-1.07)	
140-159	75	6823 5	0.91 (0.64-1.28)	0.77 (0.54-1.11)	0.78 (0.54-1.13)	0.71 (0.42-1.21)	0.83 (0.51-1.36)	0.093	0.85 (0.50-1.44)	0.81 (0.49-1.34)	0.526	0.73 (0.38-1.37)	0.77 (0.49-1.20)	0.473
160-179	28	2265 6	1.02 (0.64-1.62)	0.86 (0.54-1.39)	0.87 (0.54-1.41)	0.79 (0.40-1.58)	0.94 (0.49-1.80)		0.60 (0.23-1.57)	1.05 (0.58-1.90)		0.20 (0.03-1.63)	0.95 (0.56-1.63)	
>= 180	6	6358	0.79 (0.34-1.84)	0.65 (0.28-1.54)	0.68 (0.29-1.61)	0.20 (0.03-1.49)	1.15 (0.44-3.03)		0.48 (0.06-3.53)	0.77 (0.29-2.06)		no cases	0.72 (0.29-1.75)	
p-trend			0.704	0.213	0.276	0.057	0.98		0.341	0.561		0.247	0.492	
Diastolic Blood Pressure (mmHg)														
ESH classification														
< 80	108	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	68	6487 2	1.12 (0.83-1.53)	1.05 (0.77-1.43)	1.07 (0.77-1.47)	0.92 (0.59-1.42)	1.17 (0.76-1.80)		1.12 (0.71-1.77)	0.99 (0.65-1.50)		1.51 (0.92-2.49)	0.83 (0.56-1.24)	
85-89	48	4150 0	1.13 (0.80-1.60)	1.03 (0.72-1.46)	1.04 (0.72-1.49)	1.00 (0.62-1.61)	1.00 (0.60-1.69)		1.15 (0.66-1.99)	0.97 (0.62-1.52)		1.62 (0.92-2.85)	0.79 (0.51-1.23)	
90-99	56	5119 6	1.06 (0.76-1.47)	0.93 (0.67-1.31)	0.95 (0.67-1.35)	0.77 (0.48-1.23)	1.15 (0.71-1.86)	0.215	1.25 (0.74-2.12)	0.81 (0.53-1.26)	0.371	1.02 (0.54-1.92)	0.87 (0.58-1.29)	0.759
100-109	14	1389 6	0.96 (0.55-1.68)	0.82 (0.46-1.45)	0.88 (0.49-1.56)	0.65 (0.30-1.40)	1.05 (0.45-2.48)		0.54 (0.13-2.22)	0.89 (0.47-1.68)		0.76 (0.23-2.53)	0.80 (0.42-1.53)	
>= 110	3	3264	0.88 (0.28-2.79)	0.73 (0.23-2.32)	0.53 (0.13-2.15)	0.66 (0.16-2.73)	0.79 (0.11-5.75)		1.41 (0.19-10.26)	0.59 (0.14-2.41)		no cases	0.87 (0.27-2.79)	
p-trend			0.9	0.439	0.476	0.182	0.795		0.683	0.304		0.854	0.403	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	66	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Glioblastoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
120-139	122	1239 28	0.99 (0.73- 1.34)	0.88 (0.65- 1.20)	0.85 (0.62- 1.17)	0.99 (0.63- 1.58)	0.74 (0.48- 1.15)		0.85 (0.56- 1.30)	0.97 (0.61- 1.55)		1.05 (0.67- 1.65)	0.77 (0.50- 1.18)	
140-159	75	6823 5	0.90 (0.64- 1.28)	0.77 (0.54- 1.11)	0.78 (0.54- 1.13)	0.72 (0.42- 1.22)	0.83 (0.51- 1.35)	0.146	0.85 (0.50- 1.43)	0.81 (0.49- 1.34)	0.369	0.71 (0.37- 1.34)	0.77 (0.49- 1.21)	0.122
>= 160	34	2901 4	0.97 (0.63- 1.50)	0.82 (0.52- 1.28)	0.83 (0.52- 1.31)	0.67 (0.34- 1.31)	0.98 (0.54- 1.77)		0.58 (0.24- 1.40)	0.99 (0.56- 1.75)		0.16 (0.02- 1.19)	0.91 (0.54- 1.52)	
p-trend			0.688	0.223	0.303	0.087	0.905		0.252	0.69		0.066	0.824	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	108	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	116	1063 72	1.13 (0.86- 1.47)	1.04 (0.79- 1.36)	1.05 (0.80- 1.40)	0.95 (0.65- 1.39)	1.10 (0.75- 1.62)		1.13 (0.76- 1.69)	0.98 (0.68- 1.41)		1.55 (1.00- 2.42)	0.81 (0.58- 1.15)	
90-99	56	5119 6	1.06 (0.76- 1.47)	0.93 (0.67- 1.31)	0.95 (0.67- 1.35)	0.77 (0.48- 1.23)	1.15 (0.71- 1.86)	0.157	1.25 (0.74- 2.12)	0.81 (0.53- 1.26)	0.426	1.02 (0.54- 1.91)	0.87 (0.58- 1.29)	0.739
>= 100	17	1716 0	0.94 (0.56- 1.58)	0.80 (0.47- 1.36)	0.81 (0.47- 1.40)	0.65 (0.32- 1.31)	1.01 (0.45- 2.25)		0.68 (0.21- 2.19)	0.83 (0.45- 1.51)		0.62 (0.19- 2.07)	0.81 (0.45- 1.46)	
p-trend			0.9	0.444	0.513	0.144	0.681		0.746	0.329		0.863	0.403	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
50.0-88.3	61	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	61	7772 7	0.82 (0.57- 1.18)	0.76 (0.53- 1.08)	0.78 (0.54- 1.14)	0.68 (0.39- 1.17)	0.81 (0.50- 1.32)		0.95 (0.59- 1.54)	0.60 (0.35- 1.02)		0.77 (0.44- 1.36)	0.73 (0.45- 1.17)	
96.8-105.5	87	7632 7	1.04 (0.74- 1.46)	0.91 (0.64- 1.29)	0.91 (0.63- 1.30)	0.98 (0.59- 1.60)	0.77 (0.47- 1.26)	0.363	1.09 (0.67- 1.78)	0.79 (0.49- 1.27)	0.88	1.48 (0.88- 2.51)	0.66 (0.42- 1.04)	0.802
105.6-216.6	88	7627 3	0.96 (0.68- 1.36)	0.81 (0.56- 1.15)	0.83 (0.57- 1.20)	0.67 (0.39- 1.13)	0.96 (0.59- 1.56)		0.85 (0.48- 1.49)	0.75 (0.47- 1.21)		0.67 (0.34- 1.33)	0.78 (0.51- 1.21)	
p-trend			0.783	0.486	0.552	0.329	0.896		0.759	0.711		0.915	0.444	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	153	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	144	1331 39	1.00 (0.79- 1.26)	0.92 (0.72- 1.17)	0.94 (0.73- 1.21)	0.83 (0.59- 1.16)	1.02 (0.72- 1.45)	0.298	1.09 (0.75- 1.59)	0.85 (0.62- 1.16)	0.444	0.88 (0.58- 1.36)	0.94 (0.70- 1.27)	0.777

Glioblastoma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	132	161		178	119		190	37	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.995 (0.902-1.098)	0.955 (0.873-1.045)	0.505	0.971 (0.891-1.057)	0.969 (0.872-1.078)	0.636	0.981 (0.897-1.073)	0.922 (0.771-1.103)	0.87
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.939 (0.787-1.121)	0.975 (0.834-1.139)	0.827	0.978 (0.843-1.135)	0.919 (0.764-1.105)	0.679	0.972 (0.833-1.136)	0.750 (0.524-1.072)	0.137
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	0.966 (0.831-1.124)	0.954 (0.833-1.092)	0.829	0.967 (0.850-1.100)	0.936 (0.798-1.098)	0.634	0.972 (0.849-1.113)	0.809 (0.598-1.094)	0.446
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
120-129	0.80 (0.47-1.36)	1.02 (0.63-1.66)		0.81 (0.52-1.25)	1.01 (0.55-1.87)		0.89 (0.58-1.35)	-	
130-139	0.86 (0.50-1.46)	1.02 (0.62-1.68)		0.71 (0.44-1.13)	1.26 (0.70-2.29)		0.97 (0.63-1.49)	-	
140-159	0.72 (0.42-1.22)	0.87 (0.53-1.42)	0.636	0.68 (0.43-1.07)	0.96 (0.52-1.75)	0.844	0.90 (0.58-1.39)	-	-
160-179	1.04 (0.53-2.01)	0.78 (0.39-1.54)		0.89 (0.50-1.59)	0.88 (0.39-1.97)		0.93 (0.48-1.81)	-	
>= 180	0.80 (0.24-2.69)	0.59 (0.17-1.97)		0.71 (0.25-2.02)	0.58 (0.13-2.58)		no cases	-	
p-trend	0.637	0.271		0.253	0.565		0.439	-	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.13 (0.72-1.78)	0.98 (0.64-1.52)		1.06 (0.72-1.58)	1.02 (0.62-1.67)		0.97 (0.67-1.41)	1.58 (0.54-4.63)	
85-89	0.90 (0.52-1.55)	1.17 (0.74-1.85)		0.92 (0.57-1.48)	1.15 (0.68-1.94)		0.93 (0.60-1.45)	0.82 (0.25-2.64)	
90-99	0.95 (0.57-1.58)	0.94 (0.60-1.49)	0.844	1.12 (0.73-1.71)	0.71 (0.41-1.25)	0.445	0.89 (0.57-1.38)	0.61 (0.20-1.85)	0.161
100-109	0.85 (0.36-2.03)	0.81 (0.38-1.73)		0.81 (0.37-1.78)	0.81 (0.35-1.85)		1.09 (0.52-2.30)	0.30 (0.06-1.62)	

>= 110	0.56 (0.08-4.13)	0.85 (0.20-3.52)		0.96 (0.23-3.95)	0.47 (0.06-3.47)		no cases	1.48 (0.27-8.11)	
p-trend	0.516	0.721		0.968	0.245		0.526	0.078	
Glioblastoma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
120-139	0.82 (0.52-1.31)	1.02 (0.66-1.57)		0.76 (0.52-1.12)	1.14 (0.66-1.95)		0.92 (0.64-1.34)	-	
140-159	0.71 (0.42-1.22)	0.87 (0.53-1.42)	0.615	0.69 (0.44-1.08)	0.95 (0.52-1.74)	0.628	0.90 (0.58-1.39)	-	-
>= 160	0.98 (0.52-1.85)	0.73 (0.39-1.40)		0.85 (0.49-1.48)	0.80 (0.37-1.73)		0.75 (0.39-1.47)	-	
p-trend	0.666	0.265		0.351	0.424		0.424	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.03 (0.69-1.55)	1.06 (0.73-1.53)		1.01 (0.71-1.43)	1.07 (0.70-1.65)		0.96 (0.69-1.33)	1.17 (0.43-3.22)	
90-99	0.95 (0.57-1.58)	0.94 (0.59-1.49)	0.965	1.12 (0.73-1.71)	0.71 (0.41-1.25)	0.386	0.89 (0.57-1.39)	0.62 (0.20-1.87)	0.178
>= 100	0.80 (0.35-1.80)	0.81 (0.41-1.63)		0.84 (0.41-1.71)	0.74 (0.34-1.62)		0.90 (0.43-1.90)	0.51 (0.13-1.98)	
p-trend	0.653	0.588		0.972	0.216		0.603	0.103	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	0.93 (0.55-1.58)	0.63 (0.38-1.05)		0.79 (0.51-1.22)	0.68 (0.36-1.30)		0.88 (0.58-1.35)	-	
96.8-105.5	0.80 (0.47-1.38)	1.00 (0.63-1.58)	0.734	0.74 (0.47-1.15)	1.17 (0.66-2.09)	0.916	1.06 (0.69-1.61)	-	-
105.6-216.6	0.96 (0.56-1.64)	0.72 (0.44-1.17)		0.83 (0.53-1.30)	0.79 (0.42-1.46)		0.90 (0.56-1.44)	-	
p-trend	0.837	0.526		0.453	0.85		0.903	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.98 (0.68-1.42)	0.87 (0.62-1.21)	0.664	1.04 (0.76-1.42)	0.78 (0.53-1.14)	0.208	1 (referent)	1.17 (0.77-1.77)	

Thyroid	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			420	420	382	71	349		202	218		247	173	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	420	30738	0.995 (0.939-1.054)	1.022 (0.963-1.084)	1.034 (0.972-1.100)	1.006 (0.865-1.171)	1.026 (0.962-1.094)	0.466	1.013 (0.926-1.109)	1.027 (0.950-1.110)	0.951	1.057 (0.972-1.149)	0.991 (0.911-1.077)	0.21
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	420	30738	0.979 (0.889-1.078)	1.032 (0.934-1.141)	1.031 (0.928-1.146)	0.897 (0.696-1.156)	1.062 (0.952-1.185)	0.11	1.031 (0.888-1.197)	1.028 (0.900-1.175)	0.794	1.121 (0.983-1.280)	0.927 (0.795-1.081)	0.052
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	420	30738	0.985 (0.906-1.073)	1.033 (0.946-1.128)	1.041 (0.950-1.142)	0.948 (0.757-1.188)	1.051 (0.955-1.156)	0.197	1.026 (0.899-1.170)	1.034 (0.921-1.162)	0.86	1.104 (0.980-1.243)	0.957 (0.839-1.091)	0.084
Systolic Blood Pressure (mmHg) ESH classification														
< 120	139	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	102	66446	1.04 (0.80-1.35)	1.13 (0.87-1.48)	1.15 (0.87-1.51)	2.13 (1.00-4.51)	1.01 (0.76-1.35)		1.03 (0.72-1.48)	1.29 (0.86-1.92)		1.22 (0.89-1.67)	0.95 (0.59-1.53)	
130-139	75	57482	0.94 (0.70-1.25)	1.06 (0.78-1.42)	0.99 (0.72-1.36)	1.87 (0.83-4.18)	0.96 (0.69-1.34)		0.92 (0.60-1.42)	1.21 (0.79-1.86)		0.90 (0.60-1.35)	1.17 (0.74-1.85)	
140-159	75	68235	0.92 (0.68-1.24)	1.05 (0.77-1.44)	1.06 (0.76-1.47)	1.68 (0.72-3.91)	1.01 (0.72-1.42)	0.401	0.85 (0.52-1.40)	1.26 (0.82-1.92)	0.694	1.24 (0.81-1.89)	0.90 (0.56-1.44)	0.357

classification														
< 80	203	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	133	106372	0.83 (0.66-1.04)	0.90 (0.71-1.13)	0.94 (0.74-1.19)	0.87 (0.49-1.54)	0.90 (0.70-1.16)		1.09 (0.79-1.50)	0.74 (0.54-1.02)		1.00 (0.74-1.34)	0.77 (0.54-1.10)	
90-99	62	51196	0.87 (0.65-1.17)	0.99 (0.73-1.34)	1.03 (0.75-1.41)	1.31 (0.69-2.48)	0.89 (0.62-1.26)	0.203	1.13 (0.70-1.83)	0.86 (0.59-1.27)	0.713	1.18 (0.78-1.78)	0.79 (0.51-1.23)	0.107
>= 100	22	17160	0.99 (0.63-1.55)	1.15 (0.73-1.82)	1.19 (0.74-1.93)	no cases	1.60 (1.01-2.54)		0.69 (0.22-2.19)	1.19 (0.72-1.99)		1.53 (0.81-2.91)	0.87 (0.45-1.67)	
p-trend			0.409	0.88	0.67	0.468	0.569		0.849	0.977		0.244	0.323	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Thyroid	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	121	76991	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	114	77727	0.97 (0.75-1.26)	1.05 (0.81-1.37)	1.04 (0.79-1.38)	0.99 (0.47-2.07)	1.06 (0.80-1.40)		0.85 (0.59-1.21)	1.40 (0.92-2.13)		1.30 (0.94-1.79)	0.65 (0.41-1.03)	
96.8-105.5	94	76327	0.88 (0.66-1.16)	0.98 (0.74-1.31)	0.96 (0.71-1.30)	1.09 (0.51-2.32)	0.95 (0.70-1.31)	0.679	1.00 (0.68-1.48)	1.08 (0.69-1.69)	0.665	1.15 (0.79-1.67)	0.71 (0.46-1.11)	0.113
105.6-216.6	91	76273	0.99 (0.74-1.33)	1.16 (0.85-1.58)	1.19 (0.86-1.65)	1.15 (0.52-2.56)	1.18 (0.84-1.65)		0.96 (0.59-1.56)	1.41 (0.91-2.19)		1.47 (0.96-2.24)	0.80 (0.51-1.25)	
p-trend			0.746	0.475	0.428	0.669	0.529		0.934	0.308		0.127	0.552	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	259	174179	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	161	133139	0.99 (0.80-1.22)	1.04 (0.84-1.29)	1.03 (0.82-1.29)	0.99 (0.59-1.66)	1.06 (0.84-1.35)	0.489	0.88 (0.62-1.23)	1.16 (0.87-1.53)	0.406	1.09 (0.82-1.47)	1.00 (0.73-1.37)	0.543

Thyroid	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
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Cases	223	192		313	107		336	57	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.007 (0.928-1.094)	1.041 (0.955-1.136)	0.426	1.010 (0.943-1.083)	1.049 (0.935-1.176)	0.386	0.992 (0.922-1.066)	1.123 (0.980-1.286)	0.006
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.031 (0.899-1.182)	1.034 (0.891-1.200)	0.944	1.047 (0.932-1.176)	0.979 (0.802-1.194)	0.883	1.018 (0.905-1.147)	1.000 (0.768-1.301)	0.141
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1.021 (0.905-1.153)	1.048 (0.921-1.194)	0.662	1.032 (0.931-1.143)	1.025 (0.862-1.219)	0.723	1.004 (0.903-1.116)	1.103 (0.884-1.377)	0.023
Thyroid	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.72 (0.49-1.06)	1.77 (1.21-2.60)		1.06 (0.79-1.44)	1.34 (0.77-2.33)		1.16 (0.88-1.53)	0.77 (0.20-2.96)	
130-139	0.86 (0.58-1.29)	1.34 (0.85-2.11)		0.99 (0.70-1.39)	1.27 (0.69-2.32)		1.04 (0.75-1.44)	1.28 (0.39-4.16)	
140-159	0.94 (0.62-1.41)	1.25 (0.77-2.03)	0.442	0.99 (0.69-1.43)	1.23 (0.66-2.30)	0.36	0.97 (0.67-1.40)	1.19 (0.38-3.77)	0.006
160-179	1.15 (0.64-2.10)	1.79 (0.93-3.46)		1.32 (0.79-2.21)	1.56 (0.66-3.68)		0.99 (0.52-1.89)	2.87 (0.88-9.35)	
>= 180	0.32 (0.04-2.36)	no cases		no cases	0.79 (0.10-6.08)		no cases	0.50 (0.05-4.69)	
p-trend	0.879	0.556		0.878	0.529		0.615	0.121	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.88 (0.61-1.27)	0.91 (0.62-1.35)		0.91 (0.67-1.23)	0.95 (0.57-1.61)		1.00 (0.76-1.33)	0.56 (0.22-1.44)	
85-89	0.82 (0.52-1.28)	0.92 (0.58-1.48)		0.85 (0.58-1.24)	0.89 (0.47-1.65)		1.00 (0.70-1.43)	0.37 (0.13-1.07)	
90-99	0.86 (0.56-1.33)	1.15 (0.75-1.76)	0.684	0.95 (0.66-1.36)	1.07 (0.61-1.88)	0.813	0.88 (0.60-1.29)	0.91 (0.43-1.91)	0.079
100-109	1.56 (0.86-2.86)	0.43 (0.13-1.38)		1.31 (0.75-2.31)	0.42 (0.10-1.76)		0.94 (0.44-2.03)	0.71 (0.27-1.88)	

>= 110	1.87 (0.67-5.24)	1.25 (0.30-5.16)		1.20 (0.38-3.80)	2.34 (0.70-7.81)		2.66 (0.97-7.31)	0.91 (0.20-4.20)	
p-trend	0.672	0.86		0.908	0.973		0.979	0.977	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.78 (0.57-1.08)	1.60 (1.12-2.29)		1.03 (0.79-1.35)	1.31 (0.79-2.17)		1.11 (0.87-1.43)	1.06 (0.34-3.29)	
140-159	0.93 (0.62-1.40)	1.28 (0.79-2.07)	0.212	1.00 (0.70-1.44)	1.24 (0.67-2.31)	0.362	0.98 (0.68-1.41)	1.18 (0.37-3.73)	0.006
>= 160	0.99 (0.55-1.78)	1.46 (0.76-2.83)		1.07 (0.64-1.79)	1.42 (0.62-3.25)		0.84 (0.44-1.60)	2.23 (0.69-7.20)	
p-trend	0.806	0.214		0.862	0.426		0.828	0.061	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.86 (0.63-1.18)	0.92 (0.65-1.29)		0.89 (0.68-1.16)	0.93 (0.59-1.47)		1.00 (0.78-1.28)	0.46 (0.21-1.05)	
90-99	0.86 (0.56-1.33)	1.15 (0.74-1.76)	0.564	0.95 (0.66-1.37)	1.07 (0.61-1.89)	0.934	0.88 (0.60-1.29)	0.91 (0.43-1.93)	0.08
>= 100	1.63 (0.95-2.80)	0.58 (0.23-1.46)		1.29 (0.77-2.18)	0.83 (0.32-2.15)		1.23 (0.66-2.29)	0.75 (0.30-1.86)	
p-trend	0.597	0.731		0.827	0.917		0.928	0.897	
Thyroid	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.86 (0.59-1.24)	1.32 (0.89-1.95)		1.08 (0.80-1.45)	0.98 (0.55-1.75)		1.07 (0.81-1.41)	0.52 (0.13-2.05)	
96.8-105.5	0.91 (0.62-1.34)	1.12 (0.72-1.74)	0.438	0.93 (0.67-1.31)	1.09 (0.61-1.95)	0.35	0.98 (0.72-1.35)	0.65 (0.20-2.13)	0.017
105.6-216.6	1.04 (0.69-1.58)	1.38 (0.87-2.20)		1.11 (0.78-1.59)	1.28 (0.69-2.37)		0.97 (0.67-1.41)	1.08 (0.35-3.35)	
p-trend	0.857	0.294		0.797	0.378		0.813	0.216	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.04 (0.78-1.40)	1.07 (0.78-1.47)	0.75	1.05 (0.81-1.35)	1.03 (0.68-1.57)	0.813	1 (referent)	1.22 (0.85-1.75)	

Leukemia	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1308	1308	1179	667	641		533	775		366	942	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1308	30738	1.006 (0.977-1.036)	0.986 (0.956-1.017)	0.992 (0.960-1.025)	1.004 (0.961-1.050)	0.968 (0.927-1.012)	0.21	0.978 (0.931-1.027)	0.996 (0.957-1.036)	0.888	0.983 (0.918-1.053)	0.988 (0.954-1.023)	0.991
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1308	30738	1.021 (0.969-1.076)	0.972 (0.920-1.028)	0.985 (0.929-1.044)	0.980 (0.906-1.059)	0.965 (0.892-1.045)	0.639	0.937 (0.858-1.024)	1.004 (0.936-1.077)	0.486	0.960 (0.861-1.071)	0.978 (0.917-1.044)	0.926
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1308	30738	1.015 (0.970-1.061)	0.976 (0.930-1.023)	0.986 (0.938-1.037)	0.993 (0.928-1.062)	0.958 (0.896-1.025)	0.362	0.952 (0.883-1.027)	0.999 (0.941-1.061)	0.757	0.967 (0.877-1.067)	0.980 (0.928-1.035)	0.955
Leukemia	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	241	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	247	66446	1.01 (0.85-1.21)	0.94 (0.78-1.12)	1.01 (0.83-1.22)	1.12 (0.84-1.48)	0.84 (0.66-1.07)		0.92 (0.72-1.18)	0.97 (0.74-1.27)		1.18 (0.89-1.55)	0.81 (0.64-1.02)	
130-139	270	57482	1.11 (0.93-1.33)	1.00 (0.83-1.20)	1.00 (0.83-1.22)	1.19 (0.90-1.58)	0.90 (0.70-1.15)		0.85 (0.65-1.11)	1.16 (0.89-1.50)		1.02 (0.74-1.40)	0.96 (0.77-1.21)	
140-159	375	68235	1.09 (0.91-1.29)	0.96 (0.81-1.15)	1.02 (0.84-1.23)	1.15 (0.87-1.51)	0.86 (0.67-1.09)	0.093	0.81 (0.63-1.06)	1.13 (0.88-1.44)	0.606	1.07 (0.77-1.48)	0.90 (0.73-1.12)	0.849

classification														
< 80	479	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	471	1063 72	0.98 (0.86-1.11)	0.91 (0.80-1.04)	0.94 (0.81-1.08)	0.90 (0.75-1.09)	0.92 (0.77-1.11)		0.86 (0.70-1.04)	0.98 (0.82-1.17)		0.86 (0.68-1.10)	0.94 (0.80-1.09)	
90-99	262	5119 6	1.03 (0.89-1.21)	0.93 (0.79-1.08)	0.98 (0.83-1.16)	0.85 (0.68-1.07)	1.02 (0.81-1.28)	0.701	0.82 (0.63-1.07)	1.02 (0.83-1.24)	0.642	0.92 (0.67-1.27)	0.93 (0.77-1.12)	0.745
>= 100	96	1716 0	1.11 (0.89-1.39)	0.96 (0.76-1.21)	0.97 (0.76-1.24)	1.04 (0.78-1.38)	0.79 (0.53-1.18)		1.04 (0.70-1.57)	0.99 (0.75-1.30)		1.08 (0.67-1.71)	0.94 (0.72-1.22)	
p-trend			0.392	0.441	0.808	0.64	0.506		0.296	0.933		0.808	0.485	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	231	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	318	7772 7	1.06 (0.89-1.25)	0.98 (0.82-1.16)	0.97 (0.81-1.16)	0.98 (0.75-1.28)	0.99 (0.79-1.24)		0.98 (0.78-1.24)	0.99 (0.76-1.29)		0.87 (0.66-1.15)	1.06 (0.85-1.32)	
96.8-105.5	346	7632 7	1.01 (0.85-1.20)	0.90 (0.76-1.07)	0.89 (0.74-1.07)	0.99 (0.76-1.29)	0.83 (0.65-1.05)	0.848	0.82 (0.64-1.06)	0.99 (0.77-1.27)	0.599	0.84 (0.62-1.15)	0.94 (0.76-1.18)	0.693
105.6-216.6	413	7627 3	1.03 (0.87-1.22)	0.89 (0.74-1.06)	0.91 (0.76-1.10)	0.88 (0.67-1.15)	0.91 (0.72-1.16)		0.83 (0.64-1.08)	0.97 (0.76-1.25)		0.92 (0.66-1.28)	0.91 (0.73-1.13)	
p-trend			0.906	0.123	0.258	0.278	0.279		0.076	0.809		0.574	0.16	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	613	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	695	1331 39	1.06 (0.95-1.19)	1.01 (0.90-1.13)	1.03 (0.91-1.17)	1.08 (0.92-1.28)	0.94 (0.80-1.11)	0.156	0.90 (0.75-1.08)	1.11 (0.95-1.29)	0.198	1.09 (0.87-1.37)	0.98 (0.86-1.12)	0.335

Leukemia	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	538	754		817	491		867	205	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.972 (0.926-1.021)	0.994 (0.954-1.035)	0.759	0.981 (0.944-1.021)	0.996 (0.947-1.048)	0.784	0.969 (0.930-1.010)	0.959 (0.889-1.035)	0.898

Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.971 (0.890-1.060)	0.977 (0.908-1.050)	0.882	0.983 (0.917-1.054)	0.964 (0.880-1.057)	0.343	0.934 (0.868-1.005)	0.939 (0.814-1.083)	0.861
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	0.964 (0.895-1.040)	0.984 (0.924-1.047)	0.806	0.977 (0.920-1.038)	0.980 (0.906-1.059)	0.502	0.943 (0.885-1.004)	0.934 (0.826-1.057)	0.988
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.84 (0.63-1.11)	1.03 (0.81-1.32)		0.81 (0.65-1.02)	1.22 (0.89-1.66)		0.89 (0.73-1.09)	0.69 (0.33-1.48)	
130-139	0.87 (0.65-1.15)	1.12 (0.88-1.42)		0.93 (0.74-1.16)	1.17 (0.85-1.61)		0.98 (0.79-1.20)	0.77 (0.39-1.54)	
140-159	0.91 (0.69-1.19)	0.99 (0.78-1.26)	0.964	0.89 (0.72-1.11)	1.12 (0.83-1.53)	0.777	0.85 (0.69-1.06)	0.77 (0.40-1.48)	0.541
160-179	0.77 (0.53-1.10)	1.07 (0.79-1.44)		0.85 (0.64-1.13)	1.09 (0.74-1.61)		0.93 (0.69-1.26)	0.63 (0.31-1.25)	
>= 180	1.04 (0.62-1.73)	0.96 (0.60-1.53)		0.98 (0.64-1.51)	1.08 (0.60-1.92)		0.92 (0.54-1.55)	0.64 (0.29-1.44)	
p-trend	0.558	0.981		0.634	0.92		0.385	0.289	
Diastolic Blood Pressure (mmHg) ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.94 (0.74-1.18)	0.93 (0.77-1.14)		0.87 (0.72-1.06)	1.06 (0.83-1.34)		0.89 (0.75-1.06)	0.85 (0.52-1.40)	
85-89	0.93 (0.71-1.21)	0.81 (0.64-1.02)		1.01 (0.82-1.24)	0.66 (0.49-0.91)		0.75 (0.60-0.94)	0.95 (0.59-1.54)	
90-99	0.93 (0.72-1.19)	0.92 (0.75-1.13)	0.869	0.91 (0.74-1.11)	0.96 (0.75-1.24)	0.155	0.90 (0.73-1.10)	0.86 (0.55-1.34)	0.817
100-109	1.04 (0.71-1.52)	1.05 (0.77-1.43)		1.19 (0.88-1.60)	0.86 (0.57-1.28)		1.01 (0.71-1.44)	0.83 (0.49-1.42)	
>= 110	0.71 (0.29-1.74)	0.61 (0.29-1.31)		0.65 (0.31-1.39)	0.65 (0.27-1.60)		0.43 (0.14-1.33)	0.35 (0.11-1.15)	
p-trend	0.626	0.367		0.894	0.173		0.116	0.244	
Leukemia	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg) ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

120-139	0.85 (0.67-1.09)	1.08 (0.87-1.33)		0.87 (0.72-1.05)	1.19 (0.90-1.58)		0.93 (0.78-1.11)	0.74 (0.38-1.43)	
140-159	0.91 (0.69-1.18)	0.99 (0.78-1.25)	0.897	0.89 (0.72-1.10)	1.12 (0.83-1.53)	0.987	0.85 (0.69-1.05)	0.77 (0.40-1.48)	0.547
>= 160	0.82 (0.59-1.14)	1.04 (0.78-1.38)		0.87 (0.67-1.14)	1.09 (0.76-1.57)		0.93 (0.70-1.22)	0.63 (0.32-1.24)	
p-trend	0.407	0.885		0.391	0.885		0.277	0.225	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.93 (0.76-1.14)	0.88 (0.74-1.05)		0.93 (0.79-1.09)	0.90 (0.72-1.12)		0.84 (0.72-0.98)	0.90 (0.59-1.38)	
90-99	0.93 (0.72-1.19)	0.92 (0.75-1.13)	0.999	0.91 (0.74-1.11)	0.97 (0.75-1.25)	0.409	0.90 (0.73-1.10)	0.86 (0.55-1.34)	0.703
>= 100	0.98 (0.68-1.41)	0.97 (0.72-1.30)		1.08 (0.81-1.44)	0.82 (0.56-1.21)		0.92 (0.65-1.29)	0.73 (0.44-1.24)	
p-trend	0.68	0.58		0.808	0.465		0.221	0.25	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	0.93 (0.72-1.22)	1.02 (0.81-1.28)		0.90 (0.73-1.11)	1.15 (0.85-1.57)		0.96 (0.79-1.17)	0.94 (0.42-2.11)	
96.8-105.5	0.82 (0.63-1.08)	0.95 (0.75-1.20)	0.763	0.80 (0.64-0.99)	1.15 (0.84-1.56)	0.657	0.87 (0.71-1.07)	0.86 (0.41-1.84)	0.852
105.6-216.6	0.85 (0.64-1.11)	0.92 (0.73-1.17)		0.87 (0.70-1.08)	0.97 (0.71-1.34)		0.83 (0.67-1.03)	0.79 (0.38-1.64)	
p-trend	0.178	0.374		0.181	0.526		0.059	0.329	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.00 (0.83-1.20)	0.99 (0.85-1.16)	0.991	1.02 (0.88-1.18)	1.00 (0.83-1.21)	0.474	1 (referent)	1.14 (0.95-1.37)	

Multiple Myeloma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			475	475	434	250	225		191	284		127	348	
Cohort size			307318	307318	301857	112591	194727		146326	160992		153303	154015	

Mean Systolic Blood Pressure continuous (per 10mmHg increase)	475	3073 18	1.024 (0.976 - 1.075)	0.995 (0.945-1.047)	1.002 (0.949-1.057)	1.004 (0.934-1.080)	0.983 (0.914-1.058)	0.537	0.991 (0.912-1.076)	1.015 (0.951-1.083)	0.431	1.028 (0.919-1.151)	0.987 (0.932-1.046)	0.721
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	475	3073 18	1.079 (0.989 - 1.176)	1.012 (0.923-1.109)	1.029 (0.935-1.132)	0.970 (0.854-1.102)	1.059 (0.929-1.208)	0.607	1.006 (0.868-1.165)	1.050 (0.936-1.178)	0.555	0.976 (0.811-1.173)	1.025 (0.923-1.139)	0.584
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	475	3073 18	1.057 (0.982 - 1.138)	1.002 (0.926-1.084)	1.015 (0.935-1.102)	0.988 (0.885-1.103)	1.014 (0.907-1.135)	0.967	0.996 (0.878-1.129)	1.036 (0.939-1.144)	0.457	1.006 (0.854-1.185)	1.002 (0.916-1.096)	0.892
Systolic Blood Pressure (mmHg) ESH classification														
< 120	79	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	87	6644 6	1.07 (0.78-1.45)	0.97 (0.71-1.32)	1.01 (0.73-1.39)	1.09 (0.68-1.77)	0.89 (0.59-1.35)		1.02 (0.68-1.54)	0.98 (0.61-1.58)		1.57 (0.97-2.55)	0.71 (0.47-1.06)	
130-139	108	5748 2	1.32 (0.98-1.78)	1.16 (0.86-1.57)	1.10 (0.80-1.52)	1.34 (0.84-2.13)	1.04 (0.69-1.56)		1.01 (0.65-1.57)	1.38 (0.89-2.14)		1.06 (0.59-1.88)	1.11 (0.78-1.59)	
140-159	138	6823 5	1.20 (0.90-1.61)	1.02 (0.75-1.37)	1.07 (0.78-1.46)	1.23 (0.78-1.95)	0.85 (0.56-1.28)	0.334	1.05 (0.68-1.61)	1.14 (0.74-1.76)	0.19	1.56 (0.90-2.70)	0.84 (0.59-1.20)	0.578
160-179	44	2265 6	1.04 (0.71-1.53)	0.87 (0.58-1.29)	0.93 (0.61-1.40)	0.93 (0.52-1.68)	0.84 (0.49-1.45)		0.64 (0.30-1.33)	1.09 (0.65-1.83)		1.18 (0.44-3.15)	0.74 (0.48-1.16)	
>= 180	19	6358	1.58 (0.94-2.66)	1.32 (0.78-2.24)	1.40 (0.81-2.41)	1.59 (0.76-3.33)	1.14 (0.52-2.48)		1.08 (0.38-3.08)	1.67 (0.87-3.19)		1.13 (0.15-8.49)	1.18 (0.67-2.07)	
p-trend			0.186	0.881	0.625	0.552	0.652		0.68	0.295		0.424	0.808	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	153	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Multiple Myeloma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction

					HR (adjusted)									
80-84	108	6487 2	1.15 (0.90- 1.48)	1.07 (0.83- 1.37)	1.12 (0.86- 1.46)	1.16 (0.82- 1.65)	0.94 (0.65- 1.36)		0.97 (0.66- 1.41)	1.23 (0.87- 1.74)		0.94 (0.60- 1.49)	1.14 (0.84- 1.54)	
85-89	73	4150 0	1.13 (0.85- 1.50)	1.02 (0.77- 1.36)	1.08 (0.80- 1.46)	0.85 (0.56- 1.29)	1.25 (0.85- 1.85)		0.91 (0.57- 1.46)	1.18 (0.81- 1.71)		0.69 (0.37- 1.28)	1.16 (0.84- 1.62)	
90-99	97	5119 6	1.15 (0.89- 1.49)	1.00 (0.76- 1.30)	1.07 (0.81- 1.42)	0.89 (0.61- 1.29)	1.15 (0.78- 1.68)	0.577	0.95 (0.61- 1.48)	1.13 (0.80- 1.60)	0.641	0.89 (0.52- 1.51)	1.05 (0.77- 1.44)	0.328
100-109	38	1389 6	1.64 (1.14- 2.35)	1.36 (0.94- 1.96)	1.38 (0.93- 2.04)	1.39 (0.87- 2.23)	1.18 (0.62- 2.23)		1.61 (0.85- 3.07)	1.45 (0.92- 2.30)		1.12 (0.49- 2.55)	1.47 (0.97- 2.24)	
>= 110	6	3264	1.16 (0.51- 2.63)	0.93 (0.41- 2.13)	1.06 (0.46- 2.42)	0.64 (0.20- 2.05)	1.54 (0.48- 4.92)		0.87 (0.12- 6.28)	1.12 (0.45- 2.78)		0.69 (0.09- 5.08)	1.02 (0.41- 2.54)	
p-trend			0.045	0.525	0.311	0.808	0.238		0.696	0.309		0.62	0.307	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	79	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	195	1239 28	1.19 (0.91- 1.55)	1.06 (0.81- 1.39)	1.05 (0.79- 1.40)	1.21 (0.79- 1.87)	0.96 (0.67- 1.37)		1.02 (0.71- 1.46)	1.19 (0.79- 1.80)		1.36 (0.86- 2.14)	0.92 (0.66- 1.29)	
140-159	138	6823 5	1.19 (0.89- 1.59)	1.01 (0.75- 1.36)	1.06 (0.78- 1.45)	1.22 (0.77- 1.93)	0.84 (0.56- 1.27)	0.427	1.05 (0.68- 1.60)	1.13 (0.73- 1.74)	0.301	1.59 (0.92- 2.75)	0.83 (0.58- 1.18)	0.18
>= 160	63	2901 4	1.15 (0.81- 1.63)	0.96 (0.67- 1.49)	1.02 (0.70- 1.49)	1.06 (0.62- 1.82)	0.90 (0.54- 1.47)		0.73 (0.38- 1.38)	1.20 (0.74- 1.95)		1.20 (0.48- 2.99)	0.83 (0.55- 1.24)	
p-trend			0.451	0.691	0.891	0.939	0.474		0.583	0.678		0.207	0.269	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	153	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	181	1063 72	1.14 (0.92- 1.42)	1.05 (0.84- 1.31)	1.10 (0.87- 1.39)	1.03 (0.75- 1.42)	1.06 (0.78- 1.45)		0.95 (0.68- 1.32)	1.21 (0.89- 1.64)		0.85 (0.56- 1.29)	1.15 (0.88- 1.50)	
90-99	97	5119 6	1.15 (0.89- 1.49)	1.00 (0.76- 1.31)	1.07 (0.81- 1.42)	0.89 (0.61- 1.30)	1.14 (0.78- 1.68)	0.966	0.95 (0.61- 1.48)	1.13 (0.80- 1.60)	0.64	0.89 (0.52- 1.52)	1.05 (0.77- 1.44)	0.416
>= 100	44	1716 0	1.55 (1.10- 2.18)	1.28 (0.90- 1.82)	1.32 (0.91- 1.91)	1.25 (0.80- 1.98)	1.23 (0.69- 2.20)		1.51 (0.81- 2.80)	1.39 (0.90- 2.14)		1.05 (0.48- 2.28)	1.39 (0.93- 2.06)	
p-trend			0.026	0.379	0.228	0.732	0.382		0.588	0.228		0.801	0.245	
Mean BP (mmHg) (1/3SBP+2/ 3DBP)														
Cohort- specific quartiles														
Multiple Myeloma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2	Men HR (adjusted)	Women HR (adjusted)	Sex p- interaction	BMI <= 25 mg/m²	BMI > 25 mg/m²	BMI p- interaction	Age <= 53 yrs	Age > 53 yrs HR (adjusted)	Age p- interaction

					years of follow-up HR (adjusted)				HR (adjusted)	HR (adjusted)		HR (adjusted)		
50.0-88.3	73	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	116	7772 7	1.19 (0.89-1.60)	1.09 (0.81-1.47)	1.05 (0.76-1.43)	1.15 (0.72-1.83)	1.04 (0.70-1.55)		1.35 (0.91-2.01)	0.90 (0.57-1.41)		1.10 (0.69-1.76)	1.10 (0.75-1.63)	
96.8-105.5	125	7632 7	1.12 (0.84-1.51)	0.97 (0.72-1.31)	0.96 (0.70-1.32)	1.10 (0.69-1.74)	0.86 (0.57-1.30)	0.996	0.98 (0.63-1.53)	0.98 (0.64-1.50)	0.459	0.66 (0.37-1.16)	1.12 (0.77-1.64)	0.473
105.6-216.6	161	7627 3	1.24 (0.93-1.66)	1.02 (0.75-1.38)	1.03 (0.75-1.41)	1.00 (0.63-1.59)	1.07 (0.71-1.61)		1.08 (0.69-1.70)	1.03 (0.68-1.56)		1.01 (0.58-1.76)	1.07 (0.73-1.55)	
p-trend			0.227	0.847	0.998	0.687	0.923		0.835	0.616		0.562	0.877	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	221	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	254	1331 39	1.07 (0.89-1.30)	0.98 (0.81-1.19)	1.01 (0.83-1.24)	1.03 (0.79-1.35)	0.93 (0.70-1.23)	0.382	0.91 (0.67-1.23)	1.10 (0.85-1.41)	0.214	1.06 (0.72-1.55)	0.95 (0.76-1.19)	0.699

Multiple Myeloma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	193	277		300	175		313	87	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.975 (0.898-1.058)	1.005 (0.940-1.074)	0.809	0.997 (0.935-1.063)	0.997 (0.914-1.086)	0.222	0.986 (0.921-1.056)	0.967 (0.861-1.087)	0.946
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	1.037 (0.897-1.199)	0.994 (0.882-1.120)	0.79	1.045 (0.932-1.171)	0.967 (0.828-1.128)	0.05	0.963 (0.852-1.088)	1.019 (0.821-1.267)	0.638
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	0.998 (0.881-1.130)	1.000 (0.903-1.108)	0.981	1.019 (0.924-1.124)	0.981 (0.859-1.119)	0.083	0.970 (0.873-1.078)	0.980 (0.811-1.184)	0.774

Multiple Myeloma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	0.74 (0.45-1.22)	1.11 (0.74-1.65)		0.89 (0.60-1.32)	1.07 (0.65-1.77)		0.93 (0.66-1.31)	0.89 (0.27-3.00)	
130-139	1.10 (0.69-1.74)	1.19 (0.80-1.77)		1.18 (0.81-1.72)	1.08 (0.65-1.79)		1.18 (0.84-1.65)	0.82 (0.26-2.56)	
140-159	1.01 (0.64-1.59)	0.98 (0.66-1.45)	0.66	1.02 (0.71-1.49)	0.98 (0.60-1.62)	0.111	0.88 (0.61-1.26)	0.90 (0.31-2.61)	0.811
160-179	0.81 (0.44-1.48)	0.89 (0.53-1.50)		0.86 (0.53-1.41)	0.89 (0.46-1.71)		0.87 (0.52-1.46)	0.60 (0.19-1.88)	
>= 180	1.11 (0.47-2.60)	1.46 (0.75-2.87)		1.45 (0.76-2.75)	1.15 (0.46-2.88)		1.54 (0.74-3.18)	0.95 (0.28-3.27)	
p-trend	0.827	0.903		0.654	0.798		0.94	0.587	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.84 (0.55-1.28)	1.24 (0.90-1.70)		1.17 (0.85-1.61)	0.92 (0.61-1.38)		1.02 (0.76-1.36)	1.31 (0.54-3.18)	
85-89	1.16 (0.76-1.78)	0.86 (0.58-1.28)		1.35 (0.96-1.91)	0.55 (0.32-0.95)		0.83 (0.58-1.19)	1.84 (0.80-4.23)	
90-99	1.02 (0.67-1.55)	0.98 (0.69-1.39)	0.498	1.05 (0.74-1.48)	0.93 (0.61-1.42)	0.033	0.97 (0.70-1.36)	1.30 (0.58-2.92)	0.555
100-109	1.58 (0.90-2.75)	1.24 (0.75-2.03)		1.71 (1.09-2.69)	0.94 (0.49-1.79)		1.22 (0.70-2.12)	1.83 (0.76-4.42)	
>= 110	0.87 (0.21-3.57)	0.98 (0.35-2.69)		0.81 (0.25-2.58)	1.11 (0.34-3.58)		0.42 (0.06-3.04)	0.88 (0.18-4.21)	
p-trend	0.278	0.904		0.207	0.629		0.775	0.518	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	0.91 (0.60-1.39)	1.14 (0.80-1.63)		1.03 (0.73-1.44)	1.07 (0.68-1.68)		1.04 (0.77-1.40)	0.85 (0.29-2.50)	
140-159	0.99 (0.63-1.56)	0.97 (0.65-1.45)	0.795	1.01 (0.70-1.47)	0.98 (0.60-1.62)	0.192	0.86 (0.60-1.24)	0.90 (0.31-2.60)	0.851
>= 160	0.85 (0.49-1.49)	1.01 (0.63-1.62)		0.97 (0.62-1.52)	0.94 (0.51-1.73)		0.98 (0.61-1.57)	0.69 (0.23-2.08)	
p-trend	0.752	0.677		0.875	0.722		0.539	0.429	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	

80-89	0.97 (0.69-1.38)	1.08 (0.81-1.45)		1.24 (0.94-1.65)	0.77 (0.53-1.11)		0.94 (0.73-1.23)	1.58 (0.72-3.45)	
90-99	1.01 (0.67-1.54)	0.98 (0.69-1.40)	0.809	1.04 (0.74-1.48)	0.93 (0.61-1.42)	0.064	0.98 (0.70-1.37)	1.29 (0.57-2.90)	0.719
>= 100	1.44 (0.84-2.47)	1.20 (0.75-1.90)		1.53 (0.99-2.37)	0.97 (0.54-1.76)		1.10 (0.64-1.88)	1.63 (0.68-3.86)	
p-trend	0.353	0.69		0.189	0.893		0.957	0.551	
Multiple Myeloma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	three cases in referent	
88.5-96.6	0.85 (0.53-1.35)	1.30 (0.87-1.94)		0.93 (0.64-1.35)	1.35 (0.82-2.23)		1.15 (0.83-1.60)	-	
96.8-105.5	0.90 (0.57-1.41)	1.03 (0.68-1.55)	0.875	0.96 (0.67-1.39)	0.97 (0.57-1.64)	0.068	0.94 (0.66-1.33)	-	-
105.6-216.6	0.88 (0.56-1.40)	1.12 (0.75-1.69)		1.01 (0.70-1.46)	1.05 (0.62-1.77)		0.94 (0.65-1.37)	-	
p-trend	0.746	0.951		0.823	0.6		0.435	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.99 (0.73-1.35)	0.96 (0.74-1.23)	0.867	1.02 (0.80-1.30)	0.93 (0.68-1.28)	0.12	1 (referent)	1.28 (0.96-1.71)	

Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			1058	1058	981	504	554		470	588		351	707	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1058	30738	0.979 (0.947-1.012)	0.965 (0.932-1.000)	0.967 (0.933-1.003)	0.958 (0.910-1.009)	0.972 (0.927-1.019)	0.676	0.964 (0.914-1.017)	0.967 (0.925-1.012)	0.72	1.000 (0.935-1.070)	0.954 (0.916-0.993)	0.168
Mean Diastolic Blood Pressure continuous	1058	30738	0.985 (0.929-1.045)	0.956 (0.899-1.017)	0.961 (0.902-1.025)	0.921 (0.842-1.008)	0.995 (0.914-1.083)	0.137	0.984 (0.896-1.080)	0.938 (0.865-1.017)	0.427	1.003 (0.899-1.118)	0.935 (0.868-1.008)	0.184

(per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	1058	307318	0.977 (0.929-1.027)	0.952 (0.903-1.004)	0.956 (0.905-1.010)	0.929 (0.860-1.005)	0.975 (0.907-1.048)	0.299	0.965 (0.890-1.045)	0.945 (0.881-1.013)	0.788	1.002 (0.909-1.103)	0.932 (0.875-0.993)	0.141
Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg) ESH classification														
< 120	218	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	197	66446	0.88 (0.72-1.07)	0.84 (0.69-1.02)	0.83 (0.67-1.01)	0.93 (0.69-1.27)	0.77 (0.59-1.00)		0.74 (0.57-0.97)	0.97 (0.72-1.31)		0.87 (0.65-1.16)	0.82 (0.62-1.07)	
130-139	216	57482	0.97 (0.80-1.17)	0.90 (0.74-1.10)	0.90 (0.73-1.10)	0.92 (0.68-1.24)	0.91 (0.70-1.18)		0.78 (0.59-1.03)	1.05 (0.78-1.40)		0.76 (0.54-1.05)	0.98 (0.76-1.26)	
140-159	285	68235	0.88 (0.73-1.06)	0.82 (0.67-0.99)	0.81 (0.66-0.99)	0.87 (0.65-1.16)	0.79 (0.61-1.02)	0.727	0.85 (0.65-1.11)	0.85 (0.64-1.12)	0.818	0.81 (0.58-1.13)	0.82 (0.64-1.04)	0.414
160-179	111	22656	0.94 (0.74-1.19)	0.86 (0.67-1.10)	0.85 (0.66-1.10)	0.88 (0.61-1.27)	0.86 (0.61-1.21)		0.95 (0.65-1.39)	0.87 (0.62-1.22)		1.22 (0.76-1.97)	0.80 (0.59-1.08)	
>= 180	31	6358	0.91 (0.62-1.34)	0.84 (0.57-1.24)	0.89 (0.59-1.32)	0.70 (0.38-1.28)	1.01 (0.61-1.69)		0.48 (0.19-1.19)	1.04 (0.66-1.65)		1.41 (0.61-3.26)	0.77 (0.49-1.20)	
p-trend			0.47	0.152	0.185	0.242	0.418		0.333	0.315		0.776	0.129	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	376	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	229	64872	1.03 (0.87-1.22)	1.00 (0.85-1.18)	1.03 (0.86-1.22)	0.95 (0.74-1.22)	1.04 (0.83-1.30)		1.00 (0.78-1.28)	0.98 (0.78-1.24)		1.12 (0.84-1.48)	0.94 (0.77-1.16)	
85-89	175	41500	1.15 (0.96-1.38)	1.10 (0.92-1.32)	1.08 (0.89-1.30)	1.02 (0.78-1.34)	1.17 (0.91-1.51)		1.32 (1.01-1.73)	0.95 (0.74-1.22)		1.17 (0.84-1.62)	1.06 (0.85-1.33)	
90-99	222	51196	1.12 (0.95-1.33)	1.06 (0.89-1.26)	1.07 (0.89-1.29)	1.02 (0.80-1.31)	1.09 (0.85-1.40)	0.085	1.17 (0.89-1.53)	0.98 (0.78-1.23)	0.202	1.10 (0.79-1.52)	1.03 (0.84-1.27)	0.173
100-109	46	13896	0.83 (0.61-1.13)	0.77 (0.56-1.05)	0.75 (0.54-1.05)	0.66 (0.43-1.02)	0.92 (0.59-1.46)		0.68 (0.37-1.26)	0.78 (0.54-1.13)		0.85 (0.47-1.56)	0.74 (0.51-1.06)	

>= 110	10	3264	0.82 (0.43-1.53)	0.74 (0.39-1.39)	0.81 (0.43-1.53)	0.32 (0.10-1.02)	1.53 (0.72-3.26)		0.71 (0.17-2.85)	0.72 (0.36-1.47)		1.77 (0.77-4.06)	0.39 (0.14-1.05)	
p-trend			0.717	0.647	0.68	0.18	0.399		0.503	0.286		0.52	0.342	
Systolic Blood Pressure (mmHg) ASH classification														
< 120	218	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	413	1239 28	0.92 (0.78-1.09)	0.87 (0.73-1.03)	0.86 (0.72-1.02)	0.93 (0.71-1.22)	0.84 (0.67-1.04)		0.76 (0.60-0.95)	1.01 (0.78-1.32)		0.82 (0.63-1.06)	0.90 (0.72-1.13)	
Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
140-159	285	6823 5	0.88 (0.73-1.06)	0.81 (0.67-0.99)	0.81 (0.66-0.98)	0.87 (0.65-1.17)	0.78 (0.60-1.01)	0.96	0.85 (0.65-1.11)	0.84 (0.64-1.12)	0.955	0.81 (0.58-1.13)	0.81 (0.64-1.04)	0.224
>= 160	142	2901 4	0.93 (0.74-1.16)	0.85 (0.68-1.08)	0.85 (0.67-1.09)	0.84 (0.59-1.20)	0.89 (0.65-1.21)		0.86 (0.60-1.24)	0.91 (0.66-1.25)		1.27 (0.82-1.96)	0.79 (0.59-1.04)	
p-trend			0.355	0.108	0.123	0.284	0.254		0.357	0.202		0.999	0.058	
Diastolic Blood Pressure (mmHg) ASH classification														
< 80	376	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	404	1063 72	1.08 (0.94-1.25)	1.04 (0.90-1.20)	1.05 (0.90-1.22)	0.98 (0.79-1.22)	1.09 (0.90-1.32)		1.12 (0.91-1.38)	0.97 (0.79-1.19)		1.14 (0.89-1.45)	0.99 (0.83-1.19)	
90-99	222	5119 6	1.12 (0.95-1.33)	1.06 (0.89-1.26)	1.07 (0.89-1.28)	1.02 (0.80-1.31)	1.09 (0.85-1.40)	0.099	1.16 (0.89-1.53)	0.98 (0.78-1.23)	0.345	1.09 (0.79-1.51)	1.03 (0.84-1.27)	0.167
>= 100	56	1716 0	0.83 (0.62-1.10)	0.76 (0.57-1.02)	0.76 (0.56-1.03)	0.60 (0.39-0.90)	1.02 (0.68-1.53)		0.69 (0.39-1.21)	0.77 (0.55-1.08)		1.03 (0.62-1.71)	0.67 (0.47-0.95)	
p-trend			0.965	0.436	0.526	0.127	0.567		0.855	0.28		0.619	0.217	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles														
50.0-88.3	200	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	245	7772 7	0.95 (0.78-1.14)	0.91 (0.75-1.10)	0.94 (0.77-1.14)	0.93 (0.69-1.26)	0.88 (0.69-1.13)		0.79 (0.61-1.02)	1.04 (0.78-1.39)		0.97 (0.73-1.30)	0.86 (0.67-1.10)	

96.8-105.5	283	7632 7	0.96 (0.80- 1.15)	0.90 (0.74- 1.08)	0.91 (0.75- 1.11)	0.86 (0.64- 1.16)	0.94 (0.73- 1.21)	0.809	0.98 (0.76- 1.27)	0.85 (0.64- 1.13)	0.451	0.91 (0.67- 1.25)	0.87 (0.68- 1.11)	0.4
105.6-216.6	330	7627 3	0.95 (0.79- 1.15)	0.87 (0.72- 1.06)	0.90 (0.73- 1.10)	0.89 (0.66- 1.19)	0.86 (0.67- 1.12)		0.90 (0.69- 1.19)	0.87 (0.66- 1.15)		0.98 (0.70- 1.37)	0.82 (0.65- 1.04)	
p-trend			0.691	0.206	0.296	0.421	0.386		0.859	0.132		0.793	0.174	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	554	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	504	1331 39	0.88 (0.77- 1.00)	0.84 (0.74- 0.96)	0.83 (0.72- 0.95)	0.89 (0.74- 1.07)	0.81 (0.67- 0.97)	0.485	0.90 (0.74- 1.10)	0.81 (0.69- 0.96)	0.562	0.93 (0.74- 1.18)	0.81 (0.69- 0.94)	0.209

Lymphoma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	437	609		681	377		716	119	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	0.993 (0.940-1.048)	0.947 (0.905-0.992)	0.32	0.969 (0.928-1.012)	0.962 (0.907-1.020)	0.911	0.974 (0.931-1.019)	0.908 (0.821-1.005)	0.389
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	0.982 (0.892-1.082)	0.940 (0.867-1.019)	0.645	0.960 (0.889-1.036)	0.955 (0.860-1.059)	0.991	0.969 (0.895-1.050)	0.872 (0.720-1.057)	0.446
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	0.986 (0.907-1.071)	0.931 (0.868-0.998)	0.444	0.957 (0.896-1.022)	0.948 (0.868-1.037)	0.949	0.964 (0.900-1.033)	0.859 (0.728-1.012)	0.345
Systolic Blood Pressure (mmHg) ESH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	

120-129	0.81 (0.59-1.10)	0.85 (0.66-1.10)		0.88 (0.69-1.12)	0.76 (0.54-1.07)		0.86 (0.68-1.07)	-	
130-139	0.91 (0.67-1.24)	0.89 (0.69-1.15)		0.93 (0.73-1.19)	0.86 (0.61-1.20)		0.90 (0.72-1.14)	-	
140-159	0.89 (0.66-1.20)	0.76 (0.59-0.98)	0.495	0.87 (0.69-1.10)	0.73 (0.52-1.01)	0.945	0.79 (0.63-1.00)	-	-
160-179	0.81 (0.55-1.21)	0.89 (0.65-1.22)		0.79 (0.57-1.09)	0.97 (0.66-1.44)		1.03 (0.76-1.40)	-	
>= 180	1.14 (0.65-2.00)	0.66 (0.38-1.14)		1.03 (0.65-1.65)	0.57 (0.28-1.16)		0.86 (0.48-1.53)	-	
p-trend	0.818	0.095		0.328	0.337		0.388	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.94 (0.72-1.23)	1.06 (0.86-1.32)		0.98 (0.80-1.21)	1.04 (0.78-1.37)		1.02 (0.83-1.24)	0.63 (0.31-1.31)	
85-89	1.24 (0.94-1.64)	1.01 (0.79-1.30)		1.24 (0.99-1.55)	0.88 (0.63-1.23)		1.22 (0.98-1.51)	0.92 (0.47-1.77)	
90-99	1.10 (0.84-1.45)	1.05 (0.83-1.32)	0.388	0.99 (0.79-1.23)	1.17 (0.89-1.56)	0.882	1.06 (0.85-1.33)	1.05 (0.58-1.88)	0.417
100-109	0.84 (0.52-1.38)	0.71 (0.47-1.08)		0.87 (0.59-1.28)	0.63 (0.37-1.07)		0.78 (0.49-1.24)	0.49 (0.22-1.10)	
>= 110	1.01 (0.41-2.48)	0.60 (0.24-1.46)		0.76 (0.34-1.71)	0.69 (0.25-1.89)		0.99 (0.41-2.41)	0.18 (0.02-1.35)	
p-trend	0.597	0.343		0.87	0.637		0.735	0.295	
Lymphoma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-139	0.86 (0.66-1.12)	0.87 (0.70-1.09)		0.91 (0.74-1.11)	0.81 (0.60-1.09)		0.88 (0.72-1.07)	-	
140-159	0.89 (0.66-1.19)	0.76 (0.59-0.97)	0.663	0.87 (0.69-1.10)	0.73 (0.52-1.01)	0.869	0.79 (0.63-1.00)	-	-
>= 160	0.88 (0.61-1.26)	0.84 (0.62-1.13)		0.84 (0.62-1.12)	0.88 (0.60-1.28)		0.99 (0.74-1.33)	-	
p-trend	0.569	0.104		0.207	0.377		0.395	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.06 (0.84-1.33)	1.04 (0.86-1.26)		1.09 (0.91-1.30)	0.97 (0.76-1.25)		1.09 (0.92-1.29)	0.78 (0.43-1.42)	
90-99	1.10 (0.83-1.44)	1.05 (0.83-1.32)	0.605	0.98 (0.78-1.23)	1.18 (0.89-1.56)	0.876	1.06 (0.85-1.32)	1.04 (0.58-1.87)	0.36
>= 100	0.87 (0.56-1.35)	0.69 (0.47-1.02)		0.85 (0.59-1.21)	0.64 (0.39-1.05)		0.81 (0.53-1.23)	0.43 (0.20-0.93)	
p-trend	0.97	0.346		0.544	0.675		0.923	0.171	

Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.02 (0.76-1.38)	0.83 (0.65-1.07)		0.84 (0.67-1.06)	1.07 (0.76-1.52)		0.93 (0.75-1.15)	0.37 (0.12-1.19)	
96.8-105.5	0.99 (0.73-1.34)	0.84 (0.66-1.08)	0.501	0.91 (0.72-1.14)	0.92 (0.65-1.31)	0.867	0.94 (0.75-1.17)	0.68 (0.26-1.78)	0.962
105.6-216.6	1.00 (0.73-1.36)	0.80 (0.62-1.03)		0.85 (0.67-1.07)	0.96 (0.68-1.36)		0.91 (0.72-1.16)	0.55 (0.22-1.40)	
p-trend	0.933	0.127		0.305	0.558		0.509	0.68	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.86 (0.70-1.06)	0.83 (0.70-0.99)	0.887	0.84 (0.71-0.99)	0.86 (0.69-1.07)	0.729	1 (referent)	0.99 (0.79-1.24)	

Non-Hodgkin Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			882	882	822	409	473		400	482		290	592	
Cohort size			30738	307318	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	882	307318	0.968 (0.933-1.004)	0.957 (0.921-0.994)	0.954 (0.917-0.993)	0.963 (0.910-1.020)	0.953 (0.905-1.003)	0.83	0.951 (0.897-1.008)	0.964 (0.917-1.013)	0.458	1.005 (0.934-1.081)	0.941 (0.900-0.984)	0.124
Mean Diastolic Blood Pressure continuous	882	307318	0.977 (0.916-1.042)	0.952 (0.890-1.018)	0.947 (0.883-1.015)	0.928 (0.840-1.025)	0.981 (0.895-1.075)	0.275	0.995 (0.899-1.100)	0.926 (0.847-1.013)	0.344	1.017 (0.903-1.146)	0.924 (0.851-1.003)	0.133

(per 10mmHg increase)														
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	882	3073 18	0.965 (0.913-1.019)	0.943 (0.890-1.000)	0.939 (0.884-0.997)	0.937 (0.859-1.021)	0.954 (0.882-1.032)	0.627	0.960 (0.880-1.047)	0.936 (0.867-1.010)	0.874	1.012 (0.911-1.125)	0.917 (0.855-0.983)	0.097
Systolic Blood Pressure (mmHg) ESH classification														
< 120	185	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	169	6644 6	0.89 (0.72-1.10)	0.86 (0.69-1.06)	0.83 (0.66-1.03)	1.01 (0.71-1.42)	0.78 (0.59-1.02)		0.72 (0.54-0.96)	1.06 (0.77-1.48)		0.89 (0.65-1.22)	0.83 (0.62-1.11)	
130-139	185	5748 2	0.97 (0.79-1.20)	0.92 (0.74-1.14)	0.89 (0.71-1.10)	1.03 (0.74-1.45)	0.87 (0.66-1.15)		0.81 (0.60-1.09)	1.09 (0.79-1.50)		0.76 (0.53-1.09)	0.99 (0.76-1.30)	
140-159	225	6823 5	0.82 (0.66-1.00)	0.77 (0.62-0.94)	0.74 (0.60-0.92)	0.87 (0.62-1.22)	0.72 (0.54-0.95)	0.689	0.81 (0.60-1.08)	0.81 (0.59-1.12)	0.415	0.86 (0.60-1.23)	0.74 (0.56-0.96)	0.323
160-179	94	2265 6	0.93 (0.72-1.21)	0.87 (0.66-1.14)	0.82 (0.62-1.09)	0.99 (0.66-1.49)	0.81 (0.56-1.17)		0.90 (0.60-1.36)	0.94 (0.65-1.37)		1.05 (0.60-1.84)	0.83 (0.60-1.14)	
>= 180	24	6358	0.82 (0.53-1.27)	0.77 (0.49-1.19)	0.77 (0.49-1.21)	0.76 (0.39-1.48)	0.83 (0.46-1.50)		0.11 (0.02-0.80)	1.14 (0.69-1.88)		1.72 (0.74-4.02)	0.64 (0.38-1.07)	
p-trend			0.187	0.066	0.043	0.386	0.113		0.118	0.344		0.829	0.044	
Diastolic Blood Pressure (mmHg) ESH classification														
< 80	318	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Non-Hodgkin Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	190	6487 2	1.02 (0.85-1.22)	0.99 (0.83-1.19)	1.02 (0.84-1.23)	0.93 (0.70-1.22)	1.04 (0.82-1.33)		1.02 (0.78-1.33)	0.95 (0.74-1.23)		1.12 (0.82-1.53)	0.93 (0.74-1.16)	
85-89	151	4150 0	1.18 (0.97-1.43)	1.14 (0.93-1.39)	1.08 (0.88-1.33)	1.06 (0.79-1.43)	1.20 (0.92-1.57)		1.39 (1.04-1.85)	0.96 (0.73-1.27)		1.23 (0.86-1.75)	1.09 (0.86-1.38)	
90-99	178	5119 6	1.07 (0.89-1.29)	1.02 (0.84-1.24)	1.01 (0.83-1.24)	1.02 (0.77-1.34)	1.02 (0.77-1.34)	0.279	1.15 (0.85-1.54)	0.94 (0.73-1.20)	0.176	1.15 (0.81-1.64)	0.96 (0.77-1.21)	0.113
100-109	37	1389 6	0.79 (0.56-1.12)	0.74 (0.52-1.05)	0.69 (0.48-1.00)	0.66 (0.40-1.07)	0.87 (0.52-1.44)		0.67 (0.34-1.32)	0.75 (0.50-1.13)		0.80 (0.40-1.60)	0.72 (0.48-1.07)	

>= 110	8	3264	0.77 (0.38-1.56)	0.71 (0.35-1.44)	0.76 (0.38-1.55)	0.40 (0.13-1.25)	1.27 (0.52-3.10)		0.85 (0.21-3.42)	0.65 (0.29-1.47)		1.88 (0.76-4.68)	0.34 (0.11-1.08)	
p-trend			0.96	0.495	0.349	0.279	0.793		0.498	0.191		0.421	0.194	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	185	8614 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	354	1239 28	0.93 (0.78-1.12)	0.89 (0.74-1.07)	0.85 (0.71-1.03)	1.02 (0.75-1.39)	0.82 (0.65-1.04)		0.76 (0.59-0.97)	1.08 (0.80-1.44)		0.83 (0.63-1.10)	0.91 (0.71-1.17)	
140-159	225	6823 5	0.81 (0.66-1.00)	0.76 (0.62-0.94)	0.74 (0.59-0.92)	0.87 (0.62-1.22)	0.71 (0.54-0.94)	0.558	0.81 (0.60-1.08)	0.81 (0.59-1.11)	0.451	0.86 (0.60-1.23)	0.73 (0.56-0.96)	0.219
>= 160	118	2901 4	0.90 (0.71-1.16)	0.84 (0.65-1.09)	0.81 (0.62-1.05)	0.94 (0.63-1.39)	0.81 (0.58-1.14)		0.74 (0.49-1.12)	0.99 (0.69-1.40)		1.18 (0.72-1.94)	0.78 (0.58-1.06)	
p-trend			0.148	0.053	0.031	0.414	0.076		0.116	0.279		0.974	0.025	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	318	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	341	1063 72	1.08 (0.93-1.27)	1.05 (0.90-1.23)	1.04 (0.89-1.23)	0.98 (0.77-1.25)	1.11 (0.90-1.36)		1.16 (0.92-1.45)	0.96 (0.77-1.19)		1.16 (0.89-1.52)	1.00 (0.82-1.21)	
90-99	178	5119 6	1.07 (0.89-1.29)	1.02 (0.84-1.24)	1.01 (0.83-1.24)	1.02 (0.77-1.34)	1.02 (0.77-1.34)	0.285	1.14 (0.85-1.54)	0.94 (0.73-1.20)	0.287	1.15 (0.81-1.64)	0.96 (0.76-1.21)	0.114
>= 100	45	1716 0	0.79 (0.58-1.08)	0.73 (0.53-1.01)	0.70 (0.50-0.99)	0.60 (0.38-0.95)	0.93 (0.59-1.46)		0.70 (0.38-1.29)	0.73 (0.50-1.07)		1.00 (0.56-1.78)	0.65 (0.44-0.95)	
p-trend			0.673	0.288	0.238	0.173	0.998		0.859	0.165		0.55	0.106	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
Non-Hodgkin Lymphoma	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	168	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	208	7772 7	0.96 (0.78-1.18)	0.92 (0.75-1.14)	0.91 (0.74-1.13)	0.90 (0.64-1.27)	0.94 (0.72-1.22)		0.84 (0.64-1.11)	1.02 (0.74-1.41)		0.97 (0.71-1.34)	0.89 (0.68-1.17)	

classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-129	0.78 (0.56-1.09)	0.89 (0.67-1.18)		0.88 (0.68-1.15)	0.80 (0.55-1.15)		0.87 (0.69-1.11)	-	
130-139	0.89 (0.64-1.24)	0.93 (0.70-1.23)		0.95 (0.73-1.23)	0.88 (0.61-1.26)		0.92 (0.72-1.18)	-	
140-159	0.79 (0.57-1.10)	0.74 (0.56-0.98)	0.751	0.82 (0.63-1.06)	0.69 (0.49-0.99)	0.918	0.77 (0.60-0.99)	-	-
160-179	0.82 (0.53-1.25)	0.89 (0.63-1.27)		0.78 (0.55-1.12)	1.00 (0.66-1.53)		1.09 (0.78-1.52)	-	
>= 180	1.07 (0.58-1.99)	0.57 (0.30-1.09)		0.88 (0.51-1.52)	0.60 (0.28-1.28)		0.79 (0.41-1.53)	-	
p-trend	0.536	0.059		0.155	0.298		0.386	-	
Diastolic Blood Pressure (mmHg)									
ESH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	0.90 (0.67-1.21)	1.08 (0.85-1.37)		0.99 (0.79-1.24)	1.00 (0.74-1.36)		1.01 (0.81-1.25)	0.68 (0.31-1.50)	
85-89	1.25 (0.92-1.69)	1.07 (0.82-1.39)		1.30 (1.02-1.65)	0.89 (0.63-1.27)		1.31 (1.04-1.66)	0.76 (0.36-1.63)	
90-99	1.11 (0.83-1.50)	0.99 (0.77-1.28)	0.476	0.93 (0.72-1.19)	1.17 (0.86-1.58)	0.977	1.05 (0.82-1.35)	1.06 (0.55-2.02)	0.622
100-109	0.75 (0.42-1.31)	0.73 (0.46-1.14)		0.85 (0.55-1.31)	0.59 (0.33-1.07)		0.71 (0.42-1.20)	0.48 (0.20-1.16)	
>= 110	0.96 (0.35-2.61)	0.58 (0.21-1.57)		0.62 (0.23-1.66)	0.81 (0.30-2.22)		0.72 (0.23-2.25)	0.20 (0.03-1.54)	
p-trend	0.693	0.281		0.611	0.692		0.827	0.321	
Systolic Blood Pressure (mmHg)									
ASH classification									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-139	0.83 (0.62-1.11)	0.91 (0.71-1.16)		0.91 (0.73-1.15)	0.84 (0.61-1.15)		0.89 (0.72-1.10)	-	
140-159	0.79 (0.57-1.09)	0.74 (0.56-0.98)	0.932	0.81 (0.63-1.06)	0.69 (0.49-0.99)	0.892	0.77 (0.60-0.99)	-	-
>= 160	0.86 (0.58-1.28)	0.82 (0.59-1.15)		0.80 (0.58-1.11)	0.91 (0.60-1.37)		1.03 (0.75-1.41)	-	
p-trend	0.371	0.071		0.1	0.357		0.43	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.04 (0.81-1.33)	1.08 (0.87-1.32)		1.11 (0.92-1.35)	0.96 (0.73-1.26)		1.12 (0.93-1.35)	0.72 (0.37-1.42)	
90-99	1.11 (0.82-1.49)	0.99 (0.77-1.28)	0.755	0.92 (0.72-1.19)	1.17 (0.86-1.58)	0.77	1.05 (0.82-1.34)	1.05 (0.55-2.01)	0.684
Non-Hodgkin Lymphoma	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction

>= 100	0.78 (0.47-1.29)	0.70 (0.46-1.07)		0.81 (0.54-1.21)	0.64 (0.37-1.08)		0.71 (0.43-1.15)	0.42 (0.18-0.99)	
p-trend	0.873	0.273		0.335	0.666		0.73	0.257	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.02 (0.74-1.42)	0.87 (0.66-1.14)		0.83 (0.64-1.07)	1.15 (0.79-1.66)		0.97 (0.76-1.23)	0.50 (0.14-1.72)	
96.8-105.5	1.02 (0.74-1.42)	0.83 (0.64-1.09)	0.598	0.91 (0.71-1.17)	0.94 (0.65-1.38)	0.937	0.98 (0.77-1.25)	0.72 (0.24-2.10)	0.806
105.6-216.6	0.97 (0.69-1.36)	0.78 (0.59-1.03)		0.81 (0.62-1.04)	0.97 (0.67-1.41)		0.94 (0.72-1.21)	0.53 (0.19-1.52)	
p-trend	0.828	0.092		0.204	0.517		0.667	0.343	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	0.83 (0.67-1.04)	0.79 (0.66-0.95)	0.97	0.79 (0.66-0.95)	0.85 (0.67-1.07)	0.692	1 (referent)	0.97 (0.76-1.25)	

Other location AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Cases			406	406	380	158	248		186	220		93	313	
Cohort size			30738	30738	301857	112591	194727		146326	160992		153303	154015	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	406	30738	1.078 (1.024-1.134)	1.085 (1.030-1.142)	1.079 (1.023-1.138)	1.129 (1.038-1.227)	1.054 (0.986-1.126)	0.117	1.093 (1.013-1.179)	1.077 (1.004-1.154)	0.984	1.124 (0.996-1.269)	1.077 (1.018-1.141)	0.92
Mean Diastolic Blood Pressure continuous (per 10mmHg increase)	406	30738	1.013 (0.922-1.114)	1.028 (0.932-1.134)	1.020 (0.921-1.130)	1.164 (1.001-1.354)	0.937 (0.824-1.067)	0.022	1.059 (0.916-1.225)	1.004 (0.879-1.146)	0.746	1.191 (0.969-1.464)	0.989 (0.885-1.106)	0.433
Mean Blood Pressure (1/3SBP+2/3DBP) continuous (per 10mmHg increase)	406	30738	1.068 (0.987-1.156)	1.083 (0.998-1.175)	1.074 (0.987-1.169)	1.182 (1.040-1.344)	1.014 (0.912-1.129)	0.041	1.105 (0.979-1.246)	1.064 (0.953-1.188)	0.87	1.188 (0.994-1.420)	1.060 (0.967-1.162)	0.682
Other location AC	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
Systolic Blood Pressure (mmHg)														
ESH classification														
< 120	59	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	70	66446	1.12 (0.79-1.59)	1.17 (0.82-1.66)	1.25 (0.87-1.81)	1.45 (0.73-2.91)	1.11 (0.73-1.68)		1.01 (0.64-1.61)	1.46 (0.83-2.58)		1.67 (0.93-2.99)	1.00 (0.64-1.55)	
130-139	79	57482	1.24 (0.88-1.75)	1.31 (0.92-1.85)	1.40 (0.97-2.01)	1.71 (0.87-3.36)	1.20 (0.79-1.82)		1.21 (0.76-1.91)	1.49 (0.85-2.61)		1.51 (0.79-2.88)	1.23 (0.81-1.87)	
140-159	122	68235	1.32 (0.96-1.83)	1.41 (1.01-1.96)	1.41 (1.00-2.00)	1.84 (0.96-3.54)	1.25 (0.84-1.88)	0.142	1.26 (0.81-1.98)	1.66 (0.97-2.84)	0.803	1.93 (1.01-3.68)	1.26 (0.85-1.87)	0.905

classification														
< 80	146	1325 90	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	152	1063 72	0.98 (0.78-1.24)	1.01 (0.80-1.28)	0.99 (0.77-1.26)	1.42 (0.93-2.17)	0.87 (0.65-1.16)		0.95 (0.68-1.33)	1.06 (0.76-1.47)		1.07 (0.65-1.74)	1.00 (0.76-1.31)	
90-99	76	5119 6	0.91 (0.68-1.20)	0.93 (0.70-1.25)	0.89 (0.66-1.21)	1.46 (0.91-2.35)	0.70 (0.47-1.04)	0.041	1.00 (0.65-1.56)	0.90 (0.61-1.32)	0.762	1.37 (0.75-2.52)	0.85 (0.61-1.18)	0.721
>= 100	32	1716 0	1.13 (0.76-1.66)	1.16 (0.78-1.72)	1.13 (0.75-1.70)	1.62 (0.89-2.93)	0.94 (0.53-1.67)		1.40 (0.73-2.66)	1.06 (0.64-1.76)		1.34 (0.51-3.53)	1.11 (0.71-1.72)	
p-trend			0.973	0.865	0.946	0.089	0.189		0.59	0.824		0.318	0.776	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Cohort-specific quartiles														
50.0-88.3	57	7699 1	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	94	7772 7	1.21 (0.86-1.68)	1.26 (0.90-1.76)	1.34 (0.95-1.89)	1.10 (0.55-2.20)	1.37 (0.94-2.02)		0.99 (0.64-1.52)	1.81 (1.02-3.25)		1.43 (0.80-2.55)	1.22 (0.81-1.84)	
96.8-105.5	117	7632 7	1.29 (0.93-1.78)	1.36 (0.98-1.89)	1.37 (0.97-1.93)	1.78 (0.94-3.39)	1.20 (0.80-1.78)	0.066	1.15 (0.75-1.77)	1.81 (1.03-3.18)	0.726	1.50 (0.80-2.80)	1.34 (0.90-1.98)	0.954
105.6-216.6	138	7627 3	1.25 (0.91-1.73)	1.33 (0.95-1.86)	1.32 (0.93-1.86)	1.71 (0.90-3.25)	1.15 (0.77-1.73)		1.35 (0.88-2.08)	1.58 (0.89-2.78)		1.63 (0.83-3.17)	1.27 (0.86-1.89)	
p-trend			0.207	0.125	0.23	0.034	0.822		0.126	0.499		0.161	0.29	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	168	1741 79	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Hypertensive	238	1331 39	1.26 (1.03-1.55)	1.30 (1.05-1.60)	1.24 (1.00-1.54)	1.56 (1.10-2.22)	1.14 (0.87-1.49)	0.106	1.46 (1.08-1.98)	1.16 (0.87-1.55)	0.377	1.61 (1.05-2.49)	1.22 (0.96-1.55)	0.545

Other location AC	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	126	277		254	152		283	53	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.131 (1.031-1.241)	1.059 (0.994-1.129)	0.285	1.071 (1.003-1.145)	1.101 (1.013-1.197)	0.736	1.128 (1.057-1.203)	1.040 (0.901-1.200)	0.479

< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
120-139	1.30 (0.72-2.36)	1.18 (0.82-1.70)		1.20 (0.82-1.75)	1.31 (0.76-2.25)		1.28 (0.90-1.81)	-	
140-159	1.60 (0.86-3.01)	1.26 (0.85-1.87)	0.125	1.30 (0.86-1.97)	1.57 (0.89-2.78)	0.772	1.69 (1.15-2.47)	-	-
>= 160	2.61 (1.33-5.12)	1.40 (0.88-2.20)		1.63 (1.02-2.61)	1.93 (1.03-3.64)		2.10 (1.33-3.32)	-	
p-trend	0.003	0.149		0.041	0.027		0.0004	-	
Diastolic Blood Pressure (mmHg)									
ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	0.92 (0.60-1.41)	1.06 (0.80-1.40)		0.87 (0.65-1.17)	1.28 (0.86-1.91)		1.03 (0.78-1.35)	0.69 (0.31-1.53)	
90-99	0.79 (0.46-1.36)	0.97 (0.69-1.38)	0.924	0.88 (0.61-1.27)	1.02 (0.63-1.66)	0.347	1.23 (0.87-1.73)	0.56 (0.24-1.30)	0.24
>= 100	1.55 (0.81-2.95)	0.97 (0.59-1.62)		1.00 (0.59-1.70)	1.44 (0.78-2.65)		1.43 (0.83-2.46)	0.75 (0.29-1.89)	
p-trend	0.704	0.873		0.651	0.487		0.138	0.48	
Mean BP (mmHg) (1/3SBP+2/3DBP)									
Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	two cases in referent	
88.5-96.6	1.17 (0.64-2.15)	1.25 (0.84-1.88)		1.09 (0.73-1.62)	1.75 (0.92-3.33)		1.15 (0.79-1.68)	-	
96.8-105.5	1.24 (0.68-2.26)	1.36 (0.92-2.02)	0.614	1.18 (0.79-1.75)	1.87 (1.00-3.53)	0.392	1.45 (1.00-2.11)	-	-
105.6-216.6	1.48 (0.82-2.68)	1.21 (0.80-1.81)		1.15 (0.77-1.72)	1.82 (0.96-3.43)		1.53 (1.04-2.26)	-	
p-trend	0.176	0.468		0.486	0.146		0.015	-	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.36 (0.92-2.01)	1.22 (0.95-1.58)	0.564	1.24 (0.95-1.62)	1.36 (0.96-1.92)	0.621	1 (referent)	0.79 (0.57-1.09)	

classification														
< 80	868	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
Other location or morphology	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI ≤ 25 mg/m² HR (adjusted)	BMI > 25 mg/m² HR (adjusted)	BMI p-interaction	Age ≤ 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
80-84	555	64872	1.09 (0.98-1.21)	1.04 (0.93-1.16)	1.04 (0.93-1.16)	0.96 (0.82-1.13)	1.12 (0.96-1.30)		1.14 (0.97-1.34)	0.96 (0.83-1.12)		1.04 (0.86-1.26)	1.05 (0.92-1.20)	
85-89	384	41500	1.11 (0.99-1.26)	1.05 (0.93-1.19)	1.04 (0.91-1.18)	0.96 (0.80-1.14)	1.14 (0.96-1.36)		1.22 (1.01-1.47)	0.94 (0.80-1.11)		1.07 (0.85-1.35)	1.04 (0.90-1.21)	
90-99	495	51196	1.10 (0.98-1.23)	1.01 (0.90-1.14)	1.03 (0.92-1.17)	0.91 (0.77-1.07)	1.14 (0.96-1.34)	0.118	1.03 (0.85-1.25)	0.98 (0.84-1.13)	0.52	1.06 (0.85-1.32)	1.00 (0.87-1.15)	0.661
100-109	160	13896	1.28 (1.08-1.52)	1.15 (0.97-1.37)	1.18 (0.98-1.41)	1.06 (0.84-1.33)	1.26 (0.96-1.66)		1.02 (0.72-1.43)	1.16 (0.94-1.42)		0.97 (0.65-1.44)	1.21 (0.99-1.47)	
≥ 110	30	3264	1.07 (0.74-1.54)	0.94 (0.65-1.35)	0.79 (0.52-1.21)	0.83 (0.52-1.33)	1.09 (0.60-1.98)		1.43 (0.74-2.77)	0.80 (0.51-1.24)		1.05 (0.49-2.24)	0.91 (0.60-1.38)	
p-trend			0.011	0.438	0.414	0.521	0.047		0.345	0.789		0.691	0.465	
Systolic Blood Pressure (mmHg)														
ASH classification														
< 120	438	86141	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	977	123928	1.15 (1.03-1.30)	1.08 (0.96-1.21)	1.07 (0.94-1.21)	1.02 (0.85-1.22)	1.12 (0.96-1.31)		1.10 (0.94-1.30)	1.04 (0.88-1.24)		1.01 (0.85-1.20)	1.16 (0.99-1.37)	
140-159	692	68235	1.13 (1.00-1.29)	1.03 (0.90-1.18)	1.03 (0.90-1.19)	0.93 (0.77-1.14)	1.13 (0.95-1.35)	0.258	1.10 (0.91-1.33)	0.98 (0.81-1.17)	0.407	1.01 (0.81-1.27)	1.10 (0.92-1.30)	0.126
≥ 160	385	29014	1.30 (1.12-1.51)	1.18 (1.01-1.37)	1.21 (1.04-1.42)	1.02 (0.82-1.28)	1.34 (1.09-1.65)		1.32 (1.04-1.67)	1.09 (0.89-1.34)		0.94 (0.65-1.35)	1.29 (1.07-1.55)	
p-trend			0.003	0.122	0.054	0.753	0.012		0.049	0.645		0.888	0.047	
Diastolic Blood Pressure (mmHg)														
ASH classification														
< 80	868	132590	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	939	106372	1.10 (1.00-1.21)	1.04 (0.95-1.15)	1.04 (0.94-1.15)	0.96 (0.84-1.11)	1.13 (0.99-1.28)		1.17 (1.02-1.35)	0.95 (0.84-1.09)		1.05 (0.89-1.25)	1.05 (0.93-1.18)	
90-99	495	51196	1.10 (0.98-1.23)	1.01 (0.90-1.14)	1.03 (0.92-1.17)	0.91 (0.77-1.07)	1.14 (0.96-1.34)	0.135	1.03 (0.85-1.25)	0.98 (0.84-1.13)	0.667	1.06 (0.85-1.32)	1.00 (0.87-1.15)	0.553
≥ 100	190	17160	1.24 (1.06-1.45)	1.11 (0.94-1.31)	1.10 (0.93-1.31)	1.01 (0.82-1.26)	1.23 (0.96-1.59)		1.08 (0.79-1.47)	1.09 (0.90-1.32)		0.98 (0.68-1.41)	1.15 (0.96-1.38)	

p-trend			0.008	0.353	0.302	0.615	0.038		0.395	0.602		0.742	0.338	
Mean BP (mmHg) (1/3SBP+2/3DBP)														
Other location or morphology	Cases	Cohort	HR (crude)	HR (adjusted)	Excluding first 2 years of follow-up HR (adjusted)	Men HR (adjusted)	Women HR (adjusted)	Sex p-interaction	BMI <= 25 mg/m ² HR (adjusted)	BMI > 25 mg/m ² HR (adjusted)	BMI p-interaction	Age <= 53 yrs HR (adjusted)	Age > 53 yrs HR (adjusted)	Age p-interaction
50.0-88.3	408	76991	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
88.5-96.6	565	77727	1.10 (0.96-1.25)	1.04 (0.91-1.18)	1.03 (0.89-1.18)	0.99 (0.81-1.21)	1.07 (0.90-1.27)		1.02 (0.86-1.22)	1.03 (0.85-1.26)		0.83 (0.68-1.01)	1.25 (1.05-1.49)	
96.8-105.5	695	76327	1.18 (1.04-1.33)	1.09 (0.95-1.23)	1.10 (0.96-1.26)	0.97 (0.80-1.19)	1.19 (1.00-1.41)	0.022	1.17 (0.97-1.39)	1.02 (0.85-1.23)	0.359	1.07 (0.87-1.31)	1.18 (0.99-1.40)	0.265
105.6-216.6	824	76273	1.19 (1.05-1.35)	1.07 (0.94-1.22)	1.08 (0.94-1.24)	0.90 (0.74-1.10)	1.26 (1.06-1.50)		1.11 (0.92-1.35)	1.03 (0.85-1.24)		0.92 (0.73-1.17)	1.21 (1.02-1.43)	
p-trend			0.005	0.292	0.199	0.208	0.005		0.134	0.884		0.918	0.187	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)														
Normotensive	1166	174179	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Hypertensive	1326	133139	1.07 (0.99-1.16)	1.02 (0.94-1.11)	1.04 (0.95-1.13)	0.95 (0.84-1.07)	1.11 (0.98-1.25)	0.234	1.05 (0.92-1.19)	1.01 (0.90-1.13)	0.786	0.96 (0.82-1.13)	1.05 (0.95-1.16)	0.214

Other location or morphology	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
Cases	951	1507		1538	954		1687	370	
Cohort size	141931	160623		205214	102104		227336	37017	
Mean Systolic Blood Pressure continuous (per 10mmHg increase)	1.015 (0.980-1.053)	1.018 (0.990-1.047)	0.799	1.028 (0.999-1.057)	1.001 (0.966-1.037)	0.416	1.013 (0.984-1.043)	1.019 (0.966-1.076)	0.548
Mean Diastolic Blood	1.034 (0.969-1.104)	1.008 (0.958-1.061)	0.654	1.029 (0.979-1.082)	1.001 (0.939-1.068)	0.61	1.019 (0.968-1.073)	1.039 (0.935-1.154)	0.712

Pressure continuous (per 10mmHg increase)									
Mean Blood Pressure (1/3SBP+2/3 DBP) continuous (per 10mmHg increase)	1.029 (0.974- 1.088)	1.018 (0.975- 1.063)	0.904	1.036 (0.992- 1.081)	1.001 (0.948- 1.058)	0.479	1.020 (0.976- 1.066)	1.037 (0.948- 1.133)	0.569
Other location or morphology	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p- interacti on	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p- interacti on	No antihypertens ive treatment HR (adjusted)	Antihyperte nsive treatment HR (adjusted)	Treatme nt p- interacti on
Systolic Blood Pressure (mmHg) ESH classificatio n									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-129	1.17 (0.94- 1.45)	0.91 (0.76- 1.08)		0.93 (0.79- 1.10)	1.16 (0.93- 1.46)		0.95 (0.82- 1.10)	1.26 (0.59- 2.71)	
130-139	1.17 (0.94- 1.46)	1.16 (0.98- 1.38)		1.11 (0.94- 1.32)	1.25 (1.00- 1.57)		1.12 (0.96- 1.30)	1.54 (0.75- 3.13)	
140-159	1.14 (0.92- 1.41)	0.99 (0.83- 1.17)	0.913	1.05 (0.89- 1.23)	1.06 (0.85- 1.33)	0.563	0.97 (0.84- 1.14)	1.54 (0.78- 3.07)	0.276
160-179	1.36 (1.05- 1.76)	1.13 (0.92- 1.38)		1.18 (0.96- 1.44)	1.30 (1.00- 1.70)		1.19 (0.97- 1.47)	1.69 (0.84- 3.39)	
>= 180	1.11 (0.72- 1.69)	1.12 (0.82- 1.52)		1.27 (0.94- 1.72)	0.90 (0.59- 1.39)		1.07 (0.75- 1.54)	1.47 (0.69- 3.14)	
p-trend	0.135	0.21		0.035	0.644		0.247	0.197	
Diastolic Blood Pressure (mmHg) ESH classificatio n									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-84	1.05 (0.88- 1.26)	1.03 (0.89- 1.18)		1.02 (0.89- 1.18)	1.08 (0.90- 1.30)		1.00 (0.88- 1.14)	1.11 (0.75- 1.64)	
85-89	1.11 (0.91- 1.35)	1.00 (0.85- 1.18)		1.03 (0.88- 1.20)	1.09 (0.89- 1.33)		1.08 (0.93- 1.25)	1.01 (0.68- 1.50)	
90-99	1.06 (0.88- 1.28)	0.98 (0.84- 1.14)	0.858	1.01 (0.87- 1.17)	1.02 (0.85- 1.23)	0.722	0.99 (0.86- 1.15)	1.15 (0.81- 1.63)	0.849
100-109	1.05 (0.78- 1.43)	1.21 (0.97- 1.50)		1.30 (1.04- 1.62)	0.98 (0.74- 1.30)		1.25 (0.98- 1.59)	1.06 (0.70- 1.60)	
>= 110	1.16 (0.66- 2.02)	0.78 (0.47- 1.29)		0.84 (0.50- 1.41)	1.06 (0.62- 1.78)		0.80 (0.43- 1.50)	1.20 (0.65- 2.21)	
p-trend	0.425	0.78		0.312	0.97		0.434	0.594	
Systolic Blood Pressure (mmHg) ASH classificatio n									
< 120	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
120-139	1.17 (0.97- 1.42)	1.03 (0.89- 1.20)		1.02 (0.88- 1.17)	1.21 (0.98- 1.48)		1.03 (0.90- 1.17)	1.44 (0.72- 2.88)	

140-159	1.14 (0.92-1.41)	0.97 (0.82-1.15)	0.526	1.04 (0.88-1.22)	1.06 (0.85-1.33)	0.831	0.97 (0.83-1.13)	1.54 (0.78-3.06)	0.208
>= 160	1.31 (1.02-1.68)	1.11 (0.91-1.35)		1.19 (0.98-1.43)	1.21 (0.93-1.56)		1.16 (0.95-1.41)	1.63 (0.81-3.26)	
p-trend	0.085	0.546		0.102	0.571		0.452	0.191	
Diastolic Blood Pressure (mmHg) ASH classification									
< 80	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
80-89	1.07 (0.92-1.25)	1.02 (0.90-1.15)		1.03 (0.91-1.16)	1.09 (0.93-1.27)		1.03 (0.92-1.15)	1.06 (0.75-1.50)	
90-99	1.06 (0.88-1.28)	0.98 (0.84-1.14)	0.907	1.01 (0.87-1.17)	1.02 (0.85-1.23)	0.612	0.99 (0.86-1.15)	1.15 (0.81-1.63)	0.859
>= 100	1.07 (0.81-1.41)	1.13 (0.92-1.38)		1.21 (0.99-1.50)	0.99 (0.76-1.29)		1.17 (0.93-1.48)	1.09 (0.73-1.61)	
Other location or morphology	Never smokers HR (adjusted)	Ever smokers HR (adjusted)	Smoking p-interaction	Alcohol <= 12g HR (adjusted)	Alcohol > 12g HR (adjusted)	Alcohol p-interaction	No antihypertensive treatment HR (adjusted)	Antihypertensive treatment HR (adjusted)	Treatment p-interaction
p-trend	0.49	0.57		0.216	0.996		0.453	0.567	
Mean BP (mmHg) (1/3SBP+2/3DBP) Cohort-specific quartiles									
50.0-88.3	1 (referent)	1 (referent)		1 (referent)	1 (referent)		1 (referent)	1 (referent)	
88.5-96.6	1.09 (0.88-1.35)	1.03 (0.87-1.22)		0.99 (0.84-1.16)	1.16 (0.92-1.45)		0.97 (0.84-1.13)	1.71 (0.71-4.14)	
96.8-105.5	1.22 (0.99-1.51)	1.03 (0.87-1.22)	0.321	1.07 (0.91-1.25)	1.14 (0.91-1.43)	0.704	1.02 (0.88-1.19)	2.10 (0.91-4.83)	0.075
105.6-216.6	1.19 (0.96-1.47)	1.02 (0.86-1.20)		1.08 (0.92-1.27)	1.09 (0.87-1.37)		1.02 (0.87-1.19)	2.14 (0.94-4.87)	
p-trend	0.095	0.909		0.211	0.791		0.624	0.077	
Hypertension (SBP >= 140 mmHg, or DBP >= 90 mmHg, or self-reported)									
Normotensive	1 (referent)	1 (referent)		1 (referent)	1 (referent)		-	-	
Hypertensive	1.07 (0.93-1.23)	0.99 (0.89-1.11)	0.569	1.07 (0.96-1.19)	0.96 (0.84-1.11)	0.33	1 (referent)	1.11 (0.97-1.26)	

Supplemental Table 6. Description of 29 studies from 20 meta-analyses of type 2 diabetes and cancer incidence, mortality or both included in umbrella review

Author, Year	Cancer site	Grade of evidence	No. Studies	no. cases/population	Fixed effects	Random effects	Largest study
Cancer incidence							
Gong, 2015	Oral	Weak	10	3014/2177373	1.11 (1.00, 1.23)	1.11 (1.00, 1.23)	1.20 (1.00, 1.40)
Miao, 2017	Gastric	NS	15	14028/7132872	1.13 (1.09, 1.17)	1.10 (0.94, 1.29)	1.12 (1.05, 1.19)
Ying Jiang, 2011	Colorectal	Strong	30	62163/8244227	1.25 (1.22, 1.29)	1.27 (1.21, 1.34)	1.41 (1.32, 1.50)
Wang, 2011	Hepatocellular	Highly suggestive	25	27440/7193072	1.67 (1.62, 1.71)	2.23 (1.68, 2.96)	1.21 (1.17, 1.25)
Jing, 2012	Cholangiocarcinoma	Weak	5	674/2169590	1.78 (1.53, 2.08)	1.77 (1.27, 2.45)	2.10 (1.60, 2.50)
Ren, 2011	Biliary tract	Suggestive	9	3101/3595095	1.40 (1.29, 1.51)	1.42 (1.19, 1.70)	1.24 (1.10, 1.41)
Gu, 2015	Gallbladder	Highly suggestive	11	1078/2831965	1.62 (1.47, 1.78)	1.73 (1.40, 2.14)	1.30 (1.10, 1.50)
Lee, 2013	Lung cancer	NS	21	198771/1.53e+07	0.88 (0.87, 0.89)	1.03 (0.94, 1.13)	0.79 (0.77, 0.80)
Larsson, 2007	Breast cancer	Highly suggestive	20	30680/1384861	1.19 (1.16, 1.23)	1.20 (1.12, 1.28)	1.20 (1.10, 1.20)
Liao, 2014	Endometrial	Highly suggestive	22	16224/5396342	1.65 (1.59, 1.71)	1.65 (1.50, 1.81)	1.61 (1.51, 1.72)

Wang, 2017	Ovarian	Weak	14	6050/3708307	1.15 (1.07, 1.24)	1.19 (1.06, 1.34)	1.05 (0.93, 1.20)
Xu, 2013	Localized stage prostate	Suggestive	8	16933/863286	0.74 (0.70, 0.78)	0.80 (0.70, 0.90)	0.71 (0.65, 0.76)
Bansal, 2013	Total prostate	NS	29	118003/7796267	0.90 (0.88, 0.91)	0.92 (0.81, 1.05)	0.89 (0.87, 0.91)
Bao, 2013	Kidney	Weak	19	12714/8415738	1.36 (1.30, 1.42)	1.27 (1.02, 1.57)	1.09 (1.03, 1.16)
Yeo, 2014	Thyroid	Suggestive	7	3197/7359294	1.18 (1.09, 1.28)	1.18 (1.09, 1.28)	1.17 (1.05, 1.31)
Castillo, 2012	Non-hodgkins Lymphoma	Weak	11	12495/5480097	1.10 (1.05, 1.14)	1.28 (1.03, 1.59)	0.96 (0.91, 1.01)
Castillo, 2012	Myeloma	NS	6	5226/5154566	1.09 (1.02, 1.16)	1.16 (0.86, 1.57)	0.98 (0.91, 1.06)
Castillo, 2012	Leukemia	Weak	8	10733/5989385	1.30 (1.24, 1.37)	1.35 (1.07, 1.70)	1.18 (1.11, 1.25)
Cancer incidence/mortality							
Huang, 2011	Esophageal	Suggestive	11	1743/1789501	1.27 (1.15, 1.41)	1.26 (1.10, 1.45)	1.66 (1.35, 2.05)
Ben, 2011	Pancreatic	Highly suggestive	35	21698/8769939	2.21 (2.15, 2.29)	1.94 (1.66, 2.27)	3.22 (3.03, 3.42)
Xu, 2017	Bladder	Suggestive	21	51215/1.12e+07	1.09 (1.06, 1.13)	1.23 (1.12, 1.35)	0.96 (0.92, 1.01)
Zhao, 2015	Glioma	Weak	11	15327/6418416	0.88 (0.82, 0.95)	0.79 (0.67, 0.93)	0.95 (0.86, 1.05)
Cancer mortality							
Gong, 2015	Oral	Suggestive	5	1851/2325984	1.41 (1.16, 1.72)	1.41 (1.16, 1.72)	1.44 (1.07, 1.94)

Miao, 2017	Gastric	NS	9	3168/2581220	1.69 (1.61, 1.76)	1.28 (0.93, 1.76)	2.25 (2.12, 2.39)
Ying Jiang, 2011	Colorectal	Weak	11	11002/4090537	1.34 (1.27, 1.40)	1.20 (1.03, 1.40)	1.54 (1.44, 1.65)
Wang, 2011	Hepatocellular	Weak	7	292/1156796	2.22 (1.95, 2.53)	2.43 (1.67, 3.55)	2.48 (2.07, 2.97)
Gu, 2015	Gallbladder	Weak	6	1601/2223468	1.30 (1.07, 1.59)	1.30 (1.07, 1.59)	1.13 (0.78, 1.64)
Larsson, 2007	Breast	NS	5	4538/1082084	1.22 (1.10, 1.34)	1.24 (0.95, 1.62)	1.27 (1.11, 1.45)
Liao, 2014	Endometrial	Suggestive	5	2070/1093630	1.32 (1.13, 1.55)	1.32 (1.13, 1.55)	1.33 (1.07, 1.56)

Supplemental Table 7. AMSTAR quality assessment of Meta-Analyses included in umbrella review of type 2 diabetes and cancer incidence

Author, Year	Cancer site	1	2	3	4	5	6	7	8	9	10	11	AMSTAR score
Cancer incidence													
Luo, 2016	Colorectal	NO	NO	YES	NO	NO	YES	YES	YES	YES	YES	NO	6
Wang, 2016	Hepatocellular	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Wang, 2016	Hepatocellular	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Jing, 2012	Cholangiocarcinoma	NO	YES	YES	NO	NO	YES	NO	NO	YES	YES	NO	5
Ren, 2011	Biliary tract	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Batabyal, 2014	Pancreatic	NO	NO	YES	NO	NO	YES	NO	NO	YES	NO	NO	3
Lee, 2013	Lung	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	NO	8
Larsson, 2007	Breast	YES	NO	NO	NO	NO	YES	NO	NO	YES	YES	NO	4
Anothaisintawee, 2013	Breast	NO	NO	YES	NO	NO	YES	NO	NO	YES	NO	NO	3
Zhang, 2017	Ovarian	YES	YES	NO	NO	NO	YES	YES	YES	YES	YES	NO	7
Wang, 2017	Ovarian	NO	YES	YES	YES	NO	YES	YES	YES	YES	YES	NO	8
Xu, 2013	Localized stage prostate	NO	YES	YES	NO	NO	YES	YES	YES	YES	YES	NO	7
Bansal, 2013	Total prostate	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	NO	5
Bao, 2013	Kidney	NO	NO	NO	NO	NO	YES	YES	YES	YES	YES	NO	5
Yeo, 2014	Thyroid	NO	NO	YES	NO	NO	YES	YES	YES	YES	YES	NO	6
Schmid, 2013	Thyroid	NO	NO	YES	NO	NO	YES	YES	YES	YES	YES	NO	6
Castillo, 2012	Non-hodgkins Lymphoma	NO	YES	YES	NO	NO	YES	YES	YES	YES	NO	NO	6

Castillo, 2012	Myeloma	NO	YES	YES	NO	NO	YES	YES	YES	YES	NO	NO	6
Castillo, 2012	Leukaemia	NO	YES	YES	NO	NO	YES	YES	YES	YES	NO	NO	6
Cancer incidence/mortality													
Gong, 2015	Oral	NO	YES	YES	NO	NO	YES	YES	YES	YES	YES	NO	7
Huang, 2012	Esophageal	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Miao, 2017	Gastric	NO	YES	YES	NO	NO	YES	YES	YES	YES	YES	NO	7
Jiang, 2011	Colorectal	NO	YES	YES	NO	NO	YES	YES	YES	YES	YES	NO	7
Wang, 2012	Hepatocellular	NO	YES	NO	NO	NO	YES	NO	NO	YES	YES	NO	4
Gu, 2016	Gallbladder	NO	NO	YES	NO	NO	YES	YES	YES	YES	YES	NO	6
Ben, 2011	Pancreatic	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Liao, 2014	Endometrial	NO	YES	YES	YES	NO	YES	YES	YES	YES	YES	NO	8
Xu, 2017	Bladder	NO	YES	YES	YES	NO	YES	YES	YES	YES	YES	NO	8
Zhu, 2013	Bladder	NO	YES	YES	NO	NO	YES	NO	NO	YES	YES	NO	5
Zhao, 2015	Glioma	NO	NO	YES	NO	NO	YES	YES	YES	YES	YES	NO	6
Cancer mortality													
Wang, 2016	Hepatocellular women	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4
Wang, 2016	Hepatocellular men	NO	NO	YES	NO	NO	YES	NO	NO	YES	YES	NO	4

^a AMSTAR items:

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."*

2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.*

3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: If at least 2 sources + one supplementary strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary).*

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for “grey literature” or “unpublished literature,” indicate “yes.” SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*

5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided. *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no.”*

6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. *Note: Acceptable if not in table format as long as they are described as above.*

7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. *Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (“low” or “high” is fine, as long as it is clear which studies scored “low” and which scored “high”; a summary score/range for all studies is not acceptable).*

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. *Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7.*

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). *Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.*

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). *Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.*

11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.*

Supplemental Table 8. Description of 10 duplicate studies from 7 meta-analyses of type 2 diabetes and cancer incidence, mortality or both included in sensitivity analysis.

Study	Association between diabetes and *	Grade of evidence	no. cases/population	Summary relative risk		
				Fixed effects	Random effects	Largest study
Cancer incidence						
Luo, 2016	Colorectal cancer incidence	Strong	26046/2335605	1.34 (1.27, 1.40)	1.38 (1.27, 1.50)	1.19 (1.09, 1.29)
Wang, 2016	HCC cancer incidence women	Suggestive	2809/1769494	1.87 (1.72, 2.02)	1.85 (1.40, 2.44)	3.40 (2.90, 3.90)
Wang, 2016	HCC cancer incidence men	Highly Suggestive	11752/7547775	2.20 (2.12, 2.29)	2.16 (1.74, 2.68)	1.95 (1.82, 2.09)
Batabyal, 2014	Pancreatic cancer incidence	Highly Suggestive	39835/1.33e+07	1.57 (1.53, 1.61)	1.87 (1.67, 2.09)	1.05 (1.01, 1.11)
Anothaisintawee, 2013	Breast cancer incidence	Weak	32108/1305304	1.13 (1.08, 1.19)	1.20 (1.09, 1.31)	1.07 (1.00, 1.15)
Zhang, 2017	Ovarian cancer incidence	Weak	4114/2198773	1.20 (1.15, 1.26)	1.24 (1.06, 1.44)	1.23 (1.15, 1.32)
Schmid, 2013	Thyroid cancer incidence	Not suggestive	1015/912857	1.18 (0.98, 1.41)	1.18 (0.98, 1.41)	1.19 (0.90, 1.57)
Cancer incidence/mortality						
Zhu, 2013	Bladder cancer incidence/mortality	Weak	54187/1.15e+07	1.25 (1.22, 1.29)	1.32 (1.12, 1.56)	0.96 (0.92, 1.01)
Cancer mortality						
Wang, 2016	HCC cancer mortality women	Suggestive	1106/1229654	1.86 (1.67, 2.06)	1.79 (1.38, 2.33)	2.30 (2.00, 2.70)

Wang, 2016	HCC cancer mortality men	Suggestive	2145/1447529	2.08 (1.95, 2.22)	2.26 (1.60, 3.19)	1.59 (1.45, 1.74)
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Study	Association between diabetes and *	Fixed p value	Random p value	95% prediction interval
Cancer incidence				
Luo, 2016	Colorectal cancer incidence	0.0000	0.0000	1.07, 1.77
Wang, 2016	HCC cancer incidence women	0.0000	0.0000	0.64, 5.31
Wang, 2016	HCC cancer incidence men	0.0000	0.0000	0.83, 5.65
Batabyal, 2014	Pancreatic cancer incidence	0.0000	0.0000	0.91, 3.85
Anothaisintawee, 2013	Breast cancer incidence	0.0000	0.0001	0.90, 1.58
Zhang, 2017	Ovarian cancer incidence	0.0000	0.0066	0.76, 2.02
Schmid, 2013	Thyroid cancer incidence	0.0819	0.0819	0.95, 1.46
Cancer incidence/mortality				
Zhu, 2013	Bladder cancer incidence/mortality	0.0000	0.0011	0.57, 3.06
Cancer mortality				
Wang, 2016	HCC cancer mortality women	0.0000	0.0000	0.78, 4.10

Wang, 2016	HCC cancer mortality men	0.0000	0.0000	0.68, 7.51
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Supplemental Table 9. Description of 29 studies from 20 meta-analyses of type 2 diabetes and cancer incidence, mortality or both, restricting to cohort studies only (excluding case-control studies) included in sensitivity analysis.

Study	Cancer site	Grade of evidence	No. studies	No. cases/population	Summary relative risk		
					Fixed effects	Random effects	Largest study
Cancer incidence							
Gong, 2015	Oral	Weak	10	3014/2177373	1.11 (1.00, 1.23)	1.11 (1.00, 1.23)	1.20 (1.00, 1.40)
Miao, 2017	Gastric	Not suggestive	15	14028/7132872	1.13 (1.09, 1.17)	1.10 (0.94, 1.29)	1.12 (1.05, 1.19)
Ying Jiang, 2011	Colorectal	Strong	30	62163/8244227	1.25 (1.22, 1.29)	1.27 (1.21, 1.34)	1.41 (1.32, 1.50)
Wang, 2011	Hepatocellular	Highly Suggestive	25	27440/7193072	1.67 (1.62, 1.71)	2.23 (1.68, 2.96)	1.21 (1.17, 1.25)
Jing, 2012	Cholangiocarcinoma	Weak	5	674/2169590	1.78 (1.53, 2.08)	1.77 (1.27, 2.45)	2.10 (1.60, 2.50)
Ren, 2011	Biliary tract	Suggestive	7	2405/3593302	1.40 (1.29, 1.51)	1.42 (1.17, 1.71)	1.24 (1.10, 1.41)
Gu, 2015	Gallbladder	Highly Suggestive	11	1078/2831965	1.62 (1.47, 1.78)	1.73 (1.40, 2.14)	1.30 (1.10, 1.50)
Lee, 2013	Lung cancer	Not suggestive	21	198771/1.53e+07	0.88 (0.87, 0.89)	1.03 (0.94, 1.13)	0.79 (0.77, 0.80)
Larsson, 2007	Breast cancer	Suggestive	15	15748/1360406	1.19 (1.16, 1.23)	1.20 (1.11, 1.30)	1.20 (1.10, 1.20)

Liao, 2014	Endometrial	Highly Suggestive	21	15851/5342191	1.66 (1.60, 1.72)	1.67 (1.51, 1.84)	1.61 (1.51, 1.72)
Wang, 2017	Ovarian	Weak	14	6050/3708307	1.15 (1.07, 1.24)	1.19 (1.06, 1.34)	1.05 (0.93, 1.20)
Xu, 2013	Localized stage prostate	Suggestive	8	16933/863286	0.74 (0.70, 0.78)	0.80 (0.70, 0.90)	0.71 (0.65, 0.76)
Bansal, 2013	Total prostate	Not suggestive	29	118003/7796267	0.90 (0.88, 0.91)	0.92 (0.81, 1.05)	0.89 (0.87, 0.91)
Bao, 2013	Kidney	Weak	19	12714/8415738	1.36 (1.30, 1.42)	1.27 (1.02, 1.57)	1.09 (1.03, 1.16)
Yeo, 2014	Thyroid	Suggestive	7	3197/7359294	1.18 (1.09, 1.28)	1.18 (1.09, 1.28)	1.17 (1.05, 1.31)
Castillo, 2012	Non-hodgkins Lymphoma	Weak	11	12495/5480097	1.10 (1.05, 1.14)	1.28 (1.03, 1.59)	0.96 (0.91, 1.01)
Castillo, 2012	Myeloma	Not suggestive	6	5226/5154566	1.09 (1.02, 1.16)	1.16 (0.86, 1.57)	0.98 (0.91, 1.06)
Castillo, 2012	Leukemia	Weak	8	10733/5989385	1.30 (1.24, 1.37)	1.35 (1.07, 1.70)	1.18 (1.11, 1.25)
Cancer incidence/mortality							
Huang, 2011	Esophageal	Suggestive	11	1743/1789501	1.27 (1.15, 1.41)	1.26 (1.10, 1.45)	1.66 (1.35, 2.05)
Ben, 2011	Pancreatic	Highly Suggestive	35	21698/8769939	2.21 (2.15, 2.29)	1.94 (1.66, 2.27)	3.22 (3.03, 3.42)
Xu, 2017	Bladder	Suggestive	21	51215/1.12e+07	1.09 (1.06, 1.13)	1.23 (1.12, 1.35)	0.96 (0.92, 1.01)
Zhao, 2015	Glioma	Not suggestive	5	4189/6243834	0.96 (0.88, 1.04)	0.96 (0.88, 1.04)	0.95 (0.86, 1.05)
Cancer mortality							

Gong, 2015	Oral	Suggestive	5	1851/2325984	1.41 (1.16, 1.72)	1.41 (1.16, 1.72)	1.44 (1.07, 1.94)
Miao, 2017	Gastric	Not suggestive	9	3168/2581220	1.69 (1.61, 1.76)	1.28 (0.93, 1.76)	2.25 (2.12, 2.39)
Ying Jiang, 2011	Colorectal	Weak	11	11002/4090537	1.34 (1.27, 1.40)	1.20 (1.03, 1.40)	1.54 (1.44, 1.65)
Wang, 2011	Hepatocellular	Weak		292/1156796	2.22 (1.95, 2.53)	2.43 (1.67, 3.55)	2.48 (2.07, 2.97)
Gu, 2015	Gallbladder	Weak	6	1601/2223468	1.30 (1.07, 1.59)	1.30 (1.07, 1.59)	1.13 (0.78, 1.64)
Larsson, 2007	Breast	Not suggestive	5	4538/1082084	1.22 (1.10, 1.34)	1.24 (0.95, 1.62)	1.27 (1.11, 1.45)
Liao, 2014	Endometrial	Suggestive	5	2070/1093630	1.32 (1.13, 1.55)	1.32 (1.13, 1.55)	1.33 (1.07, 1.56)

Study	Cancer site	Fixed p value	Random p value	95% prediction interval
Cancer incidence				
Gong, 2015	Oral	0.0444	0.0444	0.98, 1.25
Miao, 2017	Gastric	0.0000	0.2290	0.61, 1.98
Ying Jiang, 2011	Colorectal	0.0000	0.0000	1.07, 1.52
Wang, 2011	Hepatocellular	0.0000	0.0000	0.58, 8.57
Jing, 2012	Cholangiocarcinoma	0.0000	0.0006	0.66, 4.72
Ren, 2011	Biliary tract	0.0000	0.0003	0.80, 2.51
Gu, 2015	Gallbladder	0.0000	0.0000	0.99, 3.05
Lee, 2013	Lung cancer	0.0000	0.4744	0.71, 1.51
Larsson, 2007	Breast cancer	0.0000	0.0000	0.97, 1.49
Liao, 2014	Endometrial	0.0000	0.0000	1.18, 2.36
Wang, 2017	Ovarian	0.0001	0.0044	0.87, 1.62
Xu, 2013	Localized stage prostate	0.0000	0.0004	0.57, 1.12
Bansal, 2013	Total prostate	0.0000	0.2209	0.48, 1.77
Bao, 2013	Kidney	0.0000	0.0303	0.53, 3.06
Yeo, 2014	Thyroid	0.0001	0.0001	1.06, 1.32

Castillo, 2012	Non-hodgkins Lymphoma	0.0000	0.0258	0.63, 2.59
Castillo, 2012	Myeloma	0.0109	0.3277	0.45, 3.03
Castillo, 2012	Leukemia	0.0000	0.0111	0.66, 2.77
Cancer incidence/mortality				
Huang, 2011	Esophageal	0.0000	0.0007	0.94, 1.69
Ben, 2011	Pancreatic	0.0000	0.0000	0.87, 4.32
Xu, 2017	Bladder	0.0000	0.0000	0.84, 1.79
Zhao, 2015	Glioma	0.2916	0.2916	0.83, 1.10
Cancer mortality				
Gong, 2015	Oral	0.0006	0.0006	1.03, 1.94
Miao, 2017	Gastric	0.0000	0.1231	0.42, 3.89
Ying Jiang, 2011	Colorectal	0.0000	0.0178	0.74, 1.94
Wang, 2011	Hepatocellular	0.0000	0.0000	0.78, 7.54
Gu, 2015	Gallbladder	0.0084	0.0084	0.99, 1.72
Larsson, 2007	Breast	0.0001	0.1105	0.49, 3.16
Liao, 2014	Endometrial	0.0005	0.0005	1.02, 1.71

Supplemental Table 10. Characteristics of the seven prospective studies included in the meta-analysis of the pre-diagnostic IL-6 concentrations and colorectal cancer risk

Author, year	Location	Population (women/men/all)	Design	No of CRC cases/cohort or controls	Results*	Matching or Adjustment factors	Quality Criteria
Il'yasova, 2005	USA	Health Aging and Body Composition Cohort (all)	Cohort	CRC: 40/2169	CRC: 1.44 (0.90-2.31)	Age, sex, race, study site†	6/9
Heikkila, 2009	England, UK	British Women's Heart and Health Study (women)	Cohort	CRC: 32/3074‡ Colon: 26 Rectum: 7	CRC: 0.92 (0.53-1.60) Colon: 1.14 (0.65-2.00) Rectum: 0.35 (0.09-1.42)	Age, BMI, smoking, socioeconomic position, physical activity, HRT use, NSAID use	6/9
Heikkila, 2009	Wales, UK	Caerphilly Cohort (men)	Cohort	CRC: 30/845‡ Colon: 20 Rectum: 12	CRC: 0.71 (0.41-1.23) Colon: 0.72 (0.36-1.46) Rectum: 0.48 (0.19-1.24)	Age, BMI, smoking, physical activity, NSAID use, socioeconomic position	6/9
Chan, 2011	USA	Nurses' Health Study (women)	Nested C-C	CRC: 346/686** Colon: 273 Rectum: 73	CRC: 1.02 (0.80-1.30) Colon: 1.15 (0.86-1.54) Rectum: 0.58 (0.32-1.07)	Age, BMI, physical activity, smoking, menopausal status, HRT use, prior endoscopy, family history of colorectal cancer, multivitamin use, aspirin/NSAIDS use, calcium, folate, red meat, alcohol consumption	8/9
Ho, 2012	USA	Women's Health Initiative Observational Study (women)	Case-cohort	CRC: 413/769 Colon: 334 Rectum: 78	CRC: 0.96 (0.76-1.21) Colon: 1.02 (0.80-1.31) Rectum: 0.75 (0.46-1.24)	Age, race, smoking, colonoscopy, estrogen, insulin, waist circumference§	7/9
Song, 2013	USA	Health Professionals Follow-up Study (men)	Nested C-C	CRC: 274/532 Colon: 142 Rectum: 53	CRC: 1.40 (1.05-1.85) Colon: 1.70 (1.16-2.48) Rectum: 0.75 (0.37-1.52)	Age, BMI, family history of CRC, prior endoscopy, smoking, alcohol, physical activity, aspirin/NSAID use, multivitamins use, folate, calcium, fiber, red meat intake	7/9
Kakourou, 2015	USA	CLUE II (all)	Nested C-C	CRC: 173/345 Colon: 124 Rectum: 48	CRC: 1.21 (0.94-1.56) Colon: 1.50 (1.12-2.01) Rectum: 0.77 (0.51-1.16)	Age, sex, race, education, BMI, smoking, NSAID/aspirin use, family history of CRC, diabetes medications, HRT or oral contraceptive use	7/9

Abbreviations: IL-6, interleukin-6; CRC, colorectal cancer; C-C, case-control; BMI, body mass index; HRT, hormone replacement therapy; NSAID, non-steroidal anti-inflammatory drug; IBD, inflammatory bowel disease; NR, not reported.

*Relative risk and 95% confidence intervals for the association between a one unit increase in the naturally logarithm transformed IL-6 concentrations and colorectal cancer risk (expressed as hazard ratios in cohort and case-cohort studies and as odds ratios in nested case-control studies).

†The authors reported that further adjustment for adiposity, smoking, physical activity, education, medical conditions and medications used did not alter the risk estimates.

‡The total number of incident cancer cases in these analysis does no add up to the total number of incident colorectal cancer cases in the published analysis because some participants had both colon and rectal cancers and were included in both analyses.

§The authors reported that colorectal cancer risk factors that were not statistically significant in multivariable modeling were excluded (e.g., family history of colorectal cancer and physical activity).

**Chan et al. provided updated data and risk estimates with more cases and controls compared to the numbers in the published paper.

Supplemental Table 11. Newcastle-Ottawa scale for the quality assessment of the seven prospective studies included in the meta-analysis of the pre-diagnostic IL-6 concentrations and colorectal cancer risk

Quality assessment criteria	Acceptable	Il'yasova	Heikkila	Heikkila	Chan	Ho	Song	Kakourou
Selection								
Representativeness of the exposed cohort?	Representative of average adult population in the community†	-	-	-	-	-	-	-
Selection of the non-exposed cohort?	Drawn from the same community as exposed cohort	+	+	+	+	+	+	+
Ascertainment of exposure?	Blinded prospective assessment with adequate quality-control statistics (CV≤10%)	+	+	+	+	+	-	+
Demonstration that outcome of interest was not present at start of study?	Yes	+	+	+	+	+	+	+
Comparability								
Study controls for age, sex, adiposity?	Yes	+	+	+	+	+	+	+
Study controls for additional risk factors?	Family history of CRC, NSAID/aspirin use, smoking, physical activity	-	-	-	+	+	+	-
Outcome								
Assessment of outcome?	Blinded and validated assessment	+	+	+	+	+	+	+
Was follow-up long enough for outcome to occur?	Mean follow-up >5 years	+	+	+	+	+	+	+
Adequacy of follow-up of cohorts?	Complete follow-up or subjects lost to follow-up unlikely to introduce bias‡	-	-	-	+	-	+	+

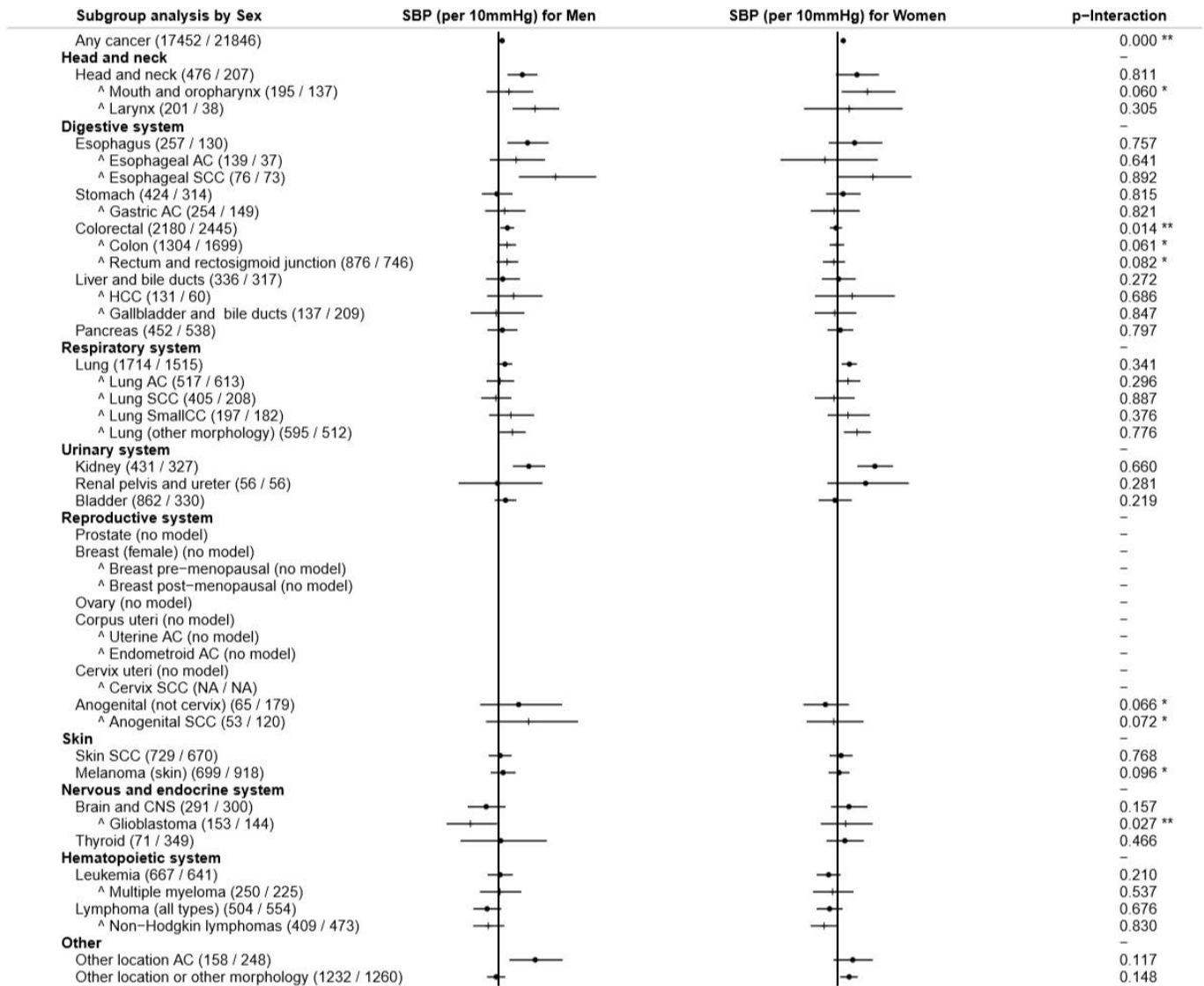
Abbreviations: IL-6, interleukin-6; CV, coefficient of variation; BMI, body mass index; CRC, colorectal cancer; NSAID, non-steroidal anti-inflammatory drug.

†All studies recruited volunteers, who may not be representative to the average adult population.

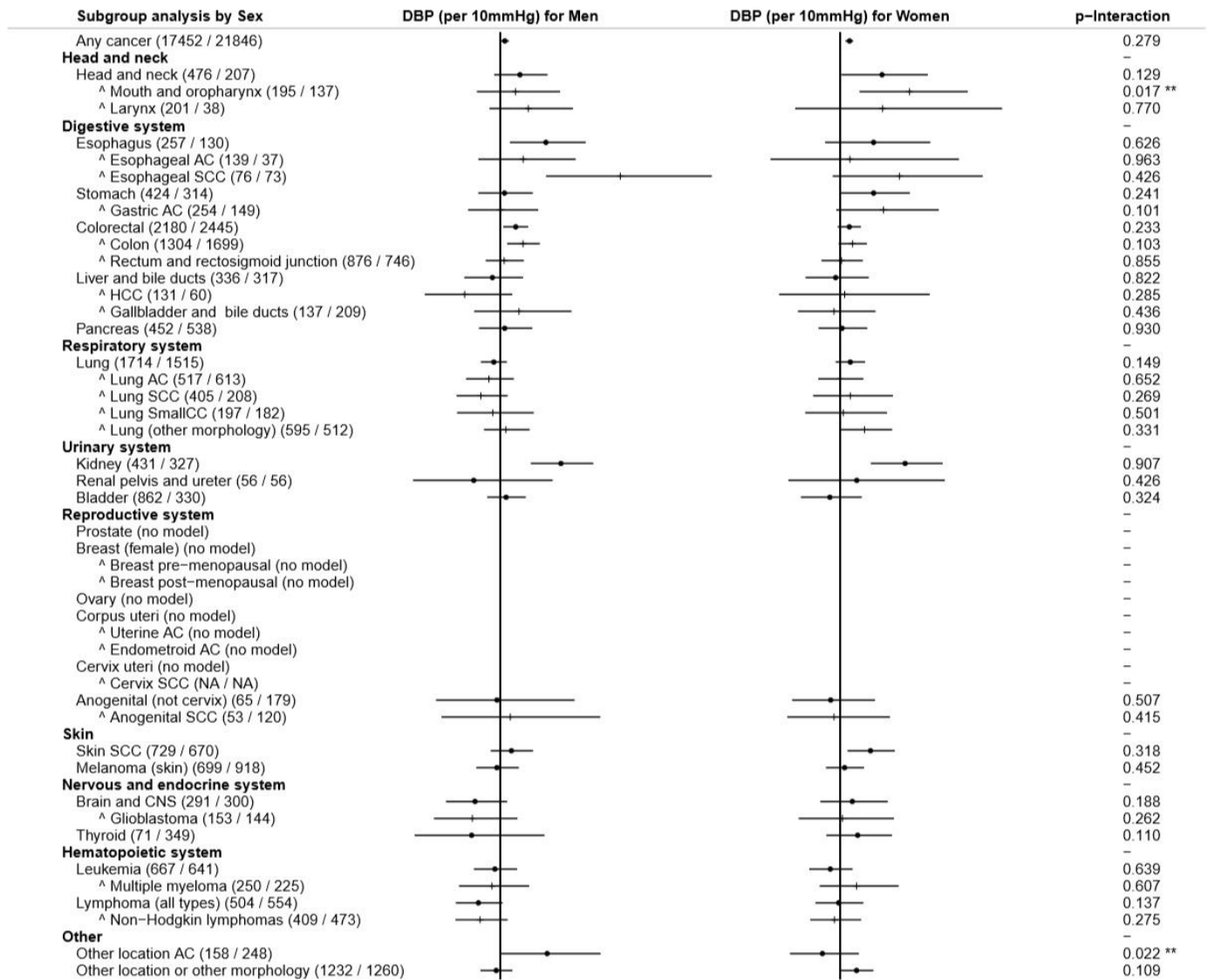
‡Four studies did not mention about the completeness of their study participants follow-up.

B) Supplementary figures

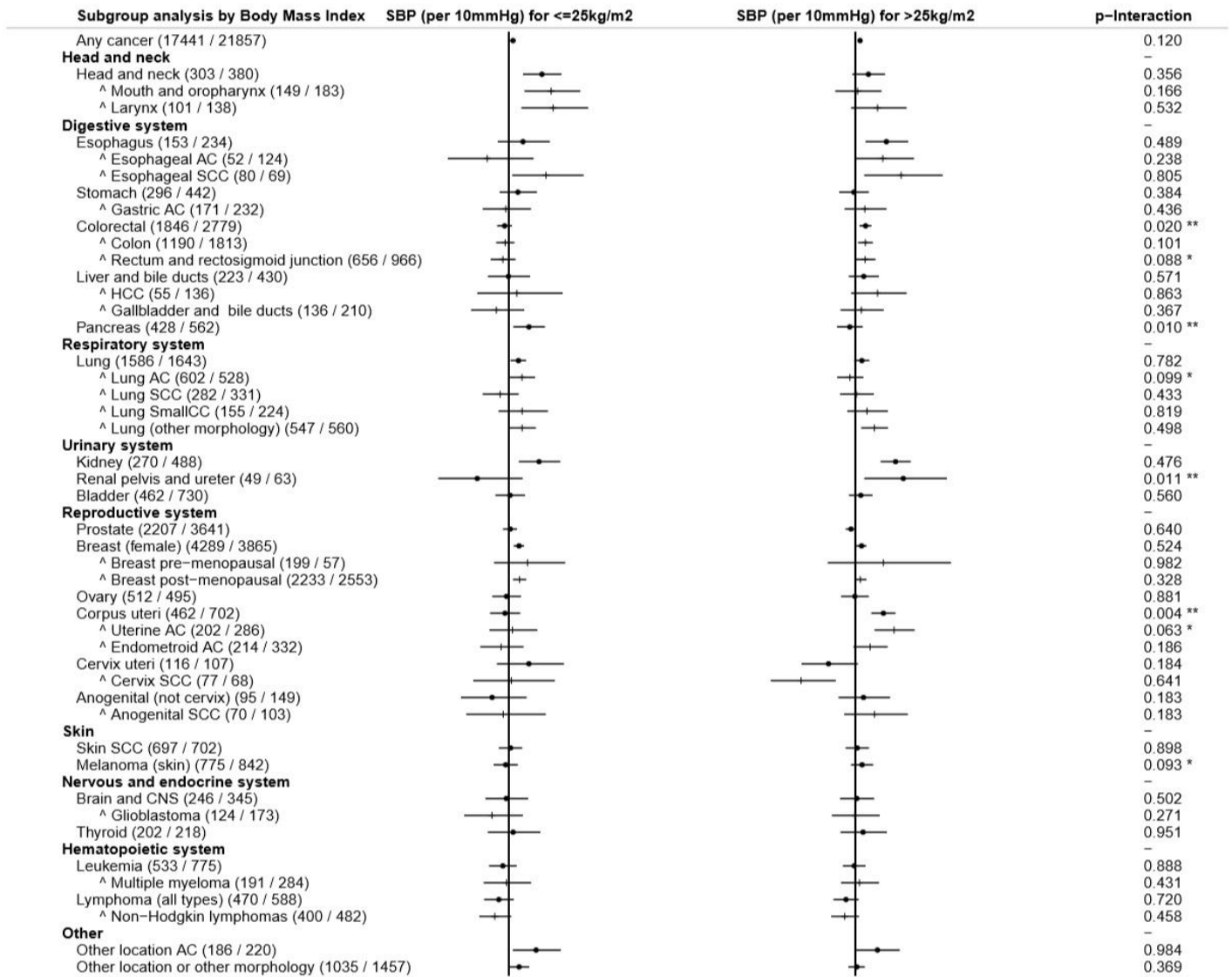
Supplemental Figure 1A: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



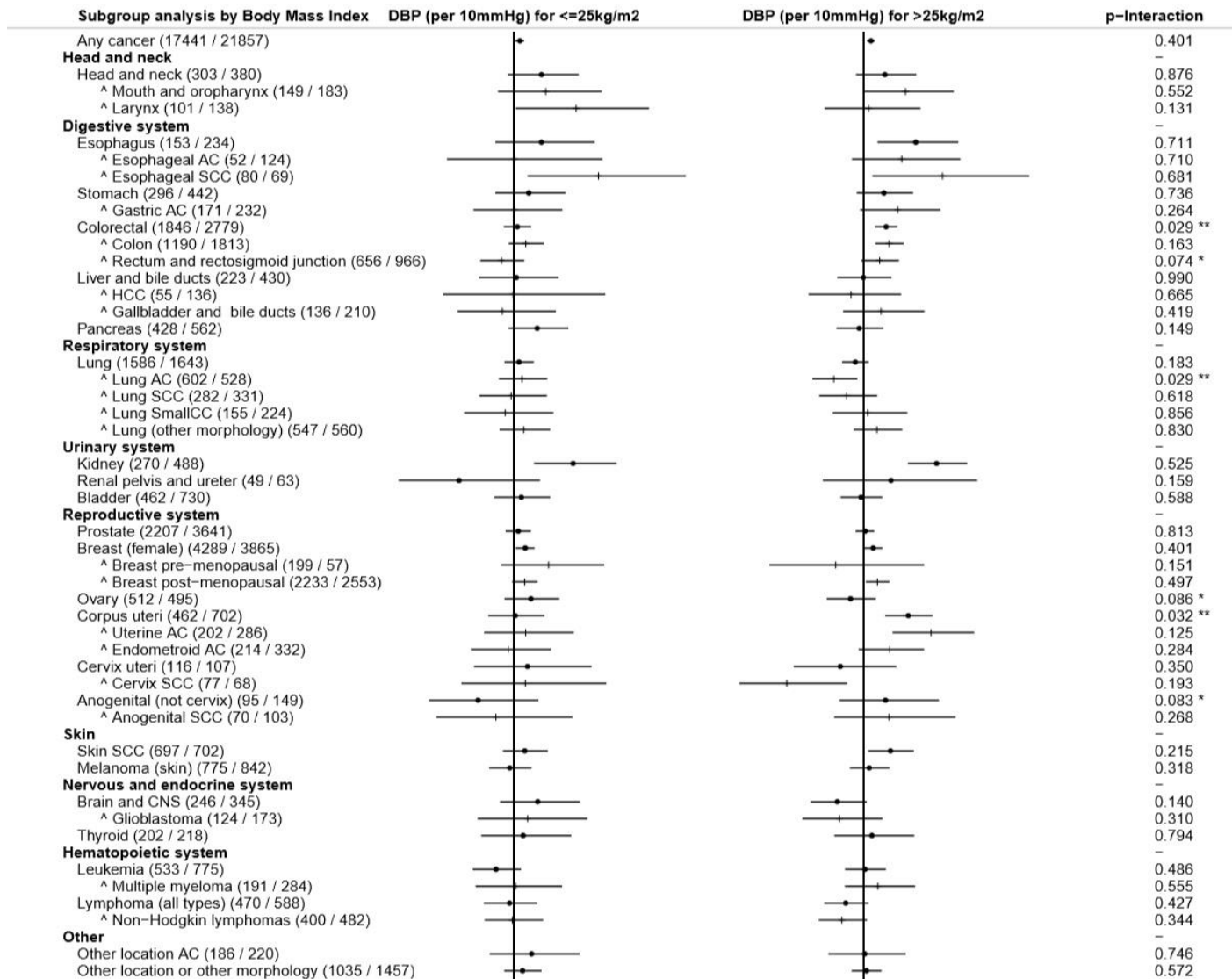
Supplemental Figure 1B: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



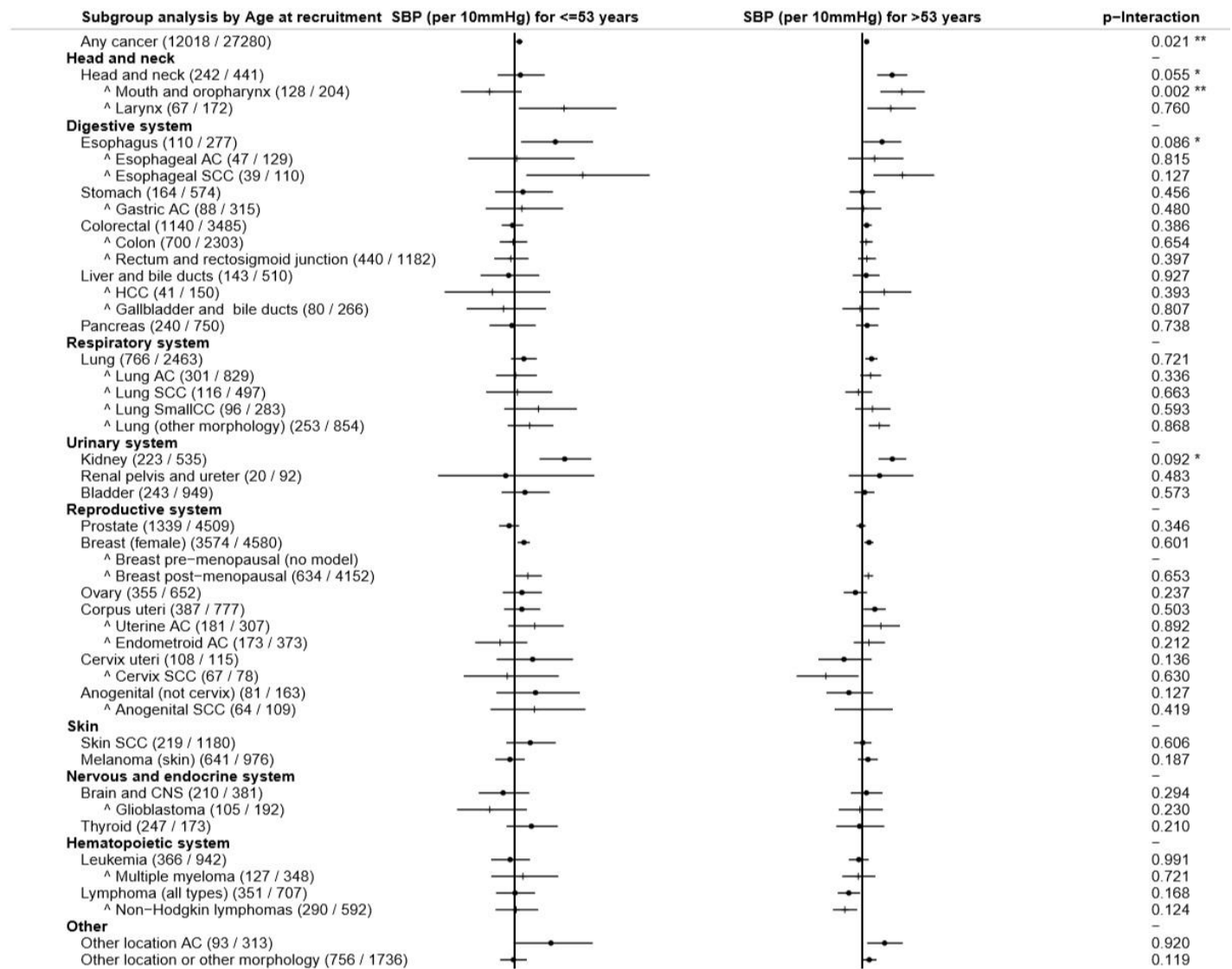
Supplemental Figure 1C: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



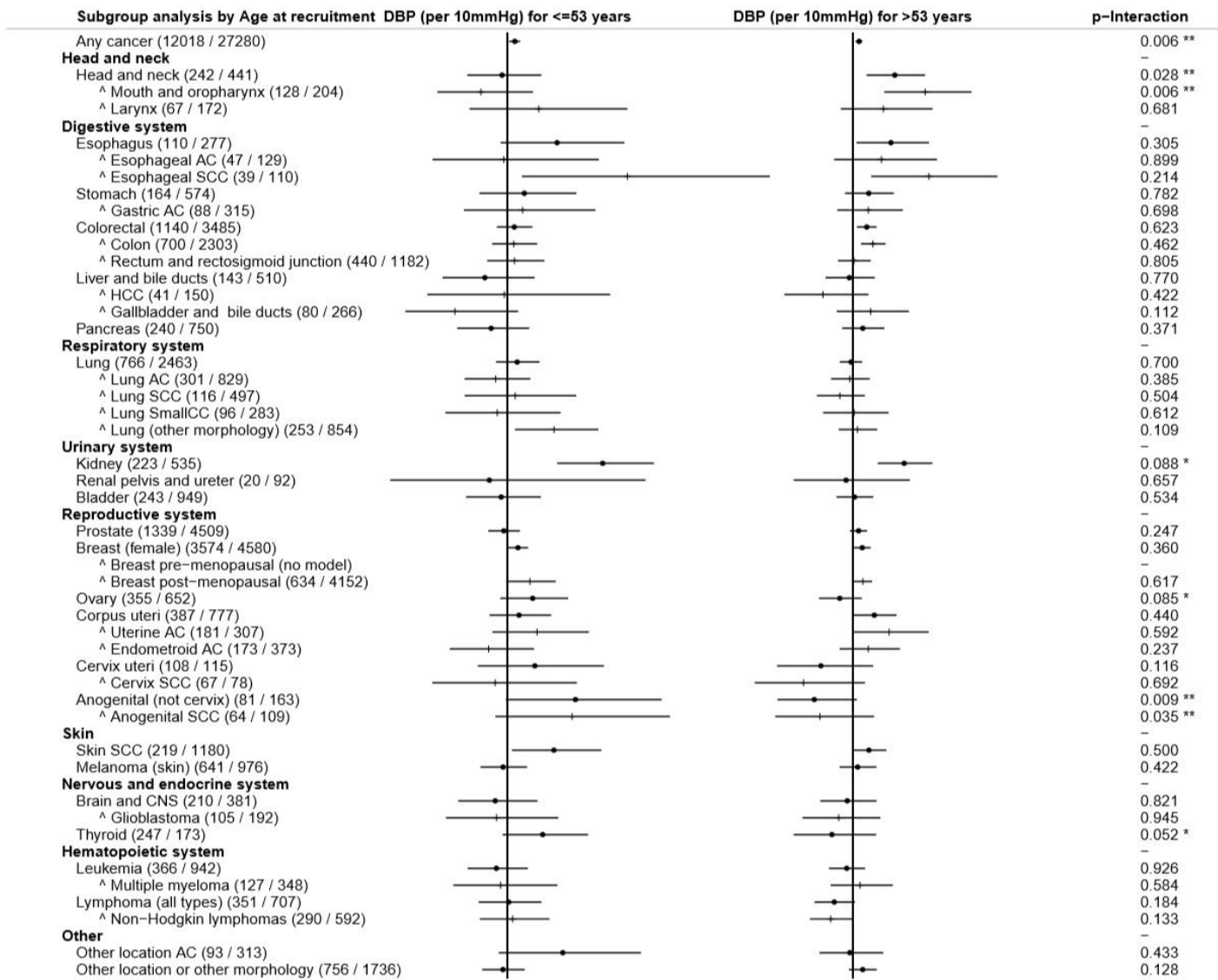
Supplemental Figure 1D: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DB in EPIC



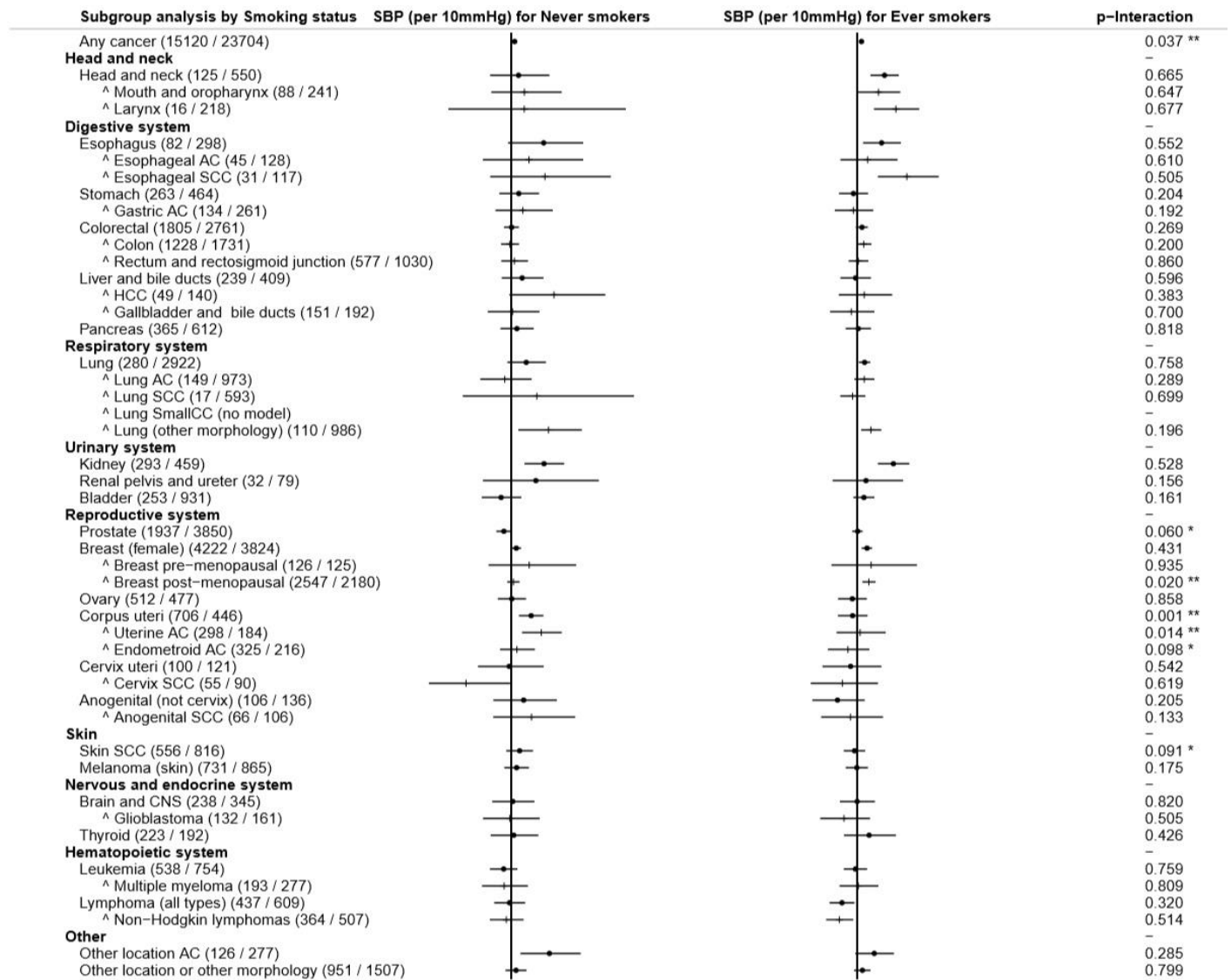
Supplemental Figure 1E: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



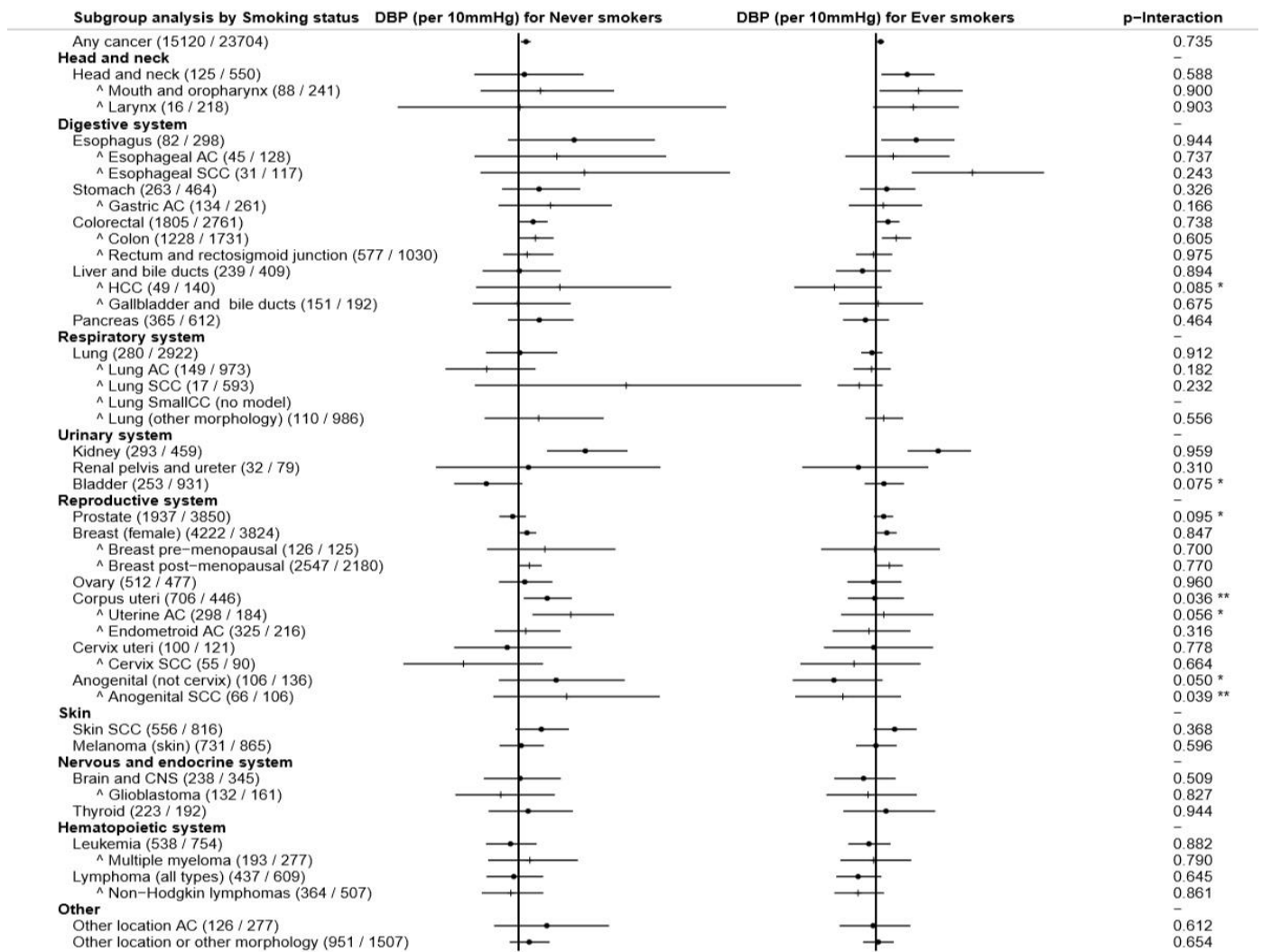
Supplemental Figure 1F: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



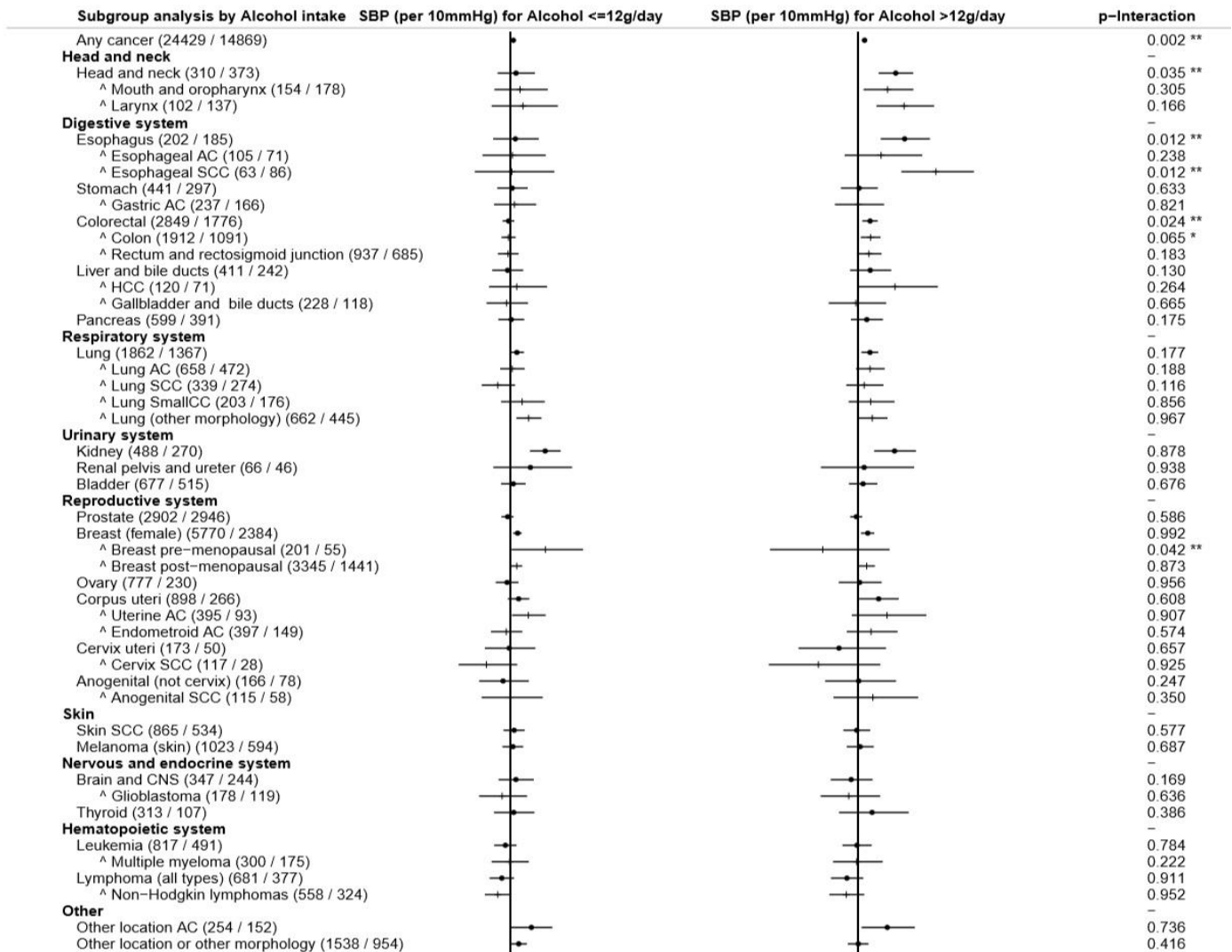
Supplemental Figure 1G: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



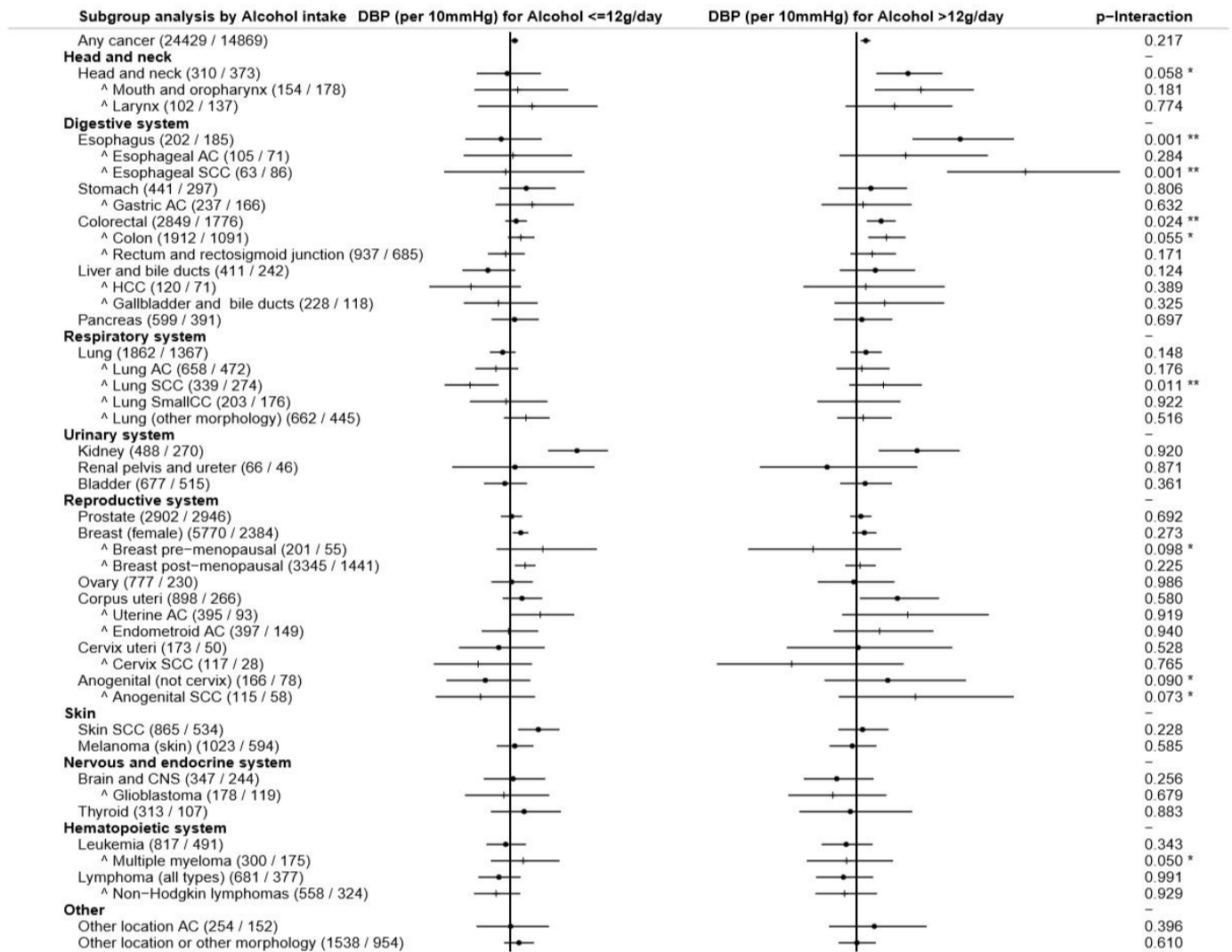
Supplemental Figure 1H: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



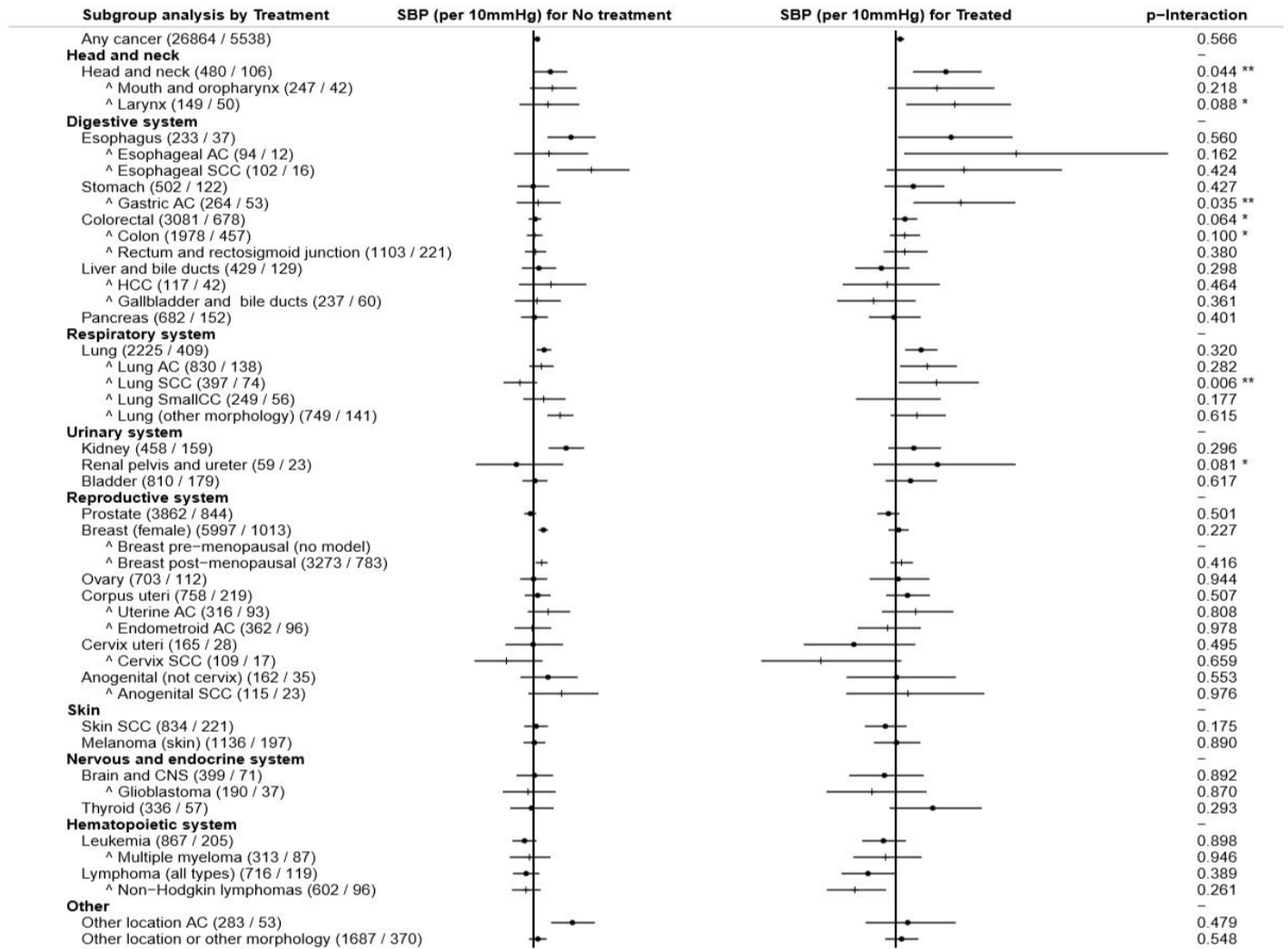
Supplemental Figure 1I: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



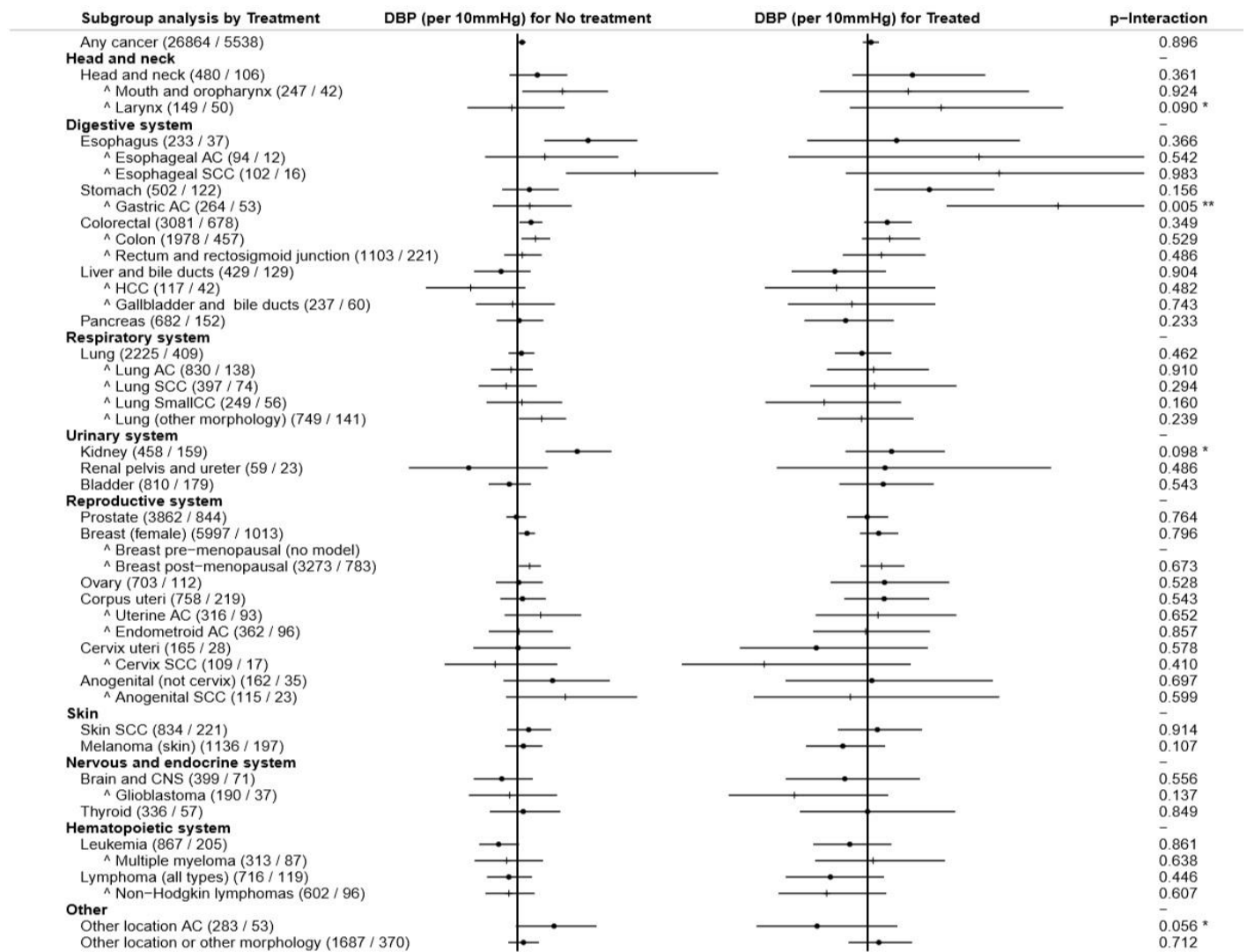
Supplemental Figure 1J: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



Supplemental Figure 1K: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC

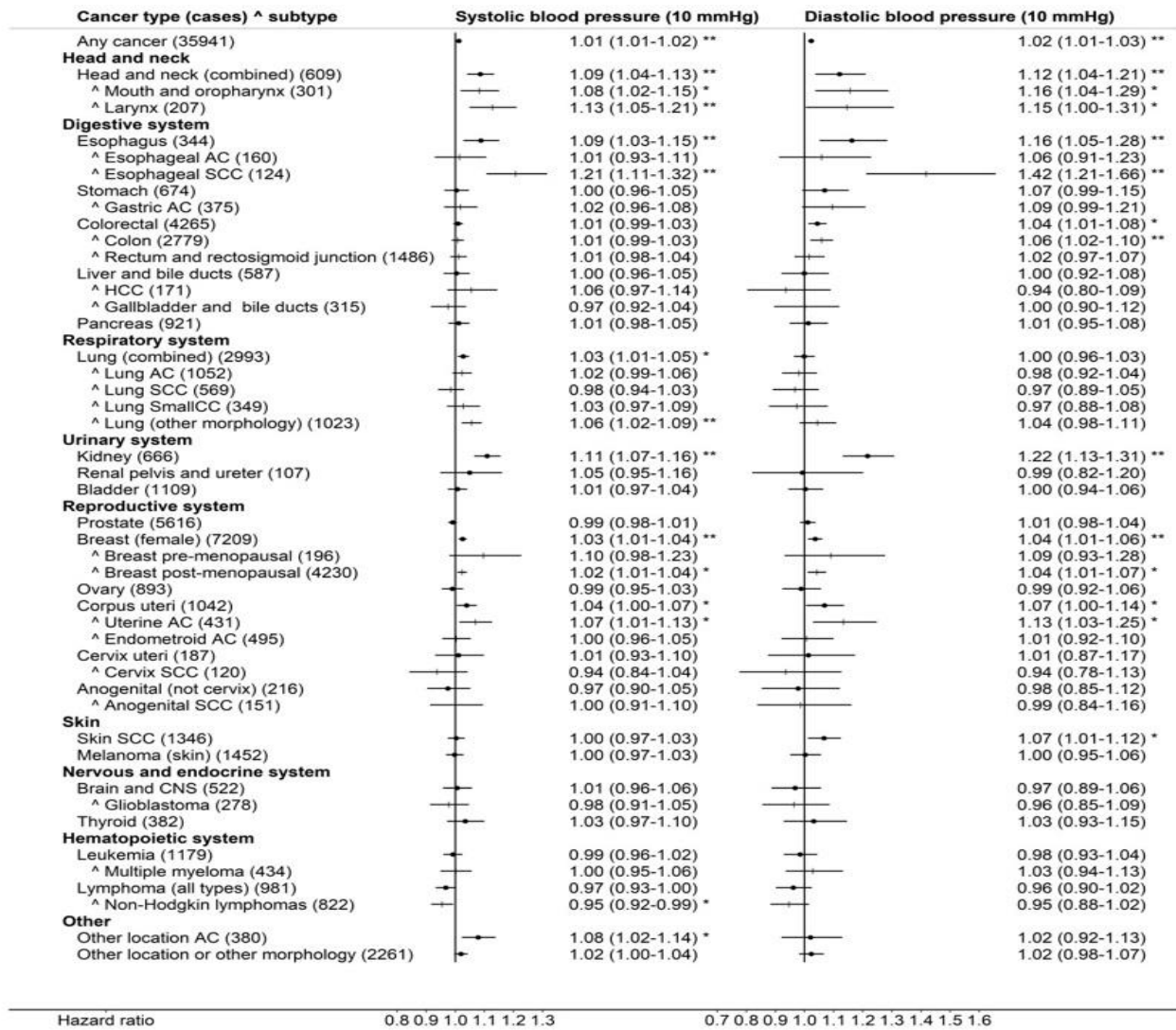


Supplemental Figure 1L: Forest plot of HR (95% CI) for sub-group analyses of continuous SBP and DBP in EPIC



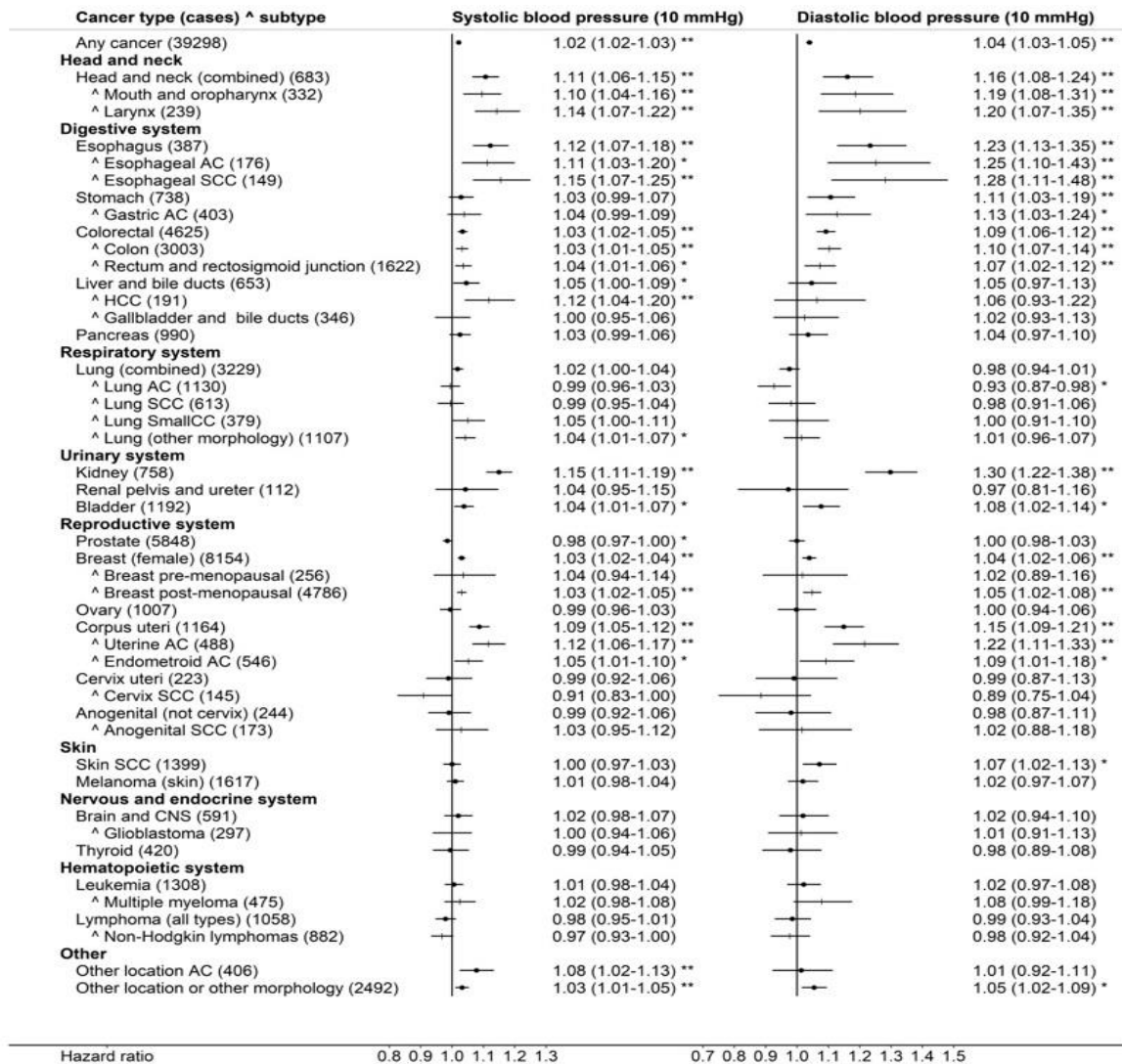
Adjusted hazard ratios (HR) (95% confidence intervals) from Cox proportional hazards models, stratified by age (5-year groups) and study centre and adjusted for confounders; Cancer types (cases per group) are described in Supplementary Table 1; AC adenocarcinoma; CNS central nervous system; HCC hepatocellular carcinoma; SCC squamous cell carcinoma; SmallCC small cell carcinoma; DBP or SBP – diastolic or systolic blood pressure; Treatment – antihypertensive treatment; Interaction p-values from likelihood ratio tests comparing nested models with and without an interaction term (multiplicative scale): * $p < 0.1$; ** $p < 0.05$. Main anatomical sites ordered by body system, as in Figure 6.

Supplemental Figure 2: Sensitivity analysis – first two years of follow-up excluded in EPIC



Hazard ratios – estimates (95% confidence intervals) (per 10mmHg higher blood pressure) derived from Cox proportional hazards models, stratified by study centre and age at recruitment (5-year categories) and adjusted for potential confounders and risk factors (Table 1); **AC** – adenocarcinoma; **CNS** – central nervous system; **HCC** – hepatocellular carcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; **Vertical order** – determined by the hazard ratio estimates for systolic blood pressure (SBP) of the main anatomical locations (**dot** symbols), each followed by the relevant specific locations or morphologies marked with ^ (+ symbols) for the main analysis (as per Figure 6) (other locations, not included in those specified, are shown last).

Supplemental Figure 3: Sensitivity analysis – crude (unadjusted) hazard ratio estimates in EPIC



Hazard ratios – unadjusted (crude) estimates (95% confidence intervals) (per 10mmHg higher blood pressure) derived from Cox proportional hazards models, stratified by study centre and age at recruitment (5year categories); **AC** – adenocarcinoma; **CNS** – central nervous system; **HCC** – hepatocellular carcinoma; **SCC** – squamous cell carcinoma; **SmallCC** – small cell carcinoma; **Vertical order** – determined by the hazard ratio estimates for systolic blood pressure (SBP) of the main anatomical locations (**dot** symbols), each followed by the relevant specific locations or morphologies marked with **^** (+ symbols) for the main analysis adjusted for potential confounders and risk factors (as per Figure 6) (other locations, not included in those specified, are shown last).

