UNIVERSITY OF IOANNINA
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

SECTOR OF SOCIAL MEDICINE AND MENTAL HEALTH
DEPARTMENT OF HYGIENE AND EPIDEMIOLOGY

MAPPING THE ASSOCIATIONS BETWEEN NON-THERAPEUTIC RISK FACTORS AND COLORECTAL CANCER PROGNOSIS

KANELLOPOULOU AFRODITI

DOCTORAL THESIS

IOANNINA 2026

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«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Ιατρικής του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα Ν. 5343/32, άρθρο 202, παράγραφος 2 (νομική κατοχύρωση του Ιατρικού Τμήματος)»

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"*Mine is not a new story, but it is for me"*

Afroditi Kanellopoulou

Ioannina, July 2026

PREFACE

Colorectal cancer was the third most common and second deadliest malignancy worldwide in 2022. Specifically, estimates of the global epidemiological burden report approximately 1.9 million new cases and about 903,000 deaths attributable to the disease. The annual number of new cases and deaths associated with colorectal cancer has been increasing at an alarming rate over time; by 2040, they are expected to exceed three million and one million, respectively.

Research findings from the past three decades indicate that the risk of carcinogenesis in the colon or rectum is shaped by the action of complex combinations of genetic, pathophysiological, sociodemographic, and lifestyle factors. Over this 30-year period, the scientific community has made remarkable progress in elucidating the etiology of the disease, a development that has contributed to more effective management and improved prognosis. In the past, colorectal cancer was characterized by high mortality rates in developed countries, such as the United States, with the five-year survival rate not exceeding 50%. Nowadays, the corresponding survival rates for individuals with stage II, III, and IV colorectal cancer reach 91%, 74%, and 15%, respectively. According to estimates by the International Agency for Research on Cancer, more than 5.7 million people worldwide were living with the disease in 2022.

The increase in life expectancy for colorectal cancer patients represents one of the most significant achievements of modern oncology. This improvement is attributed to the ability to diagnose the disease at a pre-symptomatic stage, the advancement of screening and preventive strategies, the implementation of innovative therapeutic protocols, improvements in supportive care, and, more broadly, a better understanding of the disease itself and its distinct molecular and clinical subtypes. Pathological, clinical, and therapeutic features are important prognostic factors, not only for overall survival but also for a range of other clinically relevant outcomes, including disease recurrence, and patients' overall quality of life.

In addition to the aforementioned factors, the scientific community has increasingly turned its attention to a broad range of non-therapeutic factors. However, in contrast to disease incidence, the role of these factors in prognosis appears to be largely ambiguous. More specifically, in 2018, the World Cancer Research Fund conducted an extensive review of published epidemiological studies with the primary

aim of elucidating the role of anthropometric measures, dietary habits, and lifestyle factors in the risk of developing cancer across a wide range of anatomical sites in the human body, including the colon and rectum. This comprehensive effort, widely known within the scientific community as the Continuous Update Project, concluded that there is strong evidence linking physical inactivity, body fatness, alcohol consumption, increased adult attained height, and several dietary factors (including high intake of red and processed meat, and low intake of whole grains, dietary fiber, dairy products, and calcium supplements) with colorectal cancer development. Although the scientific literature has consistently emphasized the importance of adherence, even after diagnosis, to a healthy lifestyle, as defined by recommendations for the prevention of colorectal cancer, the corresponding epidemiological associations with prognosis do not demonstrate equally high levels of evidence. This substantially complicates the development of a specific health agenda for individuals diagnosed with colorectal cancer. Accordingly, the aim of this doctoral thesis was to identify and evaluate the associations between a broad spectrum of non-therapeutic factors and the prognosis of colorectal cancer, using distinct methodological approaches.

The General Part of the thesis comprises Chapters 1 and 2. Chapter 1 provides an overview of colorectal cancer, including its definition, epidemiology and a summary of the current evidence linking various risk factors to disease prognosis. Chapter 2 outlines the objectives of the thesis. The Research Part of the thesis comprises Chapters 3, 4, and 5. Chapter 3 presents a summary and critical appraisal of the existing evidence on the associations between non-therapeutic factors examined in systematic reviews of cohort studies and the risks of mortality and disease recurrence among individuals with colorectal cancer. Chapter 4 presents the findings of a two-sample Mendelian randomization analysis regarding the associations between a wide range of genetically predicted risk factors and the risk of colorectal cancer-specific mortality among individuals with colorectal cancer. Finally, Chapter 5 summarizes the overall findings and proposes directions for future research in the field.

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LIST OF ABBREVIATIONS

AMSTAR-2	A MesaSurement Tool to Assess systematic Review 2
BMI	Body mass index
CRP	C-reactive protein
CCFR	Colon Cancer Family Registry
CRC	Colorectal cancer
CORECT	ColoRectal Transdisciplinary Study
CI	Confidence interval
CCA	Corrected Covered Area
CWLS	Corrected Weighted Least Squares
DIAGRAM	DIAbetes Genetics Replication And Meta-analysis
EPHPP	Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies
FU	Flouorouracil
GIANT	Genetic Investigation of Anthropometric Traits
GECCO	Genetics and Epidemiology of Colorectal Cancer Consortium
GWAS	Genome-wide association study
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard ratio
HbAIc	Hemoglobin A1c
HDL	High-density lipoprotein
HC	Hip circumference
HIV	Human immunodeficiency virus
INSIDE	INstrument Strength Independent of Direct Effect
IV	Instrumental variable
IGF-1	Insulin-like growth factor-1
IVW	Inverse-variance weighting
IRI	Irinotecan
LD	Linkage disequilibrium
LDL	Low-density lipoprotein
MR	Mendelian Randomization

MR-PRESSO	Mendelian Randomization Pleiotropy Residual Sum and Outlier test
OX	Oxiplatin
PRIOR	Preferred Reporting Items for Overviews of Reviews
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QUIPS	Quality In Prognosis Studies
RCT	Randomized controlled trial
ROB-NObS	Risk Of Bias for Nutrition Observational Studies
ROBINS-E	Risk Of Bias In Non-randomized Studies of Exposures
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
RR	Risk ratio
SHBG	Sex hormone-binding globulin
SIMEX	Simulation Extrapolation
SNP	Single nucleotide polymorphism
SD	Standard deviation
STROBE-MR	Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization
SWiM	Synthesis Without Meta-analysis
WC	Waist circumference
WHR	Waist-hip circumference ratio
WCRF	World Cancer Research Fund
ZEMRA	ZEro Modal Residual Assumption

GENERAL PART

CHAPTER 1

INTRODUCTION

1.1 DEFINITION OF COLORECTAL CANCER

The human gastrointestinal tract is a continuous, coiled passage made up of hollow organs extending from the mouth to the anus. It includes the mouth, esophagus, stomach, small intestine, large intestine, and anus, all connected in a long tubular system. The large intestine (or, large bowel) is the last part of the gastrointestinal tract and consists of the colon, rectum, and anal canal. The colon is further divided into the ascending colon, transverse colon, descending colon, and sigmoid colon. (**Figure 1.1**). The large intestine plays a crucial role in maintaining proper bodily function. Food that has been partly digested in the first compartments of the gastrointestinal tract passes through the cecum and then enters the colon, where water, some nutrients, and electrolytes are absorbed. The remaining waste (feces) passes through the colon and is then stored in the rectum until it is expelled during defecation through the anal canal and anus (3).

Colorectal cancer (CRC) is the term used to describe the abnormal process in which cells of the inner epithelial lining of the colon or rectum undergo a sequence of changes in their number and morphology, which may ultimately lead to the formation of one or multiple growths, also known as tumors. Over time, the tumor can invade blood and lymphatic vessels, increasing the chance of metastatic spread to distant organs (4). Tumor can be classified as in situ (abnormal cells are present in the colon or rectum but have not spread to nearby tissues), localized (limited to the place where it started, with no sign of spread), regional (has spread to nearby lymph nodes, tissues, or organs) or distant (has spread to distant organs). The tumor-node-metastasis system, as defined by the American Joint Committee on Cancer, classifies patients at diagnosis into one of four disease stages (stage I, II, III or IV) based on tumor size, the extent of lymph node involvement, and the presence of distant metastases (5).

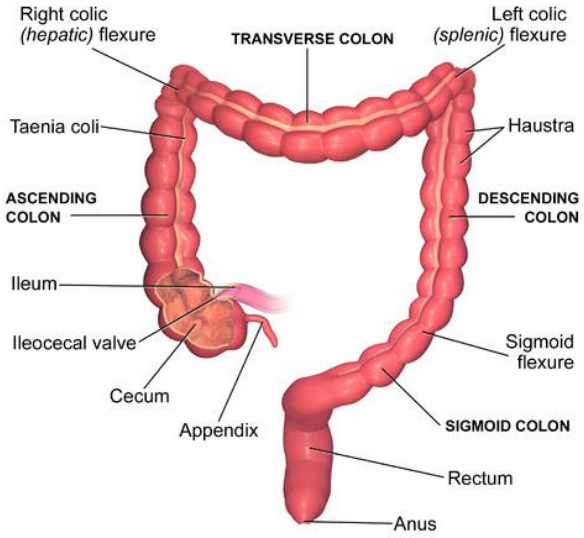

Figure 1.1: Overview of the human large intestine [*adapted from (6)*]

1.2 EPIDEMIOLOGY OF COLORECTAL CANCER

1.2.1 Estimates of global epidemiological burden

CRC is one of the most common and deadliest malignancies among adult populations worldwide, highlighting its importance as a major public health issue. Estimates of the global epidemiological burden produced by the International Agency for Research on Cancer indicate that approximately 1.9 million new cases and about 903,000 deaths were attributable to the disease during 2022, accounting for almost 10% of all cancer cases and deaths (7). These numbers show an increasing trend over time. Up to 2040, the number of new cases and deaths is expected to reach 3.2 million and 1.6 million, respectively (8). Males are more frequently diagnosed compared to females, with the age-standardized rates per 100,00 for colon and rectal cancer being equal to 12.4% and 9.1% for males, and 9.2% and 5.4% for females, respectively (7). Incidence and mortality rates vary across continents as well (**Figure 1.2**). Countries in Europe, North America, as well as New Zealand and Australia, recorded the highest colorectal cancer incidence rates in 2022, whereas countries in South-Central Asia and Africa recorded the lowest. Mortality rates present a slightly different picture, as countries primarily in Central and Eastern Europe recorded the highest numbers of deaths. This geographical variation can partially be attributed to socioeconomic differences across countries,

access to primary and secondary health care, country-specific regulations regarding CRC screening, and differences in the completeness and quality of cancer registry data (7,9).

Despite the high mortality rates, it is estimated that more than 5.7 million people diagnosed within the previous five years were living with the disease in 2022 (10). The 5-year prevalence rates were again higher in economically developed countries in Europe, North America, and Australasia (**Figure 1.3**). In the United States only, the 5-year relative survival rate during 2015-2021 was 65%, reflecting a substantial improvement in life expectancy of people living with the disease, compared with 50% during 1975-1977 (11). Survival depends heavily on the tumor stage at diagnosis, as individuals with localized, regional and distant CRC have 5-year survival rates of 91%, 74% and 15%, respectively, with no substantial differences between colon and rectal cancer (11). The improved survival rates observed over the past 50 years can be attributed to earlier diagnosis of the disease, advances in screening and prevention strategies, the implementation of innovative therapeutic approaches, improvements in supportive care, and, more broadly, a better understanding of the disease and its distinct molecular and clinical subtypes (11).

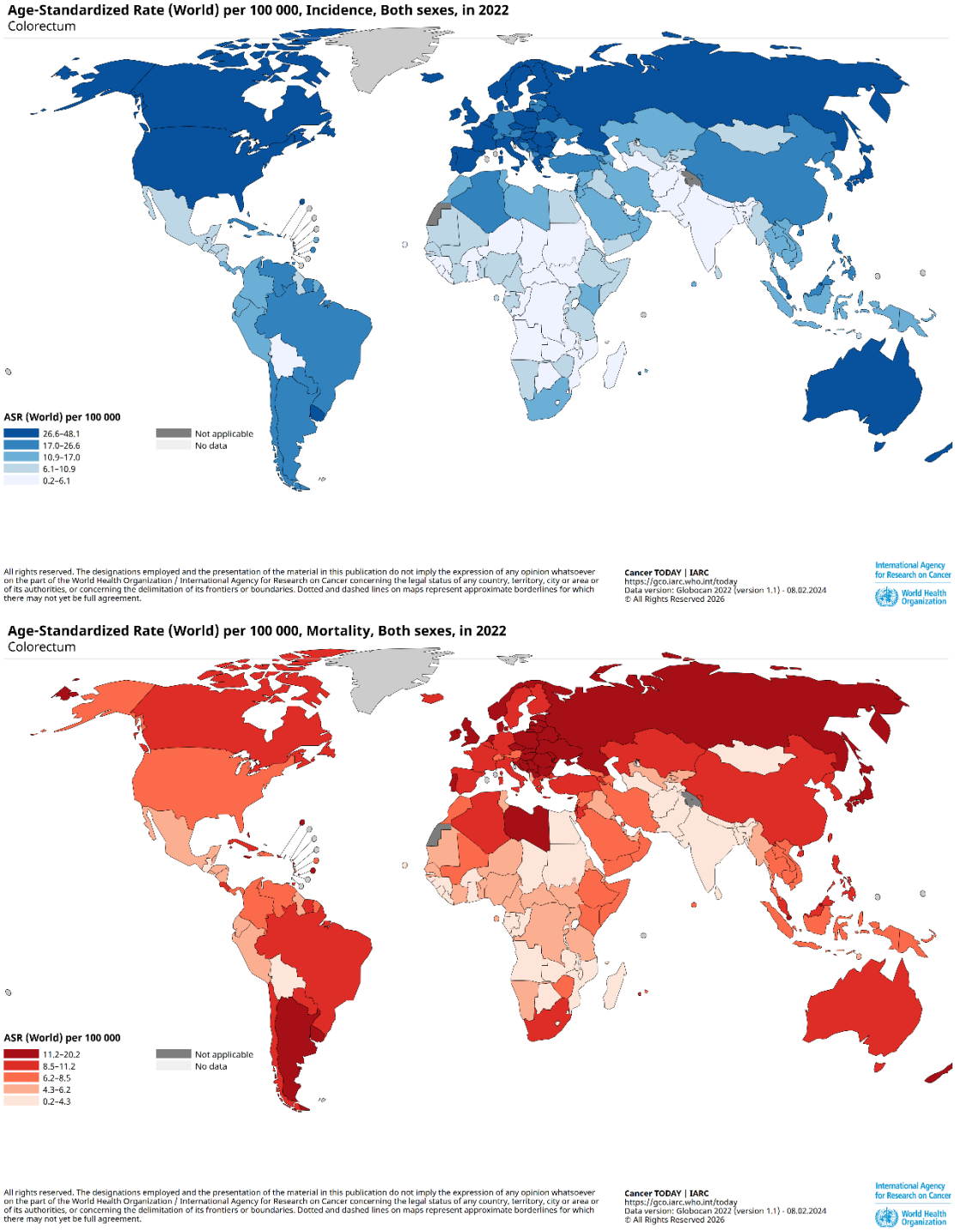

Figure 1.2: Country-specific age-standardized rates per 100,000 of CRC incidence (upper graph) and mortality (lower graph) for both sexes in 2022 [*adapted from (10)*]

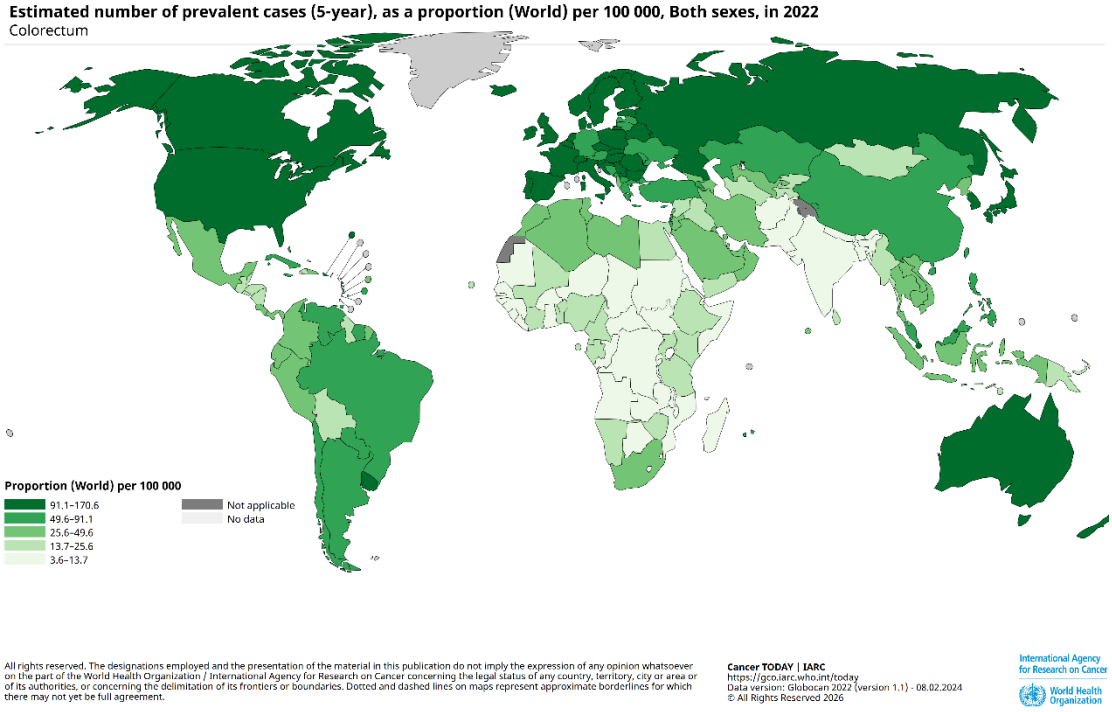

Figure 1.3: Country-specific 5-year prevalence rates (as proportions) of CRC for both sexes in 2022 [*adapted from (12)*]

1.2.2 Risk factors of disease incidence

The risk of carcinogenesis in the colon or rectum is shaped by the action of highly heterogeneous and complex combinations of genetic, pathophysiological, sociodemographic, and lifestyle factors. Colorectal polyps, which are lesions that protrude from the intestinal mucosa, are one of the most well-established precursors of CRC (13). CRC is traditionally considered an age-dependent disease, with a median age at diagnosis of 70 years in males and 72 years in females (14). More recent evidence, however, suggests an alarming increase in incidence among individuals younger than 50 years of age. This is commonly referred to as early-onset CRC and currently makes up almost 10% of all new diagnoses (15). The reasons for this phenomenon are not entirely clear yet. It has been partly attributed to inherited cancer predisposition syndromes that are involved in the development of CRC, such as Lynch syndrome. Specifically, CRC tends to occur at a younger age among individuals with Lynch syndrome than among those with no family history of CRC or any inherited genetic predisposition (45-60 versus 69 years of age) (16). Other factors currently under investigation include exposures during the prenatal or perinatal period, such as the increasing use of assisted reproductive technologies and caesarean delivery, as well as

exposures during or after adolescence, including antibiotic use, gut microbiome and lifestyle (17). Several molecular pathways have also been established in colorectal carcinogenesis, including defective DNA mismatch repair, which leads to microsatellite instability, chromosomal instability, and epigenetic alterations such as the CpG island methylator phenotype. (18). In general, the genetic architecture of CRC has largely been investigated in genome-wide association studies (GWASs) and, up to date, more than 200 independent low-penetrance genetic variants have been identified to be associated with risk of CRC development across populations of various ethnicities (19,20).

The upward trends in incidence and mortality observed over time, especially in Western countries and younger individuals, reflect also changes in population lifestyles. Over the past three decades, the global prevalence of adult obesity [defined as a body mass index (BMI) of 30 kg/m^2 or higher] has increased from 10.2% in 1990 to 20.8% in 2021 among females and from 5.8% to 14.8% among males (21). Studies have demonstrated that the increased rates of obesity and excess body weight are associated with increased rates of CRC incidence in both sexes (22). Higher measurements of other adiposity-related traits, such as body fatness, waist circumference (WC) and waist-hip circumference ratio (WHR) (22–24), as well as height (25), are associated with increased CRC risk as well. Lack of regular physical activity (26,27), alcohol consumption (28) and smoking (29) have shown to have an aggravating effect. A plethora of evidence suggests that several dietary habits increase the risk of CRC, especially high consumption of red and processed meat, and low intake of dairy products, dietary fiber and whole grains (25,30). In fact, in its 2018 report, the World Cancer Research Fund (WCRF) expert panel assessed the quality of the epidemiological evidence linking physical activity, body fatness, alcohol consumption, adult attained height, and several dietary factors (including red and processed meat, whole grains, dietary fiber, dairy products, and calcium supplements) with CRC risk, and concluded that the evidence was strong. Accordingly, the WCRF Cancer Prevention Recommendations emphasize maintaining a healthy body weight, engaging in regular physical activity, and adopting a balanced diet to reduce the risk of developing CRC (25).

Inflammatory bowel disease, including ulcerative colitis and Crohn's disease (31), and diabetes mellitus (32) are additional risk factors of CRC incidence, whereas aspirin use has been associated with a decreased risk of CRC incidence (33). Other factors which have been studied in relation to CRC incidence are insulin-like growth

factor-1 (IGF-1) (34), C-reactive protein (CRP) (35), lipids (36), circulating vitamin D (37), sex hormone-binding globulin (SHBG) and testosterone levels (38) although research is still ongoing regarding their role in CRC incidence.

1.2.3 Risk factors of disease prognosis

The course of CRC following diagnosis is mainly influenced by several pathological and clinical features. Established risk factors for important outcomes, such as all-cause mortality, CRC-specific mortality, and disease recurrence, include advanced stage at diagnosis, poorly differentiated tumor histology, lymphovascular invasion, perineural invasion, bowel obstruction or perforation at presentation, and elevated preoperative plasma levels of carcinoembryonic antigen (39,40). Molecular pathways associated with a less favorable CRC prognosis are mutations or promoter hypermethylation of DNA mismatch repair genes and loss of heterozygosity at chromosome 18q (40).

Undoubtedly, treatment plays a major role in CRC prognosis, and continuous advances in therapeutic strategies over recent years aim not only to improve survival but also other important outcomes, including patients' quality of life. Studies have demonstrated that the use of chemotherapy in patients with metastatic CRC extends survival and improves quality of life in comparison to palliative care alone. For instance, a meta-analysis of 13 randomized controlled trials (RCTs) showed that systemic chemotherapy resulted to an increase in 1-year survival from 34% to 50% whereas median survival increased by 3.7 months (41). Currently, chemotherapy for CRC includes both fluoropyrimidine-based single-agent therapy [5-fluorouracil (5-FU) or capecitabine] and combination regimens incorporating oxaliplatin (OX) and/or irinotecan (IRI). Although several studies have suggested that first-line fluoropyrimidine monotherapy may provide overall survival comparable to that of combination chemotherapy in selected patients, combination regimens, including FOLFOX (5-FU+OX), FOLFIRI (5-FU+IRI), CAPOX/XELOX (capecitabine+OX), and CAPIRI (capecitabine+IRI), remain the standard first-line treatment for most patients (42). Targeted therapies, designed to inhibit key molecular pathways involved in CRC development and progression, are also widely used in clinical practice and remain an active area of research (42). Examples include therapies targeting receptor tyrosine kinases, such as epidermal growth factor receptor and human epidermal growth

factor receptor 2 (43). Other therapeutic approaches include immunotherapy, and surgery or radiotherapy for both colon and rectal cancer (40).

In addition to the aforementioned factors that are directly related to disease characteristics, patients' clinical presentation, and the therapeutic approach, the scientific community has increasingly turned its attention to a broad range of non-therapeutic factors. However, their association with CRC prognosis has not been studied as extensively as with disease incidence, and much of the available evidence remains inconclusive. This impasse is partly attributable to the lack of evidence from RCTs. Specifically, RCTs are considered the gold standard in biomedical research and occupy the highest position in the evidence hierarchy (**Figure 1.4**). They are the main source of evidence for the benefits and safety of newly developed pharmacological or treatment-related interventions among CRC patients, but RCTs of non-therapeutic interventions have methodological and practical challenges. RCTs usually have shorter follow-up periods and smaller sample sizes than population-based observational studies, which may ultimately result in underpowered analyses due to low number of events. Their design is not appropriate or ethical for investigating some non-therapeutic factors, such as smoking initiation/cessation and alcohol consumption. To date, interventions incorporating solely lifestyle components have been highly heterogeneous, making it difficult to calculate the summaries of their relative effect estimates in the context of evidence synthesis. For instance, in a recent systematic review, the authors identified 13 RCTs evaluating dietary and lifestyle interventions for their effects on health-related quality of life and cancer-related fatigue in patients with CRC. The interventions ranged from web-based dietary and nutritional counselling to a variety of supplements, including probiotics, Korean red ginseng, and zinc. The small number of RCTs available for each intervention precluded quantitative synthesis of the findings (44). RCTs usually apply strict inclusion criteria or are conducted in highly controlled clinical settings. Consequently, their findings may not be generalizable to a broader population of CRC patients (45). Along the same lines, cancer patients of older age, those with comorbidities or those of lower socioeconomic status are usually underrepresented in relevant RCTs (45).

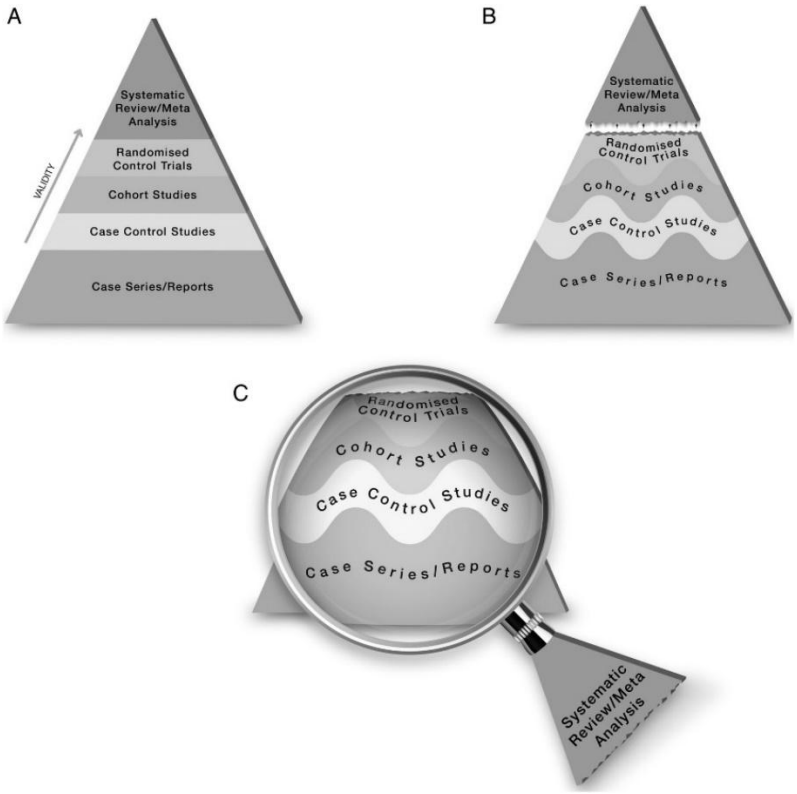

Figure 1.4: The evidence-based medicine pyramid. Transition from the traditional pyramid (A) to an updated format in which lines separating the study designs become wavy and systematic reviews are positioned outside the pyramid (B). Systematic reviews now serve as the lens through which evidence from all study designs is viewed (C) [*adapted from (46)*].

Answering many clinically relevant questions regarding non-therapeutic risk factors and CRC prognosis relies heavily on non-randomized study designs, particularly cohort studies and, less commonly, case-control studies. According to a recent meta-analysis of cohort studies, the association between BMI, assessed after diagnosis, and all-cause mortality, CRC-specific mortality, and CRC recurrence demonstrates a non-linear pattern, specifically a reverse J-shaped association with a nadir at 28 kg/m^2 (47). In simple words, a higher risk of any of those three outcomes, in relation to the nadir, was observed only for the lowest (<22 kg/m^2) and highest values (>34 kg/m^2) of the BMI distribution. The panel of experts responsible for judging the quality of the evidence concluded that no safe conclusion can be made due to concerns of reverse causation, selection bias, confounding, and errors in measuring and classifying the exposure in the underlying studies (47). Another meta-analysis showed that post-diagnosis physical activity protects against worse CRC outcomes, although the evidence was judged again to be limited because of relatively sparse data and methodological and clinical limitations of the included studies (48). Although limited

in number, other factors that have also been studied in relation to CRC outcomes following diagnosis, include aspirin use (49,50), diabetes mellitus and metformin (51), various dietary factors and circulating vitamin D (52), smoking (53) and alcohol consumption (54). Currently, the recommendations from major health organizations, such as the American Association for Cancer Research and WCRF, regarding factors, other than therapy, which may improve survival after diagnosis, are based on limited evidence and are largely aligned with those for cancer prevention. These organizations advise patients to maintain, to the extent feasible, a healthy and balanced lifestyle, including engaging in regular physical activity, following a balanced diet, avoiding smoking, and limiting alcohol consumption, always in conjunction with the treatment plan agreed upon with their treating physician (55,56).

CHAPTER 2

AIMS OF DOCTORAL THESIS

CRC is one of the most common and lethal malignancies among adults, and its prognosis is likely influenced not only by clinical, pathological, and therapeutic features but also by a wide range of non-therapeutic factors. There is a growing need to map the current state of real-world evidence regarding the associations between these factors and key CRC outcomes following diagnosis, specifically mortality and disease recurrence. Such an effort will aid researchers and policymakers in understanding what has been studied and how it has been studied, as well as in identifying gaps in the evidence and potential areas for future research. In addition, more advanced statistical techniques are needed to overcome the limitations commonly encountered in traditional observational study designs, such as confounding and reverse causation. This thesis aimed to fill these gaps by:

1. summarizing the available evidence from published systematic reviews of retrospective and prospective cohort studies which investigated the associations between non-therapeutic risk factors and mortality from any cause or from CRC, and recurrence; identifying evidence gaps; and assessing the methodological quality of the eligible reviews by conducting an overview of systematic reviews (Paper 1).
2. investigating the associations between genetically-predicted levels of a wide range of non-therapeutic risk factors and CRC-specific mortality through a two-sample Mendelian Randomization (MR) study. The risk factors examined spanned multiple domains, including anthropometry, lifestyle, sex hormones, lipids, glucose metabolism, and inflammation. Analyses were conducted for overall CRC as well as by anatomical subsite and tumor stage. A series of sensitivity analyses was also performed to evaluate the underlying MR assumptions and investigate the potential influence of collider bias (Papers 2 and 3).

RESEARCH PART

CHAPTER 3

NON-THERAPEUTIC RISK FACTORS OF MORTALITY AND RECURRENCE FOLLOWING COLORECTAL CANCER DIAGNOSIS: AN OVERVIEW OF REVIEWS

The first aim of this doctoral thesis was to conduct an overview of published systematic reviews of retrospective and prospective cohort studies which investigated the associations between non-therapeutic risk factors and mortality from any cause or from CRC, as well as disease recurrence. An overview of reviews (or, umbrella review) is an evidence synthesis approach in which systematic reviews addressing the same research question are systematically searched for, retrieved, and critically appraised. Their findings can be narratively synthesized or re-analyzed using data from the primary studies included in the reviews (57). A paper including the results of the current chapter is under preparation.

3.1 METHODS

The reporting of the current overview of reviews is in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement (58) and the Cochrane Handbook for Systematic Reviews of Interventions (59). The protocol was registered with the Open Science Framework and is freely available at: https://osf.io/3mdgr/files/hyfb2. The deviations from the protocol are presented in the **Supporting Information** of this thesis.

3.1.1 Inclusion and exclusion criteria

The population of interest comprised adults aged 18 years or older diagnosed with a malignant neoplasm of the colon or rectum (ICD-10 codes C18.0-C18.9, C19, and C20), at stages I-IV. Eligible exposures included anthropometric traits, communicable and non-communicable non-cancerous diseases, demographic characteristics (e.g., socioeconomic status), dietary factors, environmental exposures, hormones, lifestyle

factors (e.g., smoking and physical activity), non-genetic biomarkers measured systemically (i.e., in blood, serum, or urine), pharmacological agents unrelated to CRC treatment (e.g., aspirin), and reproductive factors. Exposure assessment could occur any time before diagnosis, during the peri-diagnostic period, or any time after CRC diagnosis, including before treatment initiation, during treatment, immediately after treatment, or several years following treatment. Treatment could be any recommended treatment option for CRC, such as surgery, radiotherapy, chemotherapy, targeted therapy, or immunotherapy. The outcomes of interest were total mortality, defined as death from any cause, CRC-specific mortality, defined as death due to CRC, and cancer recurrence, defined as local, regional, or distant recurrence of the tumor. Eligible study designs were systematic reviews, with or without meta-analysis, of prospective or retrospective cohort studies. We did not search for additional primary studies that were not included in the systematic reviews. No restrictions were imposed on the duration of follow-up of the included primary studies or language of publication.

On the other hand, studies of individuals younger than 18 years, healthy individuals, adults diagnosed with benign tumors or pre-malignant conditions (e.g., colorectal polyps), or adults diagnosed with malignancies other than CRC were excluded. Studies assessing pharmacological or therapeutic agents or procedures specifically designed to treat CRC, manage CRC-related symptoms, or address adverse events associated with CRC treatment were also excluded. When the purpose of a pharmacological agent was not evident from the review, its classification was confirmed using the KEGG DRUG Database (60). Studies assessing pathological characteristics of CRC, such as histological type and degree of differentiation, as well as gene mutations and other genetic alterations, as exposures were excluded. Biomarkers measured in healthy or cancerous tissues were not considered eligible. Meta-analyses of non-genetic biomarkers measured both systemically and in tissue that did not provide separate estimates for each subgroup were not considered eligible. Studies assessing outcomes unrelated to mortality or cancer recurrence, including quality of life and the incidence of second primary cancers, were excluded. Regarding study design, literature reviews and systematic reviews of cross-sectional, case-control, genetic, or interventional studies, including RCTs, were excluded. Letters to the editor, case reports, comments, editorials, conference proceedings, and unpublished reports were also excluded. Network meta-analyses were excluded, as these were expected to primarily include interventional studies.

3.1.2 Search strategy

We applied a comprehensive search strategy using the bibliographic databases PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.elsevier.com/products/embase), Scopus (https://www.elsevier.com/products/scopus) and Epistemonikos (https://www.epistemonikos.org/) from inception to November 30th, 2025. The search algorithm for each database is provided in the **Supporting Information** of this thesis (**Tables S3.1-S3.4)**. The reference lists of all selected systematic reviews were searched manually for additional reports which were potentially not identified during the database searching.

3.1.3 Selection process

Following the search, all retrieved publications were imported into Rayyan (https://www.rayyan.ai/) to identify and manage duplicate records. After de-duplication, three reviewers worked in pairs to independently screen all titles and abstracts, ensuring that each report was assessed by two reviewers using a screening form based on the eligibility criteria. Any disagreements were resolved through discussion with a fourth reviewer. Full texts of all potentially eligible records that passed the title/abstract screening stage were assessed for inclusion by two independent reviewers. Reasons for exclusion were documented and presented in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) study flow diagram (61).

When overlapping reviews of the same exposure-outcome association were identified, all relevant publications were initially included. To manage overlap among systematic reviews, we constructed a citation matrix presenting all included reviews per exposure and their primary studies (62). We then calculated the corrected covered area (CCA) as shown in the formula below, which quantifies the degree of overlap across eligible systematic reviews (62):

$$CCA = \frac{N-r}{r \cdot c-r} \quad (1)$$

N is the total number of primary studies across the systematic reviews, r is the number of unique primary studies, and c is the number of systematic reviews. Pairwise

CCA and overall exposure-specific CCA were calculated (62), while heatmaps were used to visualize the degree of overlap across reviews (63). Because CCA is not influenced by the size of individual reviews, it is expected to reflect the true extent of overlap. If high or very high overlap is detected, defined as a CCA of 10% or greater (62), we retained the review that included the largest number of studies and the most recent, if possible.

3.1.4 Data extraction

From each eligible systematic review, we extracted the following items:

- Name of the first author, year of publication, date last assessed as up-to-date, and study designs included
- Number of included studies and the number quantitatively synthesized, if applicable
- Whether a protocol was registered, databases searched, date ranges of the searches, date of the most recent search update, and whether study selection, data collection, and risk of bias/quality assessment were performed and reported by two independent reviewers
- Population characteristics: age, sex, anatomical site and stage of the tumor, and treatments received
- Exposure details: name, type (e.g., categorical or continuous), comparator, and time frame of exposure assessment (e.g., pre-, peri- or post-CRC diagnosis)
- Outcome details: outcome name, sample size and number of cases
- Risk of bias tool used and authors' risk of bias assessments of the primary studies
- Whether any framework for assessing the quality of evidence was applied, e.g., Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

From each eligible systematic review that included at least one relevant meta-analysis, we extracted where possible:

- The type of meta-analytic model used (i.e., common-effects or random-effects) and the rationale for its selection

- The summary estimate, its 95% confidence interval (CI), and the method used to calculate the CI (e.g., Wald-type, Hartung-Knapp-Sidik-Jonkman).
- To ensure the methodological rigor of the included evidence, we extracted only summary effect estimates based on study-specific estimates adjusted for potential confounders. We also extracted the covariates included in the adjustment models.
- The estimate of between-study variance and the method used to compute it, if a random-effects model was applied
- Statistical measures of between-study heterogeneity (e.g., I^2, Q-statistic, and associated p-value)
- Prediction intervals
- Any reported effect modifiers, subgroup or meta-regression estimates with their 95% CIs, the statistical test for interaction for subgroup analyses, and measures of heterogeneity within subgroups
- Statistical measures used to assess small-study effects

From each eligible systematic review that did not include a meta-analysis, we additionally extracted, where possible:

- The authors' rationale for not conducting quantitative synthesis
- The method used to present the results of primary studies [e.g., narrative synthesis following the Synthesis Without Meta-analysis (SWiM) guidelines (64)]
- Authors' concluding remarks, including the ranges of study-specific estimates along with their 95% CIs. We again extracted only the relevant study-specific adjusted effect estimates.

All associations of interest reported in each publication (i.e., one exposure with multiple outcomes or multiple exposures with a specific outcome) were extracted. If we encountered reviews that included both eligible and ineligible participants, for instance reviews including multiple cancer sites, we extracted data for the eligible subpopulations only. If relevant information was not available in the published report, we extracted it from the primary studies when possible. However, we relied solely on the methods and analyses reported in the included systematic reviews. Consequently, we did not re-analyze outcome data available only in the primary studies or assess the risk of bias or certainty of the evidence when these had not been evaluated by the review

authors. Data was independently extracted in Microsoft Office Excel ® by two reviewers from a sample of eligible studies (10%). Any disagreements in the data from this sample of eligible studies were resolved through discussions with a third reviewer until consensus was reached. When agreement was achieved, the remaining studies were extracted by a single reviewer.

3.1.5 Assessment of methodological quality

The methodological quality of the eligible systematic reviews was evaluated using AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) tool, which includes 16 items focused on key methodological issues (65): protocol registered before start of review, adequacy of literature search, justification for excluded studies, risk of bias for included studies, appropriateness of meta-analytic methods, consideration of risk of bias when interpreting results. and assessing presence and likely impact of publication bias. The overall confidence in the results of each review was rated as high, moderate, low, or critically low. An analytical plan detailing how each item was assessed can be found in the **Supporting Information** of this thesis (**Table S3.6**). The assessment was completed independently by two reviewers in a sample of eligible studies (10%). Any disagreements in the assessment of this sample of eligible studies were resolved through discussions with a third reviewer until consensus was reached. When agreement was achieved, the remaining studies were assessed by a single reviewer.

3.1.6 Data analysis

We narratively described the key characteristics of eligible systematic reviews, including population, exposures, outcomes, quality assessment, and major conclusions. This information was presented in text, tables and graphs using R packages ccaR (62), amstar2vis (66), and ggplot2 (67) (version 4.5.1).

3.2 RESULTS

3.2.1 Search results

A study flow diagram of the selection process is presented in **Figure 3.1**. Following the initial database search and de-duplication of the records, 16,974 reports were screened based on their titles and/or abstracts. In total, 1,004 reports were considered eligible for full-text screening. After excluding 18 reports for which the full text could not be retrieved, 986 reports underwent full-text assessment. Ultimately, 825 reports were

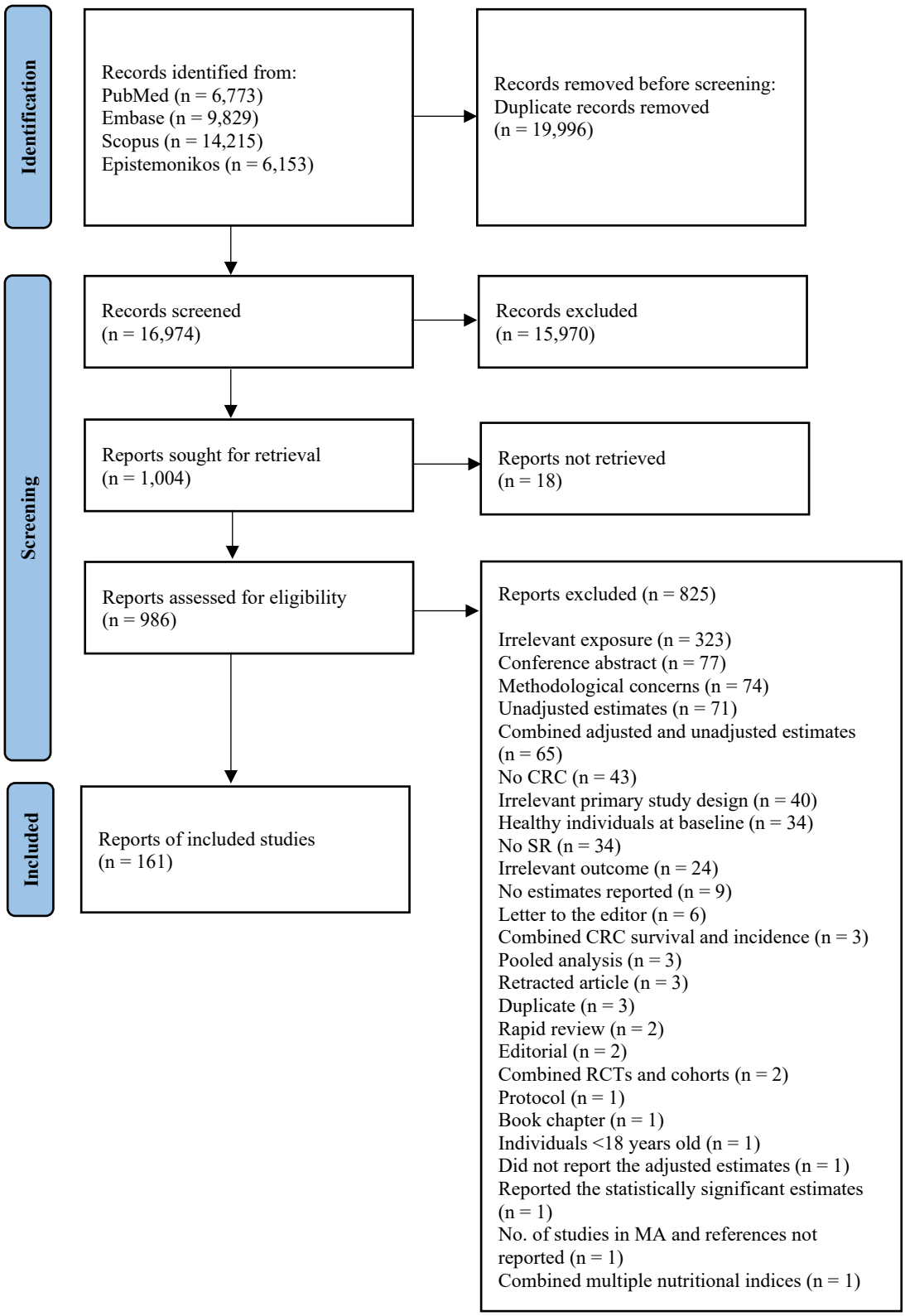

Figure 3.1: PRISMA study flow diagram for the selection of the systematic reviews investigating the association between non-therapeutic risk factors and colorectal cancer prognosis. *Abbreviations: PRISMA; Preferred Reporting Items for Systematic reviews and Meta-Analyses*

excluded. The most common reasons for exclusion were the irrelevance of the exposure (39.2%), publication as a conference abstract (9.3%), and methodological concerns regarding the identified systematic reviews (8.9%), primarily related to the potential for double counting in the meta-analyses. A complete list of the references that could not be retrieved and the excluded studies, together with the reasons for their exclusion, can be found at the following link: https://osf.io/3mdgr/files/cdu4j.

In total, 161 unique reports were considered eligible (48,49,52,54,68–225), one of which was a report summarizing the quality assessments for the exposures investigated in three independent reviews conducted by the same research team (74). We did not identify any additional relevant systematic reviews from the reference lists of the included reports that had not already been identified through the database search.

3.2.2 Characteristics of included reviews

The identified systematic reviews investigated 55 unique exposures, which can be grouped in eight broad categories, namely adiposity-related measures [BMI (n=7), subcutaneous adiposity (n=1), WC (n=2), WHR (n=1), and weight change (n=3)], comorbidities and viruses [anemia (n=1), cachexia (n=3), comorbidity (n=2), dementia (n=1), depression and anxiety (n=1), diabetes (n=5), frailty (n=3), human immunodeficiency virus (HIV) (n=1), metabolic syndrome (n=2), myosteatosis (n=1), osteopenia (n=1), sarcopenia (n=7), thrombocytosis (n=1)], drugs [aspirin (n=8), bisphosphonates (n=1), hormone replacement therapy (n=1), metformin (n=8), statins (n=7)], inflammatory biomarkers and indices [advanced cancer inflammation index (n=3), albumin to globulin ratio (n=2), controlling nutritional status (n=2), CRP (n=2), CRP to albumin ratio (n=4), fibrinogen (n=4), fibrinogen to albumin ratio (n=2), lactate dehydrogenase to albumin ratio (n=1), lymphocyte to monocyte ratio (n=6), modified Glasgow prognostic score (n=1), neutrophil to lymphocyte ratio (n=7), pan-immune inflammation index (n=1), peripheral monocyte counts (n=1), plasma d-dimer (n=3), platelet to lymphocyte ratio (n=9), prognostic nutritional index (n=2), serum albumin (n=1), systemic immune inflammation index (n=1)], lifestyle, diet and nutrition [alcohol consumption, various dietary factors and supplement intake (n=13), circulating vitamin D (n=10), geriatric nutritional index (n=5), global leadership initiative on malnutrition (n=1), physical activity (n=13), sedentary behavior (n=3), sleep (n=2), smoking (n=4)], quality of life measures (n=3), socioeconomic factors (n=2) and other

biomarkers [apolipoprotein A-1 (n=1), serum carbohydrate antigen 19-9 (n=1), serum/plasma markers of dietary phytoestrogen intake (n=1), serum/plasma tissue inhibitor of metalloproteinase-1 (n=1)] (**Figure 3.2**).

Thirty three out of the 55 unique exposures were studied in more than one systematic review. For these reviews, the CCA index ranged from 0% (e.g., for comorbidity), indicating no overlap, to 75% (e.g., for the advanced lung cancer inflammation index), indicating very high overlap (**Figure 3.2**). Overall, systematic reviews of 25 different exposures had a CCA above 10%. Therefore, we retained the systematic review that included the largest number of studies and, where possible, it was the most recent. For an additional eight exposures, namely comorbidity, CRP, neutrophil to lymphocyte ratio, patient reported outcomes, platelet to lymphocyte ratio, sarcopenia, socioeconomic factors, and WC, the systematic reviews had CCA values below 10%. In such cases, after inspecting the citation matrices and pairwise CCA values, we retained the reviews with the lowest degree of overlap. After including the exposures for which only one systematic review was identified, this process resulted in a final set of 65 systematic reviews published between 2010 and 2025 (47,48,52,54,71,72,77,78,80,85–87,94,95,99,102,113–116,119,121,122,127,128,133,135,136,140–143,147–151,159,163,165,166,168–170,173,174,186,189,190,193,197–199,201–203,206,207,209,216,217,220,222,223,225). The heatmaps in **Figures S3.1-S3.33** and **Table S3.5** in the **Supporting Information** of this thesis present the degrees of overlap between pairs of systematic reviews examining the same exposure and the rationale for selecting the systematic review for each exposure, respectively. Among the 65 systematic reviews, 55 (84.6%) (54,71,72,77,78,85–87,94,95,99,102,114–116,119,122,127,128,133,135,136,140–143,147,149–151,159,163,165,166,168–170,173,174,186,189,190,193,197,198,201–203,207,209,216,217,220,222,223) performed a meta-analysis, 7 (10.8%) (80,97,113,121,148,199,206) reported their findings narratively, and 3 (4.6%) (48,52,68) used both approaches. A clean version of the data extraction from the final included systematic reviews can be found at the following link: https://osf.io/3mdgr/files/q4t3f.

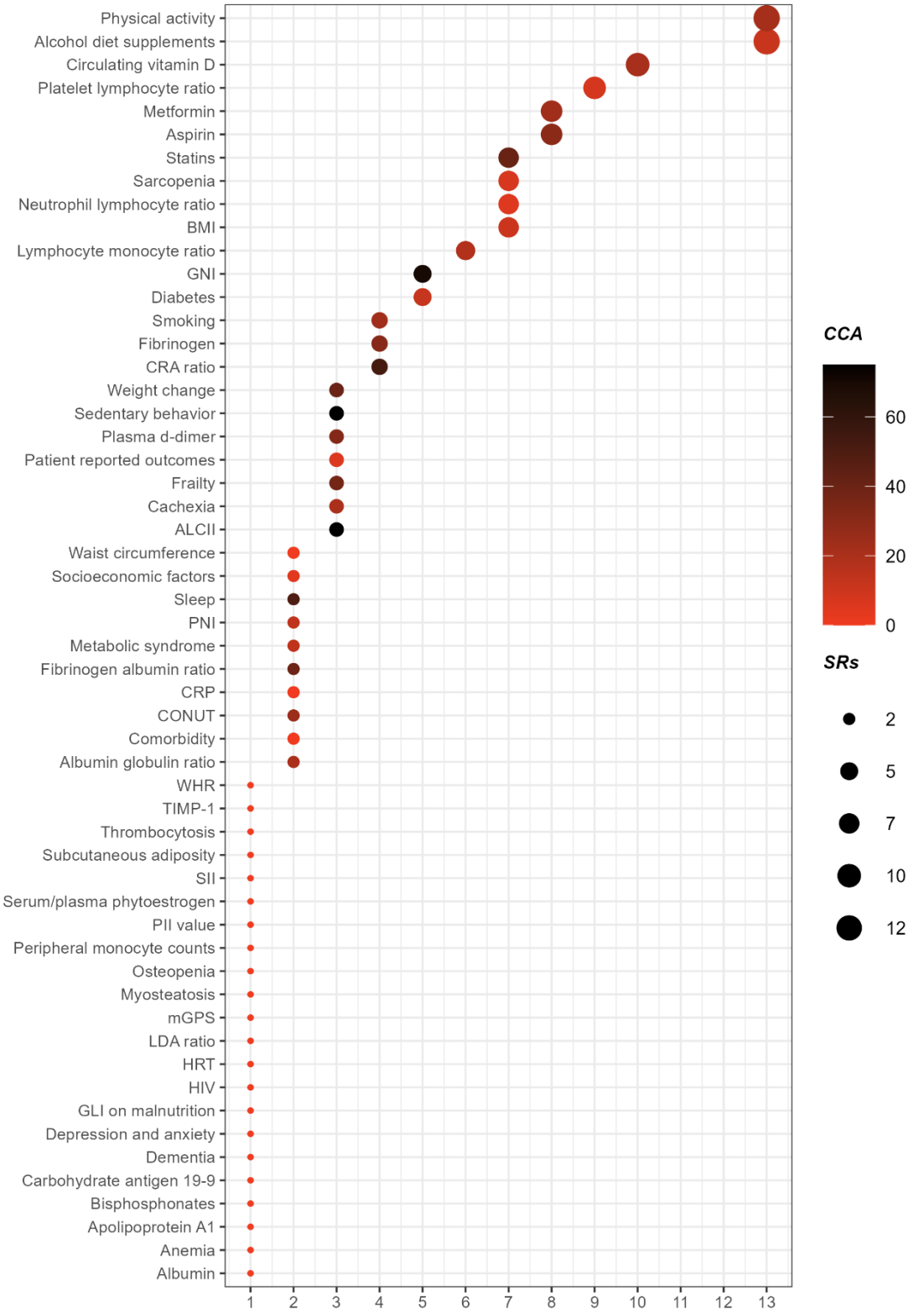

Figure 3.2: Scatterplot depicting the number of systematic reviews (SRs) identified for each of the 54 unique exposures. The size of each bubble indicates the number of reviews, while its color indicates the magnitude of the Corrected Covered Area (CCA) index, with darker colors indicating greater overlap. *Abbreviations: ALCII; advanced lung cancer inflammation index, BMI; body mass index, CONUT; controlling nutritional status, CRA; C-reactive protein to albumin, CRP; C-reactive protein, GNI; geriatric nutritional index, HIV; human immunodeficiency virus, HRT; hormone replacement therapy, LDA: lactate dehydrogenase to albumin, mGPS; modified Glasgow prognostic score, PII; pan-immune-inflammation index, PNI; prognostic nutritional index, SII; systemic immune-inflammation index, TIMP-1; tissue inhibitor of metalloproteinase-1, WHR; waist-hip circumference ratio*

Overall, we recorded 538 main associations. Most of the associations were reported for total CRC (504, 93.7%). Following authors' reporting, the most studied outcomes were all-cause mortality (192, 35.7%), overall survival (63, 11.7%) and CRC-specific mortality (63, 11.7%). We also recorded other outcomes related to mortality from other causes, and disease recurrence. We observed heterogeneity in terminology and definitions used by the included systematic reviews, particularly for recurrence outcomes (**Table 3.1**). Information on the timing of exposure assessment was available for 463 (86.1%) associations. Specifically, 126 (27.2%) about pre-diagnostic, 13 (2.8%) about pre- or peri-diagnostic, 6 (1.3%) about pre- to post-diagnostic, and 263 (56.8%) associations were about post-diagnostic exposures. The rest of the exposures were measured in relation to cancer treatment: 30 (6.5%) about pre-treatment, 4 (0.9%) about during/after treatment, 18 (3.9%) about pre-operative, and 3 (0.6%) about post-operative. An additional 81 associations were reported as part of subgroup analyses conducted by the review authors, and focused on participants of specific CRC sites and stages, or using alternative definitions of the exposures.

Table 3.1: Absolute and relative frequencies of the outcome terms used in the main associations identified across the 65 systematic reviews

All-cause mortality	192 (35.7)
Cancer-specific mortality	5 (0.9)
Cancer-specific survival	12 (2.2)
Cancer recurrence	8 (1.5)
Cardiovascular disease mortality	7 (1.3)
Cardiovascular-specific mortality	5 (0.9)
CRC-specific mortality	63 (11.7)
CRC-specific survival	1 (0.2)
CRC mortality	54 (10)
CRC recurrence/disease-free survival	5 (0.9)
CRC recurrence	3 (0.6)
CRC survival	6 (1.1)
Deaths not related to CRC or cardiovascular disease	2 (0.4)
Disease-free survival	51 (9.5)
Disease-free survival/recurrence	2 (0.4)
Disease-free survival/progression-free survival	1 (0.2)
Disease-specific survival	1 (0.2)
Non-CRC mortality	8 (1.5)
Other causes of death	5 (0.9)
Overall mortality	1 (0.2)
Overall survival	63 (11.7)

Progression-free survival	16 (3)
Recurrence	4 (0.7)
Recurrence/disease-free survival	2 (0.4)
Recurrence-free survival	21 (3.9)
Total	**538 (100)**

Abbreviations: CRC; colorectal cancer

Systematic reviews that conducted a meta-analysis reported 315 (58.6%) associations, with a median number of three estimates per association (minimum-maximum: 1-65). For meta-analyses with at least two estimates, the primary analytical approach was the random-effects model (178, 56.5%), but for 13 (7.3%) associations, the meta-analytic model used could not be determined at all. In general, we observed substantial underreporting of statistical methods. In 15 (4.8%) associations, neither the I^2 statistic nor the Q-statistic were reported. The estimator of the between-study variance was reported for only 75 of the 178 associations. None of the systematic reviews reported the method used to calculate the 95% CI of the meta-analytic summary estimate. Only three systematic reviews reported the calculation of prediction intervals.

For 223 (41.4%) associations, a meta-analysis was not conducted. Each association was informed by a median of one effect estimate (minimum-maximum: 1-14). The reasons reported for not conducting a meta-analysis were either the small number of studies available for each comparison or the substantial heterogeneity across the included studies. None of these reviews reported adhering to specific guidelines for the reporting of their methods and narrative synthesis of their results, such as the SWiM guidelines (64). Although, we must acknowledge that the specific set of guidelines was published in 2020.

Finally, only six of the 65 systematic reviews assessed the certainty of the evidence. Of these, three used the GRADE approach, while the remaining three applied the criteria developed by the independent Expert Panel of the WCRF.

3.2.3 Methodological quality of included reviews

According to the AMSTAR-2 checklist, only three systematic reviews were rated as being of moderate quality, whereas the remaining reviews were rated as critically low. Percentages for each rating by AMSTAR-2 item are presented in **Figure 3.3**, and the

detailed assessment for each review can be found at the following link: https://osf.io/3mdgr/files/8k63d.

More than half of the reviews lacked a publicly accessible pre-registered protocol (36, 55.4%). In only 11 (7%) systematic reviews, the authors searched at least two electronic databases, provided their complete search algorithms and justified any restrictions, for example, publication language or sample size of the included cohorts. In 57 (87.7%) systematic reviews, the authors did not provide a list of studies excluded after full-text screening, together with the reason for exclusion. In 16 (24.6%) reviews, the authors provided insufficient details about whether study screening and data extraction were performed in duplicate and how discrepancies were resolved. An additional issue was that authors of 34 (52.3%) reviews did not report the detailed adjustment factors per study.

The majority of systematic reviews (45, 69.2%) used the Newcastle-Ottawa scale for assessing risk of bias in the primary studies (226), which can only partially address confounding and selection bias. Review authors used various thresholds to define low risk of bias in the primary studies (e.g., >6, >7, or >9), and almost all concluded that the primary studies were generally at low risk of bias. Other tools used were the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies (EPHPP) tool (227) (1 review, 1.5%), the QUality In Prognosis Studies (QUIPS) tool (228) (5 reviews, 7.7%), the Risk of Bias in Non-Randomized Studies of Exposures (ROBINS-E) tool (229) (1 review, 1.5%), and the Risk of Bias for Nutrition Observational Studies (ROB-NObS) tool, which is a modified version of the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (230) (3 reviews, 4.6%). One review (1.5%) used criteria developed by the review team, while nine reviews (13.8%) did not perform a risk of bias assessment.

Additional methodological issues were identified in the use of statistical methods. Specifically, 36 reviews (55.4%) used a common-effects model without providing a rationale, used unadjusted effect estimates without justification, or based their choice of meta-analytic model solely on statistical measures, such as the I^2 statistic. Forty-four (67.7%) and 29 (44.6%) reviews did not comment sufficiently on inherent limitations of cohort studies, particularly residual confounding and selection bias, and publication bias, respectively. Finally, none of the included reviews explained the rationale for including retrospective and/or prospective cohort studies or extracted

information on the funding sources of the primary studies, although we acknowledge that both practices are extremely rare in systematic reviews of cohort studies.

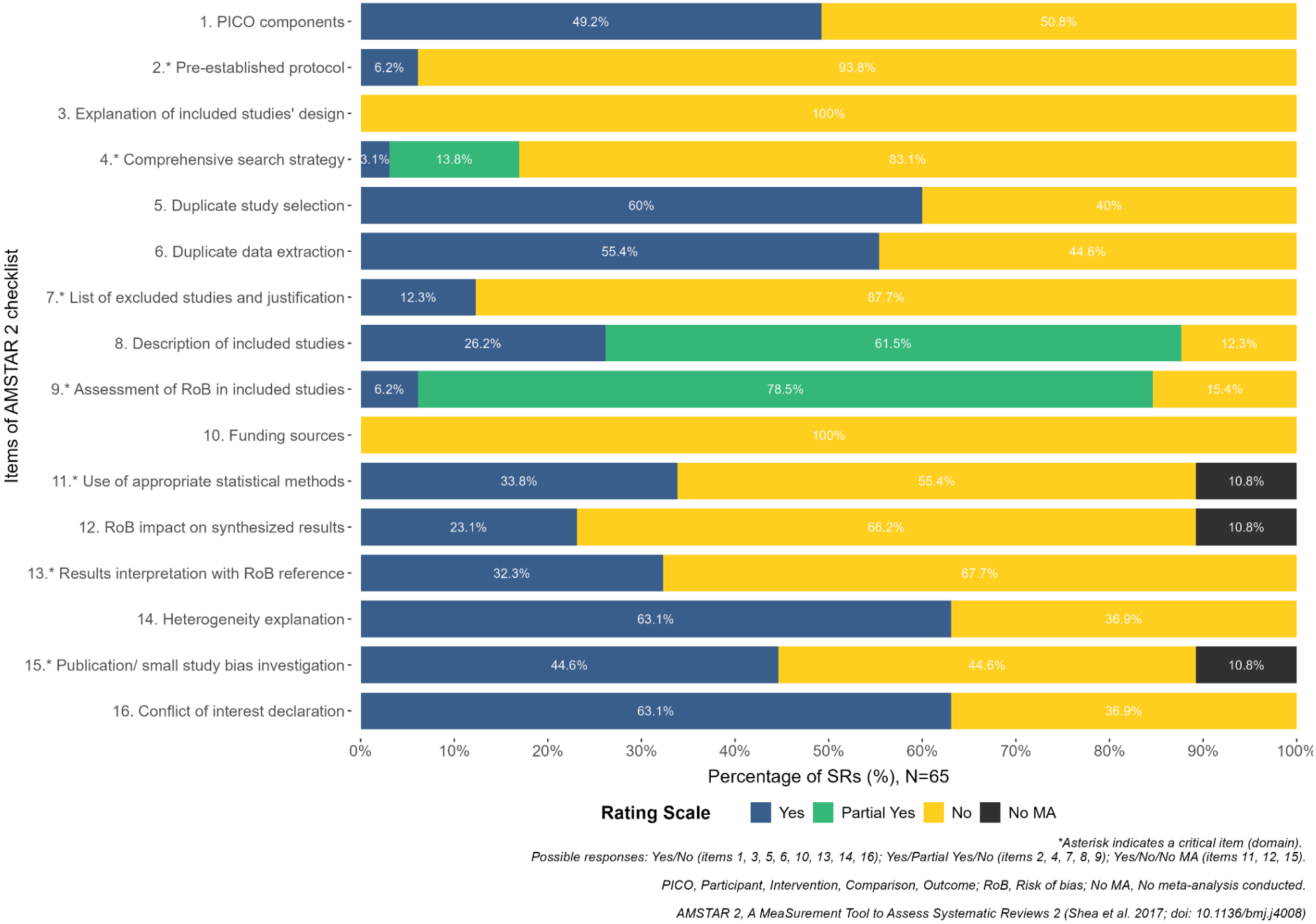

Figure 3.3: Percentages of ratings by AMSTAR-2 item across the 65 included systematic reviews

3.2.4 Findings on all-cause mortality

In the following sections, we present the results of the included systematic reviews according to the timeframe of exposure assessment. The outcome is overall survival, overall mortality or all-cause mortality. We use the term 'all-cause mortality' throughout to avoid ambiguity and ensure consistency in the presentation of the results.

3.2.4.1. Pre- and peri-diagnostic risk factors

The reported associations focused on adiposity, comorbidities, diet/nutrition, drugs and lifestyle. A single review reported all associations between various diet and nutrition-related factors, measured before diagnosis, and all-cause mortality. Each association included a small number of estimates (range: 1-3). The meta-analytic estimates ranged from 0.2 for saturated fatty acids [high vs low, number of estimates (n): 1, risk ratio (RR): 0.2, 95% CI: 0.08-0.49)] to 1.67 for folic acid (high vs low, n: 1, RR: 1.67, 95% CI: 0.74-3.78). Both lower [underweight vs normal, n: 9, hazard ratio (HR): 1.36, 95% CI: 1.21-1.52, I^2: not reported] as well as higher levels of BMI (obese vs normal, n: 15, HR: 1.14, 95% CI: 1.08-1.2, I^2: not reported) were associated with increased mortality from any cause. The association with overweight was null. CRC patients with diabetes had a higher risk from dying from any cause (diabetes vs no diabetes, n: not reported, random-effects RR: 1.21, 95% CI: 1.18-1.25, I^2: 76%) (127). Statin use decreased all-cause mortality risk (use vs no use, n: 3, random-effects HR: 0.85, 95% CI: 0.79-0.92, I^2: 5.7%). A review on pre-diagnostic alcohol consumption indicated that light (light vs no consumption, n: 8, random-effects RR: 0.87, 95% CI: 0.81-0.94, I^2: 3.8%) and moderate (moderate vs no consumption, n: 9, random-effects RR: 0.92, 95% CI: 0.85-1, I^2: 0%), but not heavy alcohol consumption (heavy vs no consumption, n: 4, random-effects RR: 0.95, 95% CI: 0.77-1.18, I^2: 50.5%), were associated with lower all-cause mortality risk (54). The latter review reported also a non-linear association between pre-diagnostic alcohol consumption and all-cause mortality. Results did not change materially by type of alcohol, except from moderate liquor consumption which was associated with increased all-cause mortality (moderate vs no consumption, n: 4, random-effects RR: 1.15, 95% CI: 1-1.32, I^2: not reported).

Regarding the results from reviews that did not perform a meta-analysis, colon cancer patients with dementia (dementia vs no dementia, n: 1, HR: 1.41, 95% CI: 1.34-

1.48) and CRC patients with higher WC (high vs low, n: 1, HR: 1.41, 95% CI: 1.12-1.77) and WHR measurements (high vs low, n: 1, HR: 1.34, 95% CI: 1.06-1.69) had a higher risk of all-cause mortality. Pre-diagnostic plasma enterolactone was not associated with all-cause mortality.

3.2.4.2. Post-diagnostic risk factors

The reported associations focused on adiposity, diet/nutrition, drugs and lifestyle. The three reviews that scored higher at the AMSTAR-2 assessments investigated post-diagnosis adiposity, physical activity and diet/nutrition. Specifically, a systematic review reported all associations between various diet and nutrition-related factors and all-cause mortality, although only results for 21 dietary factors were quantitatively synthesized. These meta-analytic estimates ranged between 0.56 for nuts and peanuts (per 0.5 servings/day, n: 3, random-effects RR: 0.56, 95% CI: 0.27-1.17, I^2: 89%) and 1.45 for dietary glycemic load (per 50 units/day, n: 3, random-effects RR: 1.45, 95% CI: 0.96-2.2, I^2: 83%). Interestingly again, alcohol consumption was associated a lower risk of all-cause mortality (per 10 g/day, n: 7, random-effects RR: 0.95, 95% CI: 0.91-1, I^2: 0%). The role of BMI was non-linearly associated with all-cause mortality. Specifically, the non-linear meta-analysis indicated a reverse J-shaped association between BMI and all-cause mortality (nadir at BMI 28 kg/m^2). The highest risk, relative to the nadir, was observed at both ends of the BMI distribution (18 and 38 kg/m^2), namely 60% and 23% higher risk for all-cause mortality. Total and recreational physical activity were associated with lower all-cause mortality, regardless of their volume and intensity, or the CRC site analyzed. On the same note, sedentary behavior, defined as the time spent sitting while watching TV/day, was associated with an increased risk of all-cause mortality (per 2 hours/day, n:3, random-effects RR: 1.13, 95% CI: 1.02-1.26, I^2: 0%). Similarly to pre-diagnosis, post-diagnostic statin use was associated with a lower risk of all-cause mortality (use vs no use, n: 9, random-effects HR: 0.86, 95% CI: 0.76-0.96, I^2: 75.3%). Finally, sleep, either lower or higher than 7-8 hour/day, was associated with an increased risk of all-cause mortality, but the 95% CIs of the corresponding estimates crossed the null value and were based only on two studies.

3.2.4.3. Pre-treatment risk factors

When the timeframe of exposure measurement was defined relative to CRC treatment, the systematic reviews investigated mainly inflammation. Specifically, the increased levels of several inflammatory biomarkers increased the risk for all-cause mortality and the meta-analytic estimates ranged from 1.28 for platelet to lymphocyte ratio (high vs low, n: 15, random-effects HR: 1.28, 95% CI: 1.03-1.59, I^2: 61.2%) (189) to 2.14 for plasma d-dimer (high vs low, n: 11, common-effects HR: 2.14, 95% CI: 1.91-2.39, I^2: 0%). On the other hand, higher lymphocyte to monocyte ratio measurements (high vs low, n: 14, random-effects HR: 0.55, 95% CI: 0.49-0.62, I^2: 37%) decreased the risk of all-cause mortality. Additional associations concerned thrombocytosis (low vs high platelet count, n: 5, common-effects HR: 2.2, 95% CI: 1.64-2.95, I^2: 28%), apolipoprotein A1 (low vs high, n: not reported, HR: 0.48, 95% CI: 0.19-0.76) (198) and serum carbohydrate antigen 19-9 (high vs low, n: 11, common-effects HR: 1.58, 95% CI: 1.3-1.93, I^2: 43.3%). Results for serum albumin were also summarized descriptively, with substantial heterogeneity across the study-specific estimates though.

3.2.4.4. Pre-operative risk factors

When the timeframe was defined according to surgery specifically, the associations concerned again inflammation and certain comorbidities. Anaemia (anaemia vs no anaemia, n: 6, common-effects HR: 1.56, 95% CI: 1.31-1.92, I^2: 86%), osteopenia (osteopenia vs no osteopenia, n: 1, HR: 5.1, 95% CI: 2.72-9.56), and sarcopenia (sarcopenia vs no sarcopenia, n: 14, random-effects HR: 1.4, 95% CI: 1.25-1.58, I^2: 54.3%) increased the risk of all-cause mortality among CRC patients. Results did not change when analyses were conducted only among colon and rectal cancer patients, CRC patients with liver metastasis, and CRC patients without distant metastasis for each one of the conditions respectively. Regarding inflammation, increased measurements of neutrophil to lymphocyte ratio (high vs low, n: 11, random-effects HR: 1.66, 95% CI: 1.36-2.02, I^2: 56.3%), platelet to lymphocyte ratio (high vs low, n: 12, common-effects HR: 1.32, 95% CI: 1.17-1.48, I^2: 41%) and systemic immune-inflammation index (high vs low, n: 3, common-effects HR: 3, 95% CI: 2.51-3.58, I^2: 32.4%) were associated with increased all-cause mortality risk.

3.2.4.5. Post-operative risk factors

Regarding post-operative exposures, only one systematic review reported the aggravating role of sarcopenia on all-cause mortality (sarcopenia vs sarcopenia, n: 6, common-effects HR: 1.76, 95% CI: 1.47-2.1, I^2: 0%). An additional systematic review descriptively summarised the effects of weight gain and weight loss on all-cause mortality, defining the timeframe as 'during/after treatment'. However, there was substantial variability across the study-specific effect estimates.

3.2.4.6. Risk factors with unknown or mixed timeframe of measurement

For the remaining associations, the timeframe of exposure assessment was not reported in the corresponding systematic reviews. This was either because it was not evident in the primary studies or because the review authors combined different timeframes. The studied factors covered all eight categories and were specifically about myosteatosis, subcutaneous adiposity, cachexia, HIV, comorbidity (using the Charlson Comorbidity Index), anxiety, depression, sarcopenia, the geriatric nutritional index, the global leadership initiative on malnutrition, bisphosphonates, hormone replacement therapy, metformin, advanced lung cancer inflammation index, CRP, fibrinogen to albumin ratio, lymphocyte to monocyte ratio, neutrophil to lymphocyte ratio, pan-immune inflammation index, peripheral absolute monocyte count, platelet to lymphocyte ratio, smoking, serum/plasma tissue inhibitor of metalloproteinase-1, quality of life (using the functioning scales of the EORTC QLQ-C30 questionnaire) and socioeconomic factors. In addition to the different CRC sites and stages that were commonly combined, unknown or mixed timeframes of exposure assessment introduced further heterogeneity, thereby limiting the interpretation of these findings.

3.2.5 Findings on colorectal cancer mortality

In the following sections, the outcome of interest is CRC-specific mortality, which was described in the systematic reviews with a variety of similar terms: cancer-specific mortality, cancer-specific survival, CRC-specific mortality, CRC-specific survival, CRC mortality, CRC survival and disease-specific survival. We used the term 'CRC-specific mortality' for a consistent presentation of the results. Again, they are presented by timeframe of exposure assessment. We also noted that many of the exposures were similar to the ones investigated in relation to all-cause mortality.

3.2.5.1 Pre- and peri-diagnostic risk factors

The reported associations focused on adiposity, diet/nutrition, drugs and lifestyle. A single review reported all associations between various diet and nutrition-related factors, measured before diagnosis, and all-cause mortality. Each association included a small number of estimates (range: 1-4). The meta-analytic estimates ranged from 0.46 for coffee (high vs low, n: 1, RR: 0.46, 95% CI: 0.24-0.87) to 1.78 for grilled food (high vs low, n: 1, RR: 1.78, 95% CI: 1.05-3.02). Similarly to all-cause mortality, lower (underweight vs normal, n: 6, HR: 1.51, 95% CI: 1.11-2.05, I^2: not reported] as well as higher levels of BMI (obese vs normal, n: 12, HR: 1.17, 95% CI: 1.08-1.27, I^2: not reported) were associated with increased mortality from any cause. The association with overweight was null. Use of statins (use vs no use, n: 5, random-effects HR: 0.82, 95% CI: 0.79-0.86, I^2: 0%) and aspirin (regular use vs no use, n: 26, random-effects HR: 0.77, 95% CI: 0.69-0.86, I^2: 91%) were associated with lower risk of CRC-specific mortality. Light alcohol consumption was associated with decreased risk of CRC-specific mortality (light consumption vs no consumption, n: 6, random-effects RR: 0.87, 95% CI: 0.78-0.98, I^2: 22.7%). Moderate and heavy alcohol consumption provided null associations and results did not change by type of alcoholic beverage.

Regarding the systematic reviews that did not perform a meta-analysis, there was limited evidence that plasma enterolactone was associated with a decreased risk of CRC-specific mortality among females but with a decreased risk among males. However, both findings were based on a single study. WC and WHR were associated with increased CRC-specific mortality, although the 95% CIs crossed the null value.

3.2.5.2 Post-diagnostic risk factors

The reported associations focused mainly on adiposity, diet/nutrition, drugs and lifestyle. The three reviews that scored higher at the AMSTAR-2 assessments investigated post-diagnosis adiposity, physical activity and diet/nutrition. The one by Chan and colleagues reported the associations between various dietary factors and CRC-specific mortality. Specifically, increased levels of circulating vitamin D (per 10 nmol/L, n: 5, random-effects RR: 0.94, 95% CI: 0.91-0.97, I^2: 0%) decreased the risk of CRC-specific mortality. Null associations were found for alcohol consumption and

supplemental calcium intake. The estimates for the rest of the studied exposures were not quantitatively synthesized. The non-linear association between BMI and all-cause mortality was observed for CRC-specific mortality too and again total and recreational physical activity were associated with lower all-cause mortality, regardless of their volume and intensity. Statin use after diagnosis (use vs no use, n: 8, random-effects HR: 0.79, 95% CI: 0.7-0.89, I^2: 55.3%) decreased the risk of CRC-specific mortality. Diagnosis of depression following CRC diagnosis was also associated with increased risk of CRC mortality (depression vs no depression, n: 5, random-effects HR: 1.79, 95% CI: 1.3-2.46, I^2: 95%) although substantial heterogeneity was observed.

Regarding the rest of the associations for which a meta-analysis was not performed, weight loss was associated with an increased risk of CRC-specific mortality. The 95% CIs of the included estimates for weight gain, sedentary behavior and serum genistein (a serum/plasma marker of dietary phytoestrogen intake) crossed the null value.

3.2.5.3 Pre-treatment risk factors

Only three associations were found for pre-treatment exposures and CRC-specific mortality and were all focused on inflammation. Higher measurements of the controlling nutritional status (high vs low, n: 3, random-effects HR: 3.93, 95% CI: 2.16-7.15, I^2: 0%) and lower measurements of the prognostic nutritional index (low vs high, n: 2, random-effects HR: 1.53, 95% CI: 1.07-2.19, I^2: 46.2%) were associated with increased CRC mortality. On the other hand, higher lymphocyte to monocyte ratio measurements were associated with lower CRC mortality (high vs low, n: 3, random-effects HR: 0.55, 95% CI: 0.32-0.95, I^2: 72%).

3.2.5.4 Pre- and post-operative operative risk factors

Only one association was identified for pre-operative exposures and CRC-specific mortality. Higher neutrophil to lymphocyte ratio is associated with increased CRC mortality risk (high vs low, n: 4, common-effects HR: 2.27, 95% CI: 1.75-2.96, I^2: 0%). An additional association was reported about the modified Glasgow Prognostic Score and CRC mortality (high vs low, n: 2, random-effects HR: 1.93, 95% CI: 1.37-2.72, I^2: 0%).

3.2.5.5 Risk factors with unknown or mixed timeframe of measurement

For the remaining associations, the timeframe of exposure assessment was not reported in the corresponding systematic reviews. The studied factors were about bisphosphonates, depression, frailty, hormone replacement therapy, lymphocyte to monocyte ratio, platelet to lymphocyte ratio, metabolic syndrome, metformin, myosteatosis, smoking, area-level socioeconomic status, human immunodeficiency virus and sarcopenia. Again, the unknown or mixed timeframe of exposure assessment limits the interpretation of the findings.

3.2.6 Findings on other causes of death

Markozannes and colleagues found that post-diagnosis physical activity decreased the risk of death from other causes, including cardiovascular mortality. However, most associations were informed by very few studies. Two additional reviews provided a descriptive summary of the associations between some dietary factors, BMI and non-CRC mortality but again the evidence was limited.

3.2.7 Findings on colorectal cancer recurrence

In the next sections, we will present the results for CRC recurrence. The review-specific terms used were cancer recurrence, CRC recurrence, CRC recurrence/disease-free survival, disease-free survival, disease-free survival/progression-free survival, disease-free survival/recurrence, progression-free survival, recurrence, recurrence/disease-free survival, recurrence/disease-free survival.

3.2.7.1 Pre- or peri-diagnostic risk factors

One review showed that obese patients had an increased risk of recurrence (obese vs normal, n: 6, RR: 1.07; 95 % CI: 1.02-1.13, I^2: not reported) and worse disease-free survival (obese vs normal, n: 5, RR: 1.07; 95 % CI: 1.01-1.13, I^2: not reported). Underweight patients also had an increased risk of recurrence (underweight vs normal, n: 6, RR: 1.13; 95 % CI 1.05-1.21, I^2: not reported) and worse disease-free survival

(underweight vs normal, n: 4, RR: 1.27; 95 % CI: 1.13-1.43, I^2: not reported). Overweight patients showed no increased risk for any of the recurrence outcomes studied.

3.2.7.2 Post-diagnostic risk factors

The available results for post-diagnostic exposures came from the three reviews that scored higher at the AMSTAR-2 assessments and investigated the role of adiposity, physical activity and diet/nutrition. Higher circulating vitamin D had a small but protective effect on CRC recurrence (per 10 nmol/L, n: 7, random-effects RR: 0.97, 95% CI: 0.93-1, I^2: 64%). The association with BMI followed a non-linear J-shaped pattern again. Total and recreational physical activity were associated with lower CRC recurrence, regardless of their volume and intensity, although associations were informed by a small number of estimates (range: 1-3). All associations for dietary factors were descriptively summarized but only healthy and unhealthy dietary and lifestyle patterns, nut and peanut intake and marine omega-3 were informed by more than two studies. The study-specific estimates demonstrated significant variability.

3.2.7.3 Pre-treatment risk factors

Almost all associations were about inflammatory biomarkers. The meta-analytic estimates ranged between 0.68 for lymphocyte to monocyte ratio and progression-free survival (high vs low, n: 3, random-effects HR: 0.68, 95% CI: 0.57-0.81, I^2: 0%) , and 3.64 for lactate dehydrogenase-to-albumin ratio and progression-free survival (high vs low, n: 1, HR: 3.64, 95% CI: 1.53-8.65). An additional association was recorded for a non-inflammatory biomarker (serum carbohydrate antigen 19-9) and disease-free survival (high vs low, n: 5, common-effects HR: 1.71, 95% CI: 1.38-2.13, I^2: 13.1%).

3.2.7.4 Pre-operative risk factors

The studied factors were certain comorbidities and inflammatory biomarkers. Anemia (anemia vs no anemia, n: 5, common-effects HR: 1.25, 95% CI: 0.98-1.58, I^2: 82%), osteopenia (osteopenia vs no osteopenia, n: 1, HR: 6.75, 95% CI: 3.62-12.59), and sarcopenia (sarcopenia vs sarcopenia, n: 7, common-effects HR: 1.49, 95% CI: 1.32-

1.68, I^2: 0%) were associated with poor disease-free survival or recurrence-free survival. Anemia was also associated with poor disease-free survival among colon and rectal cancer patients alone. For the inflammatory biomarkers, the meta-analytic estimates ranged from 1.27 for platelet to lymphocyte ratio (high vs low, n: 7, random-effects HR: 1.27, 95% CI: 1.02-1.6, I^2: 57.5%) to 2.7 for systemic immune-inflammation index (high vs low, n: 2, common-effects HR: 2.7, 95% CI: 2.28-3.19, I^2: 0%).

3.2.7.5 Post-operative risk factors

One review indicated that higher measurements of C-reactive protein were associated with increased risk of recurrence (high vs low, n: 4, random-effects HR: 2.23, 95% CI: 1.44-3.47, I^2: 0%). Weight loss and weight gain were also studied in relation to recurrence/disease-free survival but due to substantial heterogeneity, results were not synthesized. In addition, the reported timeframe of assessment was 'during/after treatment'.

3.2.7.6 Risk factors with unknown or mixed timeframe of measurement

For the remaining associations, the timeframe of exposure assessment was not reported in the corresponding systematic reviews. The studied factors were advanced lung cancer inflammation index, comorbidity (using the Charlson Comorbidity Index), neutrophil to lymphocyte ratio, fibrinogen to albumin ratio, frailty, geriatric nutritional index, lymphocyte to monocyte ratio, metabolic syndrome, pan-immune inflammation index, peripheral absolute monocyte count, platelet to lymphocyte ratio, subcutaneous adiposity and sarcopenia. Again, the unknown or mixed timeframe of exposure assessment limits the interpretation of the findings.

3.3 DISCUSSION

This overview of reviews identified 161 systematic reviews of cohort studies addressing 55 unique non-therapeutic exposures in relation to mortality from any cause, CRC-specific mortality, or disease recurrence among patients with CRC. After resolving overlap across reviews, we ultimately retained 65 systematic reviews. The final set of

included reviews presented evidence for 538 main associations, most of which involved patients with CRC regardless of tumor site or stage. The associations covered eight exposure categories including adiposity, comorbidities, drugs, inflammatory biomarkers and indices, lifestyle, diet and nutrition, quality of life, socioeconomic factors, and other biomarkers, measured at various time points before, during, or after CRC diagnosis.

To our knowledge, this is one of the few overviews of reviews that includes such a wide range of exposures and outcomes among CRC patients. Previous overviews of reviews have investigated the role of specific groups of non-therapeutic risk factors on CRC outcomes. Specifically, they focused on physical activity (231), statin use (232), metformin (233), smoking cessation (234), metabolic syndrome (235), myosteatosis (236), neutrophil to lymphocyte ratio (237,238), and sarcopenia (239) while we identified only one overview of reviews investigating multiple risk factors on CRC patients (240). Some of these overviews of reviews used a set of criteria proposed in the literature to assess the credibility of the evidence and classified the corresponding associations as providing strong, highly suggestive, suggestive, weak, or non-significant evidence (241). These criteria are based on the p-value of the summary effect estimate from the random-effects model, the number of cases, the p-value of the largest study, the percentage of total variability between study results attributed to true heterogeneity (as quantified by I^2), the prediction interval, the presence of small-study effects, excess significance bias, and the 10% credibility ceiling. Although these are not established criteria for assessing the strength of the evidence, and the individual thresholds may vary across overviews of reviews (242), we aim to apply them in the future to elucidate which associations might provide promising results. Another consideration underlying this decision is that the GRADE approach has not yet been adapted for overviews of reviews, whereas only 6 of the 65 included systematic reviews assessed the certainty of the evidence.

The methodological quality was judged to be critically low for most of the systematic reviews. This is a common finding in overviews of reviews across other research fields too, such as mental health (243) and cardiovascular diseases (244). For most of the systematic reviews included in the current overview of reviews, the critically low rating was attributable to poor methodological practices and a lack of transparent reporting. In fact, the most serious methodological issues were the lack of a pre-registered protocol, failure to report the search strategy used for each database,

whether study selection and/or data extraction were done in duplicate, the absence of a list of studies excluded during full-text screening, the use of inappropriate statistical methods (for example, choice of model based on the I^2 value), and insufficient consideration of residual confounding, selection bias, and publication bias when interpreting results. We also observed underreporting of other important information in the included systematic reviews and in most cases had to be retrieved from the primary studies, such as whether the reported effect estimates were adjusted or the study-specific adjustment factors.

Potential limitations should be considered when interpreting the findings of this overview of reviews. Some of the associations studied were informed by a small number of effect estimates. We observed that certain terms were used interchangeably to describe the same outcome, such as mortality and survival. This could potentially lead to confusion when interpreting the results. However, we carefully checked how the review authors defined and reported these outcomes. Cancer recurrence is an outcome of high clinical importance but was investigated less frequently than mortality outcomes, highlighting the potential difficulties in collecting relevant data from patients with CRC. Again, terminology and definition varied substantially, highlighting the need for a universally accepted definition of cancer recurrence. In addition, systematic reviews focusing on patients with CRC at specific cancer subsites or stages were limited, making it difficult to generalize some of our findings to these subpopulations. We decided to use the original version of AMSTAR-2 and did not make any modifications to the items considered critical, as often recommended by the AMSTAR-2 developers (65). This may have underestimated the methodological quality of some included systematic reviews, although important items that received low ratings (for example, registration of a protocol) would still be considered regardless of the classification used.

On the other hand, to our knowledge, this is one of the first overview of reviews investigating the associations between such a wide range of non-therapeutic risk factors and CRC prognosis. We applied a comprehensive search strategy and undertook measures to address the overlap of primary studies across reviews. We included systematic reviews regardless of whether they included a meta-analysis and used only adjusted effect estimates to limit the influence of residual confounding, as much as possible.

CHAPTER 4

GENETICALLY-PREDICTED RISK FACTORS OF COLORECTAL CANCER MORTALITY AFTER DIAGNOSIS: A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY

The second aim of this doctoral thesis was to investigate the associations between a wide range of genetically-predicted risk factors and CRC-specific mortality among CRC cases following the two-sample MR approach. MR uses germline genetic variants as instruments of the risk factors of interest for testing hypotheses of causal inference. This method exploits the random allocation of genetic variants at meiosis and hence mimics the structure of a "natural" randomized controlled trial (245). By using genetic variants as instrumental variables to evaluate the magnitude of association of genetically proxied lifetime exposure to a risk factor on disease outcomes, MR is less prone to residual confounding and reverse causation bias than traditional observational studies (246). Two papers have been produced from this chapter: one about adiposity-related traits has been published in the International Journal of Epidemiology (247), while the other is about IGF-1 and currently is under review at the Journal of the National Cancer Institute.

4.1. METHODS

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines (248).

4.1.1 Data on colorectal cancer survival

The Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) comprise genetic, environmental and survival data from 15 studies of 16,964 individuals of European ancestry, diagnosed with incident,

invasive CRC (50.3% males, median age at diagnosis; 67 years) out of which 4,010 died due to their disease during follow-up (**Table 4.1**) (1). Both consortia were accessed to obtain the genetic association estimates of single nucleotide polymorphisms (SNPs) with risk of CRC-specific mortality after diagnosis overall, by anatomical site [proximal colon (4,881 cases, 978 deaths), distal colon (6,214 cases, 1,433 deaths), rectum (4,749 cases, 1,045 deaths)] and tumor stage [stage I (3,338 cases, 157 deaths), stages II/III as they are both considered regional (6,420 cases, 1,209 deaths), stage IV (1,847 cases, 1,448 deaths)]. Cox proportional hazards regression models were adjusted for age at diagnosis, sex, a joint variable encompassing genotyping platform and study, and the first five principal components to account for population stratification (1).

Table 4.1: Characteristics of the studies of colorectal cancer cases included in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) (1).

Study Name	Study design	Location	Cases	Deaths	Stages	Genotyping platform
Colon Cancer Family Registry	Case-cohort	United States, Australia	2,446	538	I-IV	Illumina Human 1M or Human1M-Duo, Illumina Omni-1Quad Illumina Onco Array, Custom Affymextrix Axiom array (1.3M SNPS)
Cancer Prevention Study-II	Cohort	United States	819	186	I-IV	Illumina OncoArray + Custom iSelect array, Custom Affymetrix Axiom Array (1.3M SNPs)
Darmkrebs: Chancen der Verhutung durch Screening Study	Case-control	Germany	2,659	537	I-IV	Illumina HumanCytoSNP, Illumina HumanOmniExpress, Illumina OncoArray
Diet Activity and LifestyleStudy	Case-control	United States	1,098	210	I-IV	Illumina HumanCytoSNP, Illumina 550K, Illumina 610K
Early Detection Research Network	Case-cohort	United Stated	191	14	I-IV	Illumina OncoArray + Custom iSelect Array
European Prospective Investigation into Cancer	Cohort	Europe	1,821	471	I-IV	Illumina HumanOmn Express +ExomeChip
Health Professionals Follow-up Study	Cohort	United States	348	85	I-IV	Illumina HumanOmn Express, Illumina Human OmniExpress ExomeChip
Melbourne Collaborative Cohort Study	Cohort	Australia	750	194	I-IV	Illumina OncoArray, Custom Affymetrix Axiom Array (1.3M SNPS)
N9741 Clinicial Trial	Clinical trial	United States	426	366	IV	Illumina HumanOmn Express ExomeChip

Nurses' Health Study	Cohort	United States	591	161	I-IV	Illumina HumanOm Express, Illumina Human OmniExpress ExomeChip
Physician's Health Study	Cohort	United States	323	130	I-IV	Illumina HumanOmn Express
Prostate, Lung, COlorectal, and Ovarian Cancer Screening Trial	Case-control	United Stated	972	174	I-IV	Illumina HumanCytoSNP, Il lumina HumanHap300 and HumanHap2405, Illumina610K
UK Biobank	Cohort	United Kingdom	2,919	581	I-IV	Custom Affymetrix Axiom Array (1.3M SNPs)
VITamins and Lifestyle Study	Cohort	United States	270	67	I-III	Illumina HumanCytoSNP
Women's Health Initiative	Cohort	United States	1,331	296	I-IV	Illumina HumanCytoSNP, Illumina 550K, Illumina 610K

4.1.2. Instruments of the exposures

As already outlined in the Introduction, anthropometric and metabolic traits, dietary and lifestyle factors, sex hormones, lipids, inflammation, and glucose metabolism and insulin signaling have been studied in relation to CRC incidence, making it of particular interest to investigate their role in CRC prognosis as well. Hence, for the current MR study, the selected exposures were birth weight, BMI, basal metabolic rate, body fat percentage, height, hip circumference (HC), WC, WHR (anthropometric and metabolic traits), alcohol consumption, device-measured physical activity, lifetime smoking, circulating vitamin D (dietary and lifestyle factors), SHGB, testosterone (sex hormones), fasting total cholesterol, fasting high-density lipoprotein (HDL), fasting low-density lipoprotein (LDL), fasting triglycerides (lipids), CRP, IFG-1 (inflammation), fasting glucose, fasting insulin, hemoglobin A1c (HbA1c), type 2 diabetes, and two-hour postprandial glucose (glucose metabolism and insulin signaling).

Genetic association estimates for height were obtained from a meta-analysis of 173 studies of the Genetic Investigation of Anthropometric Traits (GIANT) consortium, including up to 4,080,687 individuals of European ancestry (249). Genetic association estimates for BMI and WHR were obtained from another GIANT Consortium GWAS meta-analysis of 806,834 individuals of European ancestry (250). Another GWAS was accessed to obtain summary genetic association estimates for WC, HC, birth weight and body fat percentage, based on a sample of 349,376 UK Biobank participants (251). Estimates for liability for type 2 diabetes were obtained from a DIAbetes Genetics

Replication And Meta-analysis (DIAGRAM) Consortium GWAS of 74,124 cases and 824,006 controls of European ancestry, and estimates for fasting glucose, fasting insulin, two-hour glucose, and HbA1c were obtained from a GWAS of up to 281,416 non-diabetic individuals (252,253). Since estimates for the latter biomarkers were derived from models adjusted for BMI, we also used instruments from alternative sources for fasting glucose, fasting insulin and HbA1c, to avoid collider bias in the marginal associations (254,255). Genetic association estimates for circulating CRP were obtained from a GWAS of up to 204,402 European individuals (256). Genetic association estimates for fasting serum lipids, namely LDL, HDL, total cholesterol, and triglycerides, were obtained from the Global Lipids Genetic Consortium GWAS including 188,577 European-ancestry individuals (257). Genetic association estimates for IGF1, testosterone, SHBG, vitamin D, device-measured physical activity and lifetime smoking were obtained from GWASs of up to 462,690 European-ancestry individuals in the UK Biobank (251,258,259). All genetic variant estimates were significant at the genome-wide significance level (p-value $< 5 \times 10^{-8}$), whereas SNPs in linkage disequilibrium (LD; $r^2 > 0.001$ within a 10 000-kb window, based on the 1000 Genome reference panel) were excluded, retaining only the SNP with the lowest p-value per locus.

4.1.3. Statistical analysis

4.1.3.1. Main analysis

We conducted a two-sample MR using the random-effects inverse variance weighted (IVW) method when the number of instrumented SNPs was larger than 3. Otherwise, we used a fixed-effect approach. In a two-sample MR, the associations between the genetic instrumental variable (IV) and the exposure, and between the genetic IV and the outcome, are obtained from different, non-overlapping samples, and summary-level data are used to derive the final estimate of the exposure-outcome association. For all exposures except type 2 diabetes, which was analyzed as a dichotomous variable, associations with CRC-specific mortality were reported as HRs per standard deviation (SD) increase in the exposure.

4.1.3.2. Sensitivity analyses

As in any MR analysis, the selected genetic variants must fall under the following criteria: i) be strongly associated with the exposure under investigation, ii) be independent of any plausible confounder of the exposure-CRC mortality association, and iii) affect CRC mortality only through the exposure being instrumented and not via any other biological pathway (e.g. existence of horizontal pleiotropy) (260). To measure the strength of the genetic instruments, we calculated the F-statistic and the proportion of the variance of the exposure explained by the corresponding genetic instrument (R^2). We pre-specified that the F-statistic should be greater than 10 to avoid the inclusion of weak instruments. To examine for the potential violation of the second and third MR assumption, we computed Cochran's Q statistic, which expresses the degree to which differences in the measures of association among the selected SNPs are due to real variation rather than sampling error (261). The potential presence of horizontal pleiotropy was further investigated using MR-Egger regression where the corresponding statistical test is based on its intercept term, when it is different from zero (262). In the presence of horizontal pleiotropy, the slope of the MR-Egger regression and the weighted median approach provide more valid MR estimates compared to IVW (262,263). Specifically, the weighted median approach provides a valid MR estimate when only half of the weight of the genetic variants meet the second and third MR assumptions (263). In case the IVW p-value was lower than 0.05, the MR pleiotropy residual sum and outlier test (MR-PRESSO) was also applied to pinpoint potential outlying SNPs and analyses were re-conducted after excluding them (264). Analyses were implemented in the statistical software R 4.0.3 using the packages MendelianRandomization (265) and MRPRESSO (266).

4.1.3.2.1. Adjustment for collider bias

As outlined in the Introduction, almost all of the genetically-predicted exposures investigated for their influence on CRC survival have also been associated with CRC incidence in the literature, thereby creating a setting in which collider bias may arise. In general, collider bias (or, index event bias) is a form of selection bias occurring when a study conditions on or adjusts for a collider. MR studies on CRC survival include only CRC cases and are prone to collider bias when the exposure of interest is also related to CRC incidence (267). Conditioning on CRC incidence can induce an association

between the genetic instrument and another measured or unmeasured cause for both CRC incidence and survival, violating the independence MR assumption (**Figure 4.1**).

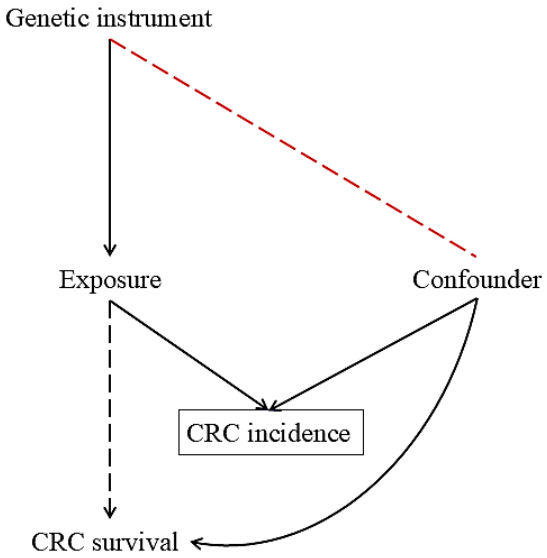

Figure 4.1: Directed acyclic graph demonstrating a typical example of collider bias in the two-sample Mendelian Randomization (MR) studies of colorectal cancer (CRC) survival. The genetic instrument is strongly associated with the exposure under investigation, the exposure is associated with risk of CRC incidence, and a measured or unmeasured confounder works as a common cause of both CRC incidence and survival (black solid lines). Conditioning on CRC incidence induces the association between the previously independent genetic instrument and the confounder (red dashed line). This would cause the violation of the second Mendelian randomization assumption, and hence threaten the validity of the MR survival estimate.

To detect whether our findings were influenced by collider bias, we applied the recently developed methods by Dudbridge and colleagues [or Simulation Extrapolation (SIMEX) method] (268), Mahmoud and colleagues (or Slope-hunter method) (269), and Cai and colleagues [or Corrected Weighted Least Squares (CWLS) method] (270).

The motivating idea of these methods is that the association between a specific SNP and CRC survival is proportional to the true effect of the SNP on CRC survival and a bias that is linear in the true effect of the SNP on CRC incidence, as shown in the following formula:

$$\beta_{survival}^{est} = \beta_{survival}^{true} + b \cdot \beta_{incidence}^{true} \quad (2)$$

where $\beta_{survival}^{est}$ is the effect estimate of the SNP on CRC survival coming from the relevant GWAS, $\beta_{survival}^{true}$ is the true effect of the SNP on CRC survival and the one we are interested in, $\beta_{incidence}^{true}$ is the true effect of the SNP on CRC incidence, and b is an estimate of the magnitude of bias called 'bias-correcting factor' and is the slope from

the regression of $\beta_{survival}^{est}$ on $\beta_{incidence}^{true}$ for all independent SNPs. Obviously, since $\beta_{incidence}^{true}$ is unknown, the effect estimate from the incidence GWAS is used.

All three methods use a set of independent SNPs to determine the bias-correcting factor. The fundamental difference between the first two methods is the assumption of collinearity between SNPs; Dudbridge and colleagues define a-priori that correlation between SNP incidence and SNP survival effects should not exist [Instrument Strength Independent of Direct Effect' (InSIDE) assumption]. Considering that certain SNPs may be involved in the etiology of both CRC incidence and progression, the Slope-hunter method attempts to overcome this limitation by categorizing SNPs into two clusters: SNPs only affecting CRC incidence ('hunted' SNPs, $p < 0.001$); and SNPs affecting both CRC incidence and survival ('pleiotropic' SNPs). It further assumes that the variance in CRC incidence explained by SNPs associated with CRC incidence only is at least as great as the variance explained by SNPs associated with CRC incidence and survival [ZEro Modal Residual Assumption (ZEMRA)]. Finally, Cai and colleagues suggested that formula (2) may have Type 1 error rates similar to those of an unadjusted analysis if weak instrument bias is not accounted for. Therefore, CWLS method was developed and is an extension of the idea proposed by Dudbridge and colleagues. It is a non-intercept model which assumes again no genetic correlation between CRC incidence and survival. All methods assume that the effect of common causes of CRC incidence and survival should be constant across all SNPs.

Bias-correcting factors were calculated by first obtaining the summary statistics for overall and site-specific CRC development, namely proximal, distal colon and rectal, in up to 58,221 cases and 67,694 controls from an analysis of the ColoRectal Transdisciplinary Study (CORECT), GECCO and CCFR (2). As genetic data for stage-specific CRC development were unavailable, stage-specific correcting factors were assessed using estimates of overall CRC. To identify independent SNPs, genetic association estimates for incidence and survival were harmonized by aligning effect estimates to the same allele and were pruned for linkage disequilibrium ($r^2 < 0.10$, 250 kb window) (**Table 4.2**). This process resulted in 350,586 SNPs for overall CRC, 350,618 for proximal colon, 350,615 for distal colon, 350,837 for rectal, 320,232 for stage I, 320,232 for stages II/III, and 320,232 for stage IV.

Table 4.2: Initial number of total SNPs of CRC incidence (2) and mortality (1), overall, by anatomical site and stage, used to calculate the bias-correcting factors.

	Incidence	Survival
Overall CRC	16,900,397	7,829,749
Proximal colon	13,802,243	7,829,749
Distal colon	13,762,711	7,829,749
Rectal	13,934,936	7,829,749
Stage I	16,900,397*	7,068,523
Stages II/III	16,900,397*	7,068,523
Stage IV	16,900,397*	7,068,523

**Genetic estimates for overall CRC were used as stage-specific CRC development data were unavailable*

Following the SIMEX method and under the assumption of no genetic correlation between CRC incidence and survival, CRC survival estimates were regressed on CRC incidence estimates using a SIMEX adjustment for regression dilution (number of simulations: 1,000) to derive the bias-correcting factors and their standard errors. In the Slope-hunter method, SNPs that only influenced CRC incidence ('hunted' SNPs) were identified by p-value thresholding ($p < 0.001$) and then a model-based clustering and boots resampling technique (number of samples: 100) were applied to each dataset to estimate the bias-correcting factors and their corresponding standard errors, respectively. Finally, under the CWLS method and assuming again no genetic correlation between CRC incidence and survival, the bias-correcting factors were computed as simple functions of the summary effect estimates, related to the Hedges-Olkin estimator of random-effects variance in meta-analysis, but extended to a weighted regression framework. The variances of the bias-correcting factors were estimated using a sandwich variance estimator, similarly scaled to correct for weak instrumental variables. The formulas for the corrected marginal survival estimates and their corresponding standard errors are available at the **Supplementary Information**. IVW MR estimates and Cochran's Q statistic were then re-calculated using the corrected estimates. We compared all bias-adjusted estimates to assess the robustness of SNP-survival effect estimates across methods. Additionally, we compared the initial IVW estimates with the bias-adjusted IVW estimates in terms of both direction and

magnitude. Analyses were conducted using the R packages indexevent (271), SlopeHunter (272) and ColliderBias (273).

4.2. RESULTS

The final number of SNPs being instrumented for each exposure is shown in **Table S4.1** and it ranged from 3 (physical activity) to 987 (height). The R^2 ranged from 0.1% (physical activity) to 32.3% (type 2 diabetes). The estimated magnitude of bias obtained from all adjustment methods ranged from -1.404 to 0.568, with most estimates being positive (**Table 4.3**).

Table 4.3: Bias-correcting factors along with their 95% confidence intervals (CIs) overall, by anatomical site and stage

	Bias-correcting factor	95% CI
Overall		
SIMEX	0.098	(0.095, 0.101)
Slope-hunter	0.468	(0.281, 0.655)
CWLS	0.105	(0.026, 0.183)
Proximal colon		
SIMEX	0.303	(0.282, 0.327)
Slope-hunter	-0.363	(-0.8, 0.075)
CWLS	0.291	(0.138, 0.445)
Distal colon		
SIMEX	0.568	(0.536, 0.604)
Slope-hunter	0.356	(-0.249, 0.962)
CWLS	0.516	(0.34, 0.691)
Rectal		
SIMEX	0.364	(0.332, 0.402)
Slope-hunter	0.564	(0.244, 0.885)
CWLS	0.294	(0.134, 0.454)
Stage 1		
SIMEX	0.353	(0.29, 0.45)
Slope-hunter	-1.404	(-2.462, -0.346)
CWLS	0.401	(-0.019. 0.822)
Stages II/III		
SIMEX	0.296	(0.284, 0.308)
Slope-hunter	0.565	(0.065, 1.064)
CWLS	0.31	(0.154, 0.467)
Stage IV		
SIMEX	-0.183	(-0.196, 0.172)
Slope-hunter	0.441	(0.132, 0.75)
CWLS	-0.181	(-0.329, -0.033)

Abbreviations: CRC; colorectal cancer, CWLS; corrected weighted least squares, SIMEX; simulation extrapolation

4.2.1 Findings on anthropometry-related traits

The associations between the genetically-predicted anthropometric traits and CRC survival overall and by CRC site are shown in **Table S4.1**. A SD higher genetically-predicted WC was associated with 22% [95% confidence interval (CI); 2%-47%, p-value; 0.03] higher risk of CRC-specific mortality among CRC cases. The weighted median approach confirmed the aforementioned association (HR; 1.43, 95% CI; 1.05-1.93, p-value; 0.02), with no evidence of horizontal pleiotropy (MR-Egger intercept p-value; 0.77). In general, positive but imprecisely estimated associations were found for most other anthropometric traits, except for height and birth weight, which yielded null and non-significant inverse results, respectively. Results did not differ by anatomical site.

Stratified analyses by CRC stage showed a positive association with CRC-specific mortality for HC (HR; 1.32, 95% CI; 1.02-1.73, p-value; 0.04) and BMI (HR;1.5, 95% CI; 1.15-1.95; p-value; 0.003) among individuals with CRC of stages II/III (**Table S4.1**). These associations were consistent in the MR-Egger and weighted median analyses with no evidence of horizontal pleiotropy (MR-Egger intercept p-value; 0.35 and 0.54 for HC and BMI, respectively). Most of the genetically-predicted anthropometric traits appeared to be associated with better survival among stage IV CRC cases, but with wide CIs, possibly due to the presence of selection bias when analyses are restricted to this subpopulation (274). The Cochran's Q statistic was not statistically significant in any of the associations mentioned above, and the MR-PRESSO analysis did not reveal any outlying SNPs.

SIMEX and CWLS provided similar estimates, and the Slope-hunter method tended to yield either larger estimates or estimates with an opposite sign. The associations between genetically-predicted anthropometry-related traits and CRC mortality among CRC cases after controlling for collider bias are shown in **Figure 4.2** and **Table S4.2**. The SIMEX and CWLS methods provided almost identical bias-adjusted estimates and concordant with the initial IVW estimates, with the magnitude of the associations between WC and CRC-specific mortality overall, and HC, BMI, and CRC-specific mortality in stages II/III ranging from 1.2 to 1.38 per SD. The Slope-

hunter method led to the attenuation of all association estimates, except for HC (HR; 1.31, 95% CI; 1-1.71, p-value; 0.05), BMI (HR; 1.32; 95% CI; 1-1.75; p-value; 0.05) and CRC-specific mortality among individuals with stage II/III disease

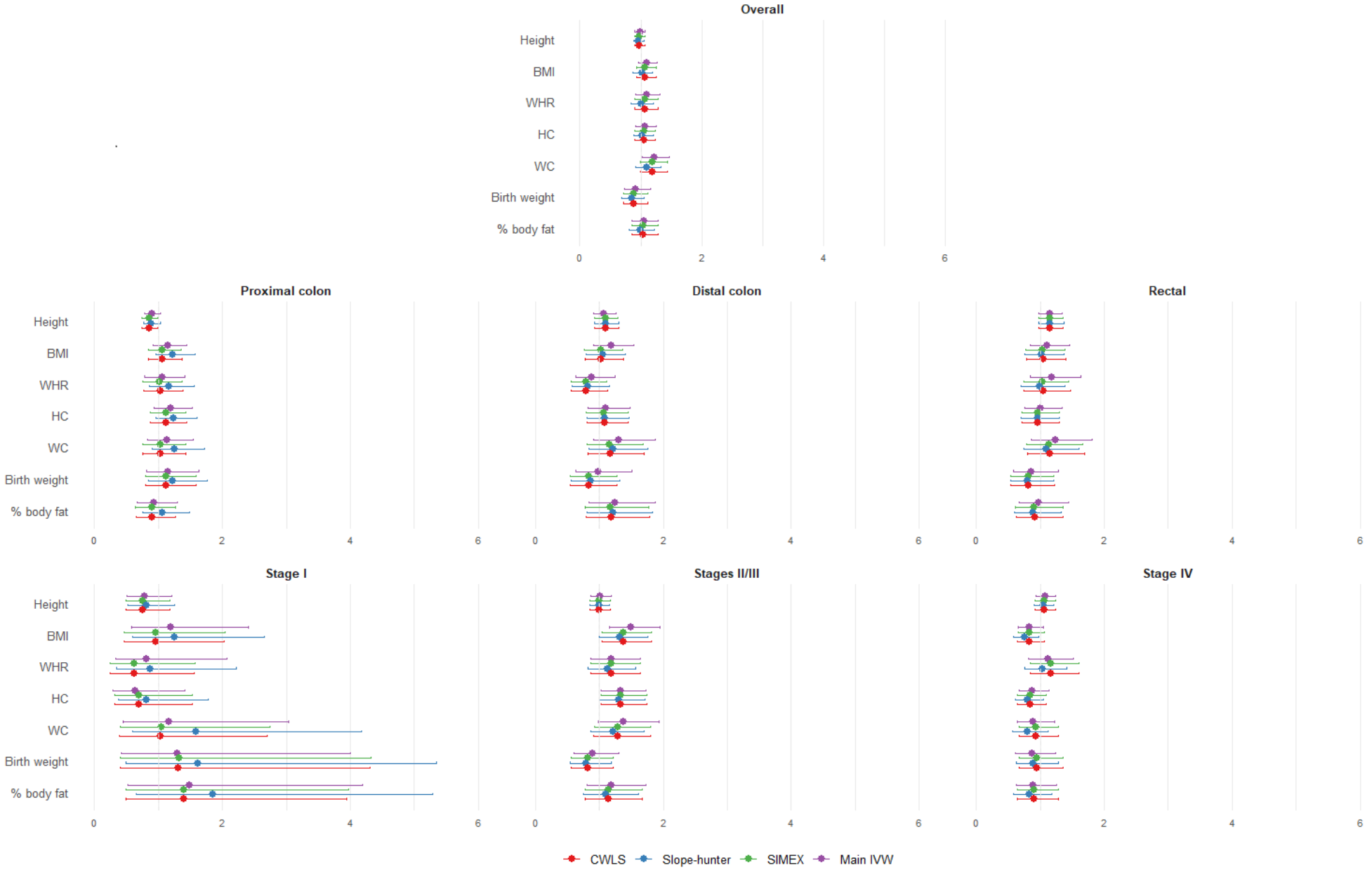

Figure 4.2: Mendelian Randomization estimates for the association between genetically-predicted anthropometric traits and colorectal cancer (CRC)-specific mortality, stratified by anatomical site and tumor stage. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are presented for each anthropometric trait using the main inverse-variance weighted (IVW) method and three approaches accounting for collider bias: Corrected Weighted Least Squares (CWLS), Slope-hunter, and Simulation Extrapolation (SIMEX). Each dot represents the HR, and horizontal lines denote 95% CIs. *Abbreviations: BMI; body mass index, HC; hip circumference, WC; waist circumference, WHR; waist-hip circumference ratio*

4.2.2 Findings on insulin-like growth factor-1

The associations between the genetically-predicted levels of IGF-1 and CRC survival overall, and by CRC site and stage are shown in **Table S4.1.** According to the IVW approach, there was an overall 17% higher risk of CRC-related death per SD increase in genetically-predicted IGF-1 concentration (HR; 1.17, 95% CI; 1.05-1.31, p-value; 0.004). The weighted median approach found a slightly attenuated but consistent effect with the IVW estimate (HR; 1.1, 95% CI; 0.91-1.33, p-value; 0.352). There was no significant evidence for horizontal pleiotropy (MR-Egger intercept p-value; 0.08).

The IVW effect estimates tended to increase in size from proximal to distal end of the bowel ranging from 1.04 to 1.24 per SD, and we also identified a 38% increased risk of death for patients diagnosed with rectal cancer (per SD increase in IGF-1 concentration; HR; 1.38, 95% CI; 1.10-1.74, p-value; 0.005). The weighted median estimate confirmed this significant effect among rectal cancer patients (HR; 1.49, 95% CI; 1.03-2.16, p-value; 0.034). The MR-Egger regression did not identify evidence for significant horizontal pleiotropy (MR-Egger intercept p-value; 0.818). In relation to tumor stage, increased genetically-predicted levels of IGF-1 had an aggravating effect on CRC-specific survival for patients of stages I, II/III and IV, although none of the associations reached statistical significance (estimates ranged from 1.09 to 1.14 per SD increase in IGF-1 concentration) (**Table S4.1**). Overall, the Cochran's Q statistic was not statistically significant in any of the associations, and the MR-PRESSO analysis did not provide evidence for any horizontal pleiotropic outlying SNPs.

The associations between genetically-predicted predicted levels of IGF-1 and CRC survival, after controlling for collider bias, are shown in **Figure 4.3** and **Table S4.2**. We found a concordant association between genetically-predicted circulating IGF-1 levels and CRC-specific survival using all three methods (HR; 1.11, 95% CI; 0.99-1.25, p-value; 0.074 for SIMEX, HR; 1.08, 95% CI; 0.96-1.22, p-value; 0.221 for Slope-hunter, HR; 1.11, 95% CI; 0.99-1.25, p-value; 0.076 for CWLS). With respect to patients diagnosed with rectal cancer, we observed concordant effect estimates of similar magnitude using the SIMEX (HR; 1.26, 95% CI; 0.98-1.61, p-value; 0.074), Slope-hunter (HR; 1.24, 95% CI; 0.96-1.6, p-value; 0.095) and CWLS (HR; 1.26, 95% CI; 0.98-1.62, p-value; 0.068) approaches**.**

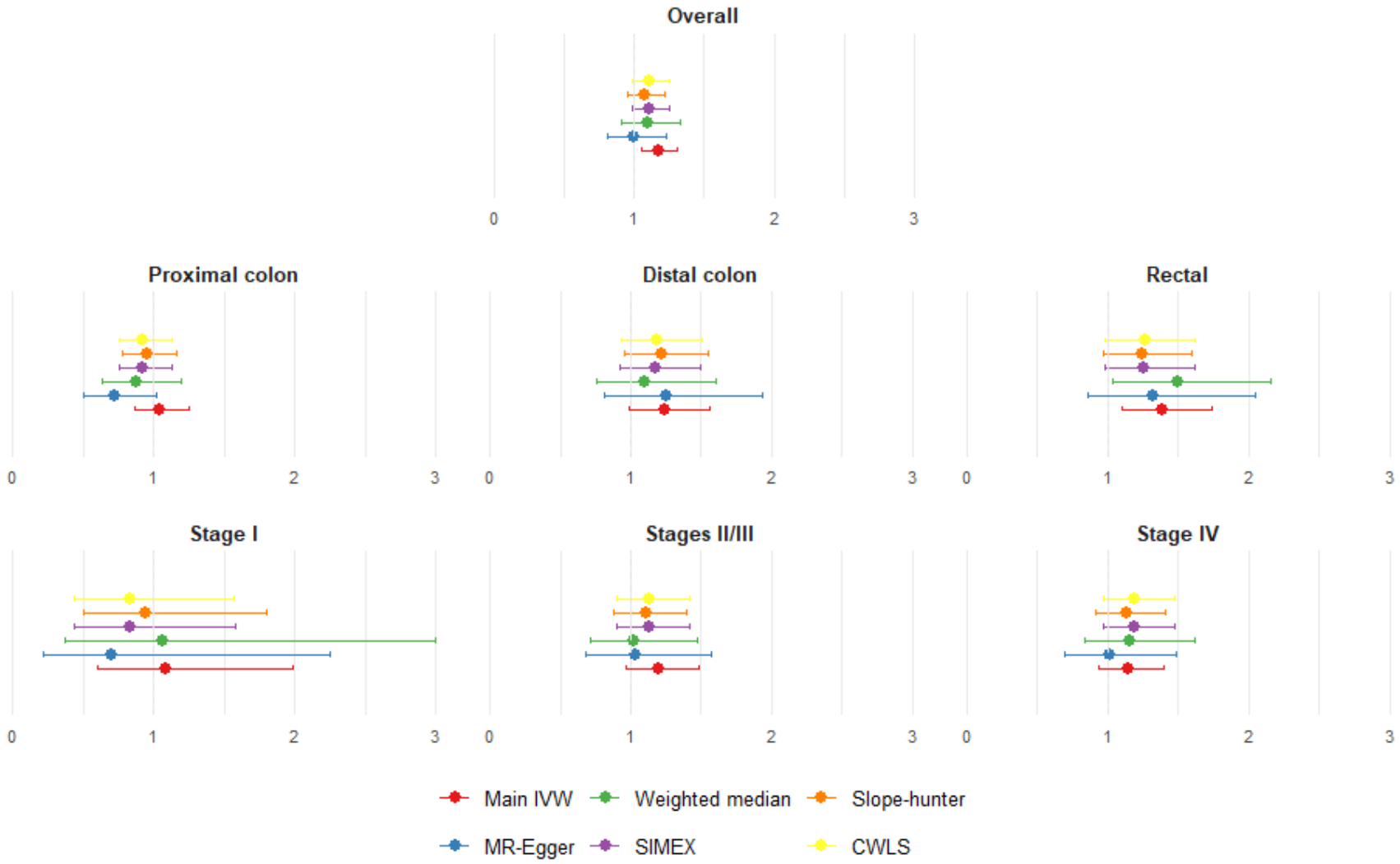

Figure 4.3: Mendelian Randomization (MR) estimates for the association between genetically-predicted levels of insulin-like growth factor-1 and colorectal cancer (CRC)-specific mortality, stratified by anatomical site and tumor stage. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) are presented using the main inverse-variance weighted (IVW) method, MR-Egger, weighted median, and three approaches accounting for collider bias: Corrected Weighted Least Squares (CWLS), Slope-hunter, and Simulation Extrapolation (SIMEX). Each dot represents the HR, and horizontal lines denote 95% CIs.

4.2.3 Findings on other exposures

Increased genetically-predicted levels of fasting glucose were associated with a decreased risk of CRC-specific mortality overall (HR; 0.73, 95% CI; 0.56-0.97, p-value; 0.028) as well as among patients with proximal colon cancer (HR; 0.57, 95% CI; 0.36-0.9, p-value; 0.016) and those with stage II/III disease (HR; 0.52, 95% CI; 0.3-0.89, p-value; 0.018) (**Table S4.1**). However, these associations were attenuated and were no longer statistically significant in either the MR-Egger or weighted median analyses, or when marginal fasting glucose estimates that were not adjusted for BMI were used. All other studied exposures yielded effect estimates close to the null. It should be noted that certain exposures, such as alcohol, physical activity and fasting insulin, yielded effect estimates with substantial uncertainty, mainly due to the limited number of SNPs being instrumented and, in some subgroups (e.g., patients with stage I disease), the low number of events.

4.3. DISCUSSION

In the current MR analysis of 25 different exposures and survival after CRC diagnosis, positive associations were observed between genetically-predicted levels of WC and IGF-1 and CRC-specific mortality overall, and HC and BMI with CRC-specific mortality in stages II/III. Higher genetically predicted IGF-1 levels were associated with increased CRC-specific mortality among patients with rectal cancer, but only in the IVW analysis. Imprecisely estimated associations were found for the rest of the exposures.

Three different methods were applied to adjust for potential collider bias in our marginal survival estimates. The SIMEX and CWLS methods yielded similar estimates of bias magnitude; therefore, the corresponding bias-adjusted estimates did not differ substantially and were highly similar to the initial IVW estimates. On the other hand, the Slope-hunter method provided slightly different bias-adjusted estimates with greater uncertainty. The differences across methods used to adjust for collider bias can potentially be explained by the core assumptions of each method. The SIMEX and CWLS methods may be more sensitive to the positive genetic correlation between CRC incidence and CRC-specific mortality (268,270), which we reasonably believe exists. In contrast, the Slope-hunter method addresses this limitation but relies on the

assumption that there are no common causes of CRC incidence and CRC-specific mortality that explain more of the variance in incidence than the SNPs that affect incidence only (269). Therefore, the results from these methods should be interpreted with caution, as the aforementioned assumptions cannot be verified using the available data.

Epidemiologic evidence on the plausible association between the studied exposures and survival among CRC patients comes primarily from observational studies, which have assessed exposures at various time points pre-, peri-, or post-CRC diagnosis. With regards to anthropometry-related traits, a recent meta-analysis of 20 observational studies concluded that higher post-diagnosis BMI was associated with higher risk of overall and CRC-specific mortality, and the shape of the associations appeared reverse J-shaped with a nadir at 28 kg/m^2 (68). While these findings highlighted the aggravating association of being high-overweight or obese with CRC outcomes, they also showed positive associations with low and low-normal BMI. As a result, the totality of this evidence was judged as limited due to methodological considerations of the included observational studies. There is very little data available on WC and CRC outcomes. A relevant meta-analysis including five prospective cohort studies assessing WC before or at diagnosis of CRC, suggested that elevated WC was associated with increased mortality from CRC (HR 1.27; 95% CI 1.08-1.49) (275). The literature on the association between HC and CRC survival is scarce as well. We identified only one cohort study involving 3,924 CRC cases, where 1,043 cases died due to CRC during a mean follow-up of 49 months, reporting that higher pre-diagnostic HC was associated with increased CRC-specific mortality (per 10 cm; HR 1.09; 95% CI 1-1.18) (276). Finally, the association of anthropometry and CRC survival by tumor stage is poorly investigated in the literature. A meta-analysis of 13 prospective and retrospective studies assessing anthropometry either pre- or post-diagnosis reported that obesity (BMI > 30 kg/m^2) was associated with worse overall survival (HR 1.10; 95% CI 1.05–1.15) in the subgroup of CRC patients of stages II/III (277). Another systematic review concluded that there was insufficient evidence for a link between adiposity measures, such as BMI, and survival among stage IV CRC patients due to inherent biases in the included studies (97). Although this evidence is generally concordant with our results, MR captures more effectively the effect of anthropometry across the lifespan and potentially helps overcome limitations arising from timing discrepancies in anthropometry assessment.

The biological mechanisms connecting anthropometry and CRC survival are not entirely understood and might be related to factors that are associated with CRC incidence. One potential biological pathway may involve IGF-1, which has also been associated with poorer CRC survival in the current study. Specifically, relevant evidence suggests that higher BMI levels are associated with increased bioavailability of IGF-1, decreased levels of IGF binding proteins, and increased production of adipokines and pro-inflammatory cytokines that may contribute to carcinogenesis and tumor progression (278). Although most of the evidence has focused on BMI, the observed effect of WC may be explained by the fact that it serves as a proxy for visceral adiposity, which is metabolically more active in terms of secreting the aforementioned adipokines and pro-inflammatory cytokines (279) and may therefore have more profound implications for CRC prognosis.

Potential limitations should be considered in the interpretation of our findings. Some of our analyses were underpowered, mainly due to the small number of deaths and SNPs instrumented. Larger GWASs on CRC patients are required to better investigate the link between the genetically-predicted exposures and CRC survival. MR analyses of summary-level data do not allow for stratified analyses by important covariates, such as sex and treatment status. Although several exposures exhibit sex-specific genetic architectures, including anthropometric traits and IGF-1 concentrations, we were unable to use sex-stratified summary statistics, as the genetic data for CRC-specific mortality were only available in a sex-combined format. An additional limitation would be that SNP-exposure estimates may differ in CRC cases compared to a generally healthy sample, as there may be effect modifications by factors relating to having the disease (267), though no exposure GWASs have yet focused on SNPs in CRC cases alone. MR analyses on CRC survival can be susceptible to survival bias, which occurs when CRC cases must survive long enough to be included in the GWASs and contribute any person-time (267,280). IVW MR methods assume linear associations between the exposure and outcome, but nonlinear analysis was not performed, as the available methods do not work well with summary-level data, and statistical power would have been limited (281). We also acknowledge that genetic correlations may exist among some studied. Future research could select and prioritize strongly correlated traits and assess their influence on CRC-specific mortality. Finally, all included GWASs had a lack of ethnic diversity in the samples studied, limiting our capability to generalize our findings to populations of non-European ancestry.

Our study has also a number of strengths. To our knowledge, this is the first two-sample MR analysis investigating the association between numerous exposures and CRC survival. We conducted stratified analyses by CRC site and stage producing novel findings, especially for stages II and III, and we were able to attenuate the effect of significant biases on our results, including reverse causation, residual confounding, and collider bias.

CHAPTER 5

CONCLUDING REMARKS

5.1 SUMMARY OF FINDINGS

In the current thesis, we investigated the role of non-therapeutic risk factors in key outcomes following a diagnosis of CRC, specifically all-cause mortality, CRC-specific mortality, and disease recurrence. We followed two distinct methodological approaches: an overview of reviews including prospective and retrospective cohort studies, and a two-sample MR analysis.

In the overview reviews, 161 systematic reviews assessed 55 unique non-therapeutic exposures spanning a wide range of categories, namely adiposity, comorbidities, diet and nutrition, drugs, inflammatory biomarkers and indices, lifestyle factors, quality of life measures, sociodemographic characteristics and other biomarkers. Thirty-three of these exposures were investigated in more than one systematic review. After calculating the CCA index, we finally retained 65 systematic reviews. In total, we recorded 538 main associations, the majority of which were reported for participants with CRC regardless of anatomical subsite or disease stage. The most studied outcome was all-cause mortality or overall survival, and more than half of the associations were about post-diagnostic exposures. In 315 associations, meta-analysis was conducted with the random-effects model being the primary approach. The systematic reviews provided evidence on multiple non-therapeutic risk factors associated with CRC outcomes after diagnosis. However, the vast majority were rated as having very low methodological quality, limiting the reliability of their findings.

In the two-sample MR analysis, we investigated the associations between genetically-predicted levels of 25 exposures and CRC-specific mortality overall, as well as by CRC subsite and tumor stage. We also conducted sensitivity analyses to assess potential violations of the MR assumptions and to adjust our estimates for potential collider bias. We found that increased genetically-predicted levels of certain anthropometric measures, such as WC, BMI, and HC, were associated with increased CRC-specific mortality overall and stage II/III disease. We also found that increased

genetically-predicted IGF-1 levels were associated with increased CRC-specific mortality among CRC patients overall and among those diagnosed with rectal cancer. All other genetically-predicted exposures yielded imprecise estimates with some of them having substantial uncertainty. Overall, we found no evidence of collider bias affecting our results. However, these findings should be interpreted with caution, as the assumptions underlying the methods used could not be evaluated using the available data.

5.2 PUBLIC HEALTH IMPLICATIONS

Our findings provide insight into the complexity of CRC prognosis and the challenges associated with studying it. Although tumor- and treatment-related characteristics are the primary drivers of CRC progression, accumulating evidence suggests that non-therapeutic factors may also contribute to disease prognosis. The overview of reviews provided extensive evidence on the role of a wide range of non-therapeutic risk factors in mortality and recurrence outcomes, including, but not limited to, obesity, inflammatory biomarkers, lifestyle factors, and comorbidities. However, it should be emphasized that the poor methodological quality of many of the included systematic reviews may have resulted in certain associations with biased or inflated estimates. In addition, potential differences in outcome definitions, particularly for recurrence, the limited representation of specific patient subgroups in many associations (e.g., patients with colon or rectal cancer), and variability or missingness in the timing of exposure assessment complicate the interpretation of the results and warrant caution when communicating these findings to individuals diagnosed with CRC. Our MR study identified adiposity- and inflammatory-related traits that may play a role in CRC prognosis. These findings show consistency with the evidence from the systematic reviews of cohort studies, which investigated adiposity measures mainly before and after diagnosis, as well as various inflammatory biomarkers measured before or after treatment initiation. In general, MR can capture more effectively the effect of exposures across the lifespan and potentially help overcome limitations arising from timing discrepancies in the assessment. However, at the same, it is important to integrate evidence from multiple and diverse study designs when informing robust, evidence-based clinical guidelines.

5.3 FUTURE RESEARCH DIRECTIONS

Considering the high degree of overlap across reviews examining the same exposures, adopting a living systematic review approach should be considered, whereby studies involving patients with CRC are identified, extracted, analyzed, and critically appraised at regular time intervals to ensure that the evidence remains up to date and to minimize research waste. The included systematic reviews provided abundant evidence supporting either an aggravating or a protective role of many of these exposures in CRC prognosis. For some exposures also, their effects were investigated at different time points in relation to tumor diagnosis or treatment initiation. However, the reviews' low methodological quality suggests that many researchers conducting and publishing systematic reviews either do not adhere to established reporting guidelines, such as PRISMA (61), or use suboptimal methodological approaches. At the same time, the use of more contemporary tools at the systematic review level for assessing the risk of bias, such as ROBINS-E (229), is recommended to enable a comprehensive evaluation of important systematic errors in the conduct, analysis and reporting of cohort studies. Future research should also focus on assessing the quality of the evidence presented in our overview of reviews.

In addition, larger GWASs on the studied exposures and outcomes may enable more efficient investigation of associations that were underpowered in our MR study. Future clinical studies may help elucidate the biological mechanisms linking anthropometric traits, inflammation, and their interplay to CRC prognosis, as the current evidence remains limited. Studies accounting for the potential genetic correlation among some of these exposures (for example, body mass index and waist circumference) may provide further insight into the observed associations. Future MR studies could leverage individual-level data to investigate the potential for collider bias in greater detail.

5.4 CONCLUSION

Despite significant progress in elucidating the aetiology of CRC incidence, its prognosis remains less well studied and more complex. This thesis aimed to provide an overview of a wide range of non-therapeutic factors that may influence mortality and

recurrence and hopefully encourage further future research into how these factors may contribute to improved outcomes following diagnosis.

ABSTRACT IN ENGLISH

Colorectal cancer (CRC) is the third most common cancer and second deadliest malignant tumor among adult populations worldwide. The prognosis of CRC is influenced by clinical, pathological, and treatment-related characteristics, as well as by a range of non-therapeutic factors. There is a clear need within the scientific community to map the associations between these non-therapeutic factors and key clinical outcomes following CRC diagnosis, such as all-cause mortality, CRC-specific mortality, and disease recurrence, as investigated in prospective and retrospective cohort studies. Furthermore, advanced statistical approaches are required to address the inherent limitations of observational studies, including confounding and reverse causation. This doctoral thesis addressed these research questions through (1) an overview of systematic reviews of prospective and retrospective cohort studies and (2) a two-sample Mendelian randomization (MR) study investigating the associations between genetically-predicted levels of a broad range of non-therapeutic factors and the risk of CRC-specific mortality.

To address the first objective, published systematic reviews of prospective and retrospective cohort studies investigating the associations between non-therapeutic risk factors and the risk of all-cause mortality, CRC-specific mortality, or disease recurrence were identified, appraised, and synthesized. The literature search yielded 161 systematic reviews investigating a total of 55 non-therapeutic exposures, which were classified into ten broad categories: anthropometric measures, inflammatory biomarkers and indices, diet and nutrition, sociodemographic characteristics, comorbidities, lifestyle, quality of life factors, drugs, and other biomarkers. Thirty-three exposures were investigated in more than one systematic review. According to the Corrected Covered Area (CCA) index, only eight exposures demonstrated low overlap across systematic reviews. For the remaining 25 exposures, the CCA reached values of up to 75%, indicating substantial overlap. In cases of substantial overlap, the systematic review including the largest number of primary studies was retained and the most recent, if possible. Overall, 65 systematic reviews were included, providing evidence on 538 main associations. Overall, 95.2% of these associations concerned CRC regardless of anatomical subsite or disease stage. The most frequently investigated outcome was all-cause mortality, while more than half of the associations involved

exposures assessed after CRC diagnosis. Meta-analysis was conducted for 315 associations, with random-effects model representing the primary analytical approach. According to the AMSTAR 2 tool, the methodological quality of 62 of the 65 included systematic reviews was judged to be critically low.

To address the second objective, the MR analysis investigated anthropometric and metabolic traits (height, body mass index, birth weight, waist circumference, hip circumference, waist-to-hip ratio, body fat percentage, and basal metabolic rate), lipid-related traits (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), glycaemic and insulin-related traits (type 2 diabetes, fasting glucose, fasting insulin, HbA1c, and 2-hour glucose following a 75-g oral glucose tolerance test), lifestyle-related factors (physical activity, smoking, alcohol consumption, and circulating vitamin D), inflammatory biomarkers [C-reactive protein and insulin-like growth factor-1 (IGF-1)], and sex hormones (testosterone and sex hormone-binding globulin). Analyses were performed overall, as well as by anatomical site and tumor stage. In addition, several sensitivity analyses were conducted to evaluate the MR assumptions and to investigate the potential impact of collider bias using three recently developed methods: Simulation Extrapolation (SIMEX), Slope-hunter, and Corrected Weighted Least Squares (CWLS). The results demonstrated that one standard deviation increment in genetically-predicted levels of waist circumference and IGF-1 levels was associated with a statistically significant 22% [hazard ratio (HR): 1.22, 95% confidence interval (CI): 1.02–1.47 and 17% (HR: 1.17, 95% CI: 1.05–1.31) increase in the risk of CRC-specific mortality, respectively. Additional significant associations were observed between genetically predicted IGF-1 levels and rectal cancer mortality (HR: 1.39, 95% CI: 1.10–1.74), as well as between hip circumference (HR: 1.33, 95% CI: 1.02–1.73) and body mass index (HR: 1.50, 95% CI: 1.15–1.95) and CRC-specific mortality among patients with stage II/III disease. Sensitivity analyses assessing the impact of collider bias yielded estimates that were largely consistent with the primary analyses.

These findings hopefully will encourage further future research into how non-therapeutic factors may contribute to improved outcomes following CRC diagnosis

ΠΕΡΙΛΗΨΗ ΣΤΑ ΕΛΛΗΝΙΚΑ

Ο καρκίνος του παχέος εντέρου είναι ο τρίτος σε επίπτωση και δεύτερος σε θνητότητα καρκίνος σε ενήλικους πληθυσμούς παγκοσμίως. Η πρόγνωση της νόσου φαίνεται να επηρεάζεται από κλινικές, παθολογικές και θεραπευτικές παραμέτρους, αλλά και από μια σειρά μη θεραπευτικών παραγόντων. Υπάρχει σαφής ανάγκη στην επιστημονική κοινότητα για τη χαρτογράφηση των συσχετίσεων μεταξύ αυτών των μη θεραπευτικών παραγόντων και βασικών κλινικών εκβάσεων μετά τη διάγνωση της νόσου, όπως οι κίνδυνοι θνητότητας και υποτροπής, όπως αυτές έχουν μελετηθεί σε προοπτικές ή αναδρομικές μελέτες κοόρτης. Επιπρόσθετα, εξελιγμένες στατιστικές προσεγγίσεις είναι αναγκαίες προκειμένου να ξεπεραστούν οι εγγενείς περιορισμοί αυτών των μελετών, όπως είναι η ύπαρξη συγχυτικής δράσης και η αντίστροφη αιτιότητα. Η παρούσα διδακτορική διατριβή επιχείρησε να απαντήσει σε αυτά τα ερευνητικά ερωτήματα μέσω της διεξαγωγής (1) μιας ανασκόπησης συστηματικών ανασκοπήσεων που περιλάμβαναν αναδρομικές ή προοπτικές μελέτες κοόρτης, όπως και (2) μιας μελέτης Μεντελιανής Τυχαιοποίησης δύο δειγμάτων στην οποία διερευνήθηκαν οι συσχετίσεις μεταξύ των γενετικά προβλεπόμενων επιπέδων ενός ευρέος φάσματος μη θεραπευτικών παραγόντων και του κινδύνου θνητότητας από καρκίνο παχέος εντέρου.

Για τις ανάγκες του πρώτου στόχου, αναζητήθηκαν, συλλέχθηκαν και αξιολογήθηκαν ως προς τη μεθοδολογική τους ποιότητα, δημοσιευμένες συστηματικές ανασκοπήσεις αναδρομικών και προοπτικών μελετών κοόρτης που διερεύνησαν τις συσχετίσεις μεταξύ μιας σειράς μη θεραπευτικών παραγόντων και του κινδύνου θνητότητας από οποιαδήποτε αιτία ή από καρκίνο του παχέος εντέρου, καθώς και υποτροπής της νόσου. Από την αναζήτηση, προέκυψαν 161 συστηματικές ανασκοπήσεις οι οποίες αφορούσαν συνολικά 55 μη θεραπευτικούς παράγοντες και οι οποίοι εντάσσονταν σε 10 ευρείς κατηγορίες: ανθρωπομετρικοί δείκτες, δείκτες φλεγμονής, διατροφή, κοινωνικοδημογραφικοί παράγοντες, συννοσηρότητες, τρόπος και ποιότητα ζωής, λήψη φαρμάκων και άλλοι βιοδείκτες. Τριάντα τρεις μη θεραπευτικοί παράγοντες μελετήθηκαν σε περισσότερες από μια συστηματικές ανασκοπήσεις. Με βάση τον δείκτη της Διορθωμένης Καλυμμένης Περιοχής (Corrected Covered Area, CCA), σε μόλις 8 μη θεραπευτικούς παράγοντες, οι συστηματικές ανασκοπήσεις παρουσίασαν χαμηλή αλληλεπικάλυψη, δηλαδή δεν περιλάμβαναν τις ίδιες πρωτογενείς μελέτες. Για τις υπόλοιπες 25, ο δείκτης έφτασε

μέχρι και το 75% συνιστώντας σημαντική αλληλεπικάλυψη. Στις περιπτώσεις σημαντικής αλληλεπικάλυψης, επιλέχθηκε η συστηματική ανασκόπηση με τις περισσότερες μελέτες και, αν ήταν εφικτό, η πιο πρόσφατη. Με βάση αυτά τα κριτήρια, συμπεριλήφθηκαν τελικώς 65 συστηματικές ανασκοπήσεις που αφορούσαν κατά βάση 538 συσχετίσεις. Το 95,2% αυτών των συσχετίσεων αφορούσε τον καρκίνο του παχέος εντέρου συνολικά, ανεξαρτήτως συγκεκριμένης ανατομικής εντόπισης ή σταδίου. Η πιο συχνά μελετώμενη έκβαση ήταν η θνητότητα από οποιοδήποτε αιτία και περισσότερες από τις μισές συσχετίσεις, αφορούσαν εκθέσεις εκτιμώμενες μετά τη διάγνωση της νόσου. Σε 315 συσχετίσεις συνολικά, πραγματοποιήθηκε ποσοτική σύνθεση των αποτελεσμάτων των πρωτογενών μελετών, με το μοντέλο των τυχαίων επιδράσεων να αποτελεί την κύρια προσέγγιση. Σύμφωνα με το εργαλείο AMSTAR-2, η μεθοδολογική ποιότητα των συστηματικών ανασκοπήσεων κρίθηκε πολύ χαμηλή στις 62 από τις 65 συστηματικές ανασκοπήσεις.

Για τις ανάγκες του δεύτερου στόχου, οι μελετώμενοι μη θεραπευτικοί παράγοντες ήταν ανθρωπομετρικοί και μεταβολικοί δείκτες (ύψος, δείκτης μάζας σώματος, βάρος γέννησης, περιφέρεια μέσης, περιφέρεια γλουτών, λόγος περιφέρειας μέσης-περιφέρειας γλουτών, ποσοστό σωματικού λίπους, βασικός μεταβολικός ρυθμός), λιπιδαιμικοί δείκτες (ολική χοληστερόλη, HDL χοληστερόλη, LDL χοληστερόλη, τριγλυκερίδια), σακχαρώδης διαβήτης και σχετικοί δείκτες (γλυκόζη νηστείας, ινσουλίνη νηστείας, γλυκοζυλιωμένη, γλυκόζη ύστερα από 2 ώρες αφού έχουν ληφθεί 75 γραμμάρια πόσιμης γλυκόζης), τρόπος ζωής (σωματική δραστηριότητα, κάπνισμα, κατανάλωση αλκοόλ, επίπεδα βιταμίνης D στο αίμα), δείκτες φλεγμονής (C-αντιδρώσα πρωτεΐνη, ινσουλινόμορφος αυξητικός παράγοντας-1) και ορμόνες φύλου (τεστοστερόνη και σφαιρίνη δεσμεύουσα στις φυλετικές ορμόνες). Οι αναλύσεις πραγματοποιήθηκαν τόσο για το συνολικό δείγμα όσο και ανά ανατομική εντόπιση και στάδιο του όγκου. Επιπλέον, πραγματοποιήθηκε μια σειρά αναλύσεων ευαισθησίας για την αξιολόγηση των βασικών παραδοχών της Μεντελιανής Τυχαιοποίησης και τη διερεύνηση της πιθανής επίδρασης της μεροληψίας λόγω επιλογής (collider bias) χρησιμοποιώντας τρεις πρόσφατα δημοσιευμένες μεθόδους [Simulation Extrapolation SIMEX, Slope-hunter, Corrected Weighted Least Squares (CWLS)]. Τα αποτελέσματα κατέδειξαν ότι για κάθε μία τυπική απόκλιση αύξησης στα επίπεδα της περιφέρειας μέσης και του ινσουλινόμορφου αυξητικού παράγοντα-1, ο κίνδυνος θνητότητας από καρκίνο παχέος εντέρου αυξήθηκε στατιστικά σημαντικά κατά 22% [λόγος αναλογικών κινδύνων (ΛΚ): 1,22, 95%

διάστημα εμπιστοσύνης (ΔΕ): 1,02-1,47] και 17% (ΛΚ: 1,17, 95% ΔΕ: 1,05-1,31) αντίστοιχα. Άλλες σημαντικές συσχετίσεις ήταν εκείνη του ινσουλινόμορφου αυξητικού παράγοντα-1 με τον κίνδυνο θνητότητας από καρκίνο στο ορθό (ΛΚ: 1,39, 95% ΔΕ: 1,1-1,74) και οι συσχετίσεις της περιφέρειας γλουτών (ΛΚ: 1,33, 95% ΔΕ: 1,02-1,73) και του δείκτη μάζας σώματος (ΛΚ: 1,5, 95% ΔΕ: 1,15-1,95) με τον κίνδυνο θνητότητας από καρκίνο παχέος εντέρου σταδίων ΙΙ και ΙΙΙ. Οι αναλύσεις ευαισθησίας για την επίδραση μεροληψίας λόγω επιλογής δεν φάνηκαν να παρουσιάζουν διαφορετικούς εκτιμητές.

Τα ευρήματα της παρούσας διατριβής μπορούν να αποτελέσουν κινητήριο δύναμη για μελλοντικές ερευνητικές δράσεις στο πεδίο της πρόγνωσης του καρκίνου παχέος εντέρου.

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SUPPORTING INFORMATION

DEVIATIONS FROM THE PROTOCOL OF THE OVERVIEW OF REVIEWS

- We included non-genetic biomarkers but further specified that only non-genetic biomarkers measured systemically (i.e., in blood, serum, or urine) were eligible. Biomarkers measured in healthy or cancerous tissues or cells were not considered eligible. Meta-analyses of non-genetic biomarkers measured both systemically and in tissue that did not provide separate estimates for each subgroup were not considered eligible.
- To ensure the methodological rigor of the included evidence, we included only meta-analyses based exclusively on adjusted effect estimates. Meta-analyses that combined adjusted and unadjusted effect estimates were excluded. When a systematic review did not perform a meta-analysis, we extracted only the study-specific adjusted effect estimates.
- If a systematic review that did not perform a meta-analysis failed to report effect estimates for all relevant studies, it was not considered eligible for that specific association.
- As we were not always able to verify the timing of exposure assessment (pre-diagnosis, at diagnosis, or post-diagnosis), we decided to include all relevant exposures regardless of when they were assessed.
- We pre-specified that the selection of the final review(s) for each exposure-outcome association would be based on the number of included studies, year of publication, and methodological quality. However, most of the identified systematic reviews were rated as having low methodological quality according to AMSTAR-2. Therefore, among overlapping reviews, the final review was selected solely on the basis of the number of included studies and the year of publication, if possible.
- Anastomotic leakage was not considered eligible, as it was not directly relevant to any of the exposures of interest. In addition, it is a short-term adverse event only associated with a specific therapeutic intervention (surgery), limiting the generalizability of the findings to a broader CRC population.

Table S3.1: Search algorithm applied in PubMed for the overview of reviews on non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

# of search	Search terms
1	Colorectal neoplasms[MeSH Terms]
2	cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR malign*[Title/Abstract]
3	colon[Title/Abstract] OR rectum[Title/Abstract] OR rectal[Title/Abstract] OR colorectum[Title/Abstract] OR colorectal[Title/Abstract] OR "large bowel"[Title/Abstract] OR "large intestine"[Title/Abstract] OR gut[Title/Abstract]
4	#2 AND #3
5	Recurrence[MeSH Terms] OR "Neoplasm Recurrence, Local"[MeSH Terms] OR "Disease Progression"[MeSH Terms] OR "Disease-Free Survival"[MeSH Terms] OR Mortality[MeSH Terms] OR "Survival Analysis" [MeSH Terms]
6	mortality[Title/Abstract] OR death[Title/Abstract] OR dead*[Title/Abstract] OR fatal*[Title/Abstract] OR surviv*[Title/Abstract] OR recurren*[Title/Abstract] OR relapse*[Title/Abstract] OR progress*[Title/Abstract] OR prognos*[Title/Abstract] OR metasta*[Title/Abstract] OR "second cancer"[Title/Abstract] OR "second cancers"[Title/Abstract] OR "secondary cancer"[Title/Abstract] OR "secondary cancers"[Title/Abstract]
7	(systematic[Title/Abstract] AND (review*[Title/Abstract] OR overview*[Title/Abstract])) OR "meta analysis"[Title/Abstract] OR "meta analyses"[Title/Abstract] OR meta-analysis[Title/Abstract] OR meta-analyses[Title/Abstract] OR "evidence synthesis" [Title/Abstract]
8	(#1 OR #4) AND (#5 OR #6) AND #7

Table S3.2: Search algorithm applied in Embase for the overview of reviews on non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

# of search	Search terms
1	colorectal cancer/ or colon carcinoma/ or colon tumor/ or colon cancer/ or rectum carcinoma/ or rectum tumor/ or rectum cancer/
2	(colorectal or colon or rectum).ab,ti.
3	(cancer$ or neoplasm$ or tumour$ or tumor$ or carcinoma$ or adenocarcinoma$ or malign$).ab,ti.
4	2 and 3
5	*Recurrent disease/
6	*Disease exacerbation/
7	Disease free survival/
8	mortality/ or all-cause mortality/ or cancer mortality/ or cardiovascular mortality/ or mortality rate/ or premature mortality/

9	Survival analysis/
10	Relapse/
11	Survivor/
12	Second cancer/
13	(mortality or death or dead$ or fatal$ or surviv$ or recurren$ or relapse$ or progress$ or prognos$ or metasta$ or (second$ adj1 cancer$)).ab,ti.
14	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	((systematic adj2 review$) or (systematic adj2 overview$) or (meta adj1 analys#s) or meta-analys#s or (evidence adj1 synthesis)).ab,ti.
16	(1 or 4) and 14 and 15

Table S3.3: Search algorithm applied in Scopus for the overview of reviews on non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

# of search	**Search terms**
1	cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malign*
2	colon OR rectum OR rectal OR colorectum OR colorectal OR “large bowel” OR “large intestine” OR gut
3	mortality OR death OR dead* OR fatal* OR surviv* OR recurren* OR relapse* OR progress* OR prognos* OR metasta* OR “second cancer” OR “second cancers” OR “secondary cancer” OR “secondary cancers”
4	(systematic AND (review* OR overview*)) OR “meta analysis” OR “meta analyses” OR meta-analysis OR meta-analyses OR “evidence synthesis”
5	#1 AND #2 AND #3 AND #4

Table S3.4: Search algorithm applied in Epistemonikos for the overview of reviews on non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

# of search	**Search terms**
1	(title:(cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malign*) OR abstract:(cancer* OR neoplasm* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR malign*))
2	(title:(colon OR rectum OR rectal OR colorectum OR colorectal OR "large bowel" OR "large intestine" OR gut) OR abstract:(colon OR rectum OR rectal OR colorectum OR colorectal OR "large bowel" OR "large intestine" OR gut))
3	(title:(mortality OR death OR dead* OR fatal* OR surviv* OR recurren* OR relapse* OR progress* OR prognos* OR metasta* OR "second cancer" OR "second cancers" OR "secondary cancer" OR "secondary cancers") OR abstract:(mortality OR death OR dead* OR fatal* OR surviv* OR recurren* OR relapse* OR progress* OR

	prognos* OR metasta* OR "second cancer" OR "second cancers" OR "secondary cancer" OR "secondary cancers"))
4	(title:((systematic AND (review* OR overview*)) OR "meta analysis" OR "meta analyses" OR meta-analysis OR meta-analyses OR "evidence synthesis") OR abstract:((systematic AND (review* OR overview*)) OR "meta analysis" OR "meta analyses" OR meta-analysis OR meta-analyses OR "evidence synthesis"))
5	#1 AND #2 AND #3 AND #4

Table S3.5: Identified systematic reviews per exposure along with the decision rationale for the overview of reviews on non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

Number of overlapping reviews	CCA	Overlapping reviews	Chosen reviews	Decision rationale
Advanced lung cancer inflammation index				
3	75%	Xie (2023) (69), Liu (2023) (70), Zhang (2023) (71)	Zhang (2023)	We chose Zhang (2023) because it included the largest number of studies.
Albumin to globulin ratio				
2	20%	Ma (2022) (72), Delladio (2024) (73)	Ma (2022)	We chose Ma (2022) because it included the largest number of studies.
Alcohol, diet and supplements				
13	11.8%	van Meer (2013) (75), Schwingshackl (2015) (76), McMenamin (2017) (77), Kim (2019) (54), Hoang (2020) (78), Kanellopoulou (2021) (79), Micek (2021) (80), Castro Espin (2022) (81), Zhao (2022) (82), Chan (2024) (52), Fretwell (2024) (83), Zhu (2024)	Kim (2019), Hoang (2020), Chan (2024)	We chose Chan (2024) because it included more studies than Schwingshackl (2015), McMenamin (2017), Kanellopoulou (2021), Fretwell (2024), Zhu (2024) and Chen (2025). As Chan (2024) focused on post-diagnostic assessments, we also chose Kim (2019) for pre-diagnostic alcohol consumption, and Hoang (2020) for pre-diagnostic dietary factors and dietary patterns. These two reviews were the most comprehensive with

		(84), Chen (2025) (85)		regards to the pre-diagnostic analyses. van Meer (2013), Micek et (2021), Castro Espin (2022) and Zhao (2024) overlapped with Hoang (2020).
Anemia				
1	-	Wilson (2017) (86)	Wilson (2017)	-
Apolipoprotein A1				
1	-	Zhang (2018) (87)	Zhang (2018)	-
Aspirin				
8	29.6%	Ye (2014) (88), Li (2015) (89), Elwood (2016) (91), Paleari (2016) (92), Lin (2020) (49), Elwood (2021) (90), Mädge (2022) (93), Petrelli (2025) (94)	Petrelli (2025)	We chose Petrelli (2025) because it was the most recent review including the largest number of studies.
Bisphosphonates				
1	-	Wen (2018) (95)	Wen (2018)	-
Body mass index				
7	10.5%	Schlesinger (2014) (96), Parkin (2014) (97), Lee (2015) (98), Doleman (2016) (99), Han (2017) (100), Becerra Tomas (2024) (68), Chen (2025) (85)	Doleman (2016), Becerra Tomas (2024)	We chose Becerra Tomas (2024) because it included the largest number of studies. Lee (2015) and Doleman (2016) reported separate analyses of pre-diagnostic and/or peri-diagnostic body mass index measurements. We chose Doleman (2016) because it was the most recent review including the largest number of studies.
Cachexia				
3	20%	Xu (2024) (101), Zhang (2024) (102),	Zhang (2024)	Xu (2024) and Zhang (2024) were published during the same year and included the largest

		Dunne (2024) (103)		number of studies. We chose Zhang (2024) as it provided the detailed adjustments per study.
Circulating vitamin D				
10	21.3%	Buttigliero (2011) (104), Pilz (2013) (105), Li (2014) (111), Maalmi (2014) (109), Toriola (2014) (112), Vaughan-Shaw (2017) (106), Maalmi (2018) (110), Xu (2018) (108), Ottaiano (2023) (107), Chan (2024) (52)	Chan (2024)	We chose Chan (2024) because it was the most recent review including the largest number of studies.
Comorbidity				
2	0%	Lee (2011) (113), Ohta (2025) (114)	Lee (2011), Ohta (2025)	There was no overlap across the reviews so we included both of them.
Controlling nutritional status				
2	25%	Takagi (2020) (129), Vatvani (2025) (128)	Vatvani (2025)	We chose Vatvani (2025) because it was the most recent review including the largest number of studies.
C-reactive protein				
2	0%	Zhao (2022) (115), Gwenzi (2023) (116)	Zhao (2022), Gwenzi (2023)	There was no substantial overlap across the reviews so we included both of them.
C-reactive protein to albumin ratio				
4	52.8%	Fan (2019) (118), Wang (2019) (117), Zhou (2019) (120), Liao (2021) (119)	Liao (2021)	We chose Liao (2021) because it was the most recent review including the largest number of studies.
Dementia				
1	-	Hopkinson (2016) (121)	Hopkinson (2016)	-
Depression and anxiety				

1	-	Xia (2024) (122)	Xia (2024)	-
Diabetes				
5	12.1%	Barrone (2008) (123), Stein (2010) (124), Li (2017) (125), Zhu (2017) (126), Petrelli (2021) (127)	Petrelli (2021)	We chose Petrelli (2021) because it was the most recent review including the largest number of studies.
Fibrinogen				
4	31.5%	Perisanidis (2015) (130), Ji (2018) (131), Lin (2018) (132), Li (2019) (133)	Li (2019)	We chose Li (2019) because it was the most recent review including the largest number of studies.
Fibrinogen to albumin ratio				
2	40%	Li (2022) (134), Su (2025) (135)	Su (2025)	We chose Su (2025) because it was the most recent review including the largest number of studies.
Frailty				
3	37.5%	Chen (2022) (136), McGovern (2022) (137), Han (2024) (138)	Chen (2022)	We chose Chen (2022) because it included the largest number of studies.
Geriatric nutritional index				
5	70%	Xie (2020) (153), Mao (2022) (155), Zhao (2022) (151), Yuan (2023) (154), Xu (2023) (152)	Zhao (2022)	Mao (2022), Zhao (2022) and Yuan (2023) included the largest number of studies. We chose Zhao (2022) as it reported the detailed adjustments per study.
Glasgow and modified Glasgow prognostic score				
1	-	Gwenzi (2023) (116)	Gwenzi (2023)	-
Global leadership initiative on malnutrition				
1	-	Zhang (2025) (150)	Zhang (2025)	-
Hormone replacement therapy				

1	-	Jang (2019) (149)	Jang (2019)	-
Human immunodeficiency virus				
1	-	Pumpalova (2021) (148)	Pumpalova (2021)	-
Lactate dehydrogenase to albumin ratio				
1	-	Dwi Purwati (2025) (147)	Dwi Purwati (2025)	-
Lymphocyte to monocyte ratio				
6	18.4%	Song (2016) (146), Guo (2017) (145), Tan (2018) (144), Portale (2023) (143), Mei (2025) (142), Meng (2025) (141)	Meng (2025), Mei (2025)	We chose Meng (2025) and Mei (2025) because they were the most recent reviews including the largest numbers of studies, and did not overlap (CCA; 0%).
Metabolic syndrome				
2	14.3%	Lu (2022) (140), Okazaki (2025) (139)	Lu (2022)	We chose Lu (2022) because it included the largest number of studies.
Metformin				
8	23.5%	Mei (2014) (51), He (2016) (224), Du (2017) (157), Meng (2017) (158), Tian (2017) (159), Deng (2020) (160), Wang (2020) (161), Georgopoulos (2023) (162)	Tian (2017)	We chose Tian (2017) because it included the largest number of studies.
Myosteatosis				
1	-	Lee (2020) (163)	Lee (2020)	-
Neutrophil to lymphocyte ratio				
7	5.2%	Malietzis (2014) (164), Mei (2017) (165), Li (2019) (166), Lee (2022) (167), Lin (2022), Zhao	Mei (2017), Li (2019), Lin (2022), Zhao (2022), Portale (2023)	There was no substantial overlap across the reviews. We did not choose Malietzis (2014) because it overlapped with Mei (2017) (CCA: 18.2%), and Lee (2022)

		(2022) (115), Portale (2023) (143)		because it overlapped with Portale (2023) (CCA; 16.7%).
Osteopenia				
1	-	Watanabe (2022) (169)	Watanabe (2022)	-
Pan-immune-inflammation index				
1	-	Yang (2022) (170)	Yang (2022)	-
Patient reported outcomes				
3	5.6%	Montazeri (2009) (171), Zylla (2017) (172), Zang (2024) (173)	Zang (2024)	Although the overall CCA was low, the pairwise CCAs were high. We chose Zang (2024) because it was the most recent review including the largest number of studies.
Peripheral monocyte counts				
1	-	Wen (2019) (174)	Wen (2019)	-
Physical activity				
13	22%	Barbaric (2010) (175), Des Guetz (2013) (176), Ballard Barbash (2013) (177), Je (2013) (178), Schmid (2014) (179), Wu (2016) (180), Zhou (2016) (181), Cormie (2017) (182), Friedenreich (2019) (183), Hong (2021) (184), Choy (2022) (185), Markozannes (2024) (48), Chen (2025) (85)	Markozannes (2024)	We chose Markozannes (2024) because it included the largest number of studies.
Plasma d-dimer				
3	32.1%	Lu (2017) (186), Lin (2018) (132),	Lu (2017)	We chose Lu (2017) because it included the

		Li (2018) (188)		largest number of studies.
Platelet to lymphocyte ratio				
9	7.9%	Gu (2016) (195), Peng (2016) (194), Chen (2017) (193), Huang (2017) (192), Wang (2021) (191), Guo (2023) (190), Portale (2023) (143), Meng (2025) (141), Yu (2025) (189)	Chen (2017), Guo (2023), Meng (2025), Yu (2025)	There was no substantial overlap across the reviews. We did not choose Gu (2016), Peng (2016) and Huang (2017) because they overlapped with Chen (2017) (CCA; 28.6%, 50%, 56.2%, respectively). We did not choose Wang (2021) because it overlapped with Guo (2023) (CCA; 17.9%). We did not choose Portale (2023) because it overlapped with Yu (2025) (CCA; 17.4%).
Prognostic nutritional index				
2	14.3%	Yang (2016) (208), Sun (2019) (207)	Sun (2019)	Both reviews included the same number of studies. We chose Sun (2019) because it was the most recent review.
Sarcopenia				
7	7.4%	Levolger (2015) (206), Sun (2018) (205), Haiducu (2021) (204), Xie (2021) (203), Zhu (2022) (202), Watanabe (2022) (169), Lin (2024) (201)	Levolger (2015), Xie (2021), Zhu (2022), Lin (2024)	There was no substantial overlap across the reviews. We did not choose Sun (2018) because it overlapped with Xie (2021) (CCA; 26.7%). We did not choose Haiducu (2021) because it overlapped with Zhu (2022) (CCA; 28.6%). We did not choose Watanabe (2022) because it overlapped with Lin (2024) (CCA; 14.3%).
Sedentary behavior				
3	75%	Swain (2019) (200), Markozannes (2024) (48),	Markozannes (2024)	We chose Markozannes (2024) because it included the largest number of studies.

		Chen (2025) (85)		
Serum albumin				
1	-	Gupta (2010) (199)	Gupta (2010)	-
Serum carbohydrate antigen 19-9				
1	-	Yu (2017) (198)	Yu (2017)	-
Serum/plasma markers of dietary phytoestrogen intake				
1	-	Micek (2021) (80)	Micek (2021)	-
Serum/plasma tissue inhibitor of metalloproteinase-1				
1	-	Lee (2011) (197)	Lee (2011)	-
Sleep				
2	50%	Stone (2019) (196), Chen (2025) (85)	Chen (2025)	We chose Chen (2025) because it was the most recent review including the largest number of studies.
Smoking				
4	23.1%	Walter (2014) (219), McMenamin (2017) (77), Caini (2022) (218), Chen (2025) (85)	McMenamin (2017)	We chose McMenamin (2017) because it included the largest number of studies.
Socioeconomic factors				
2	4.4%	Chua (2025) (217), Lawler (2025) (216)	Chua (2025), Lawler (2025)	There was no substantial overlap across the reviews so we chose both of them.
Statins				
7	41.2%	Zhong (2015) (215), Ling (2015) (214), Cai (2015) (213), Gray (2016) (212), Mei (2017) (211), Dobrzycka (2018) (210), Li (2019) (209)	Li (2019)	We chose Li (2019) because it was the most recent review including the largest number of studies.
Subcutaneous adiposity				
1	-	Cheng (2022) (220)	Cheng (2022)	-

Systemic immune-inflammation index				
1	-	Gao (2022) (223)	Gao (2022)	-
Thrombocytosis				
1	-	Wang (2019) (222)	Wang (2019)	-
Waist circumference				
2	0%	Parkin (2014) (225), Becerra Tomas (2024) (47)	Parkin (2014), Becerra Tomas (2024)	There was no overlap across the reviews so we included both of them.
Waist-hip circumference ratio				
1	-	Parkin (2014) (225)	Parkin (2014)	-
Weight change				
3	40.5%	Dunne (2024) (103), Becerra Tomas (2024) (47), Wang (2025) (221)	Becerra Tomas (2024)	We chose Becerra Tomas (2024) because it included the largest number of studies.

Table S3.6: AMSTAR-2 items and the rationale for assigning a "Yes" rating in the reviews included in the overview of reviews of non-therapeutic risk factors of survival and recurrence following colorectal cancer diagnosis.

No	Item	Decision rationale for Yes
1	Did the research questions and inclusion criteria for the review include the components of Population-Intervention-Comparator-Outcome (PICO)?	All items were described in the Methods (search strategy, inclusion/exclusion criteria, data extraction, statistical analysis).
2	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	All items [review question(s), search strategy, inclusion/exclusion criteria, risk of bias assessment, meta-analysis/synthesis plan, if appropriate, plan for investigating causes of heterogeneity, justification for any deviations from the protocol] were described in the review protocol. For search strategy specifically, we considered the full analytical algorithm used for at least one database, as sufficient information.
3	Did the review authors explain their selection of the study designs for inclusion in the review?	The review provided a clear explanation of why prospective and/or retrospective cohort studies

		were included, either in the Introduction, the search strategy, or the inclusion/exclusion criteria.
4	Did the review authors use a comprehensive literature search strategy?	All items [searched at least two databases, provided key word and/or search strategy, justified publication restrictions (eg, language), searched the reference lists/bibliographies of included studies, searched trial/study registries, included/consulted content experts in the field, where relevant, searched for grey literature, conducted search within 24 months of completion of the review] were reported in the review. For search strategy specifically, we considered the full analytical algorithm used for each database, as sufficient information.
5	Did the review authors perform study selection in duplicate?	At least two reviewers independently screened eligible studies and resolved disagreements through discussion or with the involvement of a third reviewer to reach consensus. Alternatively, two reviewers screened a sample of eligible studies and achieved good agreement (at least 80%), after which the remaining studies were screened by a single reviewer.
6	Did the review authors perform data extraction in duplicate?	At least two reviewers independently extracted data from eligible studies and resolved disagreements through discussion or with the involvement of a third reviewer to reach consensus. Alternatively, two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80%), after which data from the remaining studies were extracted by a single reviewer.
7	Did the review authors provide a list of excluded studies and justify the exclusions?	The review provided a list of all potentially relevant studies that were read in full text form but excluded

		from the review, the reasons for exclusion of each study were reported as well.
8	Did the review authors describe the included studies in adequate detail?	All items (populations, interventions, comparators, outcomes, research designs, study's setting, timeframe for follow-up) were described in detail at the beginning of the Results section, prior to the quantitative or qualitative synthesis of effect estimates. Detailed adjustments done per study were reported as well. The presentation of some of these characteristics in tables or supplementary material was considered acceptable.
9	Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Appropriate tools for assessing risk of bias in cohort studies are ROBINS-I (282) and ROBINS-E (229). In general, the tool used to assess risk of bias needs to be endorsed by the Latitudes Network (). Considering that most of these tools are relatively new, other tools were expected to be used in reviews, such as the Newcastle-Ottawa scale. This scale, however, can partially address confounding and selection bias alone.
10	Did the review authors report on the sources of funding for the studies included in the review	The review reported on the sources of funding for individual studies included in the review. If reviewers looked for this information but it was not reported by study authors, also qualifies
11	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	The reviewers used an appropriate weighted technique to combine study results, adjusting for heterogeneity, if present. For cohort studies, a random-effects rather than a fixed-effect model was considered appropriate. The reviewers also statistically combined effect estimates from cohort studies that were adjusted for confounding,

		rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available.
12	If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	The authors performed analyses to investigate possible impact of risk of bias on summary estimates of effect, such as subgroup analyses according to risk of bias level or sensitivity analyses excluding studies at high risk of bias. We still considered this criterion to be met when reviewers used suboptimal risk of bias assessment tools, such as the Newcastle-Ottawa scale.
13	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	The reviewers discussed two major sources of bias usually present in cohort studies, these were residual confounding and selection bias, in the Results and/or Discussion sections.
14	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	The reviewers investigated potential sources of heterogeneity (for example, through prespecified subgroup analyses or meta-regression) and discussed the implications of this heterogeneity for the review findings in the Results and/or Discussion sections. Such a discussion was considered necessary even when investigation of heterogeneity was not possible (e.g., due to few studies).
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	The reviewers performed graphical and/or statistical assessments of publication bias (e.g., Egger's test, Begg's test, or visual inspection of funnel plots) and discussed the potential presence and impact of publication bias in the Results and/or Discussion sections. Such a discussion was considered necessary even when formal statistical tests or graphical assessments were not conducted.

16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	The reviewers reported no competing interests or described their funding sources and how they managed potential conflicts of interest.

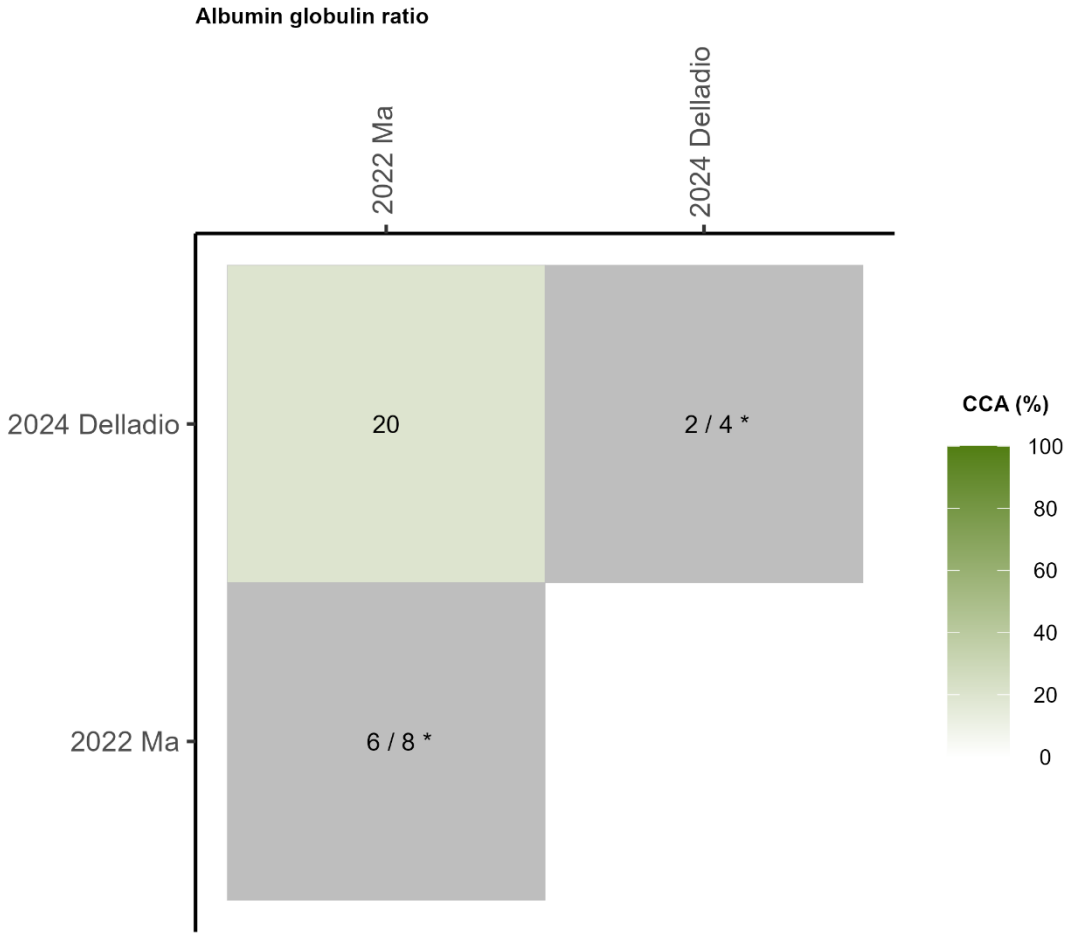

Figure S3.1: Heatmap demonstrating the degree of overlap between pairs of reviews for albumin to globulin ratio using the corrected covered area (CCA) measure.

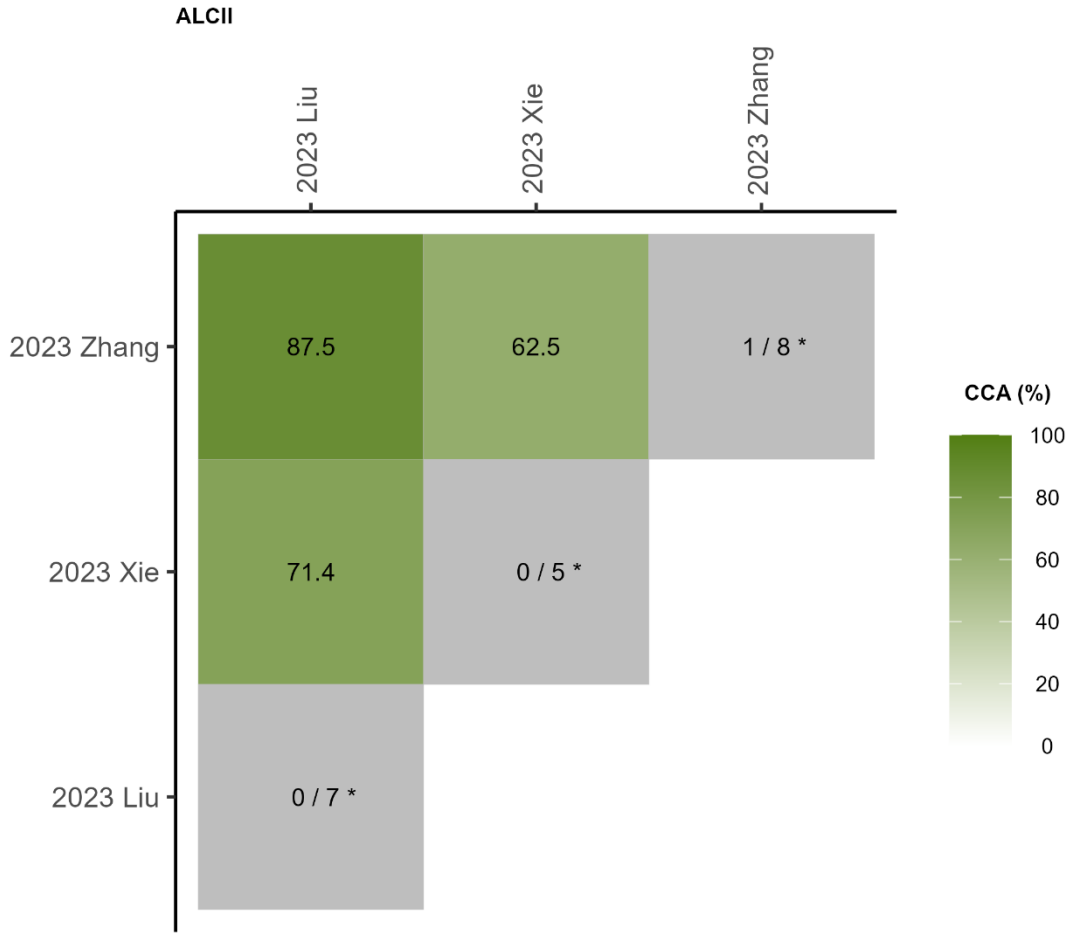

Figure S3.2: Heatmap demonstrating the degree of overlap between pairs of reviews for advanced lung cancer inflammation index (ALCII) using the corrected covered area (CCA) measure.

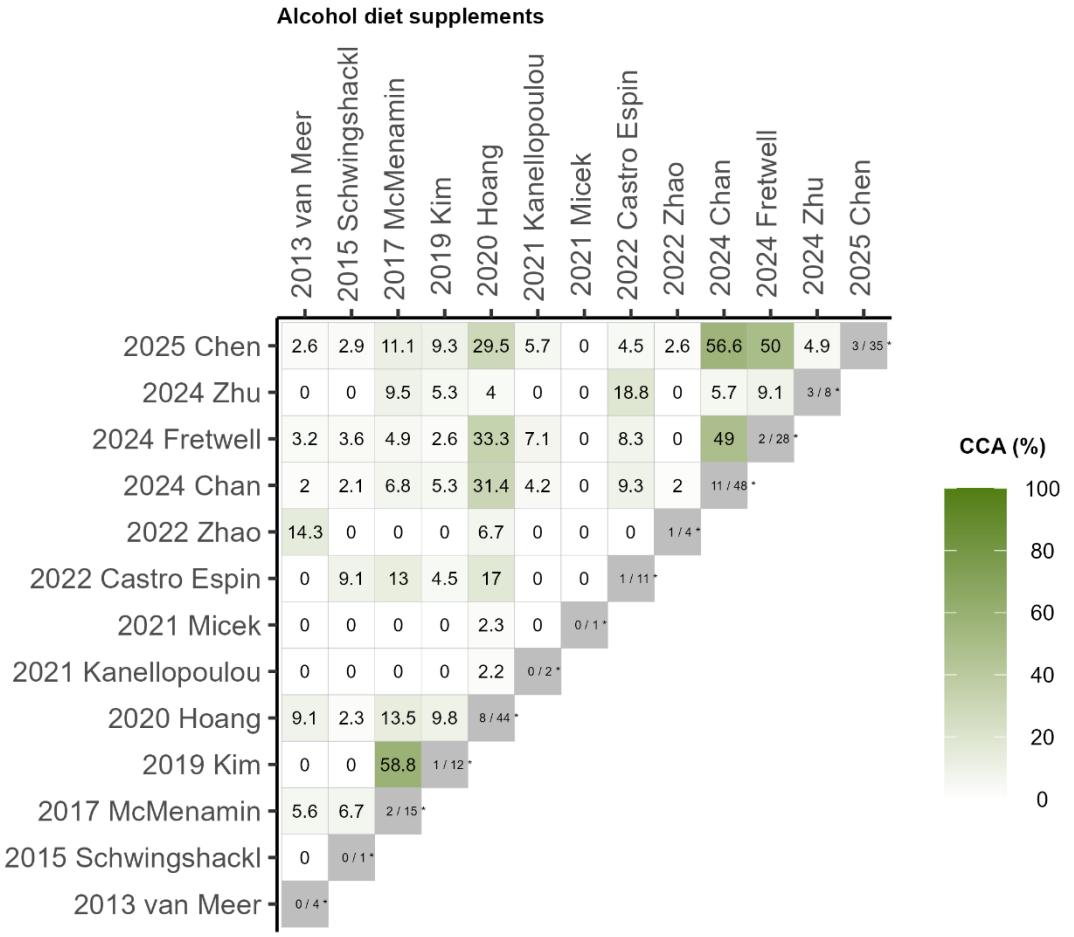

Figure S3.3: Heatmap demonstrating the degree of overlap between pairs of reviews for alcohol, diet and supplements using the corrected covered area (CCA) measure.

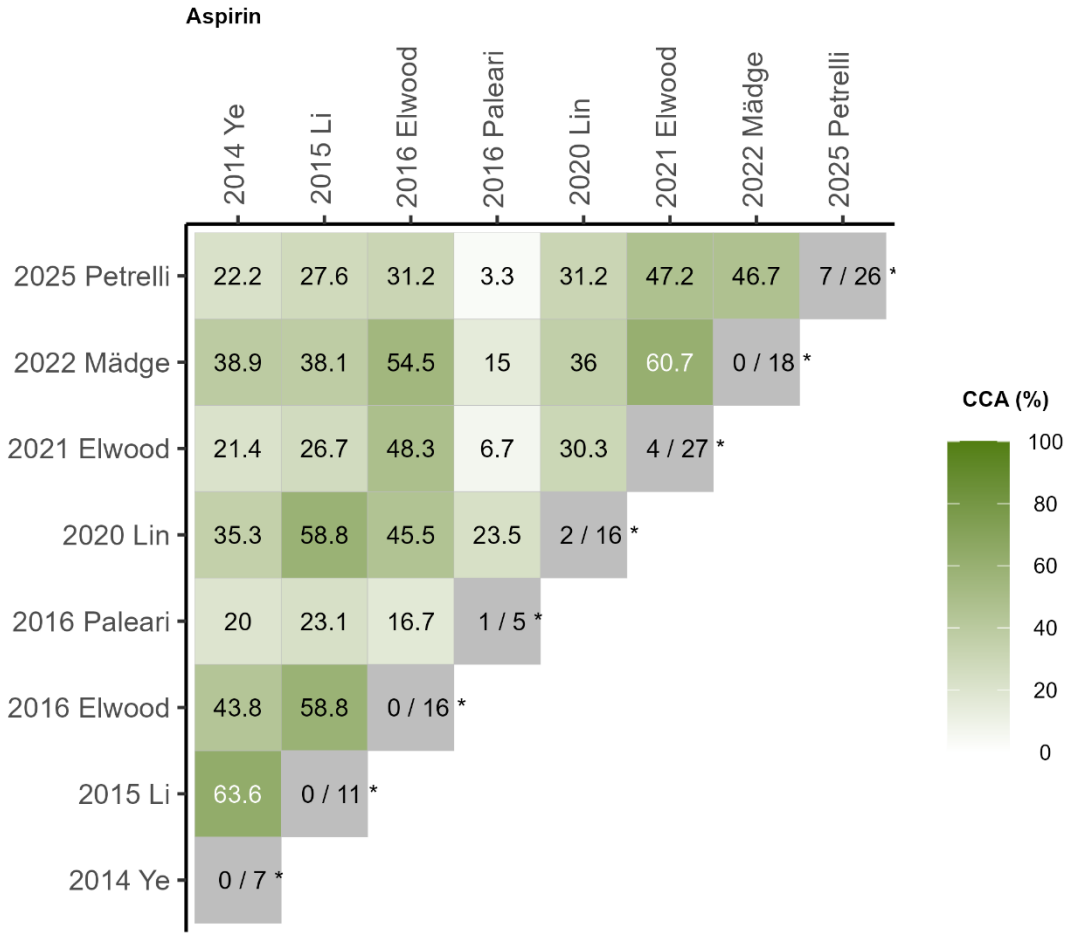

Figure S3.4: Heatmap demonstrating the degree of overlap between pairs of reviews for aspirin using the corrected covered area (CCA) measure.

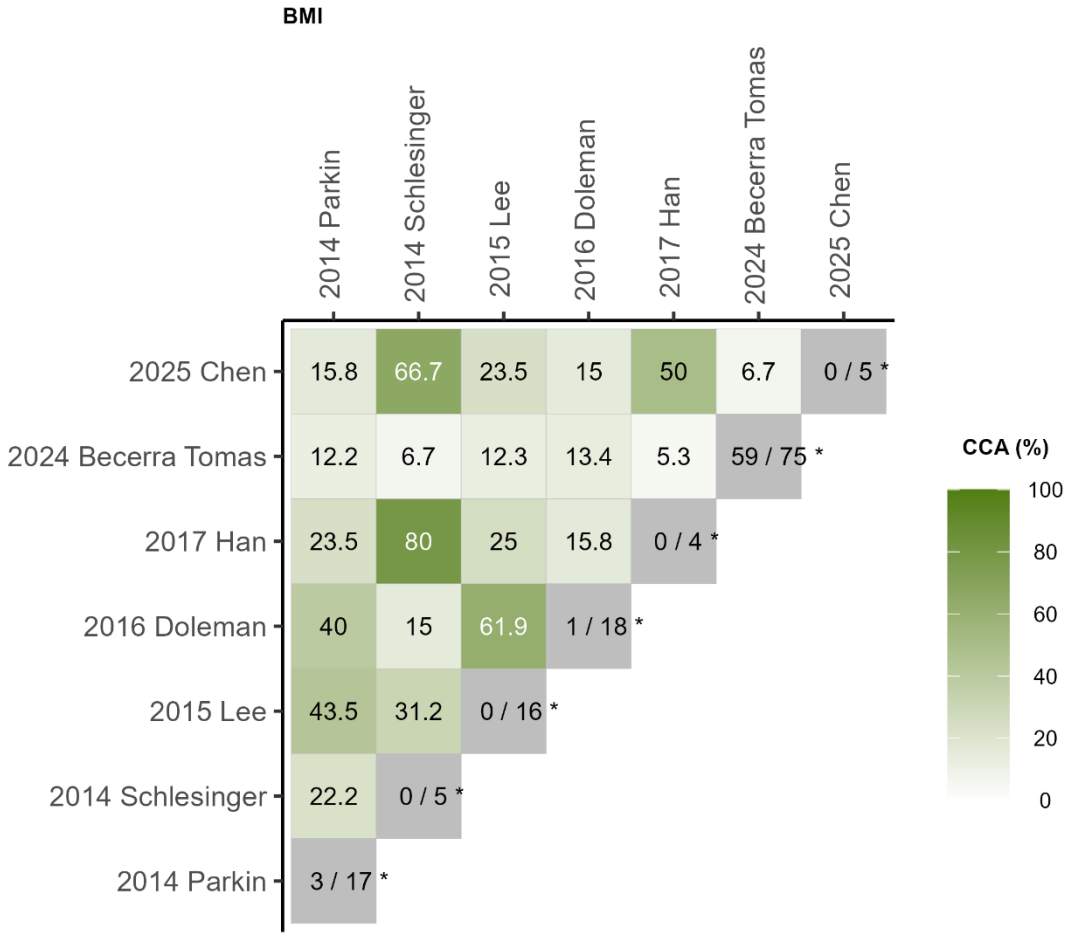

Figure S3.5: Heatmap demonstrating the degree of overlap between pairs of reviews for body mass index (BMI) using the corrected covered area (CCA) measure.

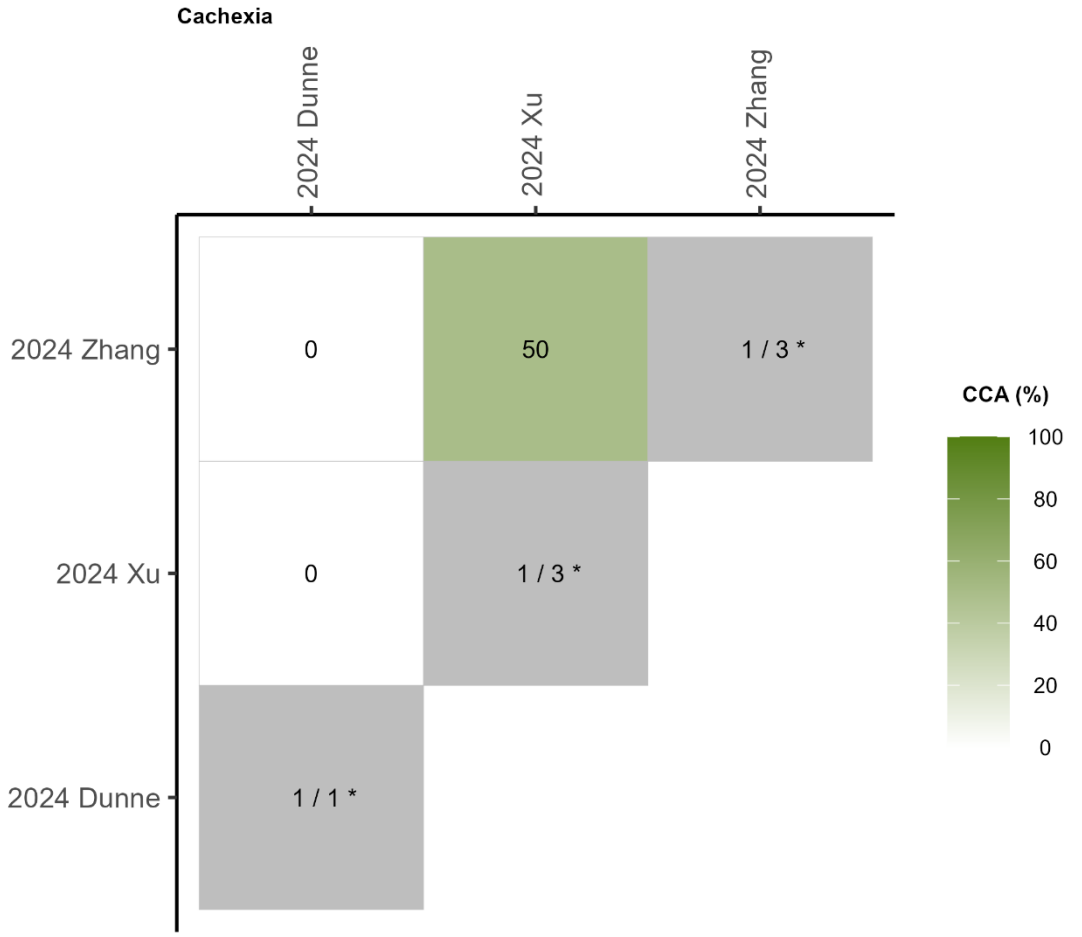

Figure S3.6: Heatmap demonstrating the degree of overlap between pairs of reviews for cachexia using the corrected covered area (CCA) measure.

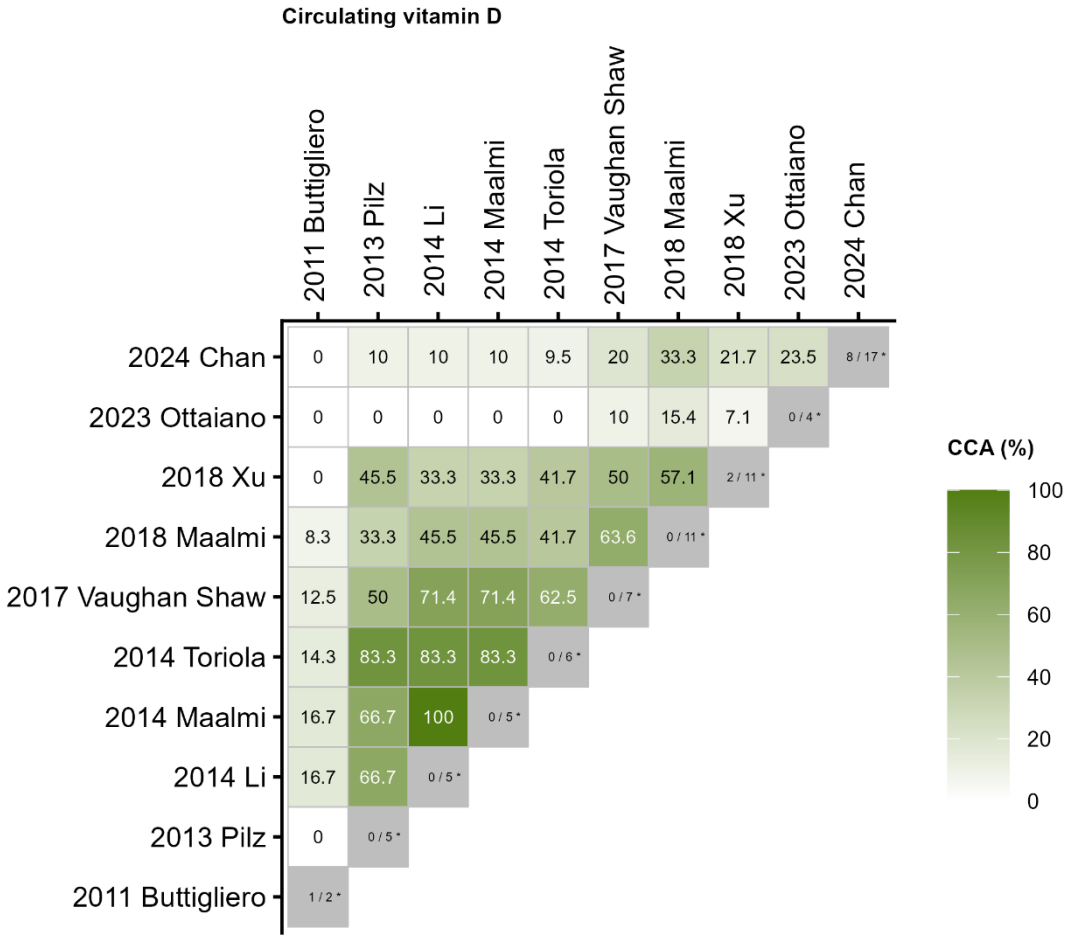

Figure S3.7: Heatmap demonstrating the degree of overlap between pairs of reviews for circulating vitamin D using the corrected covered area (CCA) measure.

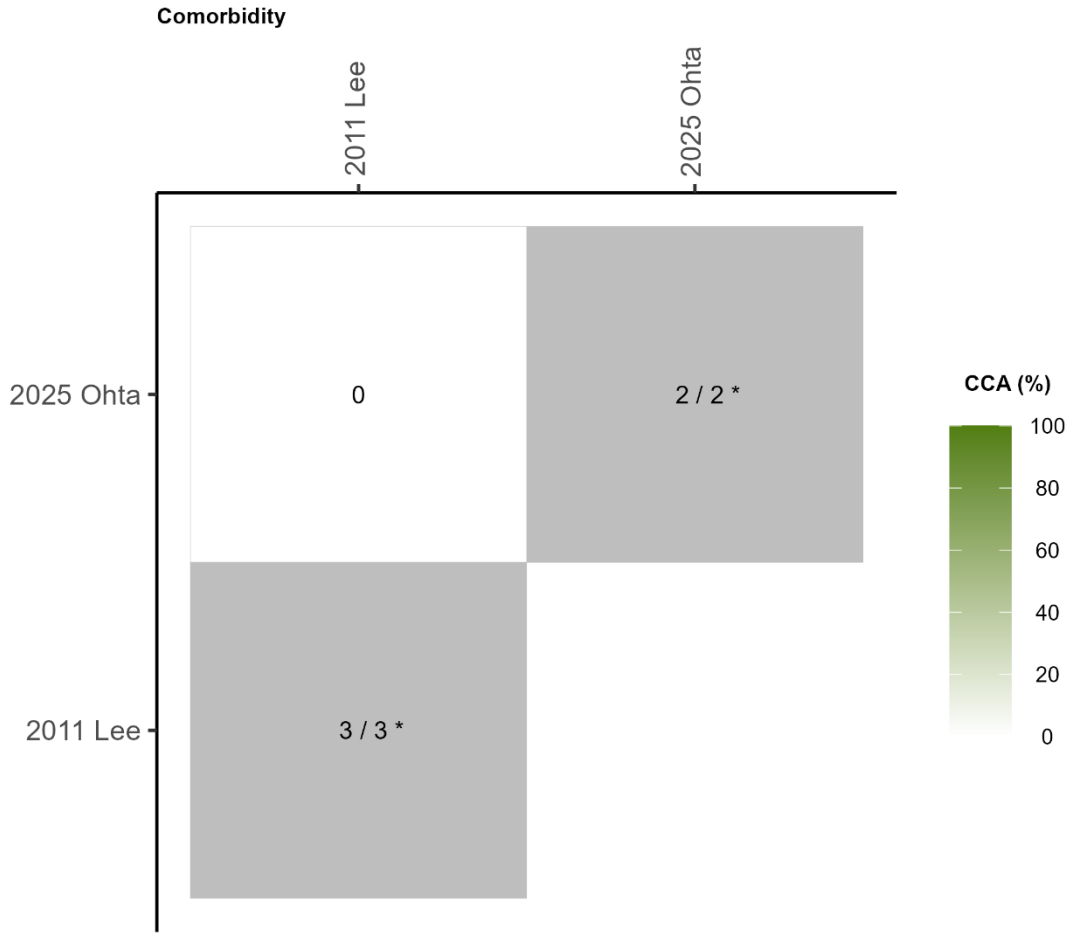

Figure S3.8: Heatmap demonstrating the degree of overlap between pairs of reviews for comorbidity using the corrected covered area (CCA) measure.

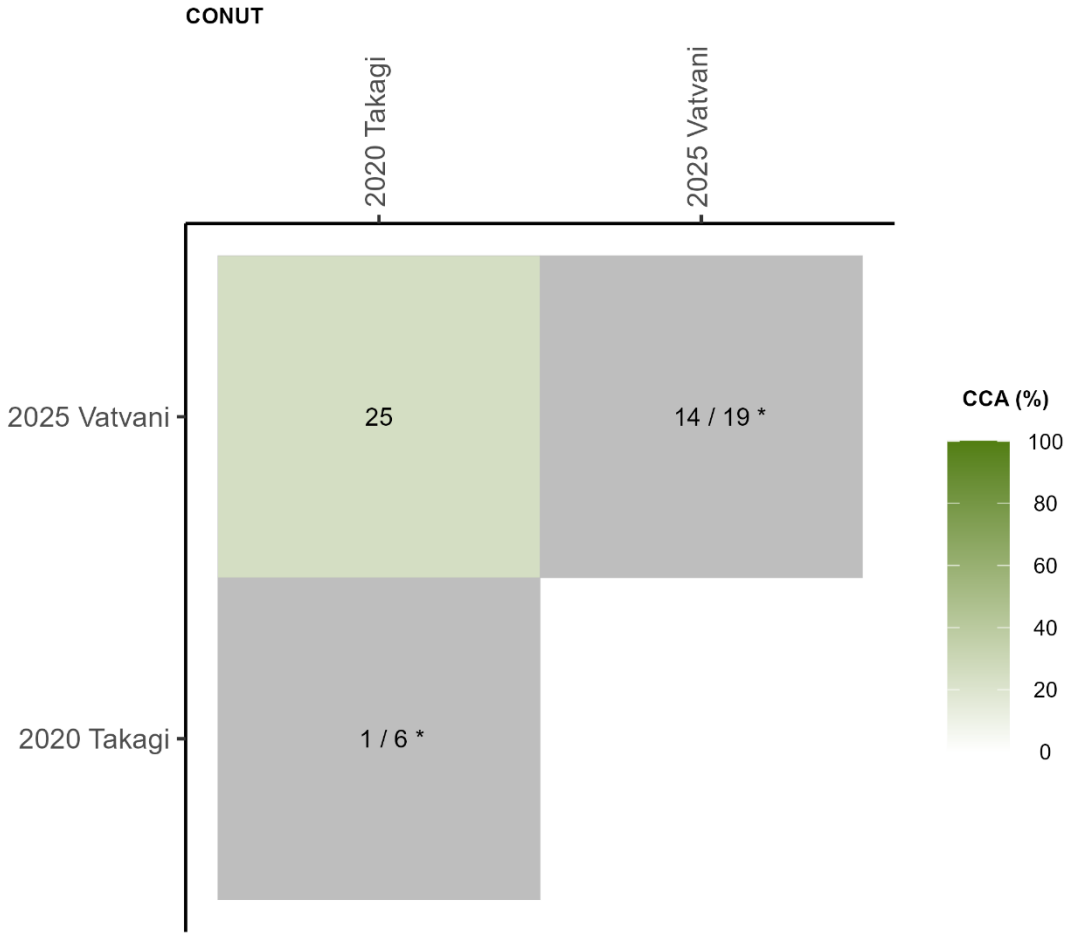

Figure S3.9: Heatmap demonstrating the degree of overlap between pairs of reviews for controlling nutritional status (CONUT) using the corrected covered area (CCA) measure.

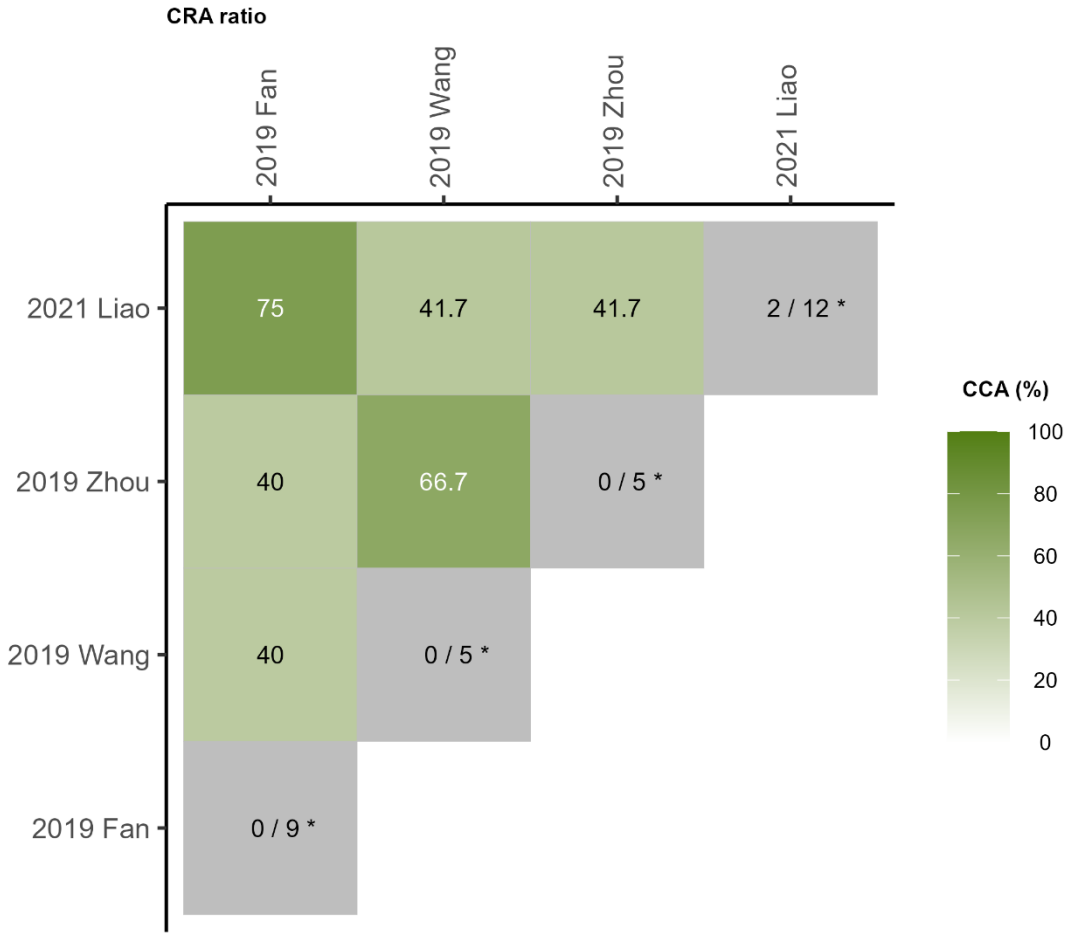

Figure S3.10: Heatmap demonstrating the degree of overlap between pairs of reviews for C-reactive protein to albumin (CRA) ratio using the corrected covered area (CCA) measure.

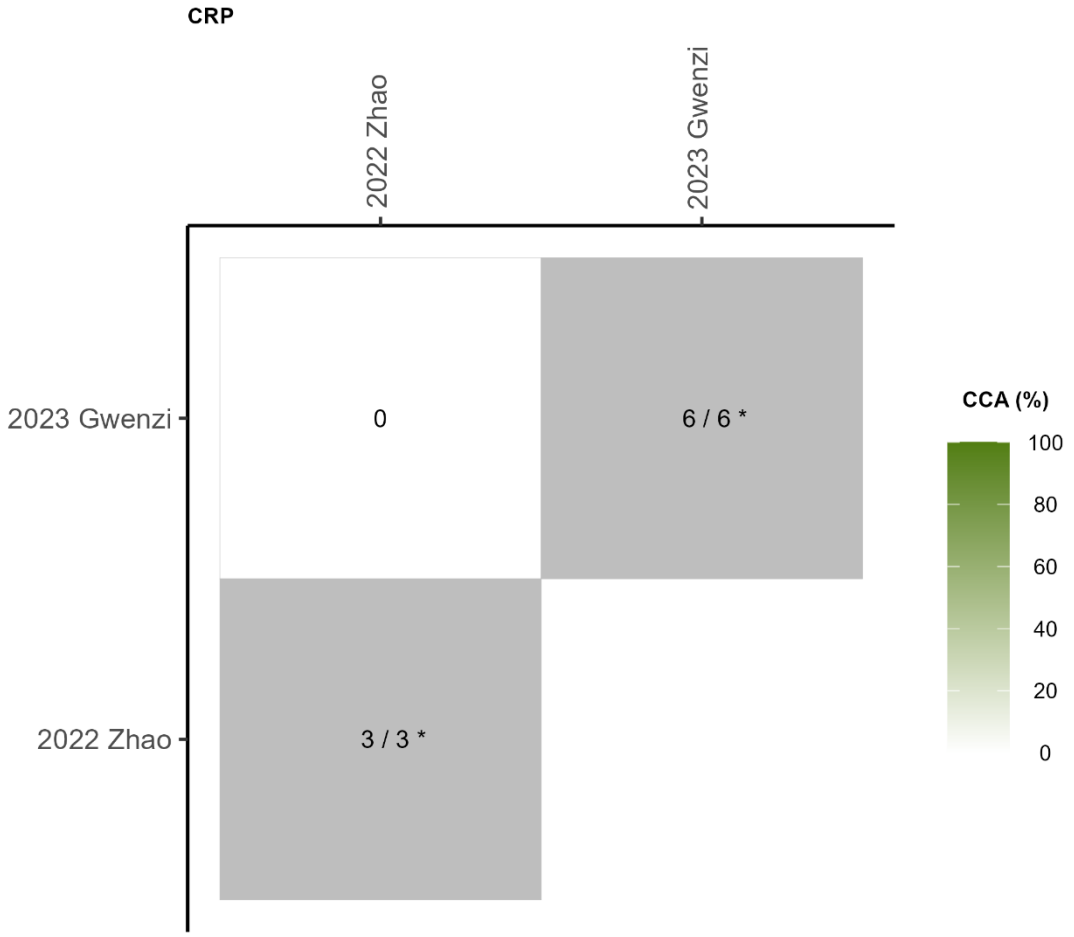

Figure S3.11: Heatmap demonstrating the degree of overlap between pairs of reviews for C-reactive protein using the corrected covered area (CCA) measure.

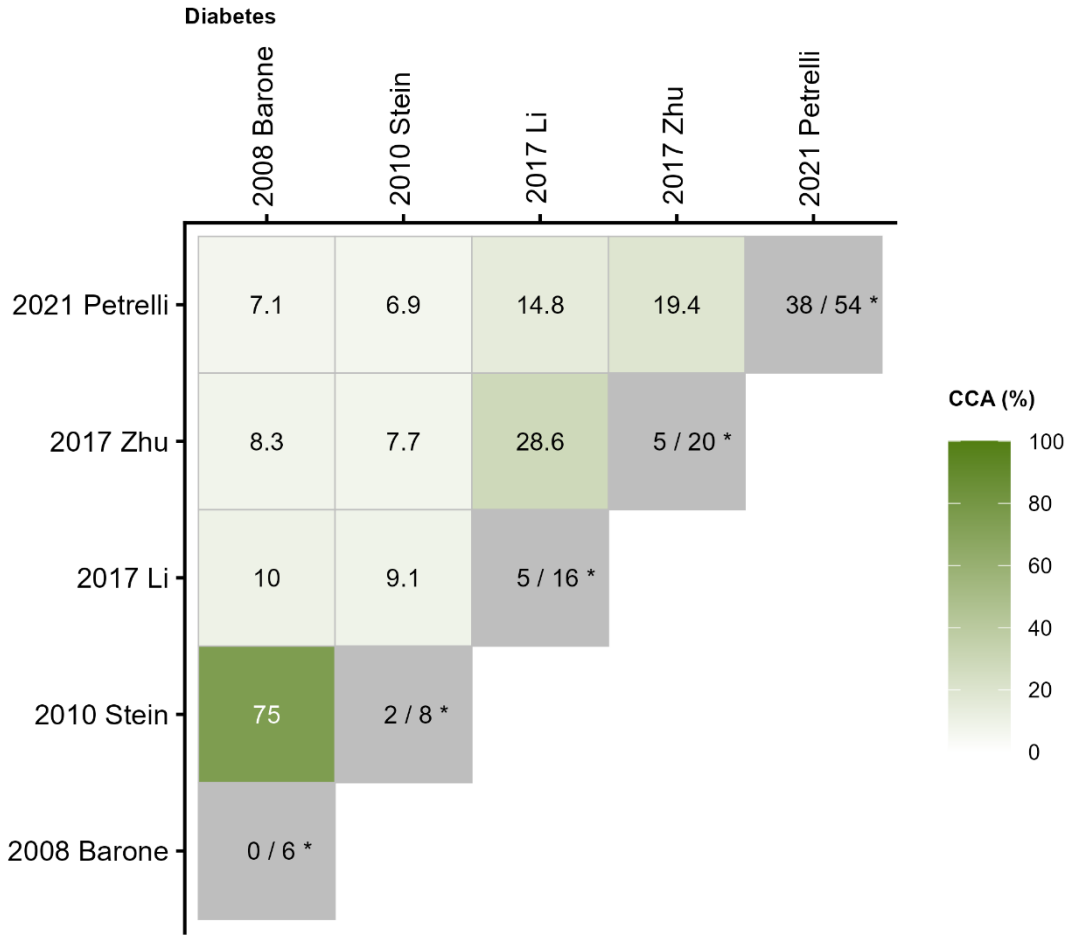

Figure S3.12: Heatmap demonstrating the degree of overlap between pairs of reviews for diabetes using the corrected covered area (CCA) measure.

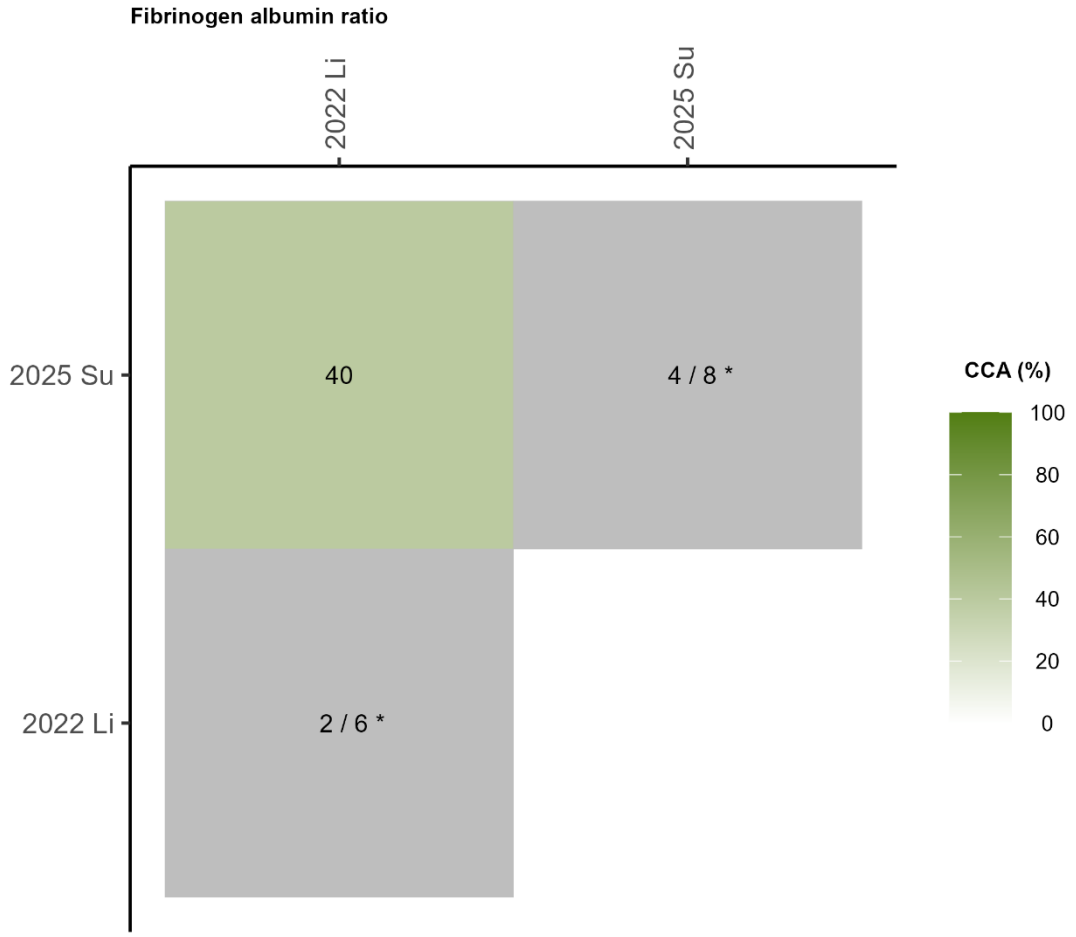

Figure S3.13: Heatmap demonstrating the degree of overlap between pairs of reviews for fibrinogen to albumin ratio using the corrected covered area (CCA) measure.

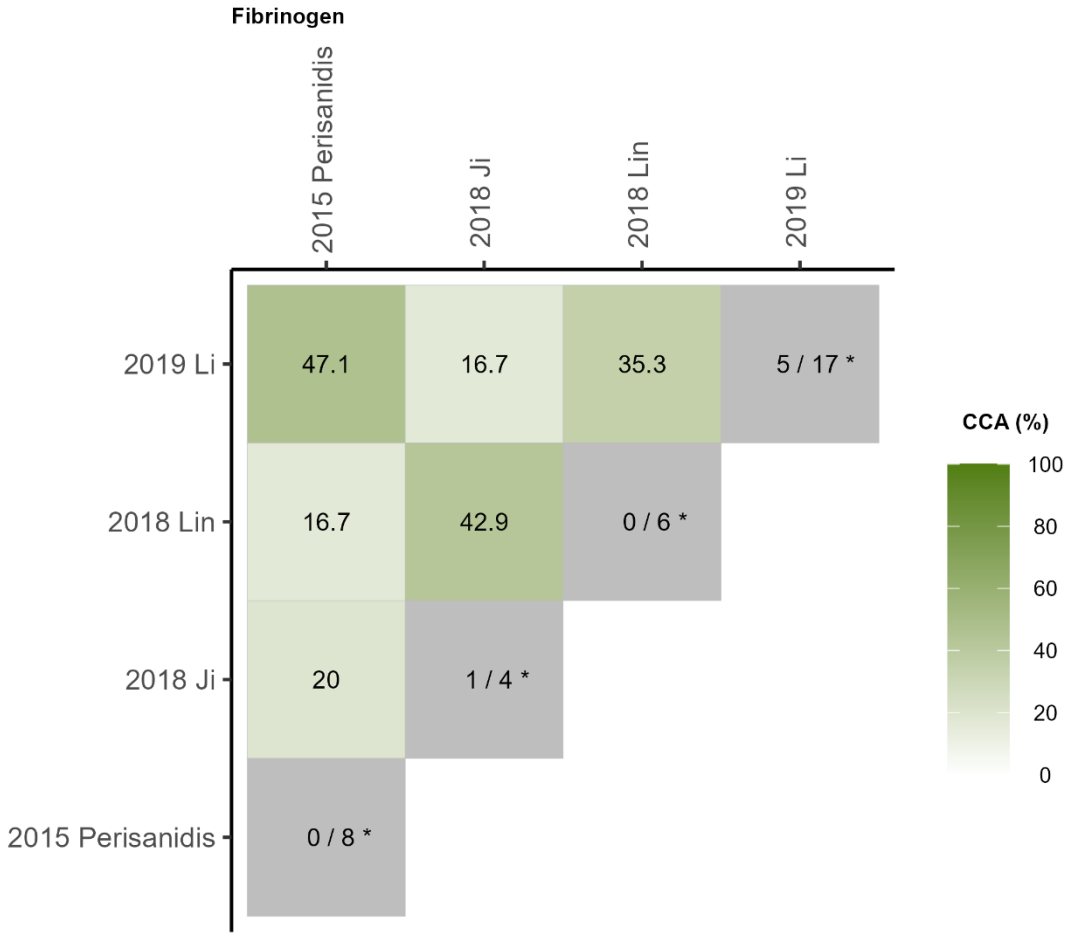

Figure S3.14: Heatmap demonstrating the degree of overlap between pairs of reviews for fibrinogen using the corrected covered area (CCA) measure.

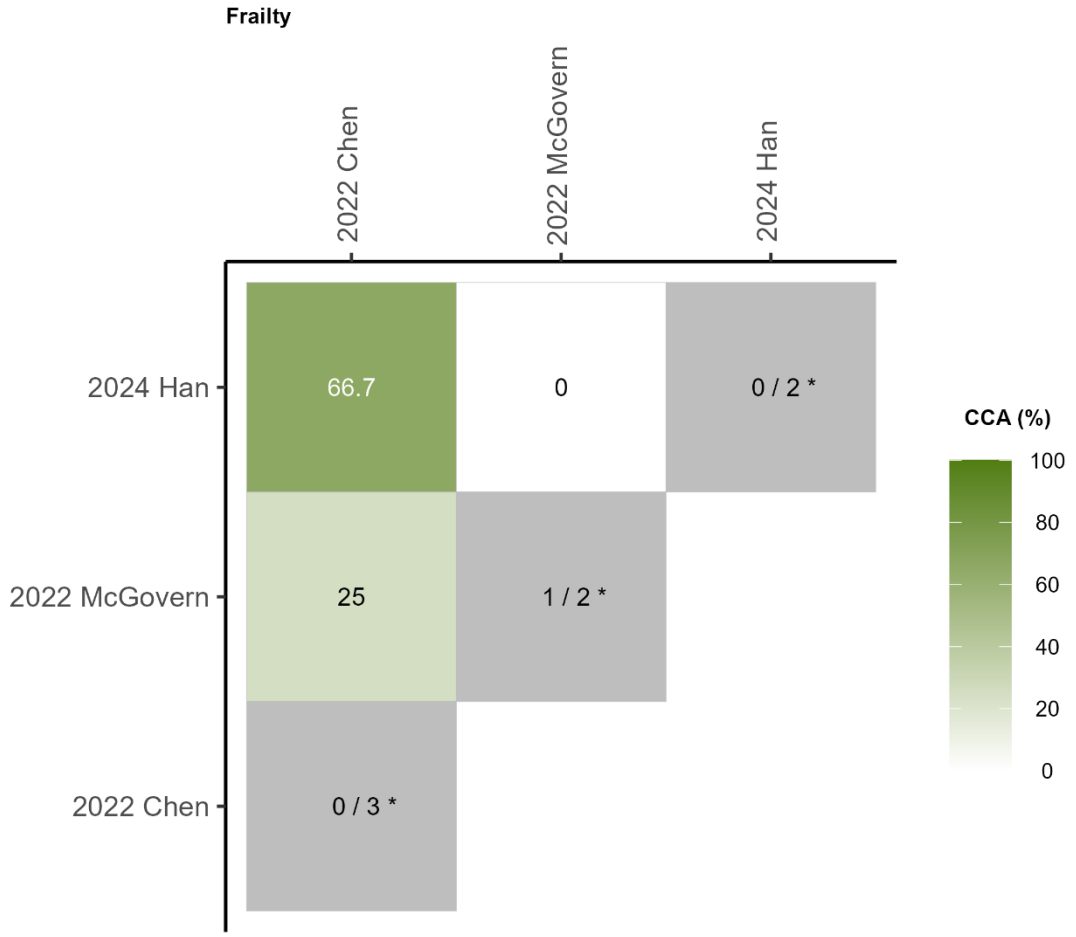

Figure S3.15: Heatmap demonstrating the degree of overlap between pairs of reviews for frailty using the corrected covered area (CCA) measure.

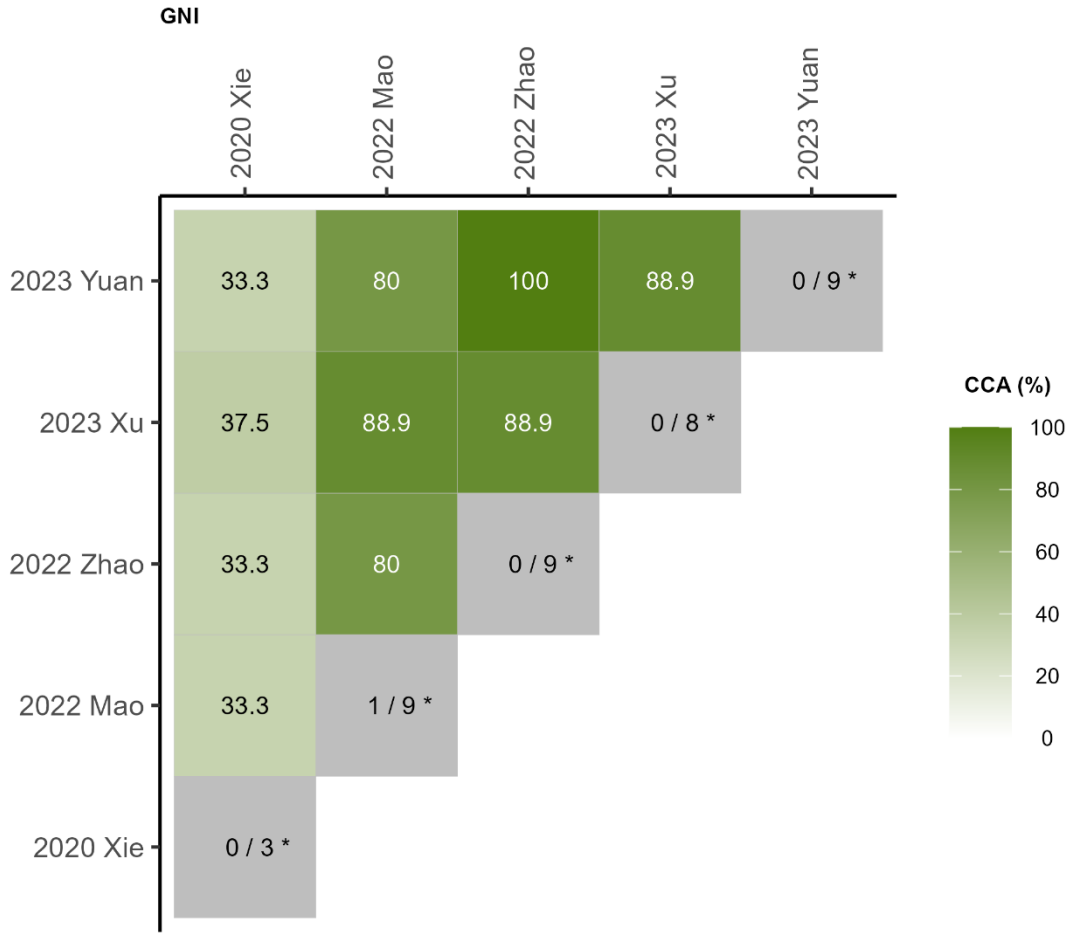

Figure S3.16: Heatmap demonstrating the degree of overlap between pairs of reviews for geriatric nutritional index (GNI) using the corrected covered area (CCA) measure.

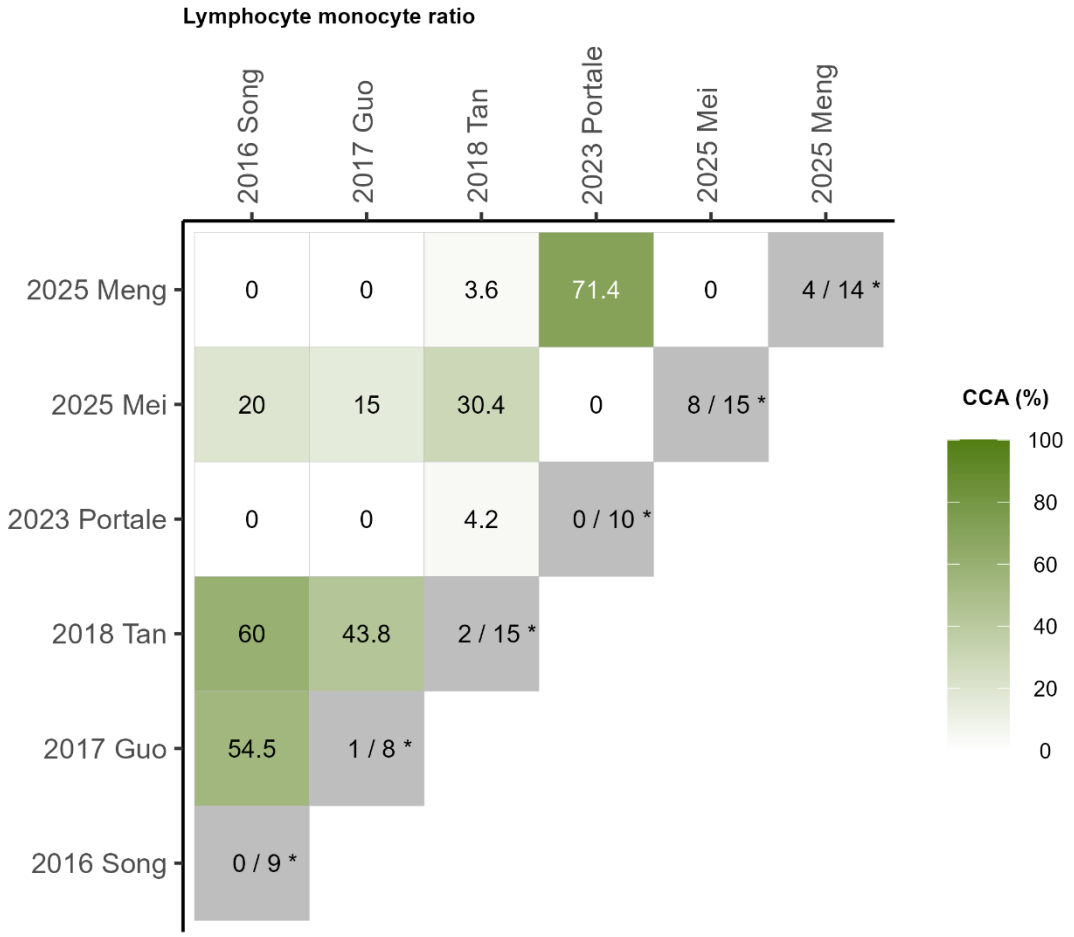

Figure S3.17: Heatmap demonstrating the degree of overlap between pairs of reviews for lymphocyte to monocyte ratio using the corrected covered area (CCA) measure.

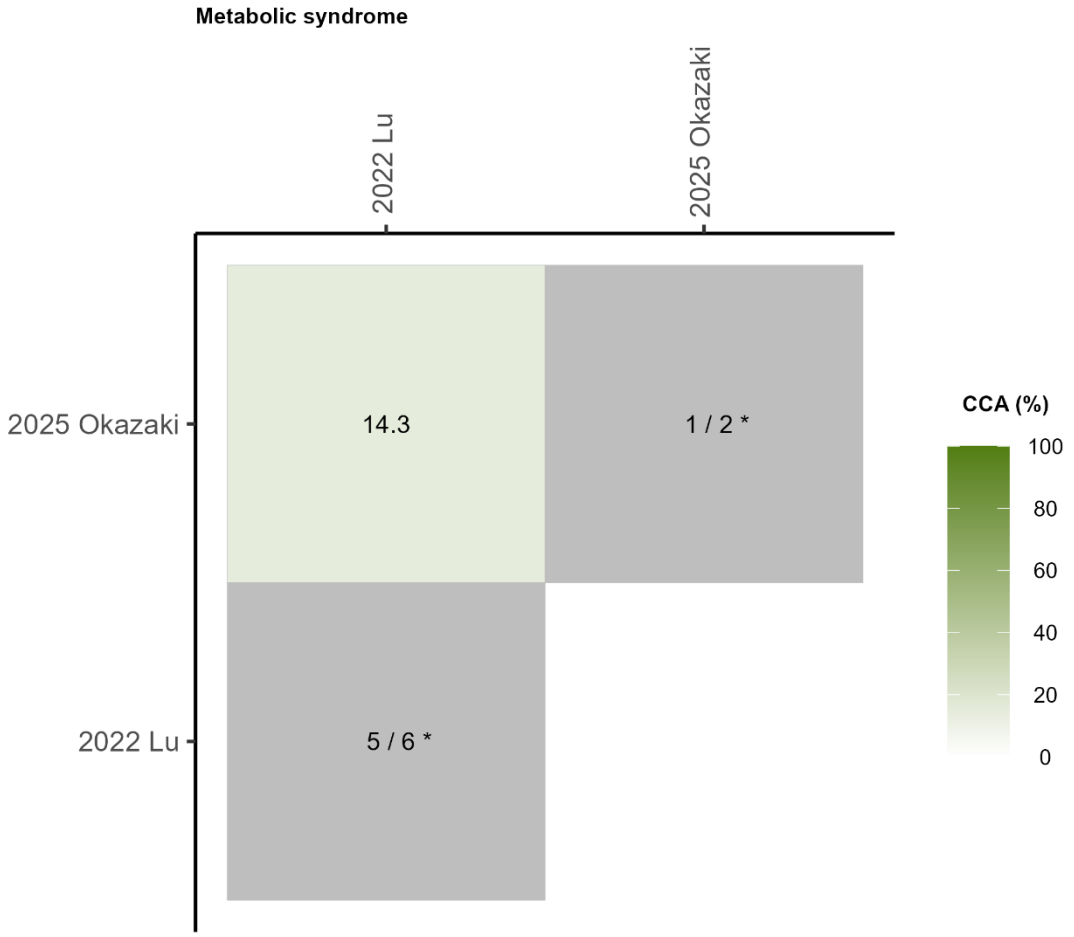

Figure S3.18: Heatmap demonstrating the degree of overlap between pairs of reviews for metabolic syndrome using the corrected covered area (CCA) measure.

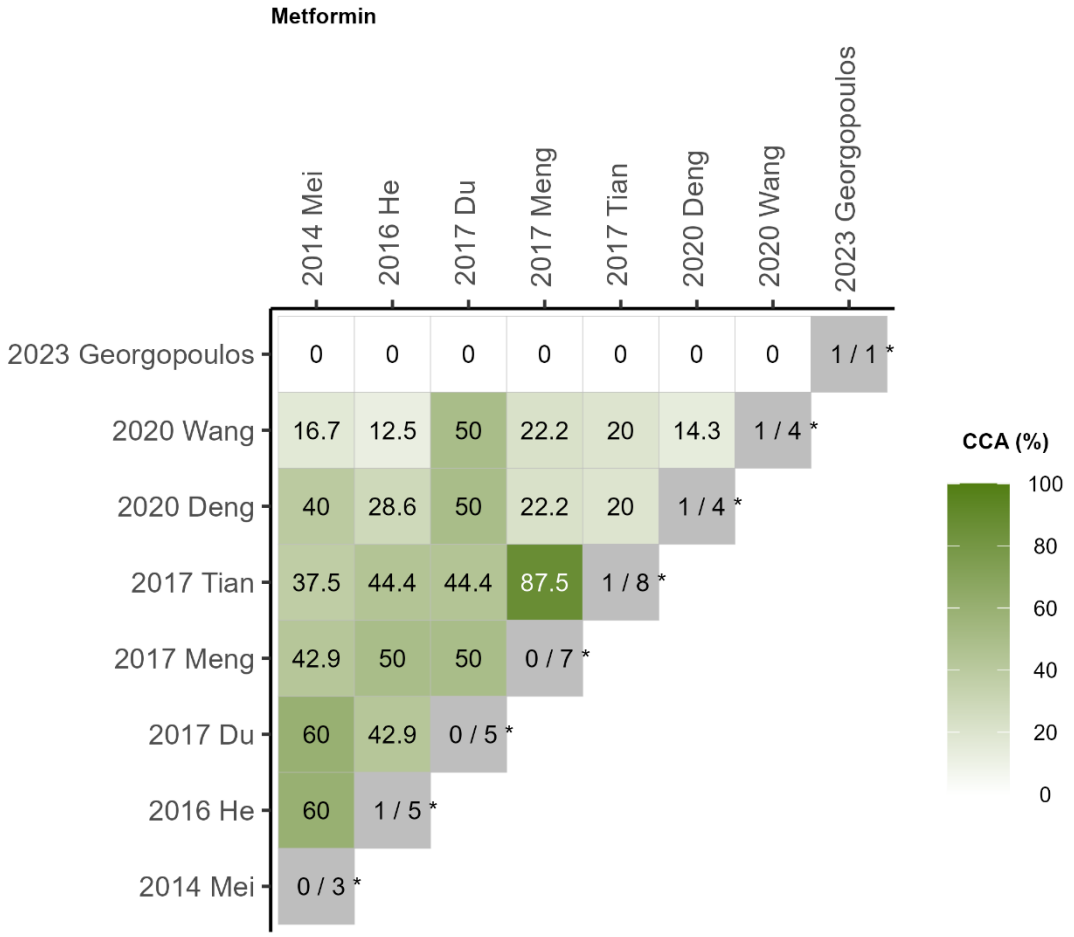

Figure S3.19: Heatmap demonstrating the degree of overlap between pairs of reviews for metformin using the corrected covered area (CCA) measure.

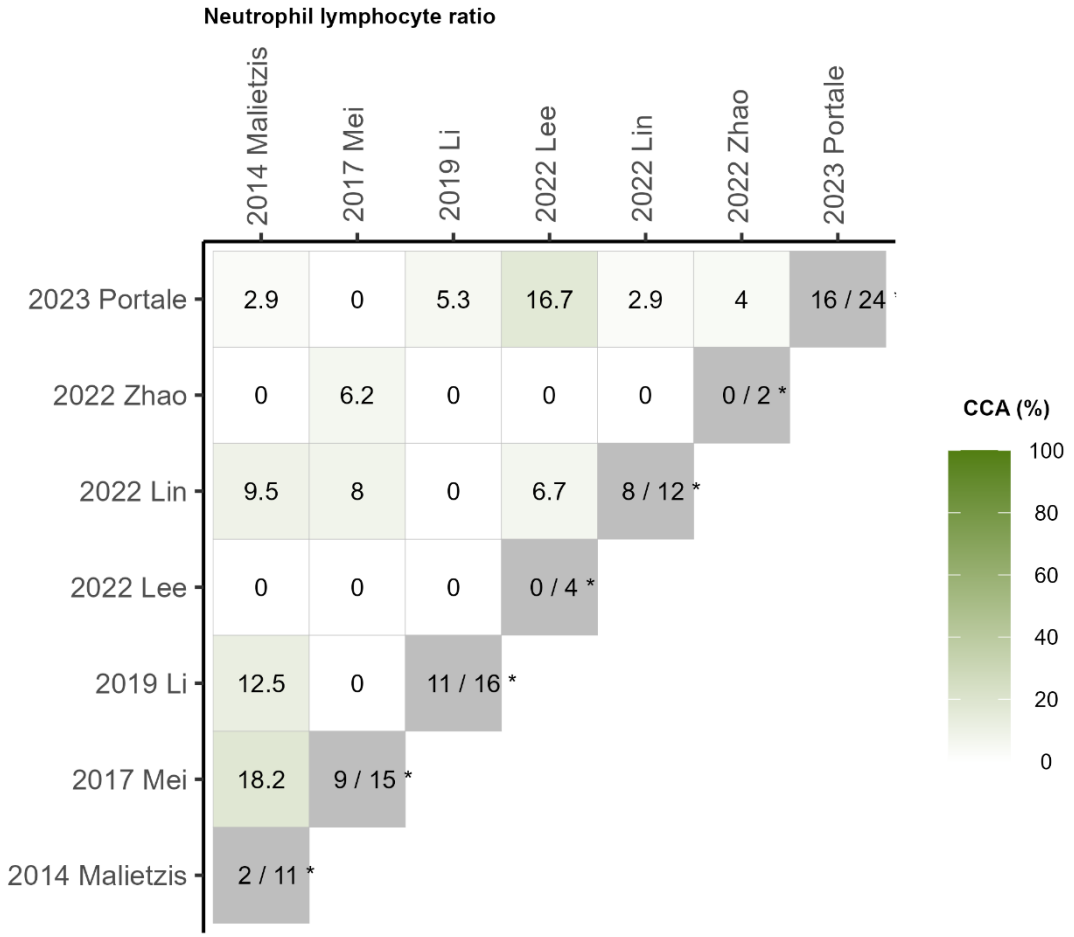

Figure S3.20: Heatmap demonstrating the degree of overlap between pairs of reviews for neutrophil to lymphocyte ratio using the corrected covered area (CCA) measure.

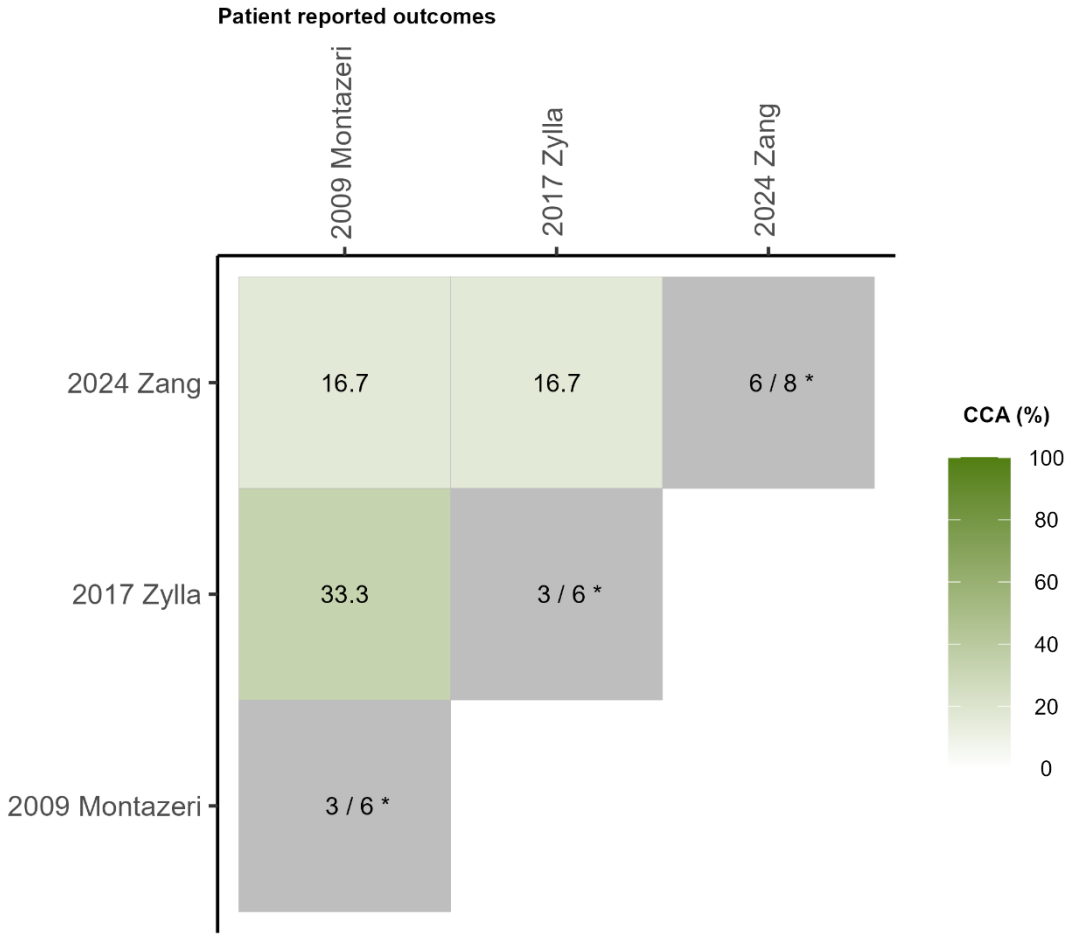

Figure S3.21: Heatmap demonstrating the degree of overlap between pairs of reviews for patient reported outcomes using the corrected covered area (CCA) measure.

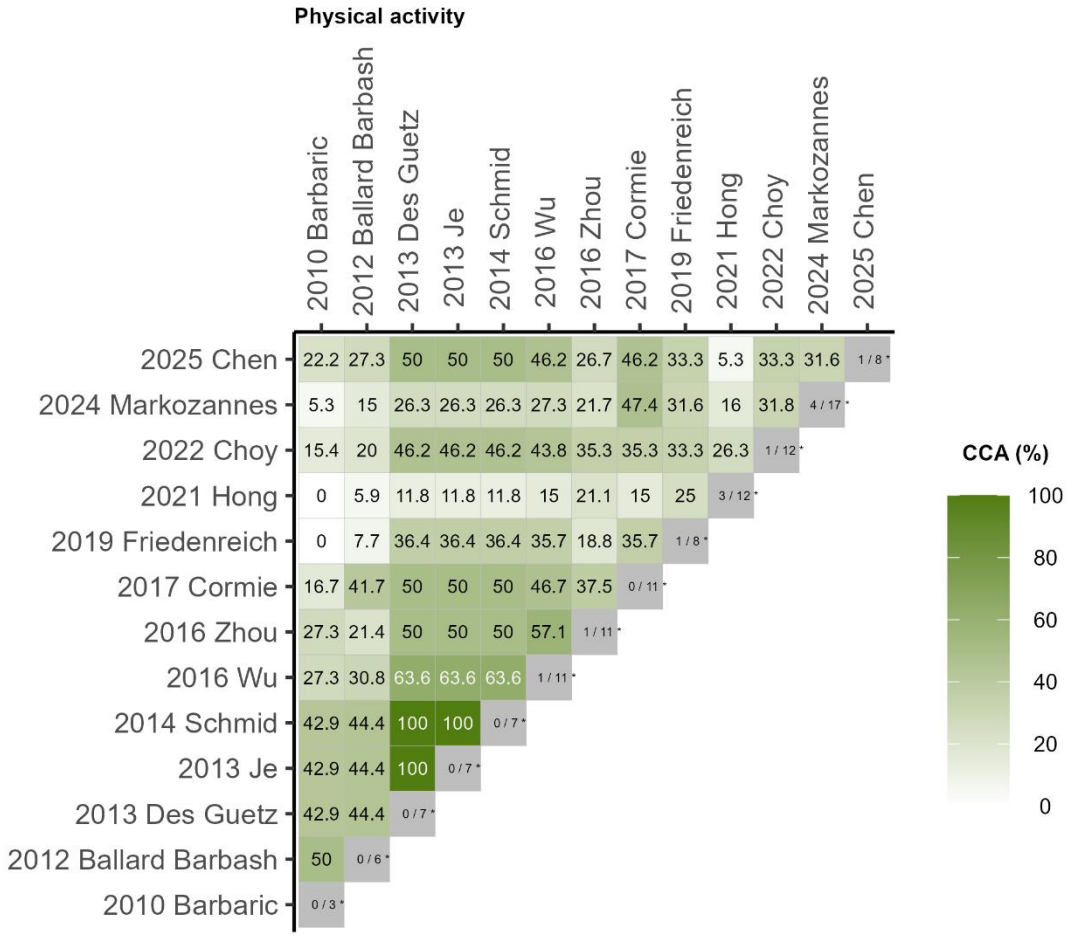

Figure S3.22: Heatmap demonstrating the degree of overlap between pairs of reviews for physical activity using the corrected covered area (CCA) measure.

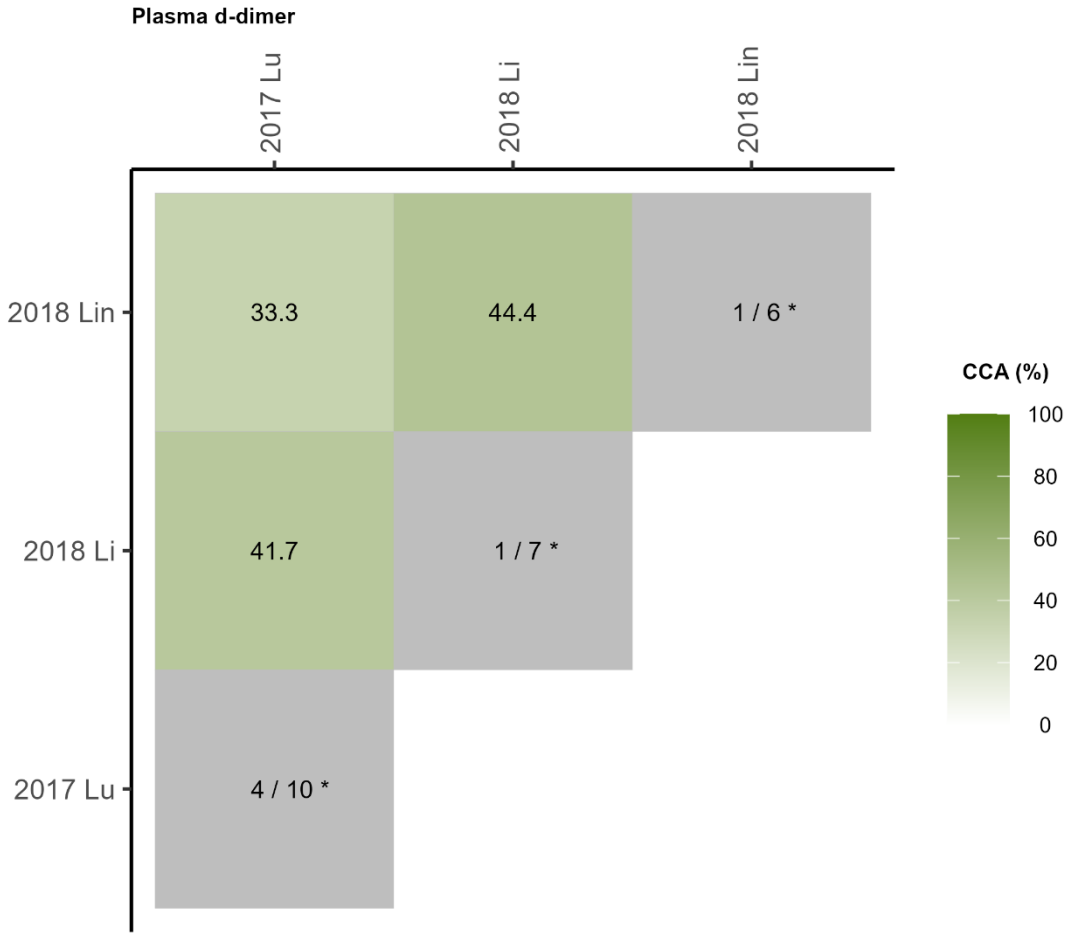

Figure S3.23: Heatmap demonstrating the degree of overlap between pairs of reviews for plasma d-dimer using the corrected covered area (CCA) measure.

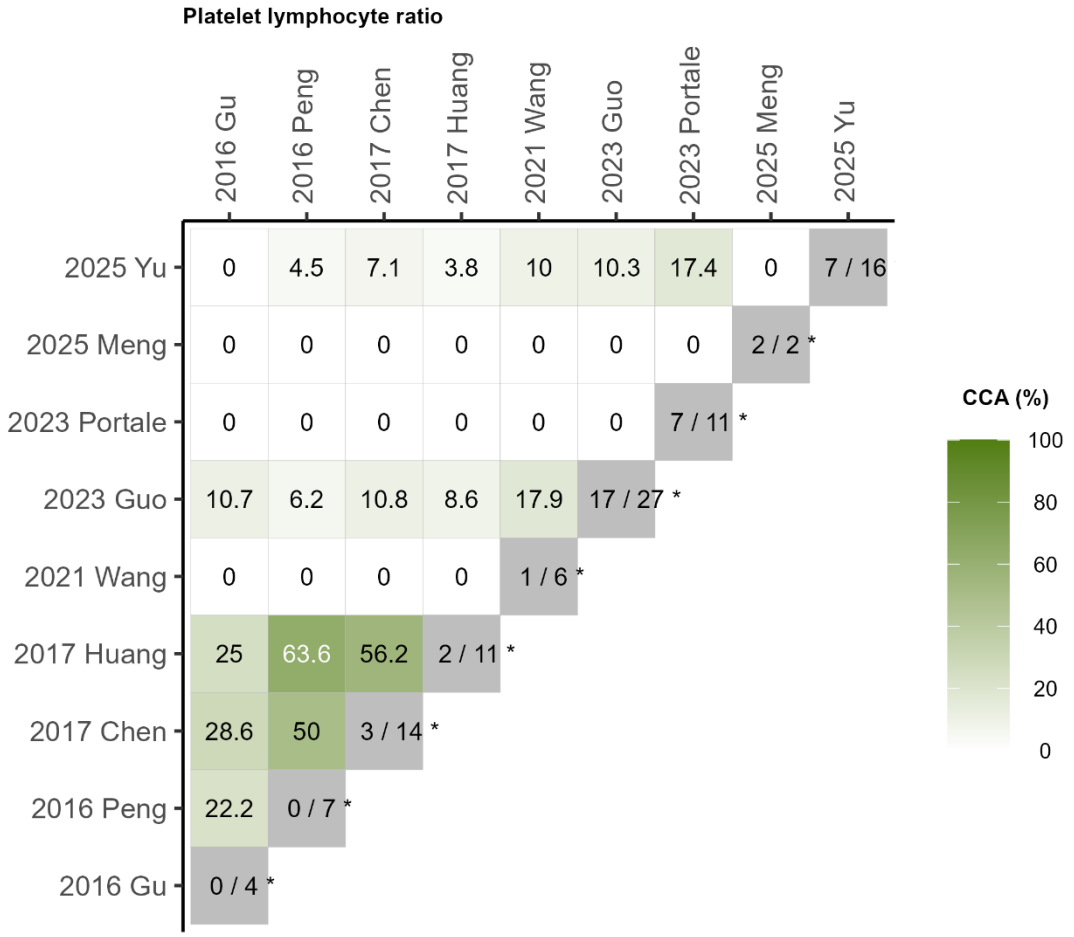

Figure S3.24: Heatmap demonstrating the degree of overlap between pairs of reviews for platelet to lymphocyte ratio using the corrected covered area (CCA) measure.

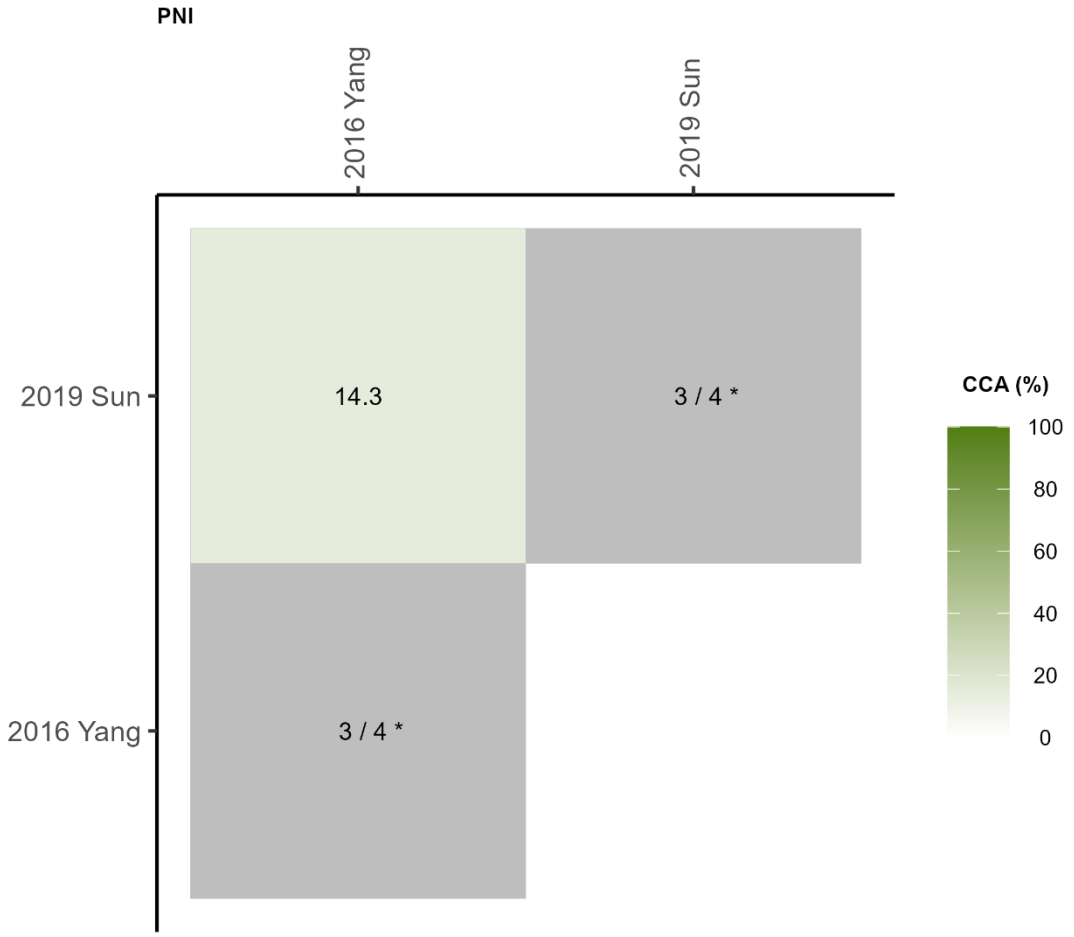

Figure S3.25: Heatmap demonstrating the degree of overlap between pairs of reviews for prognostic nutritional index (PNI) using the corrected covered area (CCA) measure.

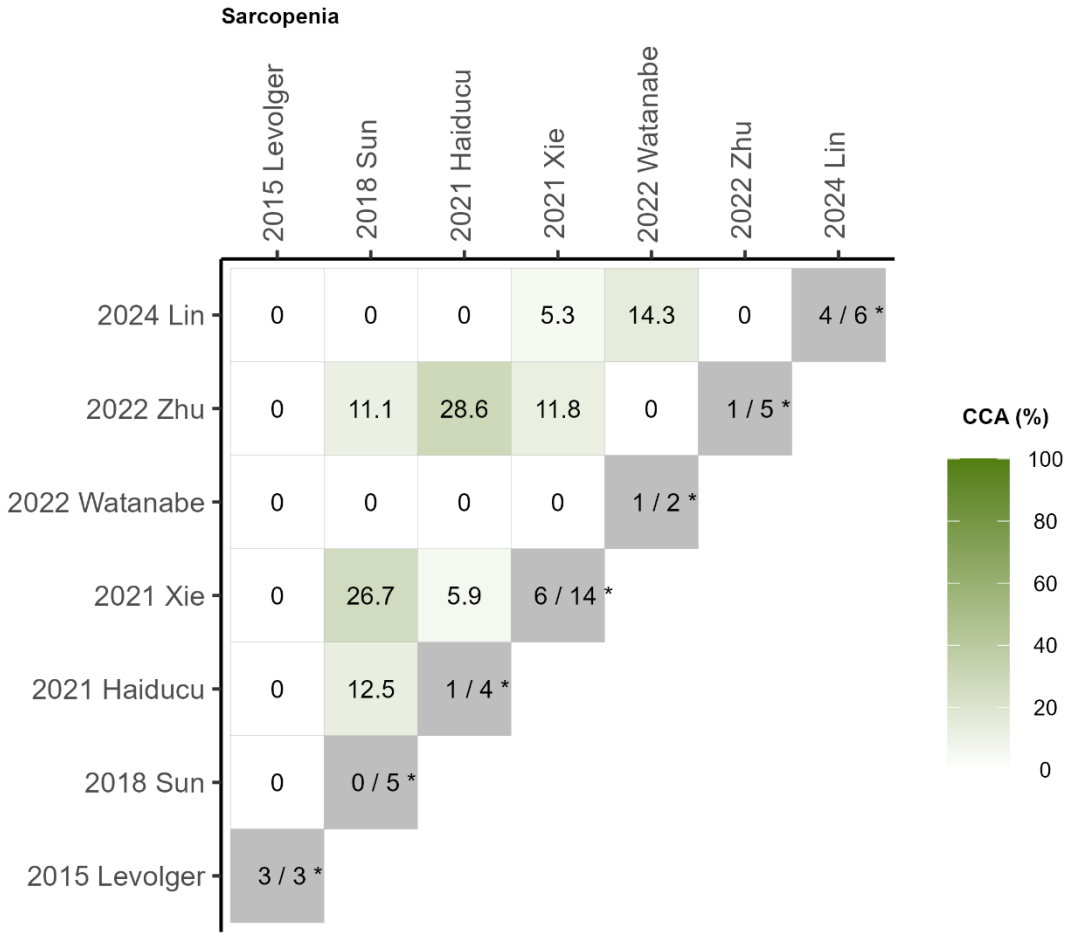

Figure S3.26: Heatmap demonstrating the degree of overlap between pairs of reviews for sarcopenia using the corrected covered area (CCA) measure.

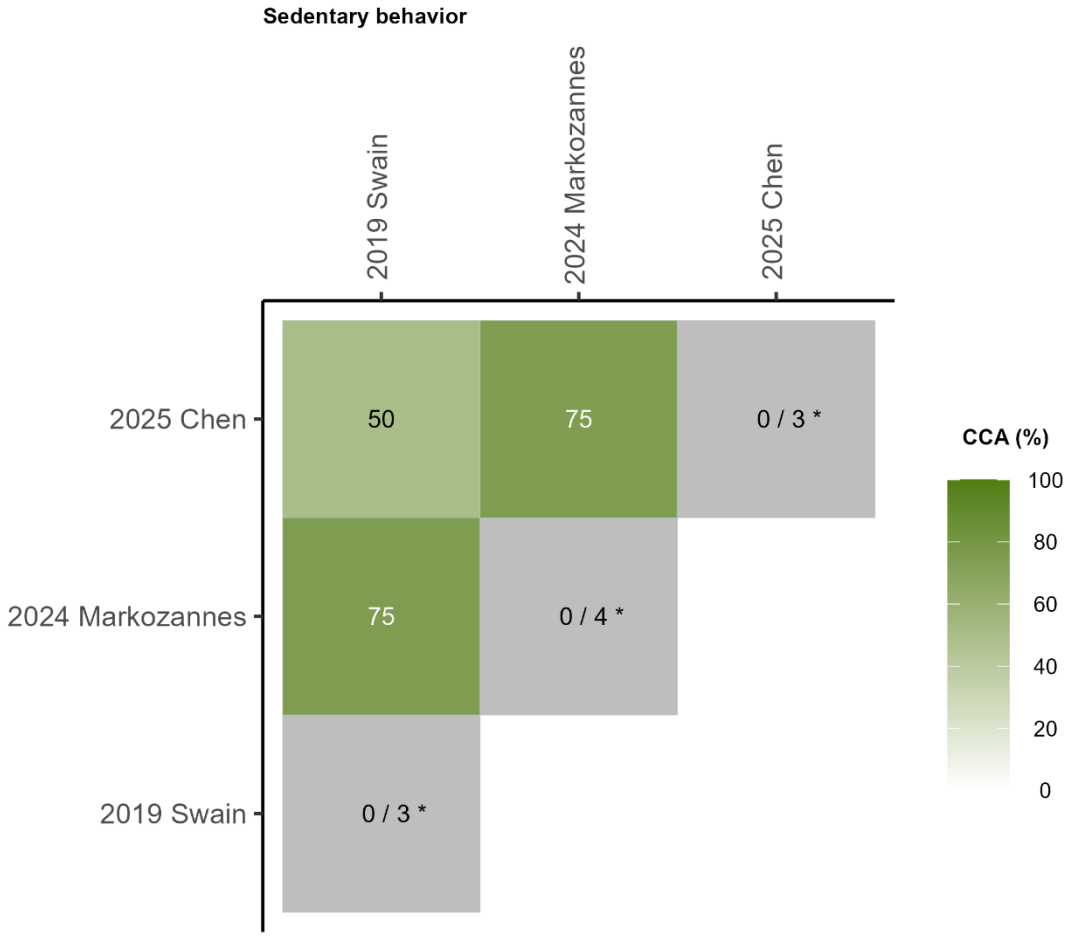

Figure S3.27: Heatmap demonstrating the degree of overlap between pairs of reviews for sedentary behavior using the corrected covered area (CCA) measure.

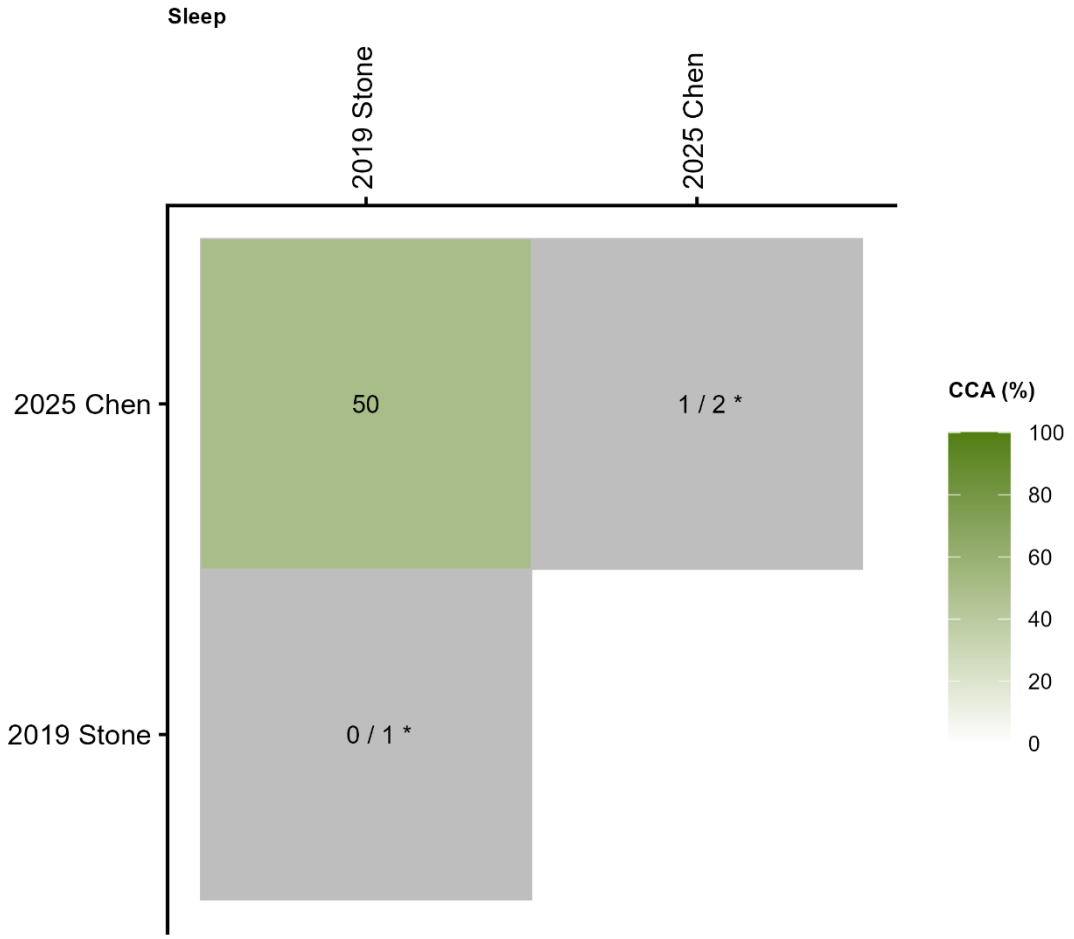

Figure S3.28: Heatmap demonstrating the degree of overlap between pairs of reviews for sleep using the corrected covered area (CCA) measure.

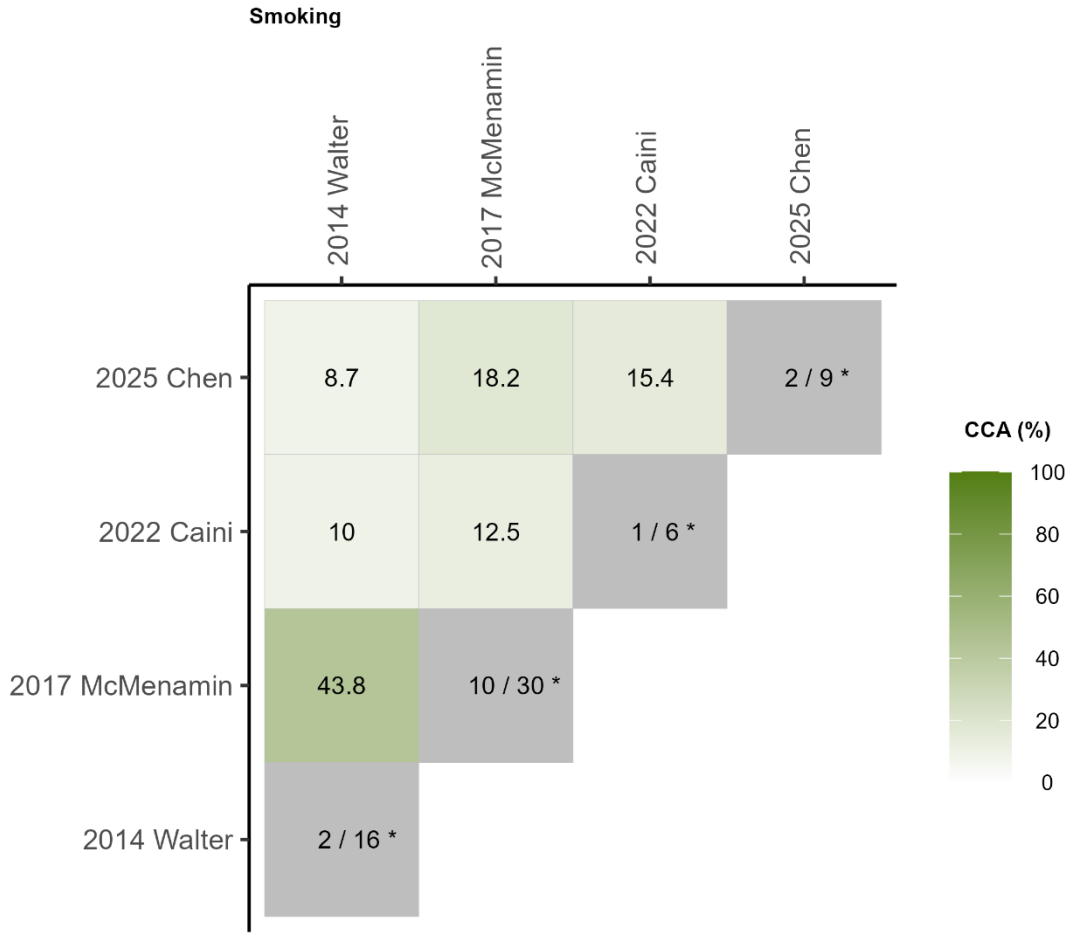

Figure S3.29: Heatmap demonstrating the degree of overlap between pairs of reviews for smoking using the corrected covered area (CCA) measure.

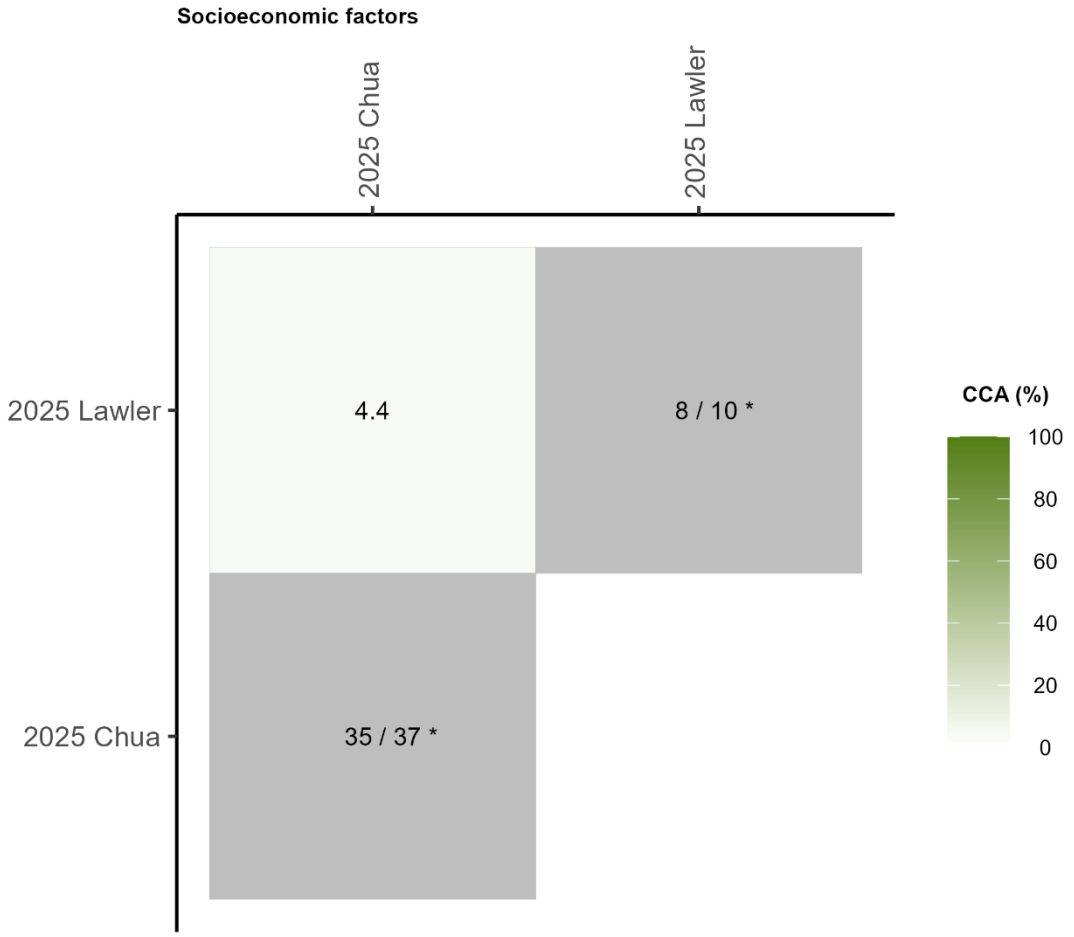

Figure S3.30: Heatmap demonstrating the degree of overlap between pairs of reviews for socioeconomic factors using the corrected covered area (CCA) measure.

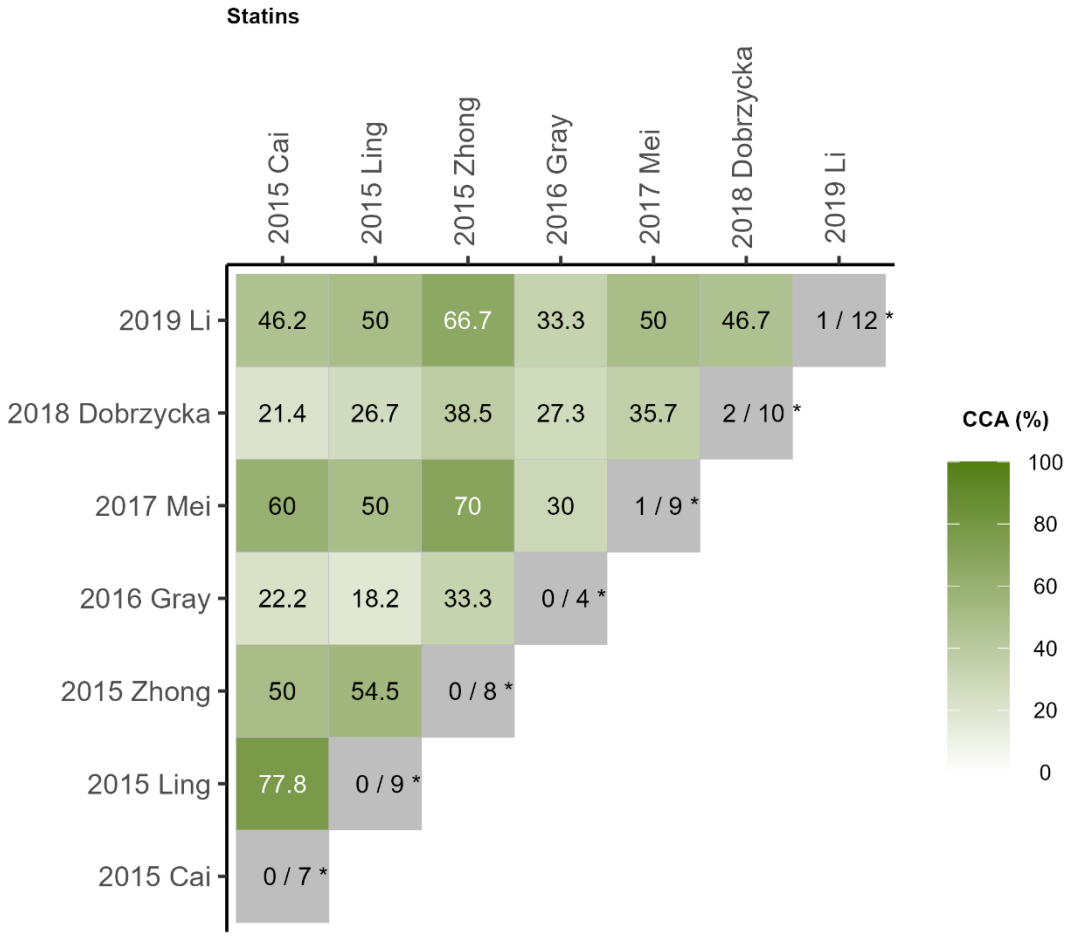

Figure S3.31: Heatmap demonstrating the degree of overlap between pairs of reviews for statins using the corrected covered area (CCA) measure.

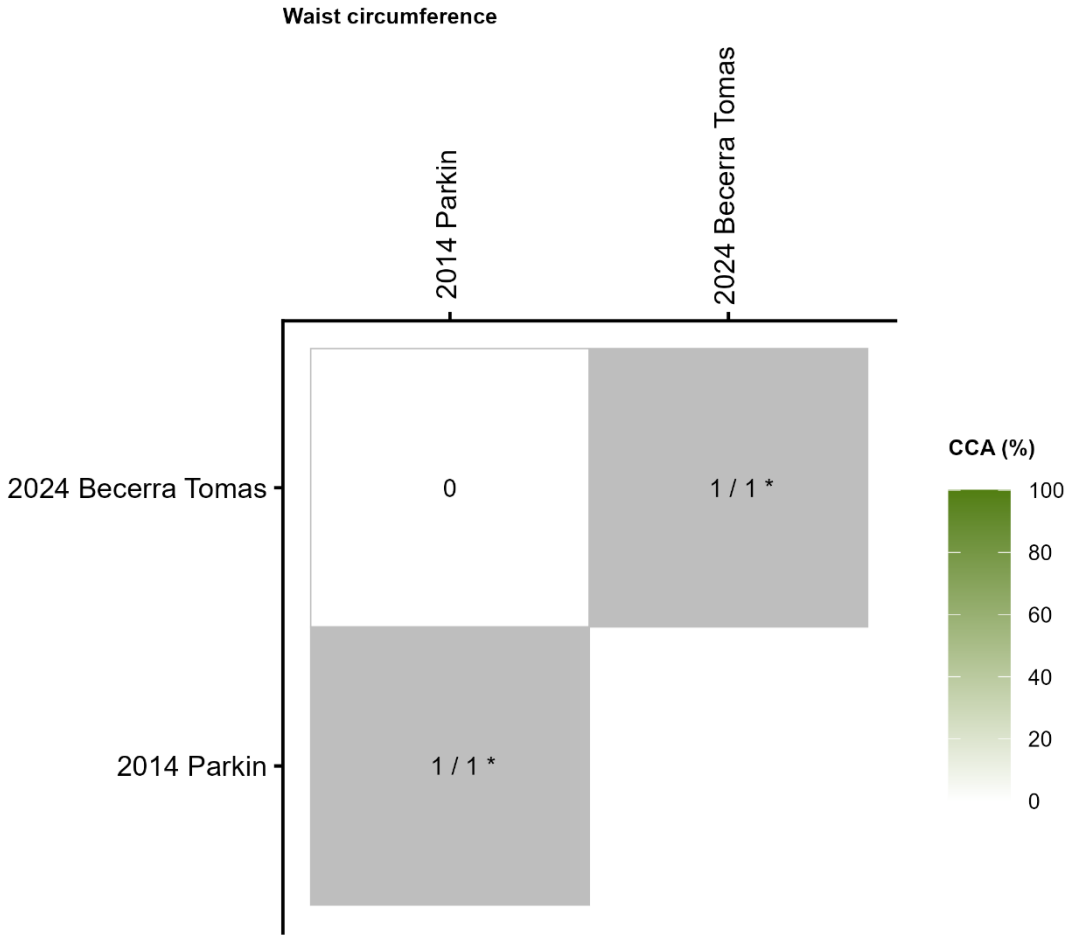

Figure S3.32: Heatmap demonstrating the degree of overlap between pairs of reviews for waist circumference using the corrected covered area (CCA) measure.

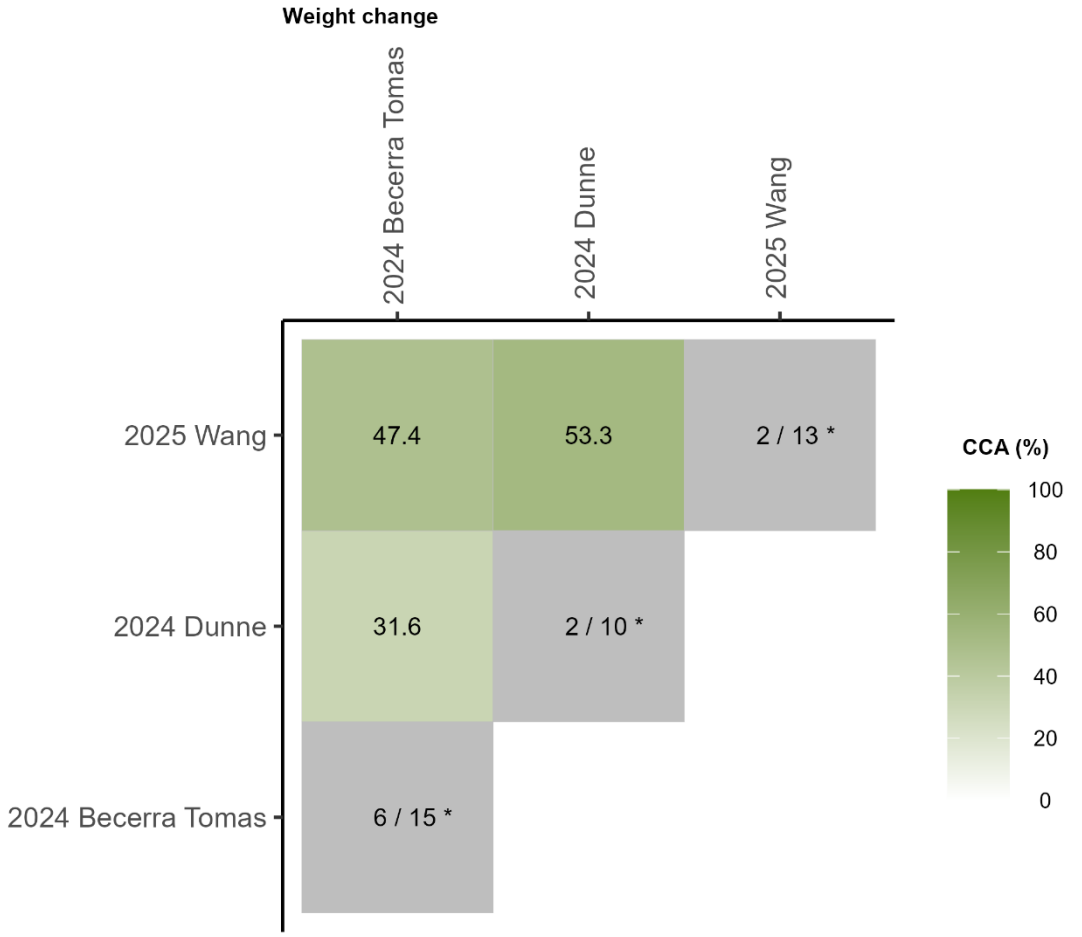

Figure S3.33: Heatmap demonstrating the degree of overlap between pairs of reviews for weight change using the corrected covered area (CCA) measure.

FORMULAS FOR THE MR SURVIVAL ESTIMATES AND THEIR STANDARD ERRORS FOLLOWING THE THREE METHODS FOR COLLIDER BIAS ADJUSTMENT

SIMEX

$$\beta_{survival}^{corrected} = \beta_{survival}^{biased} - b \cdot \beta_{incidence}^{est}$$

$$se\left(\beta_{survival}^{corrected}\right) = \sqrt{se\left(\beta_{survival}^{biased}\right)^2 + b^2 \cdot se(\beta_{incidence}^{est})^2 + se(b)^2 \cdot (\beta_{incindence}^{est})^2 + se(b)^2 \cdot se(\beta_{incidence}^{est})^2}$$

Slope-hunter

$$\beta_{survival}^{corrected} = \beta_{survival}^{biased} - b \cdot \beta_{incidence}^{est}$$

$$se\left(\beta_{survival}^{corrected}\right) = \sqrt{se\left(\beta_{survival}^{biased}\right)^2 + b^2 \cdot se(\beta_{incidence}^{est})^2 + se(b)^2 \cdot (\beta_{incindence}^{est})^2 + se(b)^2 \cdot se(\beta_{incidence}^{est})^2}$$

CWLS

$$\beta_{survival}^{corrected} = \beta_{survival}^{biased} - b \cdot \beta_{incidence}^{est}$$

$$se\left(\beta_{survival}^{corrected}\right) = \sqrt{se\left(\beta_{survival}^{biased}\right)^2 + b^2 \cdot se(\beta_{incidence}^{est})^2}$$

where $\beta_{survival}^{biased}$ is the unadjusted effect estimate of the SNP on CRC survival, $se\left(\beta_{survival}^{corrected}\right)$ is its corresponding standard error, $\beta_{incidence}^{est}$ is the effect estimate of the SNP on CRC incidence and $se(\beta_{incidence}^{est})$ is its corresponding standard error. The terms b and $se(b)$ correspond to the bias-correcting factor and its standard error, as calculated by each method.

Table S4.1: Hazard ratios and 95% confidence intervals for the associations between the genetically-predicted levels of various exposures and colorectal cancer (CRC) mortality among CRC cases overall, and by anatomical site and stage.

			MR-Egger		
Exposure	Number of SNPs	IVW	Slope	Intercept p-value	Weighted median
CRC					
Alcohol	37	1.002 (0.678, 1.482)	0.954 (0.533, 1.707)	0.823	0.856 (0.501, 1.463)
BMR	445	0.94 (0.795, 1.11)	0.982 (0.642, 1.501)	0.824	0.914 (0.701, 1.192)
Birth weight	97	0.92 (0.733, 1.155)	1.113 (0.535, 2.315)	0.592	1.028 (0.745, 1.418)

Body fat %	293	1.051 (0.859, 1.285)	1.121 (0.55, 2.286)	0.852	1.202 (0.883, 1.637)
HC	305	1.07 (0.919, 1.247)	1.072 (0.685, 1.678)	0.994	1.185 (0.935, 1.501)
Height	987	0.985 (0.907, 1.069)	0.975 (0.834, 1.14)	0.886	1.012 (0.888, 1.154)
WC	267	**1.221 (1.018, 1.465)**	1.32 (0.754, 2.311)	0.774	**1.425 (1.055, 1.926)**
WHR	353	1.099 (0.922, 1.31)	1.164 (0.707, 1.916)	0.808	1.162 (0.886, 1.524)
BMI	542	1.105 (0.961, 1.269)	1.161 (0.81, 1.665)	0.767	1.158 (0.905, 1.481)
Smoking	211	0.963 (0.659, 1.407)	1.661 (0.459, 6.014)	0.385	1.214 (0.686, 2.15)
Physical activity	3	1.33 (0.492, 3.594)	0.381 (0, 343.537)	0.716	1.295 (0.397, 4.221)
Vitamin D	51	0.889 (0.708, 1.117)	**0.613 (0.434, 0.867)**	0.007	0.742 (0.541, 1.019)
Total cholesterol	85	1.06 (0.958, 1.173)	1 (0.848, 1.178)	0.374	1.014 (0.856, 1.201)
LDL	78	0.987 (0.895, 1.088)	0.938 (0.813, 1.082)	0.342	0.893 (0.768, 1.04)
HDL	88	1.037 (0.907, 1.186)	1.007 (0.782, 1.295)	0.783	0.967 (0.79, 1.184)
Triglycerides	54	1.119 (0.973, 1.289)	1.109 (0.88, 1.398)	0.92	1.094 (0.888, 1.347)
Testosterone	89	0.856 (0.616, 1.188)	1.059 (0.594, 1.888)	0.379	0.665 (0.389, 1.138)
SHGB	236	1.002 (0.891, 1.128)	1.145 (0.926, 1.417)	0.14	0.939 (0.767, 1.151)
Fasting glucose	45	0.92 (0.761, 1.113)	1.074 (0.825, 1.399)	0.097	1.043 (0.806, 1.35)
Fasting glucose*	66	**0.734 (0.558, 0.967)**	1.211 (0.738, 1.987)	0.017	0.815 (0.496, 1.341)
Fasting insulin	13	0.987 (0.481, 2.024)	4.78 (0.186, 123.104)	0.329	1.219 (0.47, 3.159)
Fasting insulin*	35	1.381 (0.758, 2.516)	0.644 (0.097, 4.27)	0.404	0.958 (0.422, 2.173)
HbA1c	37	0.933 (0.591, 1.471)	0.784 (0.33, 1.861)	0.642	0.936 (0.458, 1.913)
HbA1c*	73	0.889 (0.608, 1.298)	0.655 (0.33, 1.299)	0.294	0.699 (0.386, 1.265)
2-hour glucose*	12	0.944 (0.738, 1.207)	0.735 (0.371, 1.456)	0.441	0.967 (0.724, 1.292)
IGF-1	308	**1.174 (1.053, 1.309)**	1 (0.811, 1.234)	0.08	1.095 (0.905, 1.325)
Type 2 diabetes	200	1.027 (0.971, 1.085)	1.005 (0.89, 1.135)	0.697	1.037 (0.928, 1.159)
CRP	40	0.949 (0.827, 1.09)	0.916 (0.739, 1.135)	0.666	1.023 (0.854, 1.225)
Proximal colon					
Alcohol	37	1.114 (0.567, 2.192)	1.343 (0.479, 3.765)	0.635	1.069 (0.421, 2.716)
BMR	445	0.984 (0.75, 1.29)	0.841 (0.423, 1.672)	0.627	0.99 (0.643, 1.524)
Birth weight	97	1.148 (0.806, 1.636)	1.16 (0.373, 3.612)	0.985	1.141 (0.68, 1.917)
Body fat %	293	0.928 (0.663, 1.297)	0.805 (0.246, 2.637)	0.807	0.992 (0.587, 1.677)

HC	305	1.191 (0.925, 1.533)	1.016 (0.484, 2.133)	0.655	1.026 (0.693, 1.517)
Height	987	0.893 (0.777, 1.025)	0.915 (0.703, 1.19)	0.83	0.922 (0.738, 1.153)
WC	267	1.129 (0.824, 1.547)	0.913 (0.347, 2.406)	0.65	0.998 (0.587, 1.698)
WHR	353	1.056 (0.788, 1.415)	1.373 (0.597, 3.155)	0.51	0.976 (0.616, 1.546)
BMI	542	1.147 (0.911, 1.445)	0.993 (0.546, 1.806)	0.607	1.081 (0.714, 1.638)
Smoking	211	0.904 (0.479, 1.705)	1.613 (0.187, 13.94)	0.581	1.02 (0.395, 2.633)
Physical activity	3	1.222 (0.231, 6.465)	0.183 (0, 17378.895)	0.743	1.097 (0.155, 7.784)
Vitamin D	51	1.109 (0.806, 1.528)	0.865 (0.517, 1.448)	0.227	1.134 (0.693, 1.856)
Total cholesterol	85	1.03 (0.87, 1.219)	1.006 (0.767, 1.321)	0.829	0.949 (0.722, 1.248)
LDL	78	0.904 (0.766, 1.066)	0.92 (0.722, 1.173)	0.844	0.898 (0.701, 1.151)
HDL	88	1.003 (0.813, 1.238)	0.915 (0.616, 1.359)	0.589	1.095 (0.793, 1.511)
Triglycerides	54	1.113 (0.88, 1.409)	1.165 (0.791, 1.715)	0.773	1.13 (0.796, 1.603)
Testosterone	89	0.776 (0.441, 1.366)	1.611 (0.604, 4.299)	0.076	0.899 (0.356, 2.268)
SHGB	236	1.047 (0.86, 1.275)	1.043 (0.732, 1.485)	0.979	0.998 (0.707, 1.408)
Fasting glucose	45	0.883 (0.641, 1.215)	1.089 (0.699, 1.696)	0.18	1.034 (0.676, 1.581)
Fasting glucose*	66	**0.565 (0.355, 0.898)**	0.707 (0.307, 1.631)	0.526	0.642 (0.321, 1.285)
Fasting insulin	13	1.264 (0.382, 4.186)	47.511 (0.222, 10182.055)	0.174	1.091 (0.222, 5.358)
Fasting insulin*	35	1.155 (0.443, 3.012)	0.246 (0.012, 4.973)	0.288	0.685 (0.182, 2.582)
HbA1c	37	0.745 (0.349, 1.592)	0.554 (0.132, 2.327)	0.634	0.8 (0.252, 2.54)
HbA1c*	73	0.63 (0.334, 1.188)	0.32 (0.102, 1.006)	0.164	0.503 (0.183, 1.383)
2-hour glucose*	12	0.878 (0.592, 1.302)	0.515 (0.175, 1.52)	0.3	0.845 (0.524, 1.365)
IGF-1	308	1.041 (0.867, 1.249)	0.72 (0.506, 1.024)	0.016	0.872 (0.639, 1.19)
Type 2 diabetes	200	1.042 (0.949, 1.143)	0.979 (0.8, 1.199)	0.502	0.95 (0.8, 1.129)
CRP	40	1.005 (0.81, 1.246)	0.964 (0.69, 1.348)	0.75	1.294 (0.927, 1.806)
Distal colon					
Alcohol	37	0.909 (0.345, 2.395)	1.002 (0.241, 4.165)	0.853	1.165 (0.414, 3.276)
BMR	445	0.941 (0.678, 1.307)	1.73 (0.753, 3.977)	0.119	1.036 (0.613, 1.75)
Birth weight	97	0.978 (0.634, 1.508)	1.074 (0.261, 4.423)	0.891	0.989 (0.528, 1.853)
Body fat %	293	1.252 (0.837, 1.872)	0.969 (0.234, 4.019)	0.713	1.404 (0.763, 2.584)
HC	305	1.103 (0.822, 1.481)	1.192 (0.502, 2.832)	0.852	1.174 (0.747, 1.845)

Height	987	1.071 (0.907, 1.265)	1.04 (0.758, 1.427)	0.83	1.036 (0.794, 1.352)
WC	267	1.304 (0.908, 1.874)	1.894 (0.621, 5.773)	0.488	1.436 (0.806, 2.56)
WHR	353	0.883 (0.629, 1.241)	0.604 (0.231, 1.579)	0.408	0.856 (0.49, 1.496)
BMI	542	1.179 (0.902, 1.541)	1.098 (0.549, 2.198)	0.828	1.178 (0.745, 1.864)
Smoking	211	0.951 (0.44, 2.057)	1.946 (0.14, 27.094)	0.577	0.946 (0.303, 2.954)
Physical activity	3	2.658 (0.352, 20.059)	0.176 (0, 186309.301)	0.698	1.925 (0.167, 22.248)
Vitamin D	51	0.877 (0.595, 1.293)	0.611 (0.327, 1.141)	0.148	0.814 (0.425, 1.56)
Total cholesterol	85	1.155 (0.932, 1.431)	0.915 (0.648, 1.292)	0.093	1 (0.702, 1.424)
LDL	78	1.113 (0.898, 1.381)	0.933 (0.68, 1.278)	0.134	0.871 (0.621, 1.222)
HDL	88	1.169 (0.912, 1.499)	1.148 (0.721, 1.829)	0.928	1.034 (0.696, 1.534)
Triglycerides	54	1.185 (0.892, 1.576)	1.039 (0.651, 1.659)	0.486	1.179 (0.759, 1.832)
Testosterone	89	0.686 (0.351, 1.339)	0.735 (0.226, 2.395)	0.888	0.53 (0.183, 1.536)
SHGB	236	0.988 (0.769, 1.269)	1.347 (0.859, 2.114)	0.105	1.019 (0.681, 1.524)
Fasting glucose	45	0.735 (0.494, 1.093)	1.075 (0.632, 1.828)	0.043	0.961 (0.574, 1.61)
Fasting glucose*	66	0.715 (0.41, 1.248)	3.239 (1.197, 8.766)	0	1.119 (0.433, 2.892)
Fasting insulin	13	0.272 (0.063, 1.169)	0.196 (0, 151.495)	0.921	0.203 (0.028, 1.456)
Fasting insulin*	35	1.312 (0.44, 3.914)	8.851 (0.293, 267.586)	0.247	0.77 (0.158, 3.764)
HbA1c	37	1.85 (0.733, 4.668)	1.851 (0.317, 10.801)	0.999	1.486 (0.347, 6.366)
HbA1c*	73	1.363 (0.632, 2.938)	1.109 (0.277, 4.44)	0.727	0.691 (0.205, 2.326)
2-hour glucose*	12	1.284 (0.753, 2.189)	1.958 (0.434, 8.837)	0.555	1.512 (0.857, 2.67)
IGF-1	308	1.243 (0.992, 1.559)	1.256 (0.813, 1.94)	0.957	1.104 (0.76, 1.603)
Type 2 diabetes	200	0.955 (0.851, 1.072)	1.004 (0.782, 1.288)	0.659	0.989 (0.817, 1.197)
CRP	40	0.994 (0.753, 1.313)	0.791 (0.519, 1.206)	0.161	0.806 (0.537, 1.211)
Rectal					
Alcohol	37	0.785 (0.349, 1.77)	0.421 (0.123, 1.436)	0.187	0.373 (0.122, 1.138)
BMR	445	0.926 (0.663, 1.293)	0.8 (0.343, 1.87)	0.714	1.011 (0.604, 1.694)
Birth weight	97	0.859 (0.577, 1.28)	1.622 (0.449, 5.852)	0.307	1.059 (0.59, 1.901)
Body fat %	293	0.978 (0.662, 1.445)	1.645 (0.418, 6.476)	0.438	1.274 (0.695, 2.333)
HC	305	1.006 (0.75, 1.348)	1.061 (0.45, 2.504)	0.896	0.906 (0.572, 1.433)
Height	987	1.146 (0.975, 1.348)	1.135 (0.834, 1.544)	0.94	1.135 (0.877, 1.471)

WC	267	1.244 (0.856, 1.808)	0.993 (0.317, 3.117)	0.683	1.633 (0.873, 3.056)
WHR	353	1.173 (0.839, 1.64)	1.223 (0.47, 3.179)	0.928	1.438 (0.858, 2.411)
BMI	542	1.113 (0.847, 1.463)	0.968 (0.478, 1.963)	0.675	1.243 (0.759, 2.036)
Smoking	211	1.016 (0.483, 2.139)	0.904 (0.073, 11.143)	0.924	1.798 (0.577, 5.603)
Physical activity	3	0.296 (0.042, 2.093)	0.121 (0, 67659.922)	0.893	0.256 (0.023, 2.893)
Vitamin D	51	0.782 (0.488, 1.251)	**0.455 (0.217, 0.956)**	0.069	0.57 (0.299, 1.085)
Total cholesterol	85	0.95 (0.778, 1.16)	0.995 (0.719, 1.376)	0.724	0.95 (0.685, 1.317)
LDL	78	0.903 (0.742, 1.099)	0.849 (0.637, 1.132)	0.564	0.874 (0.653, 1.169)
HDL	88	1.025 (0.808, 1.3)	1.064 (0.681, 1.663)	0.846	1.03 (0.701, 1.515)
Triglycerides	54	0.967 (0.733, 1.277)	0.922 (0.583, 1.46)	0.799	0.853 (0.571, 1.275)
Testosterone	89	1.297 (0.64, 2.629)	1.082 (0.31, 3.775)	0.729	0.896 (0.305, 2.631)
SHGB	236	1.029 (0.81, 1.307)	1.161 (0.753, 1.791)	0.512	1.276 (0.847, 1.92)
Fasting glucose	45	1.001 (0.688, 1.457)	0.983 (0.584, 1.656)	0.922	1.13 (0.678, 1.883)
Fasting glucose*	66	0.794 (0.462, 1.365)	0.815 (0.308, 2.159)	0.95	1.232 (0.456, 3.329)
Fasting insulin	13	1.511 (0.257, 8.884)	8.032 (0.002, 34770.641)	0.689	4.273 (0.553, 33.014)
Fasting insulin*	35	1.606 (0.556, 4.64)	0.727 (0.025, 21.075)	0.627	2.258 (0.48, 10.621)
HbA1c	37	0.795 (0.318, 1.989)	0.938 (0.161, 5.456)	0.83	0.871 (0.202, 3.746)
HbA1c*	73	1.159 (0.519, 2.59)	1.489 (0.342, 6.475)	0.689	1.618 (0.471, 5.559)
2-hour glucose*	12	0.693 (0.435, 1.102)	0.678 (0.185, 2.483)	0.972	0.573 (0.314, 1.047)
IGF-1	308	**1.383 (1.103, 1.735)**	1.323 (0.853, 2.052)	0.818	**1.492 (1.032, 2.157)**
Type 2 diabetes	200	1.02 (0.908, 1.146)	1.04 (0.806, 1.341)	0.867	1.179 (0.965, 1.44)
CRP	40	0.991 (0.73, 1.346)	0.962 (0.599, 1.546)	0.872	1.126 (0.758, 1.673)
Stage I					
Alcohol	36	**6.966 (1.092, 44.434)**	7.439 (0.578, 95.749)	0.941	7.878 (0.799, 77.669)
BMR	422	0.781 (0.337, 1.809)	0.443 (0.054, 3.621)	0.564	1.016 (0.265, 3.892)
Birth weight	91	1.297 (0.42, 4.004)	2.658 (0.08, 88.477)	0.672	0.73 (0.143, 3.726)
Body fat %	275	1.481 (0.523, 4.191)	0.352 (0.01, 11.997)	0.403	1.63 (0.33, 8.05)
HC	288	0.641 (0.291, 1.411)	0.736 (0.075, 7.273)	0.899	1.119 (0.337, 3.718)
Height	946	0.784 (0.509, 1.207)	0.961 (0.425, 2.172)	0.564	0.972 (0.485, 1.949)
WC	250	1.16 (0.443, 3.038)	0.463 (0.026, 8.294)	0.508	0.76 (0.165, 3.495)

WHR	340	0.817 (0.324, 2.063)	0.456 (0.03, 7.002)	0.656	0.372 (0.093, 1.497)
BMI	485	1.185 (0.585, 2.403)	0.77 (0.126, 4.699)	0.611	0.874 (0.25, 3.049)
Smoking	198	0.928 (0.124, 6.965)	8.616 (0.009, 7857.426)	0.502	0.26 (0.013, 5.283)
Physical activity	3	0.457 (0.003, 62.325)	0 (0, 92275696.008)	0.336	0.1 (0, 61.421)
Vitamin D	42	0.61 (0.227, 1.644)	0.274 (0.055, 1.363)	0.213	0.337 (0.077, 1.487)
Total cholesterol	77	1.274 (0.68, 2.386)	0.993 (0.29, 3.398)	0.644	0.789 (0.297, 2.096)
LDL	70	0.947 (0.495, 1.811)	1.272 (0.417, 3.875)	0.523	0.961 (0.347, 2.663)
HDL	80	1.287 (0.66, 2.509)	1.456 (0.425, 4.994)	0.815	1.596 (0.577, 4.419)
Triglycerides	45	1.024 (0.481, 2.182)	1.615 (0.472, 5.521)	0.357	1.765 (0.581, 5.36)
Testosterone	77	2.257 (0.356, 14.297)	0.25 (0.011, 5.852)	0.094	1.629 (0.066, 39.924)
SHGB	211	1.108 (0.581, 2.112)	1.073 (0.348, 3.307)	0.946	0.971 (0.336, 2.809)
Fasting glucose	42	1.098 (0.414, 2.912)	1.527 (0.393, 5.929)	0.493	1.009 (0.276, 3.695)
Fasting glucose*	62	1.5 (0.363, 6.206)	12.589 (0.984, 161.047)	0.049	5.881 (0.726, 47.614)
Fasting insulin	12	0.28 (0.003, 23.566)	2325.452 (0, 638719501745.996)	0.35	0.152 (0.001, 38.774)
Fasting insulin*	31	0.11 (0.004, 2.898)	0 (0, 0.311)	0.064	0.265 (0.004, 18.408)
HbA1c	34	1.599 (0.108, 23.781)	0.394 (0.003, 61.717)	0.519	1.987 (0.052, 76.414)
HbA1c*	68	1.192 (0.131, 10.808)	0.302 (0.006, 15.136)	0.405	0.625 (0.025, 15.351)
2-hour glucose*	10	0.963 (0.292, 3.176)	3.608 (0.061, 213.862)	0.507	1.528 (0.298, 7.825)
IGF-1	265	1.09 (0.598, 1.986)	0.7 (0.218, 2.251)	0.387	1.064 (0.374, 3.027)
Type 2 diabetes	182	1.205 (0.899, 1.614)	1.049 (0.568, 1.936)	0.614	1.119 (0.616, 2.033)
CRP	35	0.625 (0.3, 1.3)	0.471 (0.139, 1.593)	0.568	0.726 (0.261, 2.02)
Stages II/III					
Alcohol	36	0.88 (0.426, 1.814)	0.679 (0.231, 1.995)	0.525	0.681 (0.247, 1.88)
BMR	422	1.049 (0.773, 1.425)	1.529 (0.705, 3.316)	0.299	1.219 (0.753, 1.972)
Birth weight	91	0.892 (0.608, 1.308)	0.619 (0.185, 2.079)	0.534	0.822 (0.467, 1.447)
Body fat %	275	1.179 (0.807, 1.722)	2.916 (0.798, 10.648)	0.152	1.429 (0.81, 2.52)
HC	288	**1.328 (1.018, 1.731)**	1.875 (0.869, 4.044)	0.348	1.427 (0.941, 2.165)
Height	946	1.012 (0.866, 1.182)	0.98 (0.73, 1.317)	0.806	1.089 (0.846, 1.403)
WC	250	1.378 (0.984, 1.931)	2.15 (0.781, 5.915)	0.361	1.9 (1.122, 3.218)

WHR	340	1.19 (0.862, 1.643)	0.926 (0.372, 2.303)	0.563	1.259 (0.744, 2.13)
BMI	485	**1.497 (1.152, 1.945)**	1.232 (0.63, 2.409)	0.536	**1.84 (1.187, 2.852)**
Smoking	198	1.669 (0.818, 3.403)	13.759 (1.249, 151.529)	0.071	2.446 (0.815, 7.342)
Physical activity	3	1.411 (0.23, 8.644)	0.004 (0, 1133.99)	0.356	1.159 (0.116, 11.624)
Vitamin D	42	0.892 (0.618, 1.288)	0.748 (0.41, 1.363)	0.465	0.865 (0.517, 1.447)
Total cholesterol	77	1.146 (0.925, 1.42)	1.392 (0.918, 2.111)	0.284	1.314 (0.948, 1.821)
LDL	70	1.015 (0.819, 1.258)	1.092 (0.759, 1.572)	0.623	0.975 (0.703, 1.354)
HDL	80	1.119 (0.891, 1.405)	1.155 (0.76, 1.753)	0.859	0.919 (0.631, 1.338)
Triglycerides	45	1.013 (0.775, 1.325)	1.105 (0.717, 1.703)	0.618	1.029 (0.685, 1.545)
Testosterone	77	0.722 (0.379, 1.375)	0.557 (0.182, 1.703)	0.576	0.745 (0.256, 2.171)
SHGB	211	1.016 (0.813, 1.27)	1.222 (0.828, 1.806)	0.256	0.879 (0.582, 1.328)
Fasting glucose	42	0.826 (0.575, 1.187)	0.866 (0.52, 1.442)	0.797	1.016 (0.643, 1.607)
Fasting glucose*	62	**0.518 (0.3, 0.893)**	0.573 (0.212, 1.548)	0.812	0.615 (0.282, 1.342)
Fasting insulin	12	2.223 (0.566, 8.731)	45.569 (0.124, 16710.279)	0.303	2.728 (0.413, 18.008)
Fasting insulin*	31	1.732 (0.515, 5.826)	5.783 (0.114, 293.29)	0.526	1.315 (0.281, 6.148)
HbA1c	34	0.793 (0.339, 1.851)	1.021 (0.209, 5)	0.71	0.829 (0.219, 3.134)
HbA1c*	68	0.974 (0.478, 1.985)	0.632 (0.178, 2.241)	0.418	0.855 (0.266, 2.751)
2-hour glucose*	10	0.859 (0.482, 1.531)	1.629 (0.207, 12.848)	0.525	0.84 (0.44, 1.603)
IGF-1	265	1.201 (0.968, 1.489)	1.036 (0.685, 1.567)	0.414	1.022 (0.711, 1.467)
Type 2 diabetes	182	0.994 (0.885, 1.117)	1.219 (0.954, 1.559)	0.065	1.205 (0.99, 1.466)
CRP	35	1.027 (0.778, 1.355)	0.969 (0.607, 1.546)	0.759	0.875 (0.559, 1.372)
Stage IV					
Alcohol	36	0.874 (0.402, 1.902)	0.527 (0.164, 1.692)	0.256	0.582 (0.223, 1.521)
BMR	422	0.858 (0.635, 1.16)	0.82 (0.379, 1.775)	0.901	0.7 (0.448, 1.094)
Birth weight	91	0.874 (0.614, 1.243)	1.025 (0.336, 3.123)	0.767	0.931 (0.555, 1.56)
Body fat %	275	0.886 (0.626, 1.256)	1.289 (0.388, 4.281)	0.523	0.817 (0.472, 1.415)
HC	288	0.87 (0.669, 1.13)	0.82 (0.382, 1.761)	0.872	0.928 (0.619, 1.391)
Height	946	1.071 (0.926, 1.24)	0.844 (0.64, 1.113)	0.047	1.032 (0.818, 1.302)
WC	250	0.882 (0.635, 1.225)	0.926 (0.343, 2.5)	0.92	0.76 (0.443, 1.304)
WHR	340	1.115 (0.817, 1.522)	2.113 (0.878, 5.089)	0.127	0.811 (0.513, 1.283)

BMI	485	0.832 (0.657, 1.054)	1.075 (0.587, 1.971)	0.368	0.796 (0.513, 1.236)
Smoking	198	1.165 (0.599, 2.269)	3.863 (0.406, 36.763)	0.275	1.426 (0.531, 3.832)
Physical activity	3	1.116 (0.214, 5.819)	13.409 (0, 806677.876)	0.654	1.755 (0.237, 13.017)
Vitamin D	42	1.045 (0.696, 1.569)	0.848 (0.438, 1.643)	0.431	1.255 (0.691, 2.279)
Total cholesterol	77	0.998 (0.82, 1.215)	0.874 (0.598, 1.278)	0.423	0.91 (0.671, 1.235)
LDL	70	0.996 (0.821, 1.21)	0.831 (0.6, 1.151)	0.174	0.935 (0.695, 1.258)
HDL	80	0.877 (0.7, 1.098)	1.201 (0.801, 1.802)	0.069	1.023 (0.73, 1.432)
Triglycerides	45	1.095 (0.843, 1.422)	0.841 (0.554, 1.277)	0.116	0.862 (0.598, 1.242)
Testosterone	77	0.974 (0.544, 1.742)	1.017 (0.367, 2.823)	0.919	0.688 (0.26, 1.821)
SHGB	211	0.918 (0.745, 1.13)	0.718 (0.497, 1.038)	0.113	0.838 (0.595, 1.178)
Fasting glucose	42	1.186 (0.853, 1.648)	1.118 (0.703, 1.778)	0.722	1.04 (0.675, 1.602)
Fasting glucose*	62	1.018 (0.636, 1.629)	0.847 (0.361, 1.988)	0.614	1.09 (0.499, 2.381)
Fasting insulin	12	1.533 (0.433, 5.421)	1.047 (0.004, 267.893)	0.89	2.906 (0.526, 16.044)
Fasting insulin*	31	1.556 (0.608, 3.983)	0.317 (0.016, 6.347)	0.273	0.885 (0.237, 3.302)
HbA1c	34	1.012 (0.454, 2.257)	0.445 (0.101, 1.955)	0.197	0.559 (0.159, 1.959)
HbA1c*	68	0.822 (0.427, 1.583)	0.331 (0.104, 1.054)	0.062	0.453 (0.157, 1.303)
2-hour glucose*	10	1.014 (0.678, 1.517)	0.35 (0.088, 1.39)	0.114	1.051 (0.613, 1.803)
IGF-1	265	1.144 (0.939, 1.395)	1.016 (0.695, 1.484)	0.47	1.161 (0.832, 1.619)
Type 2 diabetes	182	1.051 (0.953, 1.159)	0.941 (0.763, 1.161)	0.246	0.932 (0.795, 1.094)
CRP	35	0.825 (0.645, 1.056)	0.716 (0.474, 1.08)	0.397	0.886 (0.631, 1.245)

Abbreviations: BMI; body mass index, BMR; basal metabolic rate, CRC; colorectal cancer, CRP; C-reactive protein, HbA1c; hemoglobin A1c, HC; hip circumference, HDL; high-density lipoprotein, IGF-1; insulin-like growth factor-1, IVW; inverse variance weighted, LDL; low-density lipoprotein, MR; Mendelian Randomization, SHGB; sex hormone binding globulin, SNPs; single nucleotide polymorphisms, WC; waist circumference, WHR; waist-hip circumference ratio
Bolds indicate statistically significant estimates (p-value<0.05)
**The marginal associations for the exposure were adjusted for BMI*

Table S4.2: Hazard ratios and 95% confidence intervals for the associations between the genetically-predicted levels of various exposures and colorectal cancer (CRC) mortality among CRC cases overall, and by anatomical site and stage, after adjustment for collider bias.

Exposure	Number of SNPs	SIMEX	Slope-hunter	CWLS
CRC				
Alcohol	35	1.014 (0.675, 1.524)	1.104 (0.71, 1.716)	1.016 (0.675, 1.527)

BMR	441	0.94 (0.795, 1.112)	0.894 (0.753, 1.062)	0.939 (0.794, 1.111)
Birth weight	94	0.889 (0.712, 1.11)	0.847 (0.68, 1.055)	0.888 (0.711, 1.109)
Body fat %	290	1.045 (0.853, 1.28)	0.991 (0.801, 1.225)	1.044 (0.852, 1.279)
HC	304	1.058 (0.907, 1.234)	1.028 (0.878, 1.204)	1.057 (0.906, 1.233)
Height	982	0.98 (0.903, 1.065)	0.964 (0.887, 1.049)	0.98 (0.902, 1.064)
WC	263	1.199 (0.997, 1.442)	1.104 (0.914, 1.335)	1.197 (0.995, 1.44)
WHR	354	1.075 (0.9, 1.282)	1.006 (0.841, 1.203)	1.073 (0.899, 1.281)
BMI	475	1.076 (0.929, 1.247)	1.02 (0.877, 1.187)	1.075 (0.928, 1.246)
Smoking	176	1.042 (0.692, 1.57)	0.915 (0.603, 1.388)	1.04 (0.69, 1.566)
Physical activity	1	1.115 (0.195, 6.374)	1.485 (0.251, 8.799)	1.121 (0.196, 6.408)
Vitamin D	43	0.905 (0.702, 1.168)	0.909 (0.696, 1.187)	0.905 (0.701, 1.169)
Birth weight	80	1.045 (0.939, 1.161)	1.022 (0.917, 1.138)	1.044 (0.939, 1.161)
LDL	75	0.972 (0.88, 1.073)	0.953 (0.861, 1.054)	0.971 (0.879, 1.073)
HDL	85	1.072 (0.935, 1.229)	1.084 (0.945, 1.244)	1.072 (0.935, 1.229)
Triglycerides	54	1.122 (0.974, 1.291)	1.129 (0.978, 1.304)	1.122 (0.974, 1.291)
Testosterone	70	0.803 (0.553, 1.166)	0.742 (0.502, 1.097)	0.802 (0.552, 1.164)
SHGB	203	0.958 (0.84, 1.093)	0.936 (0.816, 1.074)	0.958 (0.839, 1.093)
Fasting glucose	40	0.864 (0.703, 1.061)	0.846 (0.686, 1.044)	0.863 (0.703, 1.061)
Fasting glucose*	61	0.56 (0.408, 0.768)	0.557 (0.403, 0.768)	0.56 (0.408, 0.768)
Fasting insulin	13	0.975 (0.475, 2.001)	0.933 (0.449, 1.941)	0.974 (0.475, 1.999)
Fasting insulin*	33	1.24 (0.662, 2.322)	1.013 (0.523, 1.961)	1.235 (0.659, 2.315)
HbA1c	36	0.95 (0.599, 1.506)	0.981 (0.614, 1.567)	0.951 (0.6, 1.507)
HbA1c*	66	0.824 (0.558, 1.218)	0.814 (0.547, 1.212)	0.824 (0.558, 1.217)
2-hour glucose*	11	0.998 (0.751, 1.327)	1.001 (0.744, 1.347)	0.998 (0.751, 1.327)
IGF-1	259	1.113 (0.989, 1.252)	1.078 (0.956, 1.215)	1.112 (0.989, 1.251)
Type 2 diabetes	161	1.019 (0.958, 1.083)	1.01 (0.949, 1.075)	1.019 (0.958, 1.083)
CRP	39	0.941 (0.815, 1.085)	0.941 (0.807, 1.097)	0.941 (0.815, 1.085)
Proximal colon				
Alcohol	35	1.176 (0.566, 2.444)	1.019 (0.501, 2.075)	1.173 (0.565, 2.436)
BMR	441	0.934 (0.71, 1.228)	1.066 (0.808, 1.407)	0.936 (0.712, 1.231)

Birth weight	94	1.12 (0.791, 1.585)	1.218 (0.845, 1.755)	1.122 (0.792, 1.588)
Body fat %	290	0.903 (0.642, 1.268)	1.053 (0.75, 1.48)	0.905 (0.644, 1.271)
HC	304	1.113 (0.865, 1.432)	1.237 (0.957, 1.598)	1.115 (0.866, 1.434)
Height	982	0.857 (0.745, 0.984)	0.89 (0.773, 1.024)	0.857 (0.746, 0.985)
WC	263	1.033 (0.749, 1.425)	1.249 (0.904, 1.725)	1.036 (0.752, 1.429)
WHR	354	1.022 (0.76, 1.373)	1.156 (0.858, 1.558)	1.024 (0.762, 1.376)
BMI	475	1.065 (0.835, 1.359)	1.227 (0.962, 1.565)	1.067 (0.837, 1.362)
Smoking	176	1.015 (0.509, 2.023)	1.279 (0.638, 2.566)	1.019 (0.512, 2.03)
Physical activity	1	0.97 (0.05, 18.686)	0.617 (0.031, 12.257)	0.963 (0.05, 18.518)
Vitamin D	43	1.216 (0.868, 1.704)	1.172 (0.835, 1.647)	1.216 (0.868, 1.703)
Birth weight	80	1.012 (0.847, 1.209)	1.012 (0.842, 1.217)	1.012 (0.847, 1.209)
LDL	75	0.889 (0.752, 1.05)	0.9 (0.755, 1.073)	0.889 (0.753, 1.051)
HDL	85	1.059 (0.854, 1.312)	1.014 (0.808, 1.271)	1.058 (0.853, 1.312)
Triglycerides	54	1.117 (0.881, 1.415)	1.111 (0.875, 1.412)	1.117 (0.881, 1.415)
Testosterone	70	0.784 (0.409, 1.501)	0.832 (0.442, 1.568)	0.784 (0.41, 1.502)
SHGB	203	1.046 (0.839, 1.304)	1.066 (0.853, 1.332)	1.046 (0.84, 1.304)
Fasting glucose	40	0.865 (0.612, 1.224)	0.844 (0.595, 1.198)	0.865 (0.611, 1.223)
Fasting glucose*	61	0.518 (0.304, 0.883)	0.462 (0.27, 0.792)	0.517 (0.304, 0.881)
Fasting insulin	13	1.183 (0.355, 3.948)	1.375 (0.407, 4.65)	1.186 (0.356, 3.956)
Fasting insulin*	33	0.843 (0.314, 2.264)	1.275 (0.471, 3.449)	0.849 (0.316, 2.278)
HbA1c	36	0.823 (0.381, 1.779)	0.667 (0.306, 1.456)	0.82 (0.379, 1.773)
HbA1c*	66	0.644 (0.334, 1.242)	0.611 (0.314, 1.188)	0.644 (0.334, 1.241)
2-hour glucose*	11	0.91 (0.588, 1.409)	0.889 (0.558, 1.417)	0.91 (0.587, 1.409)
IGF-1	259	0.922 (0.757, 1.125)	0.955 (0.782, 1.167)	0.923 (0.757, 1.125)
Type 2 diabetes	161	1.053 (0.95, 1.167)	1.059 (0.954, 1.175)	1.053 (0.95, 1.167)
CRP	39	1 (0.798, 1.253)	0.976 (0.786, 1.211)	0.999 (0.798, 1.252)
Distal colon				
Alcohol	35	0.979 (0.367, 2.617)	0.93 (0.347, 2.491)	0.966 (0.361, 2.581)
BMR	441	0.873 (0.625, 1.219)	0.917 (0.656, 1.281)	0.882 (0.632, 1.231)
Birth weight	94	0.828 (0.541, 1.267)	0.857 (0.56, 1.313)	0.836 (0.546, 1.278)

Body fat %	290	1.174 (0.779, 1.769)	1.209 (0.802, 1.823)	1.182 (0.785, 1.78)
HC	304	1.074 (0.795, 1.449)	1.09 (0.81, 1.465)	1.077 (0.799, 1.453)
Height	982	1.093 (0.923, 1.296)	1.102 (0.93, 1.306)	1.096 (0.925, 1.298)
WC	263	1.163 (0.804, 1.684)	1.218 (0.841, 1.763)	1.177 (0.814, 1.703)
WHR	354	0.789 (0.559, 1.113)	0.817 (0.579, 1.153)	0.796 (0.565, 1.122)
BMI	475	1.02 (0.765, 1.359)	1.056 (0.793, 1.407)	1.029 (0.772, 1.37)
Smoking	176	0.717 (0.308, 1.671)	0.805 (0.345, 1.875)	0.737 (0.317, 1.712)
Physical activity	1	2.906 (0.079, 107.481)	2.311 (0.06, 89.236)	2.747 (0.075, 100.656)
Vitamin D	43	0.875 (0.561, 1.366)	0.877 (0.569, 1.353)	0.877 (0.564, 1.365)
Birth weight	80	1.052 (0.846, 1.31)	1.077 (0.864, 1.342)	1.059 (0.851, 1.318)
LDL	75	1.021 (0.823, 1.265)	1.042 (0.839, 1.293)	1.026 (0.828, 1.272)
HDL	85	1.268 (0.983, 1.635)	1.252 (0.97, 1.615)	1.264 (0.98, 1.629)
Triglycerides	54	1.184 (0.887, 1.581)	1.191 (0.89, 1.594)	1.184 (0.888, 1.58)
Testosterone	70	0.522 (0.244, 1.117)	0.574 (0.266, 1.238)	0.534 (0.25, 1.141)
SHGB	203	0.844 (0.64, 1.113)	0.858 (0.652, 1.13)	0.848 (0.644, 1.118)
Fasting glucose	40	0.672 (0.442, 1.022)	0.672 (0.442, 1.023)	0.672 (0.443, 1.022)
Fasting glucose*	61	0.49 (0.256, 0.939)	0.491 (0.256, 0.944)	0.492 (0.257, 0.941)
Fasting insulin	13	0.26 (0.059, 1.142)	0.265 (0.06, 1.171)	0.261 (0.06, 1.142)
Fasting insulin*	33	0.933 (0.3, 2.905)	1.049 (0.334, 3.29)	0.958 (0.309, 2.973)
HbA1c	36	1.735 (0.672, 4.477)	1.716 (0.665, 4.429)	1.735 (0.674, 4.466)
HbA1c*	66	1.09 (0.488, 2.432)	1.116 (0.499, 2.495)	1.1 (0.494, 2.448)
2-hour glucose*	11	1.223 (0.636, 2.352)	1.227 (0.644, 2.34)	1.225 (0.639, 2.348)
IGF-1	259	1.177 (0.925, 1.499)	1.214 (0.953, 1.548)	1.185 (0.931, 1.507)
Type 2 diabetes	161	0.927 (0.815, 1.054)	0.936 (0.825, 1.064)	0.929 (0.818, 1.056)
CRP	39	0.985 (0.75, 1.294)	0.984 (0.751, 1.29)	0.985 (0.751, 1.293)
Rectal				
Alcohol	35	0.83 (0.368, 1.871)	0.851 (0.378, 1.918)	0.822 (0.364, 1.856)
BMR	441	0.945 (0.671, 1.329)	0.945 (0.669, 1.335)	0.945 (0.672, 1.328)
Birth weight	94	0.811 (0.541, 1.217)	0.805 (0.534, 1.213)	0.813 (0.543, 1.219)
Body fat %	290	0.909 (0.613, 1.349)	0.889 (0.597, 1.324)	0.917 (0.619, 1.358)

HC	304	0.963 (0.713, 1.3)	0.956 (0.705, 1.296)	0.965 (0.716, 1.301)
Height	982	1.157 (0.982, 1.362)	1.158 (0.981, 1.366)	1.157 (0.983, 1.361)
WC	263	1.14 (0.781, 1.665)	1.097 (0.748, 1.609)	1.157 (0.793, 1.687)
WHR	354	1.031 (0.736, 1.446)	0.99 (0.704, 1.392)	1.046 (0.747, 1.466)
BMI	475	1.037 (0.773, 1.391)	1.019 (0.757, 1.372)	1.043 (0.778, 1.398)
Smoking	176	0.896 (0.399, 2.013)	0.82 (0.361, 1.862)	0.925 (0.413, 2.072)
Physical activity	1	0.306 (0.01, 9.154)	0.328 (0.011, 10.176)	0.299 (0.01, 8.868)
Vitamin D	43	0.773 (0.467, 1.28)	0.786 (0.473, 1.307)	0.769 (0.465, 1.273)
Birth weight	80	0.933 (0.755, 1.152)	0.918 (0.741, 1.136)	0.938 (0.76, 1.158)
LDL	75	0.887 (0.725, 1.085)	0.875 (0.714, 1.072)	0.891 (0.728, 1.09)
HDL	85	1.01 (0.789, 1.292)	1.002 (0.781, 1.286)	1.012 (0.792, 1.294)
Triglycerides	54	0.992 (0.75, 1.312)	1.006 (0.758, 1.335)	0.987 (0.747, 1.305)
Testosterone	70	1.229 (0.535, 2.819)	1.168 (0.503, 2.712)	1.251 (0.547, 2.862)
SHGB	203	1.007 (0.769, 1.319)	0.987 (0.751, 1.298)	1.015 (0.776, 1.328)
Fasting glucose	40	0.921 (0.612, 1.386)	0.9 (0.595, 1.361)	0.929 (0.618, 1.396)
Fasting glucose*	61	0.536 (0.287, 1.003)	0.52 (0.276, 0.98)	0.542 (0.29, 1.012)
Fasting insulin	13	1.497 (0.249, 9.006)	1.487 (0.242, 9.142)	1.5 (0.251, 8.969)
Fasting insulin*	33	1.355 (0.455, 4.038)	1.207 (0.4, 3.647)	1.412 (0.475, 4.197)
HbA1c	36	0.865 (0.347, 2.157)	0.855 (0.339, 2.156)	0.868 (0.349, 2.16)
HbA1c*	66	1.016 (0.461, 2.238)	0.983 (0.446, 2.168)	1.028 (0.467, 2.267)
2-hour glucose*	11	0.755 (0.461, 1.235)	0.755 (0.462, 1.233)	0.755 (0.46, 1.237)
IGF-1	259	1.256 (0.978, 1.613)	1.241 (0.963, 1.6)	1.261 (0.983, 1.618)
Type 2 diabetes	161	1.006 (0.886, 1.142)	1.005 (0.883, 1.143)	1.007 (0.888, 1.142)
CRP	39	0.982 (0.717, 1.345)	0.98 (0.716, 1.343)	0.983 (0.718, 1.346)
Stage I				
Alcohol	34	7.275 (1.049, 50.465)	4.907 (0.709, 33.98)	7.353 (1.059, 51.08)
BMR	419	0.727 (0.313, 1.69)	0.955 (0.408, 2.235)	0.721 (0.31, 1.677)
Birth weight	87	1.321 (0.403, 4.326)	1.61 (0.485, 5.341)	1.313 (0.401, 4.304)
Body fat %	275	1.401 (0.495, 3.966)	1.849 (0.648, 5.279)	1.39 (0.491, 3.936)
HC	286	0.701 (0.32, 1.532)	0.808 (0.367, 1.779)	0.698 (0.319, 1.527)

Height	938	0.76 (0.493, 1.173)	0.81 (0.523, 1.255)	0.759 (0.492, 1.171)
WC	249	1.044 (0.399, 2.736)	1.582 (0.599, 4.179)	1.032 (0.394, 2.704)
WHR	339	0.625 (0.247, 1.579)	0.866 (0.338, 2.219)	0.619 (0.245, 1.565)
BMI	423	0.964 (0.457, 2.033)	1.253 (0.59, 2.658)	0.957 (0.454, 2.018)
Smoking	165	1.026 (0.107, 9.792)	1.956 (0.211, 18.129)	1.007 (0.105, 9.631)
Physical activity	1	0.012 (0, 41.972)	0.003 (0, 11.945)	0.012 (0, 43.616)
Vitamin D	36	0.637 (0.228, 1.778)	0.629 (0.224, 1.769)	0.638 (0.229, 1.778)
Birth weight	72	1.142 (0.581, 2.242)	1.278 (0.645, 2.532)	1.138 (0.579, 2.236)
LDL	67	0.863 (0.444, 1.675)	0.962 (0.49, 1.888)	0.86 (0.443, 1.67)
HDL	79	1.472 (0.747, 2.901)	1.416 (0.712, 2.816)	1.473 (0.747, 2.904)
Triglycerides	45	1.033 (0.485, 2.203)	0.99 (0.461, 2.126)	1.035 (0.485, 2.206)
Testosterone	60	1.57 (0.204, 12.099)	2.066 (0.256, 16.675)	1.557 (0.202, 11.995)
SHGB	181	1.243 (0.593, 2.608)	1.354 (0.639, 2.872)	1.24 (0.591, 2.601)
Fasting glucose	37	0.896 (0.31, 2.588)	0.964 (0.331, 2.806)	0.894 (0.309, 2.583)
Fasting glucose*	58	0.703 (0.135, 3.646)	0.719 (0.137, 3.785)	0.702 (0.135, 3.644)
Fasting insulin	12	0.27 (0.003, 24.596)	0.328 (0.005, 21.652)	0.269 (0.003, 24.753)
Fasting insulin*	29	0.085 (0.003, 2.707)	0.219 (0.007, 7.102)	0.083 (0.003, 2.641)
HbA1c	33	1.348 (0.089, 20.516)	1.251 (0.085, 18.376)	1.351 (0.089, 20.624)
HbA1c*	61	1.461 (0.151, 14.121)	1.563 (0.155, 15.763)	1.459 (0.151, 14.103)
2-hour glucose*	10	1.077 (0.318, 3.643)	1.161 (0.339, 3.972)	1.075 (0.318, 3.636)
IGF-1	225	0.832 (0.439, 1.576)	0.946 (0.497, 1.801)	0.829 (0.438, 1.571)
Type 2 diabetes	145	1.129 (0.818, 1.558)	1.144 (0.827, 1.583)	1.128 (0.818, 1.557)
CRP	34	0.601 (0.287, 1.259)	0.61 (0.289, 1.287)	0.601 (0.287, 1.259)
Stages II/III				
Alcohol	34	0.902 (0.43, 1.889)	0.958 (0.446, 2.058)	0.905 (0.431, 1.898)
BMR	419	1.029 (0.755, 1.402)	0.993 (0.726, 1.357)	1.027 (0.753, 1.399)
Birth weight	87	0.82 (0.556, 1.211)	0.798 (0.538, 1.184)	0.819 (0.555, 1.209)
Body fat %	275	1.141 (0.78, 1.669)	1.095 (0.744, 1.613)	1.138 (0.778, 1.665)
HC	286	1.336 (1.022, 1.745)	1.309 (0.999, 1.714)	1.334 (1.021, 1.743)
Height	938	1 (0.855, 1.169)	0.99 (0.845, 1.159)	1 (0.855, 1.169)

WC	249	1.286 (0.917, 1.805)	1.21 (0.86, 1.704)	1.282 (0.914, 1.799)
WHR	339	1.19 (0.863, 1.642)	1.131 (0.818, 1.564)	1.187 (0.86, 1.637)
BMI	423	1.377 (1.044, 1.817)	1.324 (1.003, 1.749)	1.374 (1.042, 1.813)
Smoking	165	1.667 (0.766, 3.628)	1.515 (0.692, 3.314)	1.658 (0.762, 3.609)
Physical activity	1	0.544 (0.022, 13.709)	0.67 (0.025, 17.66)	0.551 (0.022, 13.876)
Vitamin D	36	0.93 (0.619, 1.397)	0.932 (0.618, 1.406)	0.93 (0.619, 1.398)
Birth weight	72	1.089 (0.866, 1.369)	1.07 (0.849, 1.349)	1.088 (0.865, 1.368)
LDL	67	0.981 (0.787, 1.222)	0.965 (0.774, 1.204)	0.98 (0.786, 1.221)
HDL	79	1.147 (0.908, 1.448)	1.153 (0.911, 1.459)	1.147 (0.908, 1.449)
Triglycerides	45	1.02 (0.78, 1.334)	1.03 (0.785, 1.352)	1.02 (0.78, 1.335)
Testosterone	60	0.904 (0.435, 1.879)	0.852 (0.407, 1.784)	0.901 (0.434, 1.873)
SHGB	181	1.093 (0.852, 1.404)	1.081 (0.839, 1.392)	1.093 (0.851, 1.403)
Fasting glucose	37	0.816 (0.548, 1.214)	0.804 (0.539, 1.199)	0.815 (0.547, 1.213)
Fasting glucose*	58	0.458 (0.245, 0.857)	0.453 (0.243, 0.844)	0.458 (0.245, 0.856)
Fasting insulin	12	2.153 (0.542, 8.556)	2.103 (0.513, 8.626)	2.149 (0.54, 8.553)
Fasting insulin*	29	1.287 (0.381, 4.341)	1.111 (0.325, 3.796)	1.276 (0.378, 4.307)
HbA1c	33	0.835 (0.352, 1.982)	0.851 (0.355, 2.04)	0.836 (0.352, 1.985)
HbA1c*	61	0.99 (0.475, 2.064)	0.983 (0.468, 2.063)	0.99 (0.475, 2.064)
2-hour glucose*	10	0.948 (0.6, 1.497)	0.937 (0.598, 1.469)	0.947 (0.601, 1.493)
IGF-1	225	1.128 (0.897, 1.419)	1.105 (0.876, 1.393)	1.127 (0.896, 1.418)
Type 2 diabetes	145	1.03 (0.906, 1.17)	1.026 (0.902, 1.168)	1.03 (0.906, 1.17)
CRP	34	1.032 (0.777, 1.369)	1.032 (0.778, 1.369)	1.032 (0.777, 1.369)
Stage IV				
Alcohol	34	0.865 (0.39, 1.921)	0.993 (0.438, 2.253)	0.866 (0.39, 1.923)
BMR	419	0.85 (0.629, 1.149)	0.774 (0.572, 1.048)	0.85 (0.629, 1.149)
Birth weight	87	0.948 (0.662, 1.357)	0.889 (0.62, 1.276)	0.948 (0.662, 1.356)
Body fat %	275	0.909 (0.643, 1.287)	0.826 (0.578, 1.18)	0.909 (0.642, 1.286)
HC	286	0.84 (0.644, 1.096)	0.801 (0.611, 1.05)	0.84 (0.644, 1.095)
Height	938	1.069 (0.921, 1.241)	1.046 (0.901, 1.216)	1.069 (0.921, 1.241)
WC	249	0.926 (0.668, 1.284)	0.801 (0.573, 1.12)	0.926 (0.668, 1.283)

WHR	339	1.165 (0.848, 1.599)	1.032 (0.751, 1.42)	1.164 (0.848, 1.599)
BMI	423	0.829 (0.647, 1.063)	0.756 (0.586, 0.974)	0.829 (0.646, 1.063)
Smoking	165	1.242 (0.606, 2.545)	0.989 (0.477, 2.054)	1.241 (0.606, 2.542)
Physical activity	1	1.504 (0.093, 24.3)	2.438 (0.147, 40.45)	1.507 (0.093, 24.345)
Vitamin D	36	1.054 (0.678, 1.637)	1.058 (0.673, 1.665)	1.054 (0.678, 1.637)
Birth weight	72	1.068 (0.866, 1.317)	1.028 (0.832, 1.269)	1.067 (0.866, 1.316)
LDL	67	1.028 (0.842, 1.255)	0.99 (0.81, 1.211)	1.027 (0.841, 1.254)
HDL	79	0.853 (0.677, 1.075)	0.864 (0.685, 1.089)	0.853 (0.677, 1.075)
Triglycerides	45	1.09 (0.834, 1.423)	1.109 (0.861, 1.427)	1.09 (0.834, 1.423)
Testosterone	60	0.881 (0.439, 1.768)	0.77 (0.383, 1.547)	0.88 (0.438, 1.767)
SHGB	181	0.908 (0.719, 1.147)	0.883 (0.698, 1.117)	0.908 (0.719, 1.147)
Fasting glucose	37	1.12 (0.78, 1.608)	1.086 (0.749, 1.574)	1.12 (0.78, 1.608)
Fasting glucose*	58	0.785 (0.458, 1.345)	0.776 (0.451, 1.335)	0.785 (0.458, 1.345)
Fasting insulin	12	1.568 (0.443, 5.554)	1.452 (0.406, 5.19)	1.568 (0.443, 5.552)
Fasting insulin*	29	1.793 (0.685, 4.697)	1.275 (0.483, 3.365)	1.791 (0.684, 4.69)
HbA1c	33	1.021 (0.452, 2.307)	1.067 (0.454, 2.507)	1.021 (0.452, 2.307)
HbA1c*	61	0.669 (0.34, 1.314)	0.659 (0.334, 1.3)	0.669 (0.34, 1.314)
2-hour glucose*	10	1.019 (0.675, 1.539)	0.991 (0.654, 1.501)	1.019 (0.674, 1.539)
IGF-1	225	1.191 (0.965, 1.471)	1.135 (0.918, 1.404)	1.191 (0.965, 1.471)
Type 2 diabetes	145	1.048 (0.941, 1.168)	1.038 (0.931, 1.157)	1.048 (0.941, 1.168)
CRP	34	0.826 (0.644, 1.061)	0.823 (0.64, 1.058)	0.826 (0.644, 1.061)

Abbreviations: BMI; body mass index, BMR; basal metabolic rate, CRC; colorectal cancer, CRP; C-reactive protein, CWLS; corrected weighted least squares, HbA1c; hemoglobin A1c, HC; hip circumference, HDL; high-density lipoprotein, IGF-1; insulin-like growth factor-1, LDL; low-density lipoprotein, MR; Mendelian Randomization, SHGB; sex hormone binding globulin, SIMEX; simulation extrapolation, SNPs; single nucleotide polymorphisms, WC; waist circumference, WHR; waist-hip circumference ratio

Bolds indicate statistically significant estimates (p-value<0.05)

**The marginal associations for the exposure were adjusted for BMI*