



**ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ**

ΤΟΜΕΑΣ ΚΟΙΝΩΝΙΚΗΣ ΙΑΤΡΙΚΗΣ ΚΑΙ ΨΥΧΙΚΗΣ ΥΓΕΙΑΣ

ΕΡΓΑΣΤΗΡΙΟ ΥΓΙΕΙΝΗΣ & ΕΠΙΔΗΜΙΟΛΟΓΙΑΣ

**Εμπειρική αποτίμηση και συστηματική ανασκόπηση προγνωστικών δεικτών
και προγνωστικών μοντέλων για χρόνια νοσήματα.**

ΣΕΡΕΤΗΣ ΑΡΙΣΤΕΙΔΗΣ

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Ι Ω Α Ν Ν Ι Ν Α 2 0 2 0



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*Αφιερώνεται στους γονείς μου Γιώργο και Αναστασία,
στις αδελφές μου Χριστίνα και Σοφία,
και σε όσους με στήριξαν υπομονετικά μέχρι το τέλος.*

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Πρόλογος

Η καρδιαγγειακή νόσος και ο καρκίνος αποτελούν τις δύο πρώτες κύριες αιτίες θανάτου παγκοσμίως, αριθμώντας σχεδόν 30 εκατομμύρια θανάτους καθ'έτος, με μεγάλο οικονομικό αντίκτυπο για τη διάγνωση και τη θεραπεία τους. Οι δύο αυτές νόσοι μοιράζονται πολλούς κοινούς παράγοντες κινδύνου, όπως το κάπνισμα, η παχυσαρκία, η έλλειψη φυσικής άσκησης, η ανθυγιεινή διατροφή και ο διαβήτης. Επομένως, η έρευνα σχετικά με την πρόγνωση και τα προγνωστικά μοντέλα, (δηλαδή του συνδυασμού πολλαπλών παραγόντων κινδύνου), είναι καίρια για τη συμβουλευτική των ασθενών και τη λήψη κλινικών αποφάσεων. Για πολλά χρόνια στον τομέα της πρόγνωσης δεν υπήρχε μία ενοποιημένη ταξινόμηση ή ένας σαφής διαχωρισμός μεταξύ των διαφόρων ειδών προγνωστικής έρευνας. Ωστόσο, από το 2013 έχουν προταθεί τέσσερα διακριτά, αλλά συγγενή, είδη έρευνας σε αυτό το πεδίο: η γενική προγνωστική έρευνα, η έρευνα προγνωστικών παραγόντων, η έρευνα προγνωστικών μοντέλων και η έρευνα προγνωστικών παραγόντων απάντησης στη θεραπεία.

Πρώτος στόχος της παρούσας μελέτης ήταν η εκτίμηση της ποικιλίας των πληθυσμών και των εκβάσεων για τις οποίες ένα από τα σημαντικότερα προγνωστικά μοντέλα καρδιαγγειακής νόσου, το Framingham Risk Score, έχει χρησιμοποιηθεί στην ιατρική βιβλιογραφία. Στο δεύτερο μέρος της μελέτης έγινε προσπάθεια ταυτοποίησης μελετών οι οποίες αναπτύσσουν ή επικυρώνουν προγνωστικά μοντέλα για την εκτίμηση δυσμενών εκβάσεων υγείας σε ασθενείς με ήδη εγκατεστημένη καρδιαγγειακή νόσο (μοντέλα δευτερογενούς πρόληψης). Τέλος, μελετήθηκε η σχέση μεταξύ της υπέρτασης, ενός ευρέως χρησιμοποιούμενου προγνωστικού δείκτη, και της έκβασης διαφόρων ειδών καρκίνου. Συνοπτικά, μέσα από την έρευνά μας αυτή προσπαθήσαμε να εκτιμήσουμε τη σωστή ή πολλές φορές αδόκιμη χρήση προγνωστικών μοντέλων στην ιατρική βιβλιογραφία, να εντοπίσουμε και να καταγράψουμε προγνωστικά μοντέλα δευτερογενούς πρόληψης και τέλος να μελετήσουμε τη σχέση μεταξύ ενός προγνωστικού παράγοντα και της εκδήλωσης μιας χρόνιας νόσου, προσφέροντας ένα ολοκληρωμένο πρότυπο έρευνας σχετικά με τα στα προγνωστικά μοντέλα και τους προγνωστικούς παράγοντες χρόνιων νόσων.

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«Empirical evaluation and systematic review of prognostic factors and prognostic models for chronic diseases. »

PART I

PROGNOSIS IN CHRONIC DISEASES

1. INTRODUCTION

Prognosis, the likelihood of a person displaying a condition at a specific time period based on his clinical or non-clinical profile, is fundamental to making sound clinical decisions and properly informing patients. Correct estimate of prognosis can help clinicians make the right decisions for treatment or diagnosis while also providing insight into the expected future course of a patient's illness. The research interest in improving predictive ability by the use of biomarkers (genetic or environmental) or prognostic models is of increasing interest in the medical literature. Progress over the last decade in the laboratory measurement of biomarkers and other possible risk factors as well as genetic polymorphisms, is constantly increasing expectations for a better, even personalized prognosis.

To date, prognostic studies have been associated with a significant number of methodological constraints that can affect both designing and analyzing a study, and ultimately describing its results. These methodological constraints cast doubt on the true predictive ability of many markers and models as well as on their clinical utility. Many predictive markers and models are only considered by a single study without further validation while systematic reviews are absent. An example of a widely used predictive model is the "Framingham Risk Score" which is one of the most widespread and widely validated prognostic model in medicine. However, systematic reviews of its predictive value are absent from the literature and there are concerns about its use in populations and outcomes beyond those for which it has been created. In other areas, such as melanoma or breast cancer, prognostic models have been proposed, but lacking broad validation and systematic review.

The two main aspects of prognostic research are the *prognostic factor research* studies and the *prognostic model research* studies. The prognostic factor research studies are divided into *exploratory* studies, which are hypothesis-free studies and identify new factor-outcome associations, and *confirmatory* studies, where new identified factors are validated in data and populations derived from different studies. On the other hand, prognostic model research studies are consisted of *model development*, where a new model is created based on known risk factors for a disease outcome, *external validation* studies in which a model's performance is assessed in a different setting, and finally in *model impact* studies that assess the impact of a new model in everyday clinical practice.

2. CARDIOVASCULAR DISEASES AND CANCER

2.1. Chronic Diseases

Although there is not a universally accepted definition of chronic disease (1), most chronic conditions share some common characteristics. So, by the term of chronic disease we usually refer to all those conditions that have a prolonged development period with probably an asymptomatic stage and no definite cure. They have multiple factors leading to their onset, result in other health complications, and often lead to disability or functional impairment (2).

The time period for a disease to be characterized is not well-defined fluctuating from more than 3 months to more than 1 year of illness (3, 4). The list of diseases under the umbrella of the term of chronic diseases is also not unanimous ranging from cardiovascular to mental and autoimmune diseases. However, according to World Health Organization the 4 main types include cardiovascular, cancer, chronic respiratory diseases and diabetes (4). Our main focus will be cardiovascular diseases and cancer.

2.2. Cardiovascular Diseases (CVDs)

2.2.1. Introduction

Cardiovascular diseases are diseases of heart and blood vessels that among other include coronary heart disease (e.g. myocardial infarction), hypertensive heart disease, heart failure and cardiomyopathies, cerebrovascular disease (e.g. stroke), aortic aneurysms and peripheral arterial disease, congenital heart disease, rheumatic heart disease, and finally pulmonary embolism and deep vein thrombosis.

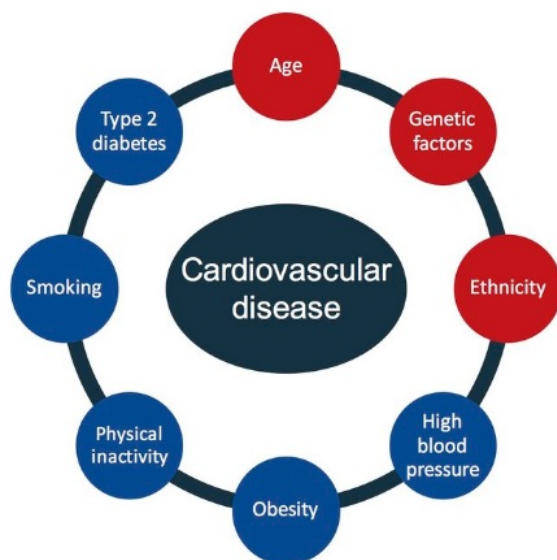
Cardiovascular diseases (CVDs) are the number 1 cause of death globally. About 18 million people died from CVDs in 2016. 85% of these deaths are due to heart attack and stroke and most of these are in low and middle-income countries. Most CVDs can be prevented using primary prevention measures against well-established risk factors such as smoking, obesity, unhealthy diet, sedentary lifestyle and alcohol overconsumption. People with other known risk factors like hypertension, diabetes, dyslipidemia, metabolic syndrome, kidney disease or already suffering from cardiovascular disease need proper identification and management with lifestyle measures and appropriate medication. Such lifestyle modifications include smoking cessation, regular physical activity, weight reduction, alcohol and salt reduction, and healthy diet with fruits and vegetables. In addition, diseases linked to CVDs often require medications such as insulin and anti-diabetic drugs, anti-hypertensive agents, statins for dyslipidemias, antiplatelets and anti-coagulants.

Unfortunately, for cardiovascular disease there are often no specific symptoms and a hard outcome may be the first manifestation of the disease. Such events may include a heart attack with pain or discomfort on chest, abdomen, jaw, back, or upper limbs or shortness of breath, nausea, and acute pulmonary edema in case of acute heart failure. However, many times a myocardial infarction may be expressed with death or malignant arrhythmias and the patient may never reach the hospital. In case of a stroke, the patient may feel numbness, confusion, difficulty speaking or seeing, headache, fainting or once more death may be immediate. Other types of CVDs may have various symptoms according to the specific disease.

It is crucial that individuals with risk factors for CVDs be early identified and managed with lifestyle modifications or drugs when necessary as primary prevention of hard events is much more cost-effective and provides better life quality than facing the consequences of an event. However, once CVD has been manifested there are often costly and time-consuming procedures and surgeries that can meliorate the state of the patient like bypass or other heart surgeries, catheterization and percutaneous angioplasty of heart and brain vessels, valve replacement or repair, heart transplantation, kidney dialysis as well as rehabilitation procedures for heart failure and stroke victims (5, 6).

2.2.2. Important Risk Factors

There are many risk factors associated with cardiovascular disease. Some of these, such as family history of heart disease cannot be modified, while others, such as hypertension or hyperlipidemia can be modified by treatment. The effect of these risk factors is cumulative, meaning, that the more the risk factors, the higher the risk that an individual will develop cardiovascular disease.



Modifiable (blue) and non-modifiable (red) risk factors for cardiovascular disease.

Smoking is amongst the leading and most important modifiable risk factors for cardiovascular disease and cancer globally (7). The prevalence of smoking in USA is 5.3% in ages from 12 to 17 years, and among adults 15.5% are smokers (6). Globally, smoking prevalence is 25% for males and 8% for females. Overall mortality among smokers is 3 times higher than non-smokers. On average, life expectancy is 11-12 years lower for smokers (8, 9). From 1965 to 2015 smoking rates have declined from 51% to 16.7% for men, and from 35% to 13.6% from women. Smoking seems to carry a synergistic effect in other major CVD risk factors including dyslipidemia, hypertension, and diabetes (10). The CVD risk associated with e-cigarette smoking is still unknown. However, it is already established that passive smokers, as well as low-dose smokers (1-3 cigarettes/day) carry also a very high risk for CVD. The annual cost for cigarette related cost is about 300 billion dollars in USA (11).

Physical inactivity is another major risk factor for CVD and stroke. Current European Society of Cardiology guidelines recommend at least 150 minutes of moderate or 75 minutes of vigorous-

intensity aerobic activity per week for CVD prevention (12). Physical activity does not only independently decrease the risk for CVD but also has a positive impact on other risk factors such as diabetes, hypertension and dyslipidemia. Benefits can be seen in all ages and groups, including pregnant females, and people with disabilities. The proportion of people not meeting the recommended guidelines is about 27%. Physical inactivity (<150 min/week) is the fourth leading risk factor for death with a risk of up to 8% for all-cause mortality (13). On the contrary, in a cohort meeting these guidelines, the risk for all-cause mortality was lower by 36% (14). The cost of physical inactivity related diseases is significant and accounts for 1.5 to 3% of healthcare expenditures in developed countries (15).

Nutrition is another major risk factor for CVD. It is estimated to cause about 31% of coronary heart disease and 11% of stroke worldwide. The American Heart Association recommends a diet pattern including 5 primary and 3 secondary targets for an ideal healthy diet (Figure 1)(16). In 2012, in children in the United States, the poor diet (<40% adherence) was 54.6% and in adults 41% (17).

	AHA Target
Primary dietary metrics†	
Fruits and vegetables	≥4.5 cups/d‡
Fish and shellfish	2 or more 3.5-oz servings/wk (≥200 g/wk)
Sodium	≤1500 mg/d
SSBs	≤36 fl oz/wk
Whole grains	3 or more 1-oz-equivalent servings/d
Secondary dietary metrics†	
Nuts, seeds, and legumes	≥4 servings/wk (nuts/seeds: 1 oz; legumes: ½ cup)
Processed meats	2 or fewer 1.75-oz servings/wk (≤100 g/wk)
Saturated fat	≤7% energy

Figure 1. AHA dietary targets for defining cardiovascular health.

Globally, sugar-sweetened beverage (SSB) intake increases over time (18), while mean sodium intake remains stable at 3950mg/day in 2010, but much higher than the recommended consumption (<1500mg/d) (19). The risk for hypertension increases by 8.2% for each SSB consumed daily. In addition, it is estimated that 1g/day reduction in sodium intake could lead to 50% reduction in hypertensives, and ~20% in deaths from CVD and stroke (20). Furthermore, daily fruit and vegetable intake has been associated with up to 40% lower risk of CVD (21), whole grain intake with 22% lower risk (22), ≥5 servings of nuts per day with 12% lower risk of CVD (23), and 0.25 g/day of long-chain omega-3 fatty acids from fish consumption with 35% lower risk from coronary heart disease (CHD) mortality (24). In contrast, each 50-g serving per day of processed meats (eg, sausage, bacon) was associated with a 42% (25), and each 2% of calories above 7% of daily calories with 23% higher incidence for CHD (26).

Overweigh and obesity are major risk factors for CVD including stroke, atrial fibrillation, venous thromboembolism, and heart failure. The prevalence of obesity was 39.6% in adults and 18.5% in children in 2016 in USA (27). Overweight is defined as $25.0 \leq \text{BMI} \leq 29.9 \text{ kg/m}^2$, and obesity as $\text{BMI} > 30 \text{ kg/m}^2$. In a meta-analysis of 57 prospective studies in Europe and North

America revealed a 30% higher risk for all-cause mortality for each 5-kg/m² higher than the normal weight of ≤ 25 kg/m² (28). However, in several studies underweight (BMI ≤ 18.5 kg/m²) has been associated also with an excessive mortality risk, and overweight with a lower or no change in risk of mortality. However, levels above the threshold of 30 kg/m² have been almost always associated with an increased all-cause mortality and CVD risk (29-31). The cost of obesity for healthcare systems is substantial. In the United States only, the annual medical cost of obesity was 147 billion in 2008, and the annual medical cost was 1429 \$ higher for individuals with obesity (32).

Dyslipidemia occurs when there are abnormal lipid levels (e.g. low-density cholesterol, triglycerides) in the blood. This condition is also a major risk factor for developing cardiovascular disease. Dyslipidemia has primary, usually genetic causes (e.g. familial hypercholesterolemia), and secondary causes such as hypothyroidism, diabetes, and nephrotic syndrome. It can present as chest pain due to underlying ischemic heart disease, or fat skin (xanthoma), or eye (xanthelasma) deposits. The WHO estimates that dyslipidemia is associated with more than a third of the cases of ischemic heart disease, and more than 2.6 million deaths per year globally (33). Desirable cholesterol levels depend on comorbidities and prior CVD but for primary prevention are: total cholesterol ≤ 200 mg/dL, low-density cholesterol (LDL) ≤ 100 mg/dL, high-density cholesterol ≥ 60 mg/dL, and triglycerides ≥ 150 mg/dL. A 10% reduction in serum cholesterol in men aged 40 has been reported to result in a 50% reduction in heart disease within 5 years; the same serum cholesterol reduction for men aged 70 years can result in an average 20% reduction in heart disease occurrence in the next 5 years. The prevalence of total cholesterol levels ≥ 240 mg/dL was 11.7% in 2016, an estimated of 28.5 million adults (Figure 2), decreased from 18.3% in 2000 (34). Besides lifestyle modifications there are several treatment options for high risk patients including statins, and non-statin medications such as ezetimibe, PCSK9 inhibitors, fibrates, nicotinic acid, and anacetrapib (35). However, statin treatment is very cost-effective. Although it raises treatment costs by an additional 3.9 billion, it is estimated to save more than 183,000 QALYs (quality adjusted life-years) and prevent 43,700 deaths each year (36).

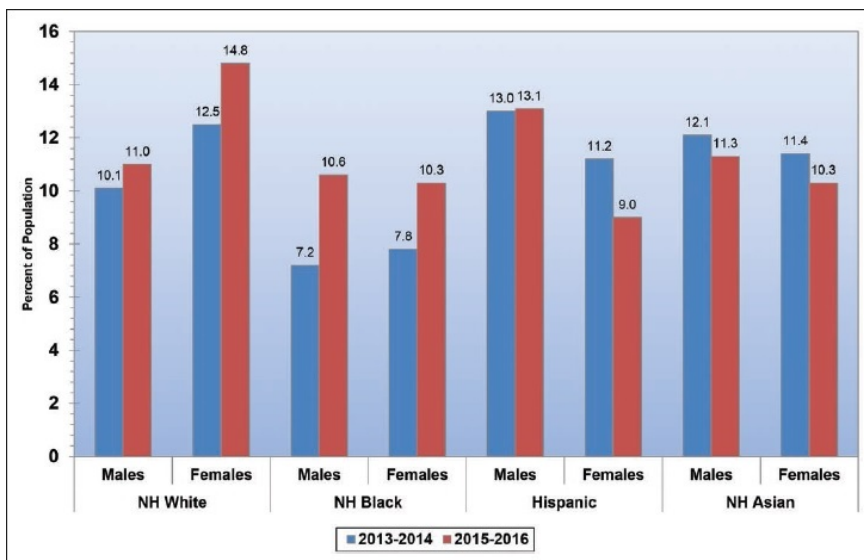


Figure 2. Age-adjusted trends in the prevalence of serum total cholesterol ≥ 240 mg/dL in adults ≥ 20 years of age by race/ethnicity, sex, and survey year (NHANES, 2013–2014 and 2015–2016) (6). NH indicates non-Hispanic; and NHANES, National Health and Nutrition Examination Survey.

Hypertension is a major risk factor for CVD and stroke. Although definitions vary in medical literature, generally, high blood pressure is defined as systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg⁽³⁷⁾. With this definition, the age-adjusted prevalence of hypertension among US adults ≥ 20 years of age was estimated to be 46.0% in NHANES in 2013 to 2016 (49.0% for males and 42.8% for females, Figure 3).

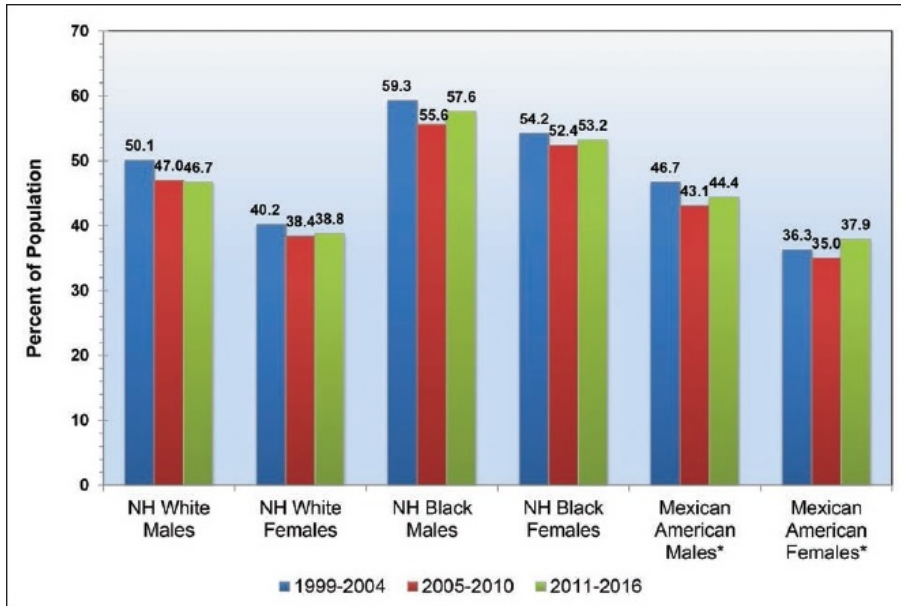


Figure 3. Age-adjusted prevalence trends for hypertension in adults ≥ 20 years of age by race/ethnicity, sex, and survey year (NHANES, 1999–2004, 2005–2010, and 2010–2016) (6). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

SPRINT trial demonstrated that an SBP goal of <120 mm Hg resulted in fewer CVD events and a greater reduction in mortality than an SBP goal of <140 mm Hg among people with SBP ≥ 130 mm Hg and increased cardiovascular risk. According to this definition the prevalence is even higher⁽³⁸⁾. In addition, hypertension has even higher prevalence in blacks (57.6% among males and 53.2% among females), and in obese patients. CHD, stroke, cancer, and diabetes accounted for 65% of all deaths with any mention of hypertension in 2013 (39). It is worth mentioning that the elimination of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females. The risk of CVD mortality doubles for every 20mmHg systolic and 10mmHg diastolic pressure increase over a baseline blood pressure of 115/75 (40). The elimination of hypertension could pose a larger impact on CVD mortality than the elimination of all other risk factors among females and all except smoking among males⁽⁴¹⁾. The estimated direct and indirect cost for hypertension treatment was \$55.9 billion in 2015 but could be more than \$220 billion in 2035⁽⁴²⁾.

The most common types of *diabetes mellitus* (DM) are diabetes mellitus type II (around 90-95% of diabetes), and diabetes mellitus type I (another 5-10%). DM is diagnosed based on fasting glucose levels \geq mg/dL, random test ≥ 200 mg/dL, 2-hour post-challenge test ≥ 200 mg/dL, or HbA1C levels $\geq 6.5\%$ (43). DM is a major risk factor for CVD (44). The prevalence of diabetes in the REGARDS study was 14% in whites and 31% among blacks in the United States (45). In a meta-analysis of 97 prospective studies DM was associated with a HR, 1.80 for all-cause mortality, HR, 1.25 for cancer death, and HR, 2.32 for vascular death. An individual with diabetes type II lives on average 6 years less (46). The number one cause of death for patients with diabetes type I is

also CVD with a ratio of 22% followed by renal death with 20% (47). In 2017 the medical cost of diabetes was \$327 billion, with these costs being 2.3 times higher for people with DM than without DM. In the same year the medical expenditure for individuals with diabetes was 16.752 dollars annually (48).

Metabolic syndrome (MetS) is diagnosed when 3 of the following risk factors are present: fasting blood glucose ≥ 100 mg/dL, HDLc ≤ 50 mg/dL in males or ≤ 40 mg/dL in females, triglycerides ≥ 150 mg/dL, SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, and waist circumference ≥ 102 cm in males or ≥ 88 cm in females. It is a multifactorial risk factor for CVD and diabetes and its total risk reflects the clustering of the individual characteristics. On the basis of NHANES the prevalence of MetS was 34.3 % (49). The risk for CVD depends on the number of components but is substantial and varies between HR, 1.8 and 2.1 (50). Overall, the cost for healthcare systems is 24% higher for each component of MetS present (51).

Chronic kidney disease (CKD) is defined as glomerular filtration rate - GFR (<60 mL. min⁻¹. 1.73/m⁻²), or excess urinary albumin excretion (≥ 30 mg/day). It is another important risk factor for CVD with great healthcare cost impact. On the other hand, many risk factors for CVD are also risk factors for CKD including DM, smoking, older age, male sex, and hypertension. CKD is categorized in several stages based on GFR and albumin excretion. Based on NHANES 2011-2014 data, the prevalence of CKD is around 15% in United States. The prevalence increases with age to 50% in individuals ≥ 80 years old (52). The cost is substantial with over \$64 billion in 2015 and over \$88.750 annually for patients on hemodialysis (6, 52). Individuals with CKD have also a very high risk of having CVD comorbidities including ischemic heart disease, heart failure, and arrhythmias. 2 out of 3 people ≥ 66 years with CKD have also CVD, in contrast to ~ 1 out of 3 people without CKD in the same age. For people with CKD, death is a more common outcome than progression to end stage renal disease, and almost 40% of these patients die due to CVD outcomes with mortality risk being higher in GFR ≤ 30 and albuminuria ≥ 300 mg/day (52) (Figure 4).

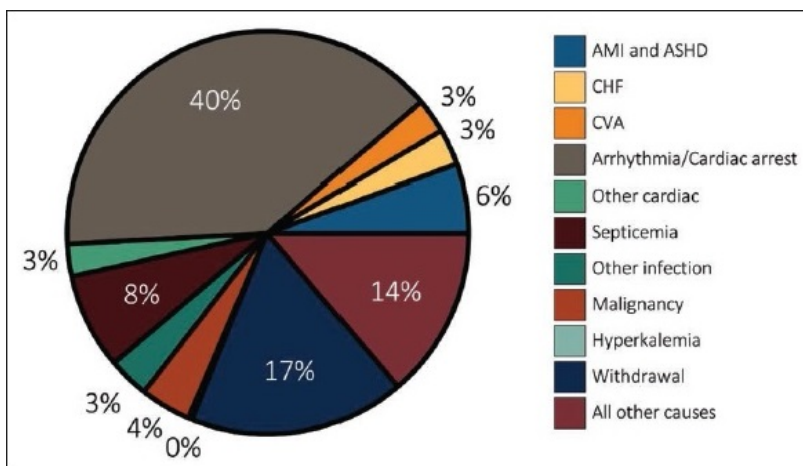


Figure 4. Causes of death in patients with end-stage renal disease (ESRD) among those with a known cause of death, 2014 (2017 USRDS Annual Data Report) (6). AMI indicates acute myocardial infarction; ASHD, atherosclerotic heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; and USRDS, US Renal Data System. Source: USRDS ESRD database

There are many more important risk factors of cardiovascular disease worth mentioning including several diseases and modifiable ones such as atrial fibrillation (53), sleep quality and obstructive sleep apnea (54), chronic obstructive pulmonary disease (55), depression (56) and non-

modifiable ones such as age (57), male sex (58), ethnicity (59), socioeconomic status (60), positive family history of CVD (61), heart rate (62), and post-menopausal status (63).

2.2.3. Cardiovascular Diseases and Prognosis

Introduction

Cardiovascular disease (CVD) is a class of diseases involving the heart and blood vessels. Although definitions often vary in medical literature, the definition generally involves coronary heart disease (CHD), cardiomyopathies and heart failure (HF), stroke, hypertensive heart disease, rheumatic heart disease, cardiomyopathies, valvular and congenital heart disease, congenital (channelopathies) and acquired arrhythmias, carditis, aortic aneurysm, peripheral artery disease (PAD), thromboembolic disease, and finally venous thromboembolism. On the basis of the data of NHANES 2013 to 2016, CVD comprising of CHD, HF, stroke, and hypertensive heart disease had an overall prevalence of 48%. Deaths attributable to CVD comprise mainly of CHD, stroke, hypertension, and heart failure (Figure 5). These most common forms of CVD are discussed below.

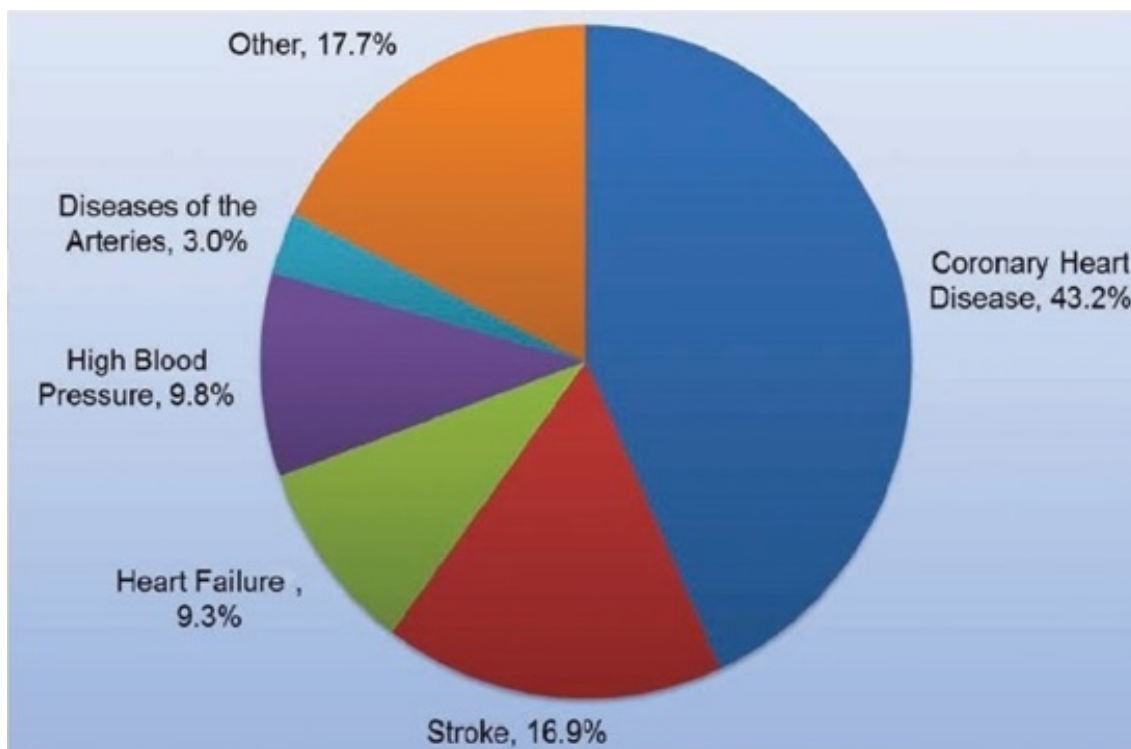


Figure 5. Percentage breakdown of deaths attributable to cardiovascular disease (United States, 2016) (6). Total may not add to 100 because of rounding. Source: National Heart, Lung, and Blood Institute from National Center for Health Statistics reports and data sets.

Coronary Heart Disease

Total CHD prevalence is 6.7% in people ≥ 20 years old with prevalence increasing with age and being higher in males than females. History of myocardial infarction (MI) has a prevalence of about 3% and angina 3.6% in US adults (Figure 6) (64). It is estimated that on average 16 years of life are lost due to a MI death. 77% of MI deaths occur outside hospital or in emergency departments. Additionally, 35% of people experiencing a MI will die as a result of it (American Heart Association – AHA computations). There is a constant decline in early MI death and heart failure death after MI in the last 2 decades, reflecting the impact of early coronary intervention strategies, of coronary care units, and of the shift of clinical presentations of MI with a decline in STEMI patients (65-67). Costs of ischemic heart disease are more than 109 billion dollars annually in US and this cost is expected to double by 2030 (68). All CVD risk factors discussed are important risk factors for MI and CHD mortality, and there are several risk-prediction tools available for the estimation of this risk, such as the Framingham Risk Score and the HEART SCORE charts, which are also recommended for clinical use in clinical practice guidelines (69).

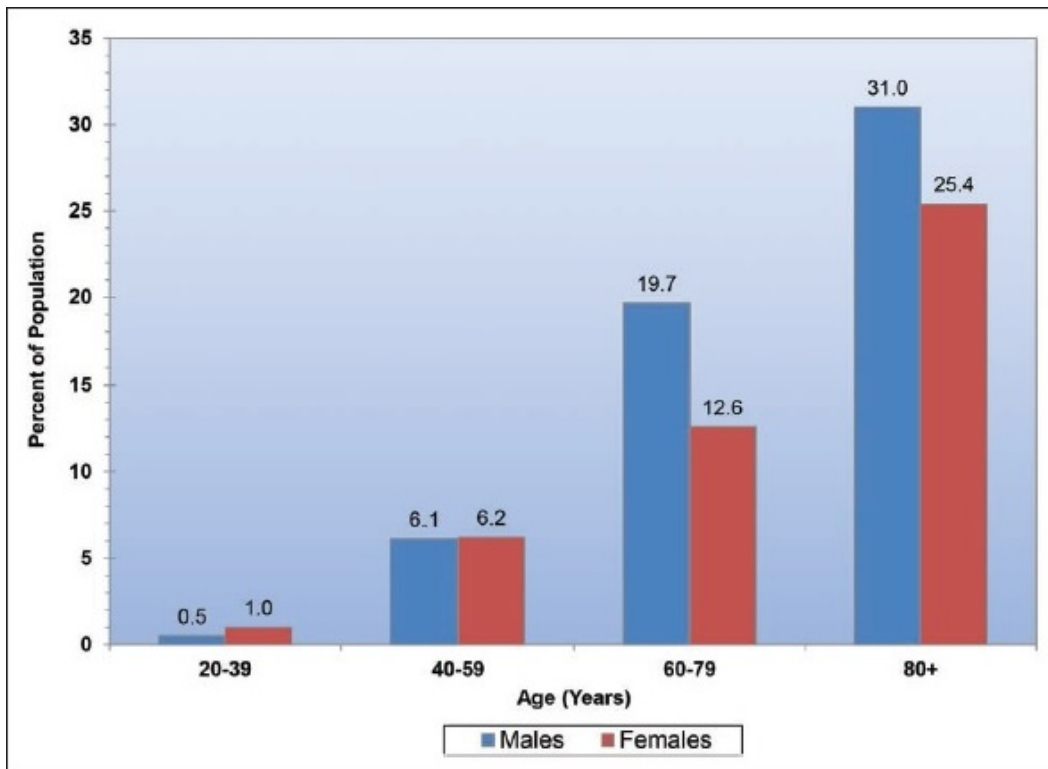


Figure 6. Prevalence of coronary heart disease by age and sex (NHANES, 2013–2016) (6). NHANES indicates National Health and Nutrition Examination Survey. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

There are several prognostic factors that define the outcome of the disease once it is already established. First of all, the specific type of coronary heart disease plays an important role on the outcome. Generally, STEMI has a greater risk for early and in hospital mortality (6.4% vs 3.4%), cardiogenic shock, and bleeding, than NSTEMI, but NSTEMI carries a greater death risk within the next 2 years (70). However, both MI presentations (STEMI and NSTEMI) carry a higher risk for hard outcomes and complications than stable coronary artery disease. The establishment of heart

failure as well as the time of this establishment confers also a negative impact on CHD prognosis (71). In the case of STEMI presentation, pain-to-angioplasty time, Killip stage, mechanical complications (such as ventricular wall rupture, ventricular tachycardia, ventricular aneurysm and pseudoaneurysm formation), left-anterior-descending culprit artery, presence of additional non-culprit lesions, TIMI flow, infarct size, hs-troponin and BNP levels, and extent of wall-motion abnormalities on echo all play an important prognostic role (72). In any case of CHD, age, male sex, presence and severity of angina symptoms, SYNTAX score and poor regulation of CVD risk factors (e.g., uncontrolled hypertension, high HbA1c levels, physical inactivity, smoking continuation etc.), depression and deprivation, ejection fraction and high heart rate have a negative impact on prognosis (73-76). Additionally, concomitant comorbidities such as diabetes, heart failure and NYHA functional class, peripheral arterial disease, chronic pulmonary disease, stroke, atrial fibrillation, and chronic kidney disease also carry an adverse prognosis (77). On the other hand, proper medication and adherence to therapy, rehabilitation, lifestyle modifications and regular physical activity, revascularization, asymptomatic disease, younger age, female sex, lack of comorbidities, low inflammatory biomarkers such as CRP and troponin/BNP levels, and lack or long-time from an index event (MI), carry a more favorable natural history and are related to better outcomes (76).

Stroke

Stroke prevalence increases with age and is about 2.5% for people ≥ 20 years old (Figure 7) (78). This ratio is probably higher since transient ischemic attacks (TIA) are often not reported (79). TIAs carry a very high short-term risk for stroke which is between 9% and 17% in the first 90-days (80). In addition, stroke recurrence rate after the diagnosis of stroke is about 5% annually, being higher in the first 2 years after the attack (81). Stroke carries the fifth place in mortality causes and 62% of deaths occur outside the hospital setting (82). All-cause mortality after a stroke is very high with 10.5% at 30 days and ~40% at 5 years, and higher for hemorrhagic than ischemic stroke (67.9% and 58.4%, respectively) (83).

There are many identified risk factors for stroke. Hypertension is an example. Anti-hypertensive therapy offers a 41% reduction in stroke risk and intense BP lowering to levels ≤ 120 mmHg offers an additional 25% benefit versus target of ≤ 140 mmHg (84, 85). Diabetes is another strong, independent risk factor for stroke in every age with a risk ratio of > 5 in ages ≤ 65 years (86). Atrial fibrillation (AF) also increases the risk of stroke by 5 times, with this risk being higher in older ages and individuals with comorbidities such as BP, DM, renal dysfunction, HF, and previous stroke (87). Total cholesterol seems to be weakly associated to the risk of ischemic stroke, but also seems to offer protection against hemorrhagic stroke (88, 89). Smoking carries also a 2 to 4 times elevated risk of stroke. Low-dose smoking or passive smoking are also associated with high stroke risk (90). On the other hand, regular physical activity in every age and Mediterranean diet are inversely associated with stroke risk (91, 92). Other risk factors for stroke incidence are obesity, renal dysfunction, black race, female sex, family history of stroke, early menopause, migraines, HIV infection, preeclampsia, air pollution, sleep disorders, and others.

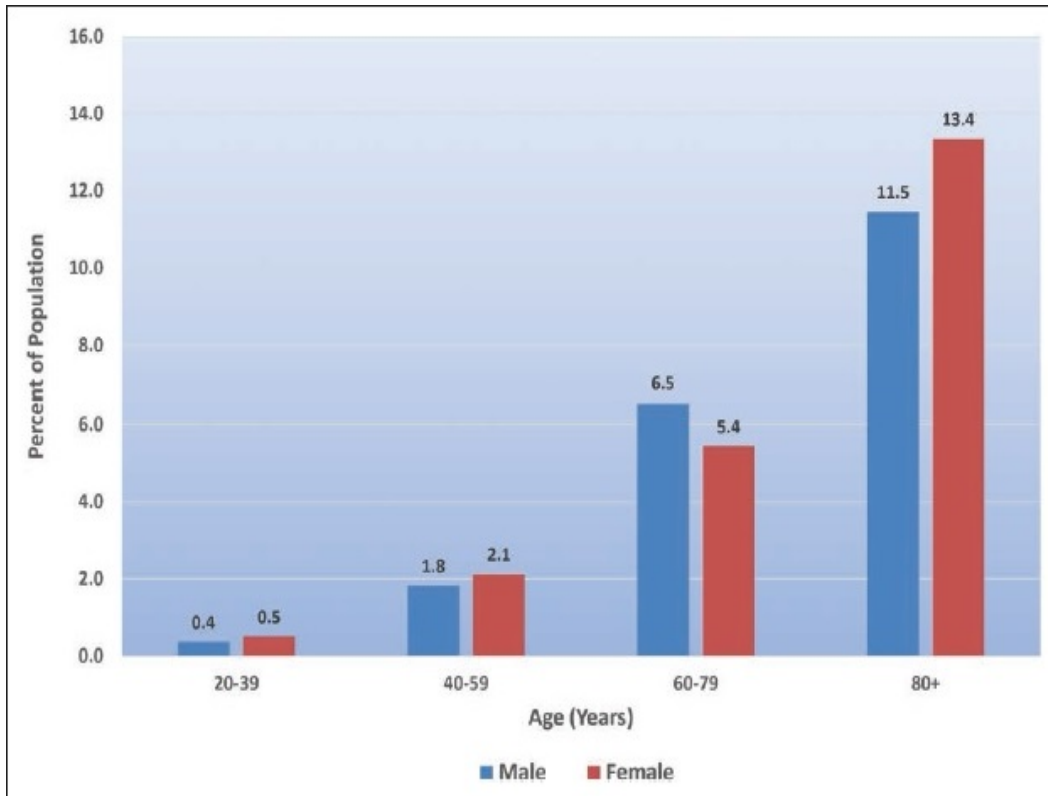


Figure 7. Prevalence of stroke by age and sex (NHANES, 2013–2016). NHANES indicates National Health and Nutrition Examination Survey (6). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Prognostic factors related to adverse stroke outcomes, that is increased mortality and decreased ability to regain independent living, include decreased level of consciousness and any degree of paralysis (e.g. hemiplegia) at first examination, advanced age, inability to walk or use hand, and urinary incompetence at 3 weeks, and pathological characteristics such as infarction extending beyond the middle cerebral artery, brain swelling, and concomitant internal carotid artery occlusion (93). Hemorrhagic versus ischemic stroke, high diastolic blood pressure and high cholesterol levels are also associated with adverse clinical outcomes (94). In addition, in ischemic stroke patients, thrombolytic treatment, stroke unit care, early rehabilitation, a large reduction of blood pressure and the use of anti-hypertensive drugs during the first 24 hours after the event, may be associated with better outcomes (95, 96). The National Institutes of Health Stroke Scale (NIHSS) score and I-score are also strong prognostic models of outcome. Based on these scores older age, male sex, severe stroke, non-lacunar stroke subtype, glucose ≥ 135 mg/dL, history of atrial fibrillation, coronary artery disease, congestive heart failure, cancer, dementia, kidney disease on dialysis, and dependency before the stroke as well as objective quantification of neurological impairment at baseline presentation using the NIHSS scale, are also important prognostic factors of mortality and disability (97-100). Finally, poor regulation of CVD risk factors (diabetes, blood pressure) after stroke incidence is also related to increased mortality and prolonged dependency (101, 102).

Heart Failure

The incidence of heart failure (HF) is 2.4% and is expected to be about 3% in 2030, reflecting an increase in elderly and an improved HF survival (103, 104). Lifetime risk for HF is high and increases with age (20-45% lifetime risk), and is higher in males than females (Chart 20-4, NHANES 2013-2016). However, this risk is higher in people with higher blood pressure (BP) and BMI in all ages, and almost doubles for individuals with BMI ≥ 30 kg/m² or BP $\geq 160/90$ mmHg (105). Traditional factors for CVD are also important factors for HF. Diabetes, hypertension, coronary heart disease, obesity, and smoking, are responsible for more than 1 out of 2 cases of heart failure (106). On the other hand, patient with HF with preserved ejection fraction (EF) tend to be older and female, and in contrast to those with HF with reduced EF, more tend to have hypertension, obesity, and anemia (107).

Moreover, some non-traditional, HF-specific risk factors have also been identified. Several circulating blood plasma markers have been identified as independent risk factors including elevated BNP, γ -GT, resistin, adiponectin, serum albumin, hs-troponin, high hematocrit levels, low omega-3 fatty acids concentration, HbA1c, albuminuria, white blood cell count, and inflammation markers such as TNF- α , CRP, and interleukin-6 (6). In addition, many echocardiography and MRI measures of systolic and diastolic dysfunction are also independent risk factors and offer additional predictive value over traditional ones (108-110).

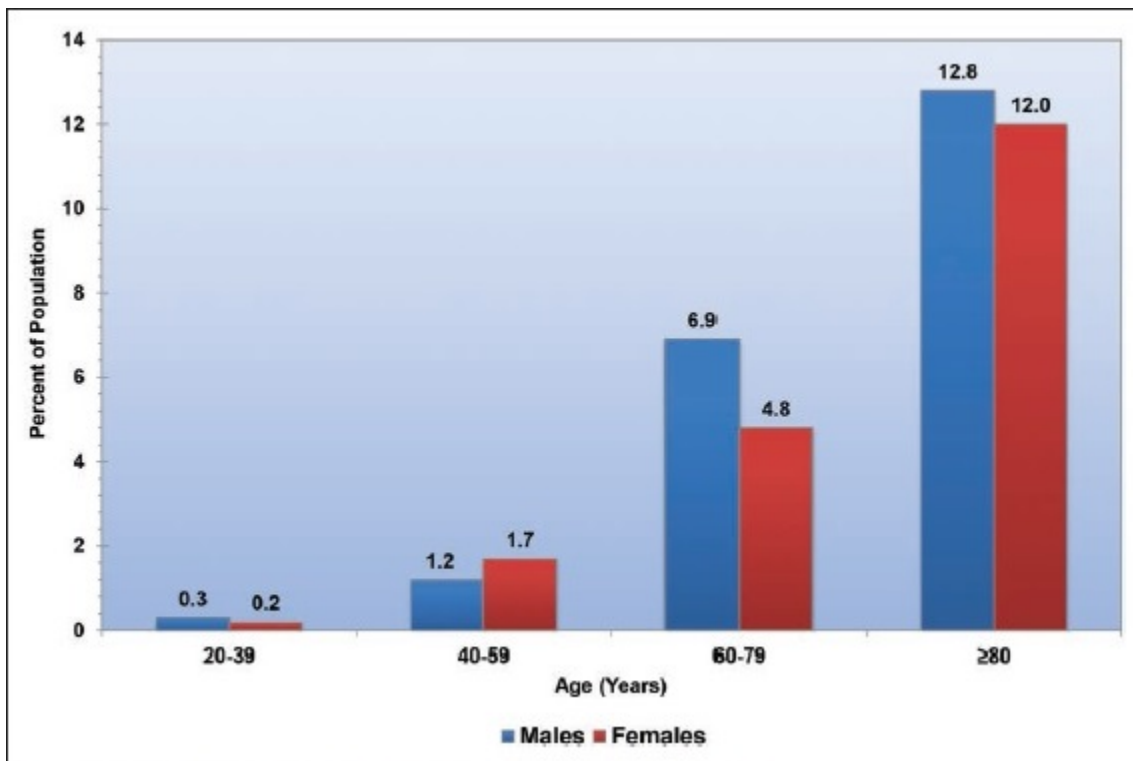


Figure 8. Prevalence of heart failure for adults ≥ 20 years by sex and age (NHANES, 2013–2016). NHANES indicates National Health and Nutrition Examination Survey (6). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

Advanced age is the most important predictor of adverse outcomes, especially in the case of comorbidities (111). Other major risk factors include reduced ejection fraction, low systolic blood pressure on admission, high natriuretic peptide levels, prior MI, prior stroke, tachycardia, hyponatremia, anemia, acute or chronic kidney disease, smoking, male sex, chronic pulmonary disease, peripheral artery disease, low or high BMI, symptoms and high stage in NYHA classification (112). The need of hospitalization is also an important risk factor of poor prognosis. Mortality rate is increased after hospitalization, and especially the first month after discharge (113). Other predictors include wide QRS and LBBB, rhythm disturbances and low total voltage on electrocardiogram, high uric acid levels, raised creatinine, high hs-CRP, ICD-shocks, poor adherence to treatment and poor control of CVD risk factors (114). Most prognostic markers are summarized in Web Table 3.5 of European Society of Cardiology guidelines on heart failure (Figure 9) (115).

Web Table 3.5 Markers of worse prognosis in patients with heart failure

Demographic data	Older age, male sex, low socio-economic status.
Severity of heart failure	Advanced NYHA Class, longer HF duration, reduced peak oxygen consumption, high VE-VCO ₂ slope, Cheyne–Stoke ventilation, short 6-minute walking distance, reduced muscle strength, poor quality of life.
Clinical status	High resting heart rate, low blood pressure, clinical features of fluid overload (both pulmonary congestion and peripheral oedema, jugular venous dilatation, hepatomegaly), clinical features of peripheral hypoperfusion, body wasting, frailty.
Myocardial remodeling and severity of heart dysfunction	Low LVEF, LV dilatation, severe diastolic LV dysfunction, high LV filling pressure, mitral regurgitation, aortic stenosis, LV hypertrophy, left atrial dilatation, RV dysfunction, pulmonary hypertension, dyssynchrony, vast area of hypo/akinesis, wide QRS complex, presumed inflammation or infiltration on CMR, inducible ischaemia and poor viability on imaging.
Biomarkers of neurohormonal activation	Low sodium, high natriuretic peptides, high plasma renin activity, high aldosterone and catecholamines, high endothelin-1, high adrenomedullin, high vasopressin.
Other biomarkers	Markers of renal function, inflammatory markers, cardiac stress markers, cardiac damage markers, metabolic markers, collagen markers, markers of organ damage/dysfunction.
Genetic testing (see section 5.10.1)	Certain mutations in inherited cardiomyopathies associated with high-risk of sudden cardiac death or rapid HF progression.
Cardiovascular co-morbidities	Atrial fibrillation, ventricular arrhythmia, non-revascularizable coronary artery disease, previous stroke/TIA, peripheral arterial disease.
Non-cardiovascular co-morbidities	Diabetes, anaemia, iron deficiency, COPD, renal failure, liver dysfunction, sleep apnoea, cognitive impairment, depression.
Non-adherence	Non-adherence with recommended HF treatment.
Clinical events	HF hospitalization, aborted cardiac arrest, ICD shocks.

CMR=cardiac magnetic resonance; COPD = chronic obstructive pulmonary disease; HF = heart failure; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; QRS = Q, R, and S waves (combination of three of the graphical deflections); RV = right ventricular; TIA = transient ischaemic attack; VE-VCO₂ = ventilatory equivalent ratio for carbon dioxide.

Figure 9. Markers of worse prognosis in patients with heart failure (115).

Hypertensive Heart Disease

Hypertension is a major risk factor for CVD, as already mentioned, resulting in serious complications and high mortality (116). Chronic blood pressure elevation increases the afterload and consequently the workload of the heart and, without appropriate treatment, induces a series of adaptive changes in three main targets: left ventricle, coronary arteries, and left atrium. As a result, three distinct and frequently combined cardiac abnormalities can occur; Heart failure, myocardial ischemia, and atrial fibrillation (117). The “VIA classification” is a simple system often used to describe these changes and quantify the severity of hypertensive heart disease. Based on this classification, each of the three variables can take a value from 0-3 according to the degree of severity: V (left ventricle), (0: none; 1: hypertrophy; 2: diastolic dysfunction; 3: systolic

dysfunction); I (myocardial ischemia), (0: none; 1: microvascular; 2: macrovascular; 3: myocardial infarction); A (atrial fibrillation), (0: none; 1: paroxysmal; 2: permanent; 3: embolic) (118).

Hypertension is responsible for about one-fourth of all causes of heart failure (HF), the end-stage of hypertensive heart disease, and precedes the development of HF by an average of 14 years (119). According to Framingham Heart Study, men with hypertension have a 2-times, and women a 3-times elevated risk to develop HF. In addition, proper anti-hypertensive treatment reduces this risk by 64% (38). The differential diagnosis of hypertensive heart disease includes several pathologies with similar clinical image, including ischemic heart disease, hypertrophic cardiomyopathy, valvular heart disease, and even sleep apnea. It is a chronic progressive disease with a significant risk of CVD death. Hypertension is a major risk factor for HF, coronary heart disease, atrial fibrillation, aortic aneurysms, stroke, peripheral artery disease, retinopathy, and renal failure. The prognosis varies and depends on the presence of other concomitant risk factors, and comorbidities, but is generally very high with a 16% risk of mortality on the stage of heart failure (with or without reduced ejection fraction) (120). However, hypertension is the most common modifiable risk factor and prevention with lifestyle modifications, or treatment after its occurrence, can prevent or delay the progression to hypertensive heart disease.

In patients with hypertensive heart disease, prognosis is mainly affected by proper antihypertensive medication and adherence to blood pressure lowering therapy. With strict blood pressure control left ventricular hypertrophy can even regress to normal values which results in a reduction in CVD events (121). Other comorbidities such as obesity, coronary heart disease, and diabetes also increase the hypertrophic response and increase the risk of progression to heart failure (122-124). Increasing age and black race has also been associated with left ventricular remodeling in hypertensive patients (125, 126). High levels of natriuretic peptides and creatinine levels, reduced ejection fraction, admissions for uncontrolled blood pressure, and chronic obstructive pulmonary disease are also associated to worse clinical outcomes and increased mortality (127).

Diseases of the Arteries

Diseases of the arteries, refers to peripheral artery disease (PAD) and aortic diseases (aneurysm, dissection etc.). Peripheral artery disease includes carotid artery disease, upper extremity arterial disease (UAED), lower extremity arterial disease (LEAD), mesenteric artery disease, and renal artery disease (RAD) (128). The prevalence of moderate to severe carotid stenosis $\geq 50\%$, increases with age. For men and women ≤ 70 years, it is 4.8% and 2.2% respectively, while for ages ≥ 70 years is up to 12.5% in males and 6.9% in females (129). Upper extremity disease usually affects the subclavian arteries and it is defined as difference of systolic blood pressure > 10 mmHg between the two arms. Its prevalence is around 2% (130). Mesenteric artery disease ($\geq 50\%$ stenosis) is very rare, except in the case of concomitant LEAD, where it coexists in as many as 27% of patients (131). Renal artery disease is defined as renal artery stenosis $\geq 60\%$ and its prevalence is 9.1% in men and 5.5% in women (132).

Finally, the simplest way to diagnose LEAD is by the use of the ankle-brachial index (ABI). ABI is an inexpensive, non-invasive tool used for the diagnosis of lower-extremity artery disease (LEAD). It is also a marker of generalized atherosclerosis and CV risk. The diagnosis of LEAD requires an ABI ≤ 0.9 and severe PAD by an ABI ≤ 0.7 , or symptoms of intermittent claudication. An ABI ≤ 0.9 is associated with a 3-fold increases risk for CV events. The prevalence of LEAD (low ABI), is estimated at 5.5% in individuals ≥ 40 years old and increases with age to 27.7% in persons ≥ 80 years. From these, only 10% have the characteristic symptom of intermittent

claudication. A 2008 meta-analysis demonstrated a 3-fold increased risk for all-cause death in males and females with $ABI \leq 3$. $ABI \geq 1.40$ is also associated with increased morbidity and mortality and reflects arterial stiffness. However, values between 1 and 1.4 appear to have the lowest mortality in a reverse J-shaped association. Progression of LEAD with demonstration of decreasing ABI, also carries a significant prognostic value for CVD death. PAD is a result of atherosclerosis and is strongly related to atherosclerosis in other vascular beds, including coronary arteries, carotids, renal arteries etc., with an elevated risk for hard outcomes (stroke, MI, death) when LEAD is combined with diagnosed atherosclerosis elsewhere.

Ageing, smoking, dyslipidemia, hypertension, and diabetes are the main risk factors of PADs. Smoking is an independent risk factor for PADs. The risk increases analogous to smoking intensity and even passive smoking is associated to carotid artery disease (133, 134). In patients with carotid artery stenosis $> 50\%$ carotid endarterectomy is required on average 7 years earlier (135). Additionally, even past smokers have an elevated risk of PAD even after cessation (130, 136). Hypertension is also associated with PADs. For example, a 20 mmHg increase in SBP is associated with an 63% increase in LEAD risk (137). Hypertension is an independent risk factor for incidence, progression and adverse outcomes for every type of PAD (138). High concentration in blood plasma LDL and LP(a) levels confer also an elevated risk for carotid artery disease and LEAD, and HDL seems to be protective (139, 140). However, triglycerides are rarely an independent risk factor for PAD. Finally, diabetes is also associated with carotid artery disease incidence but not plaque progression (141, 142). LEAD is also associated with diabetes with a 5-fold increased risk of amputation versus non-diabetic patients with LEAD (143). Other risk factors for PAD include increased levels of inflammatory biomarkers (CRP, IL6) and homocysteine, and several autoimmune diseases (LUPUS, rheumatoid arthritis) (144).

Aortic diseases contribute to the wide spectrum of arterial diseases: aortic aneurysms, acute aortic syndromes (AAS) including aortic dissection (AD), intramural hematoma, penetrating atherosclerotic ulcer, and traumatic aortic injury, pseudo-aneurysm, aortic rupture, atherosclerotic and inflammatory affections, as well as genetic diseases (e.g. Marfan syndrome) and congenital abnormalities including the coarctation of the aorta (145). The prevalence of abdominal aortic aneurysm (AAA) increases with age, and ranges from 1.3% to 12.5% in older ages for males, and 0 to 5.2% for females (146). The growth rate is higher for smokers and for people without diabetes. The global rate for rupture is higher for smokers and females (147). The global rate of death from aortic aneurysms is 2.78 per 100.000 persons per year. The in-hospital mortality for patients with the diagnosis a ruptured aortic aneurysm remains very high, (53%) (148). The treatment options include endovascular repair or open surgery. The use of endovascular repair for abdominal aneurysms has dramatically increased since 2000, and in-hospital mortality has declined. However, data for thoracic aortic aneurysms, show an increase mortality with open surgery versus endovascular repair, but also a higher 5-year survival with open surgery (6, 149) .

There are several prognostic factors defining the natural history of patients with PAD. As atherosclerosis is usually generalized, increasing age and the presence of symptomatic multisite disease, and especially coronary artery disease, greatly affects the prognosis, with significantly worse clinical outcomes (144). However, there are no indications that screening for asymptomatic concomitant PADs can alter prognosis (150). In the presence of carotid artery disease (CAD), the patients are also at increased risk for cardiac mortality with a mean rate of 2.9% per year (151, 152). In the case of LEAD, ABI is also a prognostic factor for CVD. An $ABI \leq 0.9$ is associated with more than 2-fold increased 10-year risk of MI, cardiovascular, and total mortality (153). Intermittent claudication is also associated to a worse prognosis, with one fifth of patients presenting with stroke

or myocardial infarction within 5 years (154). For patients with renal artery disease (RAD), the progression to end-stage chronic kidney disease (CKD) is related to an even greater mortality than RAD without end-stage CKD (155). Proper medication including anti-hypertensives, statins, and antiplatelet agents in case of symptomatic disease, as well as lifestyle modifications, have a positive impact on prognosis of patients with PAD (156, 157).

The rupture or dissection of a thoracic or abdominal aneurysm is related to very high mortality. The most common risk factor associated with thoracic aneurysm and dissection is uncontrolled or undiagnosed hypertension, observed in 65–75% of individuals. The mean age of rupture is 63 years; and 65% are men (158). Other risk factors include pre-existing aortic diseases or aortic valve disease, family history of aortic diseases, history of cardiac surgery, cigarette smoking, direct blunt chest trauma and use of intravenous drugs (e.g. cocaine). Approximately 20% of road accident fatalities present with aortic rupture on autopsies (159) Ultrasound screening is associated with lower rate of complications for all types of aneurysm, but not with a decrease in all-cause mortality (160). The diameter of the aneurysm is also very important as most dissections tend to occur in diameters 50 mm, and a sharp increase in aneurysms > 60mm (Figure 10). The prognosis of AD is poorer in women due to atypical presentation and delayed diagnosis (159). In case of dissection, recurrent pain, uncontrolled hypertension, early aortic expansion, malperfusion, signs of rupture (hemothorax, periaortic and mediastinal hematoma), increasing false lumen diameter, and a retrograde component of the dissection into the aortic arch, are also considered to significantly influence the patient's short-term prognosis (161).

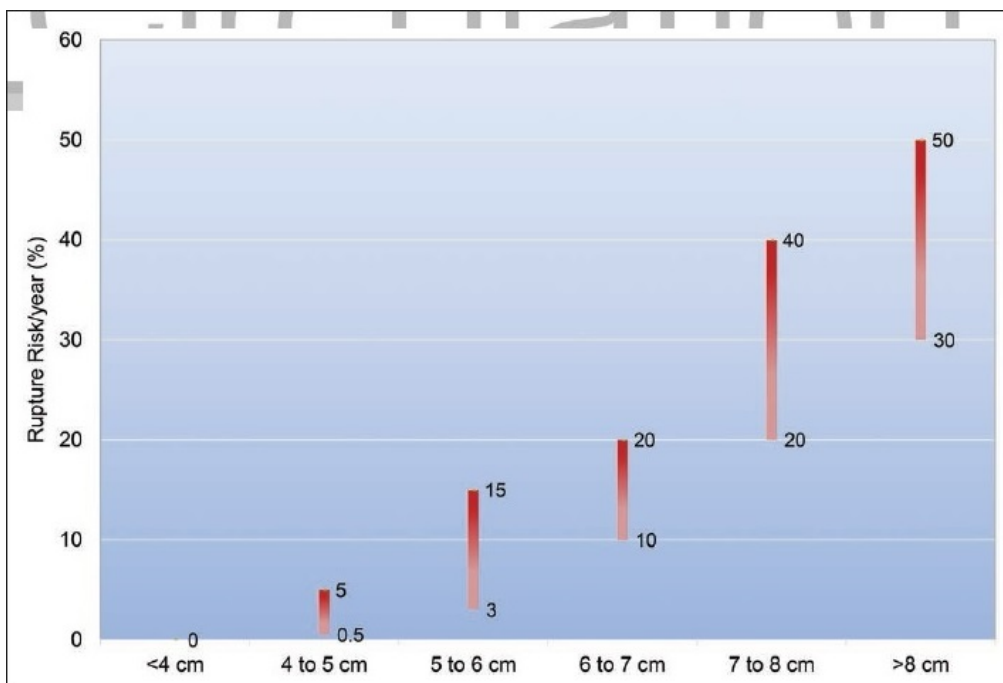


Figure 10. Association between diameter and minimum and maximum risk of abdominal aortic aneurysm rupture per year. Data derived from Brewster et al (162).

2.3. Cancer

2.3.1. Introduction

Cancer is characterized by the growth and spread of abnormal cells, and arises when normal cells are transformed into tumor cells by mutations in genes involved in proliferation or apoptosis cellular pathways. These changes are the result of the interaction between patient's genetic susceptibility and environmental carcinogens. Ageing is key risk factor for cancer development as cellular repair becomes less effective. Many of these mechanisms are similar to cardiovascular disease, including inflammation, neurohormonal stress, and angiogenesis (Figure 11).

Cancer is the second leading cause of death worldwide and 1 to 6 deaths is attributable to cancer. It was the cause of about 9.5 million deaths in 2018. 70% of these deaths occur in low or middle-income countries (163). However, according to recent data, there is a major epidemiologic transition in high-income countries where cancer has overtaken CVD as the leading cause of death (164).

Cancer shares many common risk factors with cardiovascular diseases including smoking, physical inactivity, obesity, diet low on fruits and vegetables, and alcohol use. These risk factors are responsible for about one third of cancer cases with tobacco use being the cause for most of them (165). In addition, cancer causing infections like hepatitis and human papilloma virus (HPV) are responsible for many cancer cases in low-income countries (166).

Cancer has a high economic impact for health systems. Only in USA, the cost, for cancer diagnosis and treatment was more than 1.1 trillion in 2010. However, access in cancer specific therapies and special diagnostic procedures is usually limited to high-income studies. Late-stage presentation and high mortality are much common in low and middle-income countries, and only 1 in 5 of these countries has cancer driven policy (167).

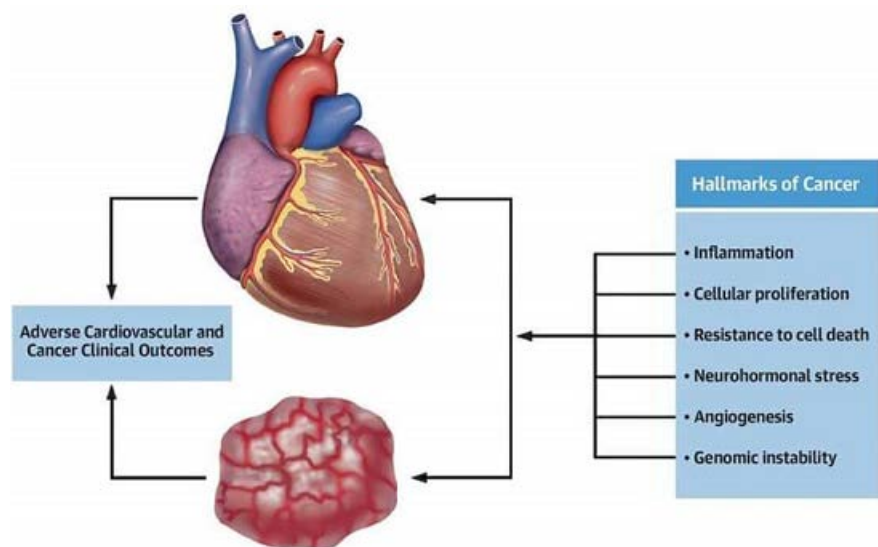


Figure 11. Shared pathophysiological mechanisms between cardiovascular disease and cancer.

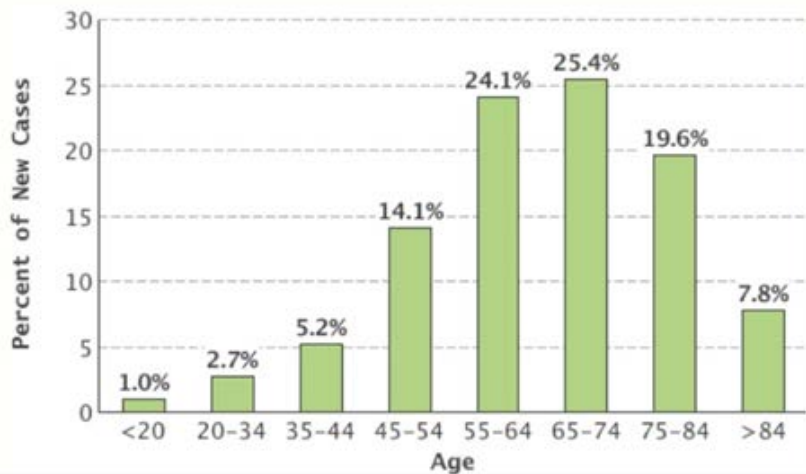
2.3.2. Cancer Risk Factors

As discussed previously, cancer is the result of patient's immune susceptibility, environmental carcinogens, and lifestyle and habits. Many of these are common between cardiovascular diseases

and cancer. There is a very large list of certain or possible carcinogens (168). The most important ones are presented here.

Age is the most important risk factor for most cancer types. It seems that cancer is a cumulative disease and the various carcinogens have an increasing impact, but also protective mechanisms seem to deteriorate with advancing age. According to the SEER database the mean age of cancer diagnosis is 66 years, but it also depends on the specific cancer type, with some cancers being more prevalent in children or younger ages (e.g. leukemia and bone cancers) (169-171).

Figure 12. Percent of new cancers by age group: All cancer sites.



SEER 18 2007-2011, All Races, Both Sexes

Smoking is a leading cause of cancer incidence and mortality. Active but also passive smokers have an elevated risk for cancer since tobacco smoke contains many substances that cause DNA damage and mutations (172). Tobacco use is related to most cancer types including lung, bladder, mouth, esophagus, stomach, pancreas, colon, rectum and kidney (173, 174). No safe limit for smoking exists and even low intensity smoking has been strongly related to cardiovascular disease and cancer (Figure 13). Individuals smoking 1 cigarette per day carry a 64% higher risk of dying earlier and 9 times higher risk for lung cancer (175).

Figure. Association Between Smoking Status and All-Cause Mortality

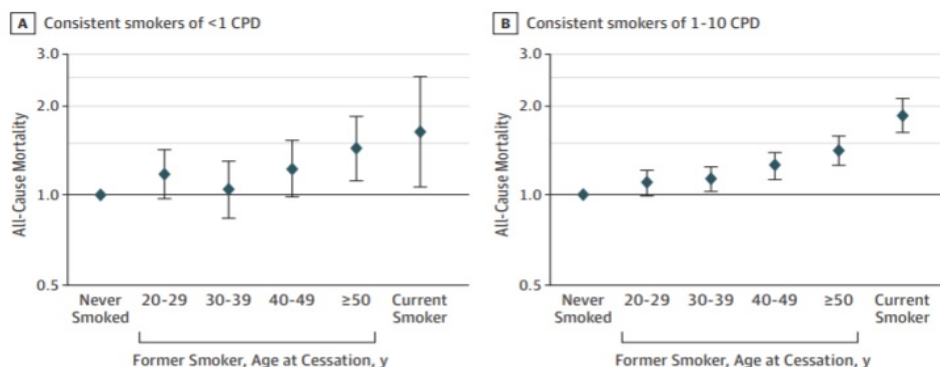


Figure 13. Association between Smoking Status and All-Cause Mortality. Hazard ratios among lifelong consistent smokers of less than 1 cigarette per day (CPD) (A) and (B) 1 to 10 CPD relative to never smokers (175).

Obesity is also a risk factor for several cancers such as breast, colon, rectum, kidney and endometrium (176). **Unhealthy diet** and **physical inactivity** are also related to obesity and elevated cancer risk (176, 177). On the other hand, regular physical activity, a healthy diet and keeping a normal weight seems to carry a protection against certain cancer types (178). These preventive measures lower also the risk for cardiovascular diseases, diabetes and hypertension (179-181).

Alcohol abuse is also another well-established risk factor for several cancers including mouth, esophagus, larynx, liver, and breast (182-185). An estimated 3.5% of cancer deaths is related to alcohol. Although up to a moderate consumption seems to offer a protection against cardiovascular diseases and even against some cancers, this should be no more than 1 unit per day for women or 2 units for men (186-188). However, it seems that even this benefit of alcohol consumption is outweighed by the harms it causes and it is included in the list of known carcinogens.

Ionizing radiation, that is radiation of certain wavelengths, has the ability to also damage DNA and cause mutations. Ionizing radiation includes high-energy radiation such as X-rays, gamma-rays and radon. Low-energy radiation like energy from Wi-Fi or cell-phones or even visible light is referred to as non-ionizing radiation and has not been linked to cancer until today. As a result, this type of carcinogen is many times iatrogenic and cumulative after X-rays and CT scans, and these exams should not be executed without specific reason (189, 190).

Other well-known risk factors (carcinogens) associated with specific cancer types include endogenous **estrogen levels** as well as **hormone replacement therapy** for the risk of breast or endometrial cancer, **sunlight UV (ultraviolet) radiation** for the risk of melanoma and other skin cancers, and **hypertension** for renal cell cancer (191-193).

Chronic inflammation has also been blamed for cancer incidence and specifically for an elevated risk for colorectal cancer in chronic inflammatory bowel diseases (e.g. Crohn and ulcerative colitis). Inflammation is normally a physiologic response to cell damage but in many autoimmune diseases this process may be expressed even without cell damage. Based on this observation, there are lately many studies investigating whether anti-inflammatory drugs such as aspirin decrease the risk of cancer. However, even **immunosuppression**, whether congenital, acquired (HIV) or iatrogenic in organ transplant recipients, carry an elevated risk for certain cancers including blood cancers, non-Hodgkin lymphoma, lung, and other cancers. As a result, it appears that there is a critical balance in the immune system to identify and attack tumor cells and not turn against normal ones (194-196).

Finally, there are several **infectious agents** that have been associated with cancer. These can be viruses, bacteria, and parasites, and most can be transmitted from one person to another through blood or body fluids. The most important ones are the Epstein-Barr virus (EBV), the hepatitis B and C viruses, the human immunodeficiency virus (HIV), the Kaposi-sarcoma associated herpesvirus and the helicobacter pylori (197-201).

2.3.3. Selected Cancers

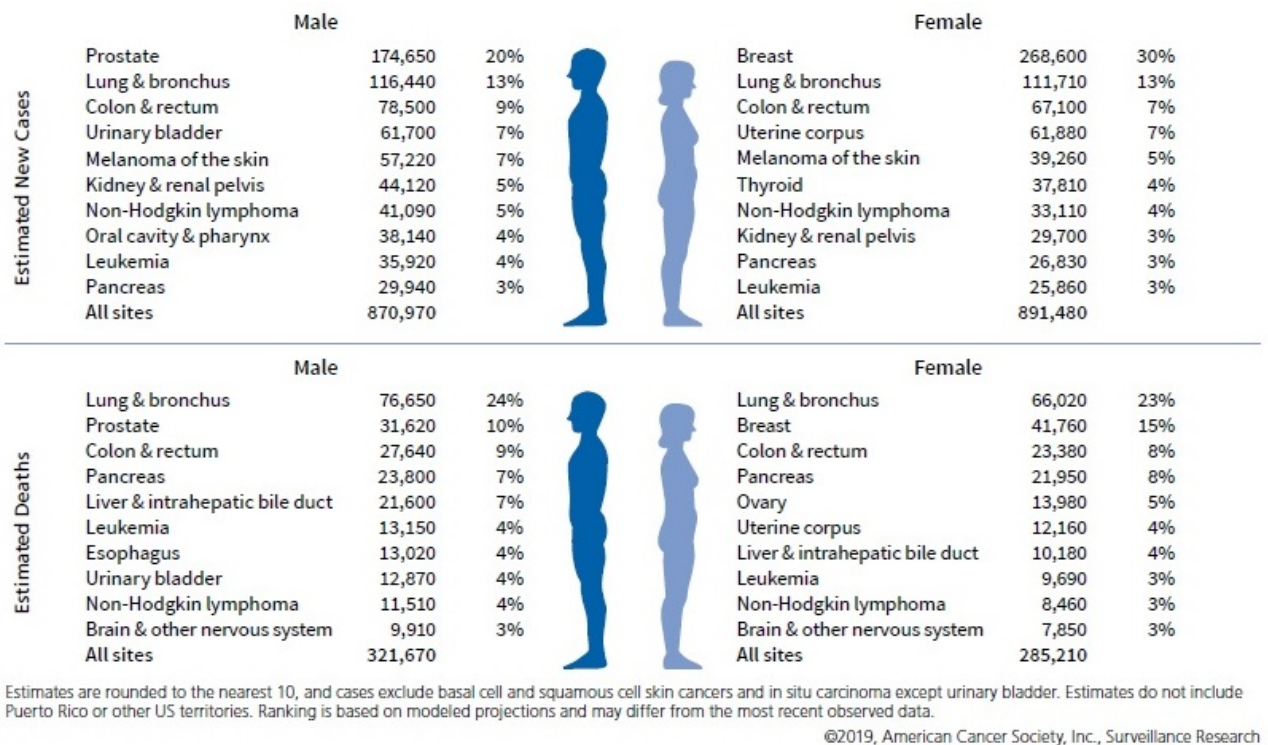


Figure 14. Leading Sites of New Cancer Cases and Deaths – 2019 Estimates (202).

Breast Cancer

Breast cancer is the most common female cancer and carries the second place in cancer mortality in females after lung cancer. Mortality from breast cancer presents a decline of up to 40% since 1989 as a result of early detection and advanced treatment strategies (202). Age and female sex are the strongest risk factors. Modifiable risk factors include obesity, alcohol consumption, physical inactivity, oral contraceptive use, and hormone replacement therapy. Non-modifiable risk factors include positive family history of breast or ovarian cancer, BRCA1 and BRCA2 mutations, high breast tissue density, history of chest radiation in younger age, long menstrual history, and not having children till 30s (203-205). Early detection strategies include mammography (low-dose X-ray) national health plans, ultrasound, and MRI screening. Often the only symptoms include a mass palpation or skin tenderness. Treatment options include local or more extensive surgery, radiation and chemotherapy according to certain tumor characteristics, lymph node involvement, and patient preference. The 5 and 10-year survival rates after diagnosis are 90% and 83% respectively.

Childhood Cancer

The most common cancers in children up to 14 years of age include leukemia (28%), central nervous system tumors (26%), neuroblastoma (a peripheral nervous system tumor, 6%), nephroblastoma or Wilms tumor (5%), non-Hodgkin and Hodgkin lymphoma, rhabdomyosarcoma, retinoblastoma, osteosarcoma, and Ewing's sarcoma (202). Symptoms are often non-specific and depend on the cancer type. Most cancers in children are spontaneous. Risk factors include radiation

history, organ transplantation, and specific congenital syndromes (ex. Down Syndrome). Overall survival has been greatly improved with 10-year survival of up to 83%.

Colon and Rectum Cancer

It is the third most common cancer type in incidence and mortality in both males and females (Figure 14). Due to the extensive screening programs of the last decades its incidence is constantly declining in ages over 55 years, but not in younger ages where it is sometimes the result of chronic bowel inflammatory diseases. The most common risk factors include obesity, physical inactivity, smoking, alcohol, processed meat intake, and lack of fruits and vegetables in everyday diet pattern. These risk factors are also modifiable. Non-modifiable ones include family history of bowel cancer, chronic inflammatory diseases (ex Crohn, ulcerative colitis), polyps, and type 2 diabetes (202, 206, 207). Early detection screening programs are now common in most national health plans, mainly by the aid of colonoscopy and certain colon specific antigens (carcinoembryonic antigen, CEA). Symptoms include rectal bleeding, change in bowel habits, decreased appetite, and weight loss, but in the early stages the disease is usually asymptomatic. Surgery is the most common treatment option. Survival for localized tumors is up to 90% in 5 years, but only ~40% of cancers are diagnosed in early stages, making screening programs completely mandatory.

Kidney cancer

Kidney cancer includes renal cell (>94%), renal pelvis (5%), and Wilms tumor (1%). The most important risk factors are male sex, obesity, smoking, hypertension, chronic kidney disease, and exposure to certain chemicals and radiation. More than half of the cases can be prevented by dealing with modifiable risk factors. Symptoms include blood in the urine, back pain, weight loss etc. Surgery and ablation therapy are the most common treatments. 5-year survival is 75% but for localized disease it is over 93% (202, 208, 209).

Leukemia

It is the most common cancer in children although most cases are still presented in older individuals. It is classified into acute and chronic myeloid leukemia (ALL, CLL) and acute and chronic lymphocytic anemia (AML, ALL) based on the cells affected. ALL is the most common type in children while CLL is the most common type in adults. Many cases are spontaneous, especially in children. Risk factors include older age, history of radiation or chemotherapy in younger age, exposure to hazardous chemicals, smoking, but also parental smoking, and genetic predisposition with the expression of the Philadelphia chromosome. Symptoms include fatigue, weight loss, and recurrent infections. Chemotherapy is the main type of therapy including targeted drugs against tumor cells or the Philadelphia chromosome. Survival depends on the specific leukemia type and is generally much better in children than in adults (202, 210, 211)

Lung Cancer

Lung cancer is the second most common cancer in new cases both in males and females and the first in cancer mortality for both sexes. Incidence has declined in the last decade mainly due to change in smoking regulations. Cigarette smoking (active and passive) is by far the most important risk factor, with more than 80% of lung cancer deaths being attributable to smoking. Other breathable chemicals related to lung cancer are radon, asbestos, arsenic and other air pollution gases. Early detection with spiral computed tomography has increase the cases diagnosed in early

stages. The disease is often expressed with persistent cough and blood, or recurrent respiratory infections. Treatment is a combination of surgery, radiation, and chemotherapy according to the stage of the disease. 5-year survival rate is only ~20% (202, 212, 213).

Liver Cancer

Liver cancer is the most rapidly increasing cancer in both men and women, with almost 3% increase per year. It is 3 times more common in men than women and it is most often presented as hepatocellular carcinoma (HCC). The most common risk factors are increased body weight, type 2 diabetes, alcohol overconsumption, hepatitis B and C infection, and smoking. Up to 70% of liver cancers can be prevented by limiting exposure to these factors. Aflatoxin seems also to increase the risk for cancer, while coffee drinking may reduce the risk. The vaccine against HBV or anti-retroviral therapy in those already infected, can further decrease the risk (214-217). Symptoms may be non-specific such as weight loss or loss of appetite, swelling and abdominal pain, or more specific due to the disruption of the normal liver function, such as jaundice and bleeding predisposition. Depending on the extension of the disease, treatment options include surgery, ablation, or embolization for localized disease, and liver transplantation, chemotherapy, or immunotherapy for more advanced stages (202, 218).

Prostate Cancer

Prostate cancer carries the first position in cancer incidence and the second in cancer mortality in men, second only to lung cancer (Figure 14). Early stage prostate cancer has no specific symptoms, so screening especially in positive family history or older ages is mandatory. This is most often done with clinical examination, prostatic specific antigen levels (PSA), and ultrasound. Sometimes symptoms may include frequent urination, pain or burning sensation, and bone pain in metastatic disease. Localized disease is treated with surgery or radiotherapy, while in metastatic disease a combination of chemotherapy, hormonal therapy, and radiotherapy may be used. Prostate cancer has been linked to black race, older age, smoking, obesity, carries of BRCA1 and BRCA2 mutations, and to positive familial history. Fortunately, most cases are discovered when cancer is still localized in which 5-year survival is almost 100%. For metastatic disease, 5-year survival decreases to just 30% (202, 219-222).

Melanoma

Melanoma consists only the 1% of all skin cancers but is responsible for the majority of cancer deaths. It is more common in younger women or older men. Risk factors for melanoma is the positive family history for melanoma, the presence of atypical moles, and exposure to UV radiation including indoor tanning (223-225). Early detection is crucial since melanoma is highly invasive with 5-year survival for localized melanoma of up to 92%. All other non-melanoma skin cancers are highly curable. New or atypical moles or other lesions insisting more than a month should be evaluated by a dermatologist. The definite treatment is the removal of the lesion but immunotherapy, radiation, or chemotherapy may be necessary for invasive melanoma with positive sentinel lymph nodes (202, 226).

Uterine Cancer

Uterine cancer is divided into uterine cervix and uterine corpus or endometrial cancer. The incidence of cervical cancer has greatly decreased since 1975. The combination of HPV (human

papilloma virus) and Pap tests for screening, offers early detection of pre-cancerous lesions. In addition, HPV vaccination protects against the 90% of the virus types that cause the cancer. HPV is by far the most important risk factor (227). Treatment is done by excision, ablation or cryotherapy for localized diseases, aided by chemotherapy or radiation for invasive disease (228). 5-year survival is 66%. On the other hand, endometrial cancer is the fourth most common female cancer, with incidence and mortality increasing over time. Modifiable risk factors include obesity, physical inactivity, and hormone replacement therapy. Other risk factors are late menopause, never having children, diabetes, Lynch syndrome, and a history of polycystic ovary syndrome. It is frequently presented with postmenopausal bleeding. Therapy depends on the stage of the disease. The 5-year survival rate is 83% (202, 229-231).

Lymphoma

Lymphoma is mainly classified to non-Hodgkin lymphoma (the most common), and Hodgkin lymphoma. Risk factor for HL is the younger age while for NHL is the advanced age. Other risk factors are related to immunity with people receiving immune-suppressants (ex. organ transplant recipients) being more susceptible, as well as people with auto-immune diseases. Epstein Barr, HIV, Helicobacter pylori and hepatitis C virus are also known risk factors. Often, the only symptoms are weight loss, fatigue, and lymphadenopathy. These patients are usually treated with chemotherapy, radiation, and stem cell transplantation. Overall, 5-year survival is between 71% (NHL) and 87% (HL) (202, 231, 232).

Pancreatic Cancer

Pancreatic cancer categorizes into exocrine tissue cancer (93%), where the enzymes for digestion are produced, and endocrine tissue tumors (7%) in cells that produce hormones. Risk factors include smoking, type 2 diabetes, obesity, chronic pancreatitis, and positive family history for pancreatic cancer. Alcohol, Lynch syndrome, and BRCA1 and BRCA2 mutations seem also to pose an increased risk (233, 234). Unfortunately, symptoms are rare and the disease is often diagnosed in advanced stages, with a 5-year survival rate of only 9%. Even in localized disease it is only 34%. Treatment is a usually combination of palliative surgery, chemotherapy and radiation therapy (202).

Other Cancers

Most types of **thyroid cancer** are highly curable with a 5-year survival rate of 98%. It is usually diagnosed in early stages, with a lump in the neck being the only symptom. Risk factors include female sex, thyroid nodules, obesity and certain genetic syndromes (235). It is treated with surgery followed by treatment with radioactive iodine (I-131), when the cancer has spread outside the thyroid gland. **Bladder cancer** is the fourth most common incident cancer in men. Male sex, white race, smoking, and frequent exposure to arsenic, aluminium, rubber, leather, and several dyes are some of the risk factors (236). It is most of times diagnosed early due to urinary symptoms and surgery is the treatment of choice with 5-year survival of 95% for localized disease. **Ovarian cancer** accounts for 5% of cancer deaths among women, more than any other gynecologic cancer. The 5-year survival is only 47% because it is often diagnosed in advanced stages since there are no specific symptoms. Treatment rarely offers a cure. Risk factors are generally the same as those for breast cancer, namely age, BRCA mutations, and family history of breast or ovarian cancer (237). Finally, **oral cavity and pharynx cancers** have been associated with smoking, alcohol consumption, and HPV infection (238). They usually present as an ulcer or thickening in the oral

cavity and are treated with surgery combined with radiation therapy. Overall 5-year survival is 65% (202).

2.3.4. Cancer Prognostic Factors

Cancer is characterized by growth, invasion, and metastasis. Although cancer is a heterogeneous group of diseases, all cancers types share some common characteristics. The prognosis of cancer patients depends on the organ of presentation (breast, prostate etc.), the histopathological traits (e.g., adenocarcinoma, sarcoma), and several prognostic factors related to the cancer (disease extent), or the specific patient (comorbidities). There are two major overlapping, proposed classifications for prognostic factors: The subject-based classification and the clinical-relevance classification. According to the most commonly used subject-based classification, prognostic factors are categorized into tumor-related, host or patient-related, and environment-related. Based on clinical-relevance classification, they are divided into essential for prognosis, additional, and promising prognostic factors (239).

In the subject-base classification, *tumor-related prognostic factors* refer to specific tumor biology and anatomic disease extent. The tumor extent of spread is most commonly described using the “TNM staging system”. T describes the size of the original (primary) tumor and whether it has invaded nearby tissue, N describes nearby (regional) lymph nodes that are involved, and M describes distant metastasis (spread of cancer from one part of the body to another). This system is globally used for the description of many solid tumors, but is not applicable to cancers like leukemia or cancers of the central nervous system (240). On the other hand, tumor biology concerns an ever-growing field of cancer biomarkers that predict the extent, recurrence, or remission of specific cancers, or the response to treatment. Such biomarkers are already used in clinical practice for diagnosis, treatment, and description of the natural history of the disease, including biomarkers such as alpha-fetoprotein (a-FP), prostate specific antigen (PSA), carcinoembryonic antigen (CEA), CA 19-9 etc. (241, 242).

Host-related prognostic factors refer to specific patient traits that affect the natural history of the disease. These include patient demographics such as age, sex, and ethnicity. Comorbidities such as coronary artery disease, diabetes, stroke, and chronic obstructive pulmonary disease have also a great impact on patient status and survival, although not directly related to cancer. Advanced age is related to poorer cancer outcomes and survival in almost all cancer types, and black race has been linked to worse outcomes in patients with prostatic cancer (243, 244). The host immune status is also a very important prognostic factor, as congenital or acquired immunodeficiency due to HIV, organ transplantation, or cortisone therapy for other reasons, is directly associated to worse clinical outcomes (245). Mental illness and depression are also associated with poorer prognosis as these patients tend to be less compliant to therapy and not seek immediate medical help (246).

Environment-related prognostic factors refer to the choice and response to treatment, access to specialized cancer care, cancer drugs, exams, technology, and health care policy factors (247-249). These factors are very important in patients living away from cancer treatment centers and especially in developing countries. These factors affect not only the treatment plan but also the ability for proper rehabilitation and follow-up for cancer recurrence.

On the other hand, in the clinical-relevance classification, the most *essential prognostic factors* are the extent of the disease quantified using the above mentioned TNM system, and the tumor histopathological characteristics such as the tumor grade and small-vessel invasion. Many tumor biomarkers play also an important role in diagnosis, quantification of disease burden, and follow-up (250). Patient age is also integral for treatment strategy in some cancers, such as thyroid or Hodgkin's lymphoma (251, 252). *Additional prognostic factors* are those factors that are not necessary for the creation of a treatment plan and are usually not considered in clinical decision making. However, they often have a great impact on the disease outcome. Such factors are the already mentioned environment-related factors. Finally, the *promising prognostic factors* are those under investigation for future application. These molecular factors may predict the response to treatment or offer targeted cancer therapy. These can be adhesion molecules, cell receptors, circulating antigens, or other proteins. There is an abundance of new promising factors in medical literature, but in order to be used in clinical practice they must first prove that can change treatment plans or alter the disease outcome, over already established ones (239).

3. A PROGNOSIS RESEARCH STRATEGY - PROGRESS

As already mentioned, prognosis research aims to predict outcomes in individuals with a disease or health condition, after a specific follow-up period, based on characteristics clearly defined at the beginning of the study (prognostic factors). Although there is a significant amount of prognosis studies published each year, a unanimous approach for addressing prognosis research questions has not existed for many years. The solution to this problem arose in 2013 when the PROgnosis RESearch Strategy (PROGRESS) was proposed. This strategy proposes a framework of four distinct but connected types of prognosis research (253-256).

In people with a specific disease or health condition, the four different types of prognosis research appeared in PROGRESS are:

Type I: Overall Prognosis Research: What is the average outcome risk in the population under study?

Type II: Prognostic Factor Research: Which characteristics (prognostic factors) are associated with a change in outcome risk?

Type III: Prognostic Model Research: How can we develop, validate, assess the performance, and evaluate the impact of models consisting of multiple prognostic factors?

Type IV: Predictors of Treatment Effect: Which characteristics predict a different response to treatment? Which treatments favor specific subgroups of patients?

OVERALL PROGNOSIS RESEARCH (PROGRESS TYPE I)

1. Definition

Overall prognosis refers to the estimation of the average risk for specific outcomes ('the endpoint') in people with a given disease or health condition ('the startpoint'), in the context, time, and setting of current healthcare (253, 257). In current healthcare systems, overall prognosis may be influenced by personal decisions, diagnostic investigations, doctor-patient interactions, available treatments and self-management. Overall prognosis refers to the mean outcome risk of all people in the specific target population and with the specific disease under investigation.

Overall prognosis is usually expressed as the average outcome probability or rate. This can take many forms like survival rate, time to recovery, complication rate or even expressed in a continuous manner (e.g. pain intensity, disability scale etc.). As a result, it may include absolute measures like average outcome risk or relative measures like mortality rate in the sample population versus mortality rate in general population. However, it is important to mention that this overall prognosis may change over time due to changes in the nature of the disease, the quality of care, new available treatments, the populations under study, and the outcome recordings.

2. Study Design

Prognosis research studies are ideally designed prospectively. The individuals with the health condition under study are identified at the startpoint and followed-up over time till the end of the follow-up period or till the occurrence of the outcome of interest. However, this prospective study design is often expensive and time consuming. Fortunately, there are usually relevant data available in national registries and healthcare and insurance records. This makes often easier and cost-effective for the researchers the conduction of retrospectively designed overall prognosis studies relying on already available data.

The startpoint and endpoint of the study should always be clearly defined avoiding complex definitions. The startpoint refers to individuals with a certain baseline health condition or disease. The endpoint can be any outcome that is considered important by the researchers as long as it is clearly defined. These outcomes can be absolute risk estimates or relative. For example, in cancer prognosis studies relative survival is typically used in the analysis of cancer registry data (258).

3. Importance

Overall prognosis studies provide descriptive information for the most likely course of a condition or a disease. Information on overall prognosis could prove very important not only for patients but also for clinicians. Through the doctor-patient interaction and communication, patients can be informed about the effective treatments, the possible complications, the expected time to treatment, the possibility of adverse outcomes etc. In addition, such information is also important for healthcare policies as well as for insurance companies (Figure 1).

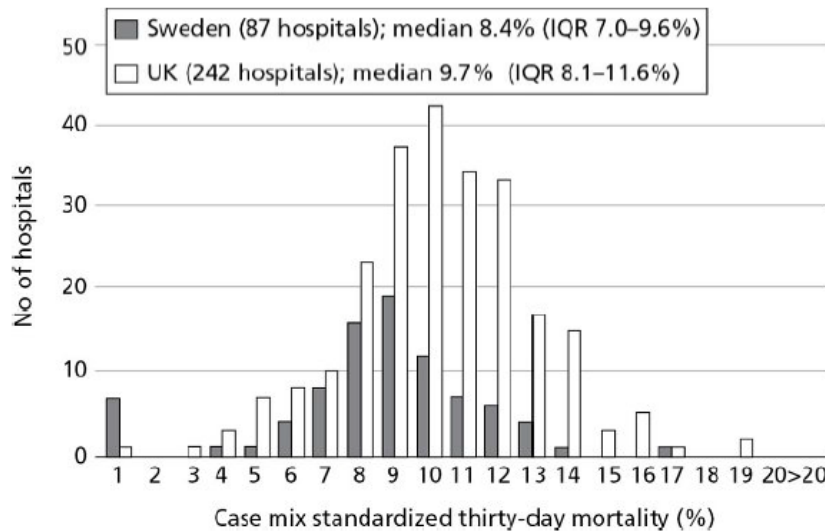


Figure 1. Example of overall prognosis research, investigating international differences in mortality rate within 30 days of admission in patients with acute myocardial infarction in the UK and Sweden.

Source: Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: Population based cohort study using nationwide clinical registries. *BMJ* (Clinical research ed).2015;351:h3913. Copyright © 2015 BMJ

Overall prognosis is also important for the definition of health conditions since prognosis and outcomes are strictly related to the pathophysiology of the disease. Diagnosis and screening are also important as long as the likely course of the disease is known. For example, even a costly and time-consuming screening program for a disease can finally prove cost-effective if the early diagnosis leads to lower impact and a better quality of life (259).

Furthermore, knowledge of overall prognosis aids in the evaluation of prognostic factors and prognostic models, assessing their impact on the physical course of the disease under investigation. Finally, it is important in the design and interpretation of randomized clinical trials because most times the aim is to prove the superiority or non-inferiority of novel therapies over already established treatments (257).

4. Statistics of overall prognosis research

Key statistical models and measures of overall prognosis research are different for continuous, binary, and time-to-event outcomes.

4.1. Continuous Outcomes

When studying continuous outcomes (e.g. blood pressure), the key summary statistics include the mean and median, combined with measures describing the variability of the outcome, such as the standard deviation (SD), interquartile range (IQR), and histograms of outcome values. The key

statistical model for summarize and predicting prognosis in terms of mean outcome values is linear regression. This is a function in the form of:

$$Y_i = \alpha + \beta_1 X_{1i} + \beta_2 X_{2i} + \dots + \beta_k X_{ki} + e_i$$

Where Y_i stands for the continuous outcome, X_{1i}, X_{2i}, \dots are the predictors, α is the “alpha hat” which represents the mean outcome value for a patient with mean outcome values, β is the “beta hat” which represents the change in mean outcome value for each one-unit increase in the corresponding predictor after adjustment for other predictors, and e_i represents the error variable that adds “noise” to the linear relationship between the outcome (dependent variable) and regressors (Figure 2).

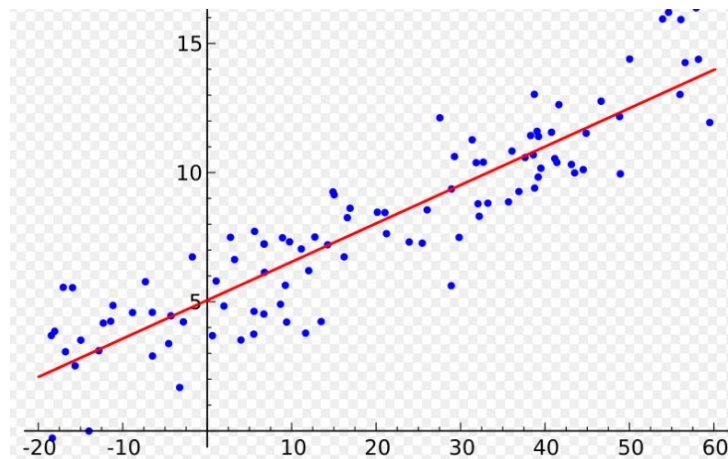


Figure 2. Example of linear regression.

4.2. Binary Outcomes

Binary outcomes are those occurring within a particular time-period (e.g. death at 5 years). Binary outcomes can be expressed by the average *absolute risk*, also known as *cumulative risk* or *incidence proportion*(257). An alternative measure is the *Odds Ratio (OR)*, which is the number of individuals with the outcome divided by the number of individuals without the outcome in a specific time-period (260). Other measures include the *Risk Difference (RD)* and the *Risk Ratio (RR)* (Figure 3).

	Exposure	No exposure	Total
Disease	a	b	a + b
No disease	c	d	c + d
Total	a + c	b + d	a + b + c + d
Risk (of disease)	a / (a + c)	b / (b + d)	
Odds	a / c	b / d	
Risk difference (RD)			(a / [a + c]) - (b / [b + d])
Risk ratio (RR)			(a / [a + c]) / (b / [b + d])
Odds ratio (OR)			(a / c) / (b / d)

Figure 3. Risk Difference, Risk Ratio, and Odds Ratio.

For binary outcomes the response (Y_i) is defined as 1 for those with the outcome or 0 for those without the outcome. In this situation, logistic regression is a more appropriate statistical model for predicting risk of outcome occurrence and for deriving odds ratios to quantify prognostic factor effects, since the response follows a Bernoulli distribution rather than a normal one (257) (Figure 4). If risk ratios are used, a Poisson or binomial regression can be used (261).

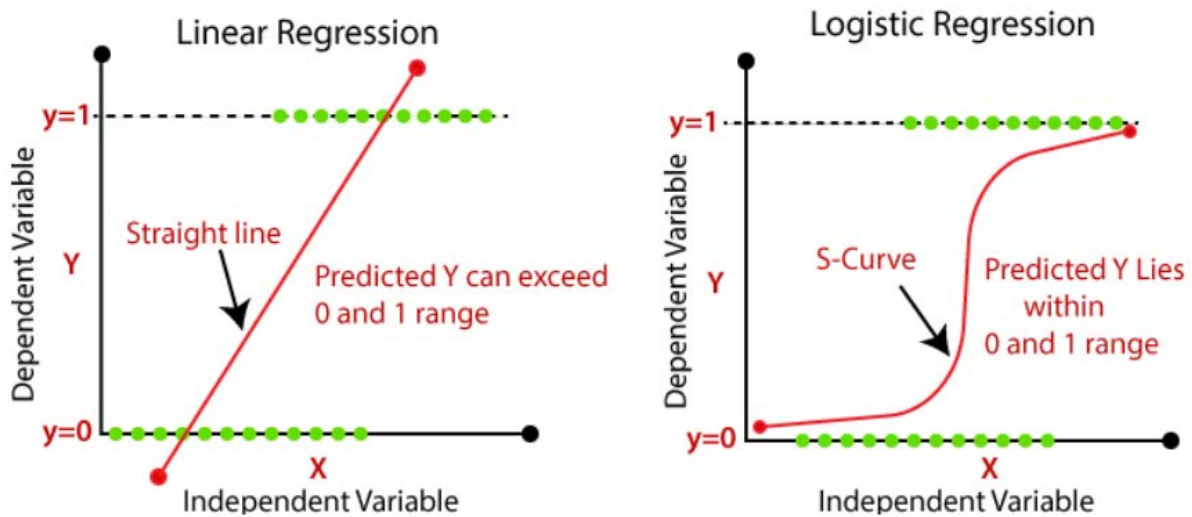


Figure 4. Linear vs Logistic Regression.

4.3. Time-to-event Outcomes

In many prognosis studies, not all individuals are followed-up for the same length of time, as many may withdraw, are lost to follow-up, die, or reach the end of the study before the outcome has occurred. In such situation it is not appropriate to exclude these individuals but rather use survival models that include them in their statistical analysis up to their censoring time (257). An important summary measure is the *incidence rate* defined as the total outcome events observed divided by the total number of person-years, which is the sum of the number of people in the study and their follow-up years.

The survival function $S(t)$ is the probability that a subject survives longer than time t . $S(t)$ is theoretically a smooth curve, but it is usually estimated using the Kaplan-Meier (KM) curve, which is a non-parametric estimation. The Kaplan-Meier curve is the visual representation of the survival function, and it shows what the probability of an event (for example, survival) is at a certain time interval. If the sample size is large enough, the curve should approach the true survival function (smooth curve) for the population under investigation (Figure 5). In addition, the survival distributions of two samples can be compared using the log-rank test. The log-rank test, also called Mantel-Cox test, is a nonparametric test that compares estimates of the hazard functions of the two groups at each observed event time. The null hypothesis is that the two groups have identical hazard functions. It is also worth mentioning that its power is maximum when the two survival curves are not crossing.

The hazard function, named $h(t)$, represents the instantaneous risk of experiencing the outcome at time (t) , while the cumulative hazard function $H(t)$, is the total hazard gathered until time (t) . On the other hand, the *hazard ratio* is the ratio of the hazard rates corresponding to the conditions described by two levels of a variable (e.g. hazard at time (t) for males divided by hazard at time (t) for females).

The most commonly used regression approach for time-to-event outcomes is the Cox proportional hazards regression. Cox regression (or proportional hazards regression) is a method for investigating the effect of several variables upon the time a specified event takes to happen. In the context of an outcome such as death this is known as Cox regression for survival analysis. It was first described by Cox and is a common approach for estimating hazard ratios to quantify prognostic factor effects (262).

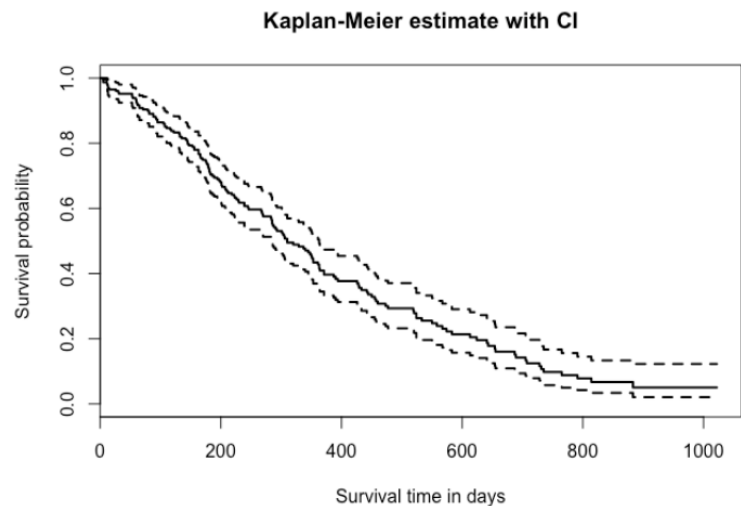


Figure 5. Kaplan-Meier curve example.

5. Sources of bias

In overall prognosis research the main sources of bias are related to selection bias and information bias and should always be taken into account. For this reason, several quality assessment tools have been developed such as the Newcastle-Ottawa Scale, the Quality In Prognosis Studies (QUIPS) tool and the Prediction model Risk Of Bias Assessment Tool (PROBAST) (263-265).

Selection bias is the bias introduced by the selection of individuals, groups or data for analysis in such a way that proper randomization is not achieved, thereby ensuring that the sample obtained is not representative of the population intended to be analyzed. The phrase "selection bias" most often refers to the distortion of a statistical analysis, resulting from the method of collecting samples. If the selection bias is not taken into account, then some conclusions of the study may be false. Selection bias can arise at baseline when participants are incorrectly identified, invited or excluded (participation bias) and during follow-up when participants may withdraw or data may be missing (attrition bias) (266).

In epidemiology, information bias refers to bias arising from measurement error. Information bias is also referred to as observational bias and misclassification. It is usually the result of poor methods for measuring outcomes resulting in over or underestimation of overall prognosis. So, in order to limit the risk for information bias the outcome and methods of measurement should be reliable, valid and clearly defined from the startpoint (267). Most quality assessment tools and checklists as those already described, include specific questions to evaluate such common sources of bias.

PROGNOSTIC FACTOR RESEARCH (PROGRESS TYPE II)

1. PROGNOSTIC FACTORS

1.1. Definition and Classification

Prognostic factors are clinical measures used to help elicit an individual patient's risk of a future outcome, such as the incidence of a disease, the recovery from a disease or its recurrence after primary treatment (268). As a prognostic factor can be considered any variable that is associated with a risk of a health outcome among people with a specific health condition (269). They are also known as prognostic markers, prognostic variables or predictors. They are used in all fields of medicine but even more in chronic diseases such as cancer, cardiovascular disease, chronic respiratory diseases and diabetes.

It is important to differentiate prognostic factors from predictive factors. Prognostic factors include those characteristics that help to define the natural history of a disease while predictive factors are those characteristics that help to define the likelihood of benefit from a specific treatment. However, some of the prognostic factors can be predictive and vice versa. Another important differentiation is between prognostic factors and risk factors. Risk factors are those that have been related to causing the disease, while prognostic factors are those that in individuals with a specific disease can influence the outcome or the natural history of the disease.

There are many different prognostic factor groups that have been suggested including clinical characteristics, demographics, symptoms, signs, co-morbidities, biometrics, biomarkers, response to treatment, molecular characteristics and genetic information, anatomic disease extent etc. However, they are mostly classified into 3 main categories including patient-related, disease-related, and treatment or environment-related factors (239, 270).

Patient or host-related factors are clinical factors. These variables include individual patient demographic characteristics such as age, sex, race, weight, height, body mass index and habits such as smoking, sedentary lifestyle etc. However, they also include biometrics, physical examination and clinical measurements like blood pressure, heart rate variability, performance index, severity and type of symptoms, clinical history and co-morbidities like diabetes, renal failure and hypertension. They can also be biomarkers like hemoglobin level, blood sugar and cholesterol levels, creatinine clearance, genes, RNA sequences, single-nucleotide polymorphisms (SNPs), imaging, electrophysiology and cardiac catheterization results etc.

Disease-related factors include those characteristics of the disease that predict the response to treatment. As a result, they depend on the chronic disease under investigation. Considering oncology, they can involve tumor characteristics like tumor classification, stage, metastases, histopathologic type, anatomical invasion, location and size but also cancer-related biomarkers like genes, hormones, proteins, receptors, antigens and other molecular markers. In cardiovascular medicine and diseases like myocardial infarction, heart failure, stroke and coronary artery disease-related prognostic factors can include left ventricular ejection fraction, rhythm disorders, type, location and number of coronary or brain arteries affected, electrocardiographic findings, and biomarkers like troponin, B natriuretic peptide, creatinine kinase and c-reactive protein levels.

Treatment-related factors relate to different treatment strategies, techniques and treatment quality. They are also mentioned as environment-related prognostic markers. Different patients have access to different experienced and technically skilled doctors due to patient choice, socioeconomic status or environmental reasons (e.g. distance). For example, highly-trained surgeons tend to operate in specialized medical centers in large cities where not all patients have access to. In addition, specific medical techniques and equipment like cardiac catheterization laboratory and high-resolution computed tomography are not available in every hospital. Also, a different type of chemotherapy, combination of drugs and dosage or follow-up period may be chosen that often has a direct result on patient outcomes (239).

1.2. Importance of Prognostic Factors

Prognostic factors are of great importance for many reasons. First of all, they are very useful in clinical practice. By identifying which markers are prognostic of a disease we gain insight on its mechanisms, biology and natural history (271). This fact aids clinicians inform the patients and their relatives on the clinical course and possible outcomes of a disease but also plan an appropriate treatment strategy based on individual patient characteristics and likelihood of recovery or future disease recurrence (272). This helps alleviating patient anxiety and explaining the different variations in disease outcome. Many prognostic factors are also useful for monitoring disease progression. Such examples are CRP for infections, HbA1c for diabetes management, CD4-count for HIV infection monitoring and several serum tumor markers for cancer monitoring and effect of treatment (254, 273-275).

In addition, prognostic markers play an important role in the design, conduct and analysis of research studies, including randomized clinical trials, and help identify targets for new interventions. The assessment of specific prognostic factors to specific disease outcomes plays a vital role in clinical research. It identifies risk groups for stratified management and helps to target specific factors for modification or to introduce new treatment approaches (264). Furthermore, they ensure comparability among different patient groups and allow researchers to examine the degree of association and dependence among significant risk factors. Finally, the combination and weighing of the effect of prognostic factors on specific diseases helps in the development of prognostic models and in evidence-based treatment strategies (stratified medicine) (253).

2. PROGNOSTIC FACTOR STUDIES

2.1. Prognostic Factor Research

Prognostic factor research aims to identify those clinical or non-clinical patient characteristics that predict the risk of future outcomes, and how these factors can be used to improve patient outcomes or treatment strategy (257). It usually involves a prospective cohort study to identify factors that have added prognostic value over already established ones.

Prognostic factor studies are the most common type of prognosis research. There is a huge variety of prognostic factors in medical literature that are associated with many different outcomes,

and there is also an increase in relevant publications each year (Figure 1). However, many of those studies are poorly conducted with low overall quality that leads to severe study limitations (264, 276, 277).

Therefore, prognostic factor research requires careful planning, strict delimitation of the aim of the study and clearly defined study design, data analysis, and reporting. There are broadly two main different study designs that often co-exist within the same study.

- *The exploratory study design* involves the identification of potential prognostic factors related to a specific outcome, without previous knowledge on this specific association.
- *The replication and confirmation design* involve the evaluation of already established factors and the assessment of their added value on known prognostic factors for the outcome under investigation.

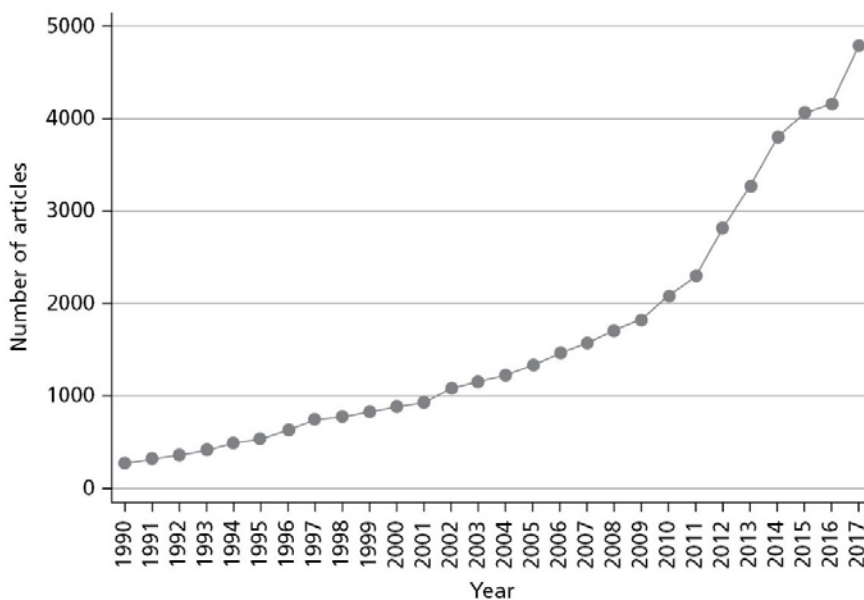


Figure 1. Number of citations identified in PubMed over time with ‘prognostic factor’ or ‘prognostic marker’ in the title or abstract.

Source: reproduced courtesy of Richard D. Riley (257).

2.2. Exploratory Studies

The second objective in the PROGRESS (PROGnosis RESearch Strategy) framework refers to identification of prognostic factors linked to a specific outcome without or with little previous knowledge on this association (254). Most diseases and especially cardiovascular diseases and cancer, are extensively studied and many factors are already identified. However, there is always the need for studies from scratch, to discover new unidentified factors.

Exploratory studies are important to identify new or the most promising prognostic factors from a large number of possible factors. They are called exploratory due to the possibility of chance

findings. These studies are also often called “agnostic” or “hypothesis-generating” studies, and were revived in the last decade by the introduction of the genome-wide association studies (GWAS), in which multiple genetic markers, entire genes and sequences are studied for a potential link to a disease or other specific outcome (278). In the same way, in other hypothesis-free studies many risk factors are collectively studied and not one by one separately, in an attempt to reach to the desired associations. However, most of times approaches to identify possible new prognostic factors incorporate some degree of biological reasoning and are based on hypothesized causal pathway from the onset of the disease to the disease outcome (254).

2.3. Confirmatory Studies

It is crucial that findings from exploratory studies are re-evaluated and validated in replication and confirmation studies. In these confirmatory studies, newly identified prognostic factors are re-assessed to validate their importance on the same outcome, and thus, to eliminate chance findings. Then, their additive value over other already established factors is assessed after appropriate adjustments. This incremental value is often assessed in prediction model using recalibration and reclassification measures such as the net reclassification index (NRI) or the integrated discrimination improvement index (IDI).

Confirmatory prognostic factor studies should be well-designed with clear methodological analysis and reporting. Factors derived from exploratory studies are assessed after adjustment for already established ones for the specific disease and outcome, and are found either with or without significant additive value. Ideally, several different confirmatory studies should be available for each new discovered prognostic factor, so that a meta-analysis could synthesize a combined effect estimate. However, this is rarely the case since there are substantially more exploratory than confirmatory prognostic studies in published medical literature.

Finally, there is also the possibility that the exploration and confirmation phases are combined within the same study. In this case, researchers, after identifying a potential new prognostic factor, perform also a systematic review and assess its prognostic value using already published data from different studies (257).

2.4. Design of Prognostic Factor Studies

The main aspects for conducting an exploratory or confirmatory prognostic factor study are common. The ideal design is the prospective cohort study design, because it enables researchers to clearly define the inclusion and exclusion criteria, the population sample under investigation, the study outcomes, the better collection of baseline and follow-up data, and the reasons for missing data or drop-out. The retrospective study design is also an acceptable alternative, but is often difficult to identify and use already recorded data for the specific population sample and for the specific outcome required. Most of times there are similar but not ideal data available for the hypothesis under study, and as a result some assumptions are required that can possibly bias and reduce the quality of the study.

Additionally, a prospective study design is usually based on a specific study protocol with clearly defined outcomes, and thus decreases the possibility of chance findings (type I errors), that

could result from using data gathered for other reasons. The prospective study design allows also measurements and outcomes to be blinded to prevent relevant biases. Other eligible designs are also the case-cohort and nested case-control designs, where only a part of the population sample is used for the derivation of results. However, the selection of a particular sample may affect the generalizability of the study for other populations besides this small sample (279).

Prospective cohort studies are costly and time consuming, and demand a high amount of dedication from researchers during the follow-up period. Luckily, in the last decades there are also extensive datasets available including huge amount of routine collected, real life data, such as insurance and national electronic health records, biobanks, mortality registries, or large-scale cohort follow-ups including entire populations (e.g. EPIC or Framingham Heart Study). These large datasets usually allow the proper identification of eligible participants for conduction of quality prognostic factor studies (nested case-control, retrospective), without having to handle every aspect from the ground-up (257, 280, 281). Moreover, many large randomized clinical trials (RCTs) may also contain the required information, since most of them study simultaneously many different risk or prognostic factors. However, there is always the possibility that combination of data from many different RCTs may be required and that these data may also not be generalizable to the general population.

2.5. Sample Size

There are many steps required for a high-quality prognostic factor study. These steps include proper recruitment strategy and setting, clearly defined inclusion and exclusion criteria, adequate sample size, definition of startpoint, endpoints and outcomes, strategy for prognostic factor measurement, and adequate follow-up period with description of the reason of possible drop-outs (264).

A participant sample is required from the target population and setting. Ideally, a consecutive sample or a random sample from consecutive patients should be chosen in order to avoid selection bias, so that the final sample will be representative of the population intended to be analyzed.

The size of this sample is also very important in prognostic factor studies because usually, for a prognostic factor to be important a large enough effect estimate is required (e.g. relative risk > 1.5 for a binary factor in exploratory studies), so that after adjustment for other established factors in confirmatory studies this effect has a chance to remain significant. Consequently, most often for detection of such large effect estimates, large enough sample sizes are required. This is usually referred as the *power* of the study, that is, the likelihood that a study will detect an effect, when there is an effect to be detected. Generally, a power of $\geq 80\%$ is considered good enough for a study, but in prognostic factor studies an even greater power is usually required.

Sample size calculations are available in most software statistical packages and are different for continuous and binary outcomes. The calculation is based on functions which require the specification the size of true prognostic effect one wishes to be able to detect, the type I error, the desired statistical power, and the standard deviation of the factor (282-284). However, the main concern is that for confirmatory prognostic factor studies an adjusted and not an unadjusted effect estimate should be in focus. Adjusted effect estimates are typically smaller than unadjusted ones, since they also take into consideration the effect estimate of other already established factors. So, the sample size in confirmatory studies should also take into consideration such correlations and be

larger than that required for unadjusted prognostic effects (exploratory studies). There are several functions and formulas in literature, so that the population sample size can be calculated (285, 286).

2.6. Analysis

There are several steps that need to be considered from the beginning of the study for the achievement of a high-quality study analysis. The study must be carefully planned and the researchers must specify the primary objectives in relation to prognostic factors and outcomes. The secondary objectives need also to be clearly stated. The objectives of the studies should not change during the study analysis in search of significant associations. The prognostic factors of interest need to be measured at the start-point, together with any other important prognostic factors that will be used for adjustment.

The statistical model that will be used should be suitable for the outcome of interest. For example, a logistic regression model should be used for a binary outcome and a Cox regression model for a survival analysis or time-to-event outcome. Although much easier, continuous variables (prognostic factors) should not be dichotomized but examined on their continuous scale (287, 288). There are several methods available for investigation of continuous variables in prognosis research, including “fractional polynomials” for limited information and simple functions, and “splines” for more extensive data and more complex functions (289, 290). In addition, researchers should focus mainly on reporting effect estimates and confidence intervals and not just the p-values (291).

The individuals lost to follow-up should be clearly stated, as well as the reasons for drop-out and the specific drop-out time. Furthermore, any missing data during the follow-up period should be handled accordingly using any of the available methods, such as the multiple imputation method for missing data. Univariate analyses should be avoided, and the prognostic factor of interest should ideally be adjusted for other already established prognostic factors. Many exploratory studies consider only unadjusted prognostic effect estimates in univariate analyses. These studies should always be accompanied by confirmatory studies (or analyses within the same study), investigating whether the new prognostic factors add any prognostic value over already established ones, after appropriate adjustments (291). The known factors that are used for adjustments should be prespecified in the study protocol based on existing medical literature. All candidate factors should be used for adjustment, and not only those that were significant based on p-values from univariate analyses performed within the same study. Treatment should also be included as an adjustment factor in cohorts where treatment varies across participants (292, 293).

For survival analyses, there is always the potential that the hazard ratios of prognostic factors may vary over time, and this should always be taken into consideration during adjustments (non-proportional hazards) (257). Finally, many prognostic factors tend to be systematically measured with error. An example is blood pressure. This error is affected by time and tends to be larger when measurements are repeated over some time period and not consecutively. This systematic error should sometimes be taken into account and not always be ignored (294).

2.7. Reporting

Full reporting is needed for all prognostic factor studies and not only for promising ones with potentially significant associations. High-quality, transparent reporting of all prognostic factor studies, even of non-significant results, promotes research as data could be used in systematic reviews and meta-analyses by other researchers. The REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) checklist guideline provides recommendations for high-quality reporting of prognostic factor studies in oncology. However, this guideline is also applicable in other diseases. It is a valuable reference of issues to consider when designing, conducting, and analyzing prognostic studies (292). In brief, the following steps have to be considered:

- **Introduction:** Statement of the prognostic marker examined, objectives, and hypothesis.
- **Materials and methods:** Description of patient characteristics, inclusion and exclusion criteria, and treatments. Description also of specimen characteristics and assay method when available, study design (prospective, retrospective), follow-up period, clinical endpoints, candidate variables, sample size, target power, and effect size. Specification of all statistical methods used, variable selection procedure, and handling of missing data.
- **Results:** Description of patient flow and reasons for exclusion. Report of demographic characteristics, prognostic variables, and number of missing values. Presentation of univariable analyses showing the relation between the prognostic factors and the outcome, including all the variables analyzed. Performance of multivariable analyses with report of effect estimates and confidence interval for at least the prognostic factor and the final model. All results should be provided regardless of statistical significance, promoting further research.
- **Discussion:** Interpretation of the results in context of the hypothesis and comparison with other relevant studies. Discussion of study limitations and implications for future research.

PROGNOSTIC MODEL RESEARCH (PROGRESS TYPE III)

1. PROGNOSTIC MODELS

1.1. Definition

A prognostic or risk prediction model is a mathematical function that relates certain risk factors (covariates) to the probability (risk) of a particular outcome happening in a well-defined population and within a specific time period (295, 296). Prediction models are more and more used in modern medicine to guide clinical decision making (69).

Risk prediction models are used in all fields of medicine and especially in cardiovascular disease and cancer. Known models for cardiovascular disease are the Framingham Risk Score (297),

SCORE (298), CHA2DS2-VASc Score (298) and HAS-BLED Score (299), and for cancer are the Nottingham Prognostic Index (NPI) (300), Adjuvant! (301), The Bach Model (302), and CRC-PRO (303).

The scope of risk prediction models is to guide and aid in clinical decision making, by providing physicians with objective probabilities for specific outcomes based on individual patient characteristics (255, 304, 305). However, their independent use away from professional clinical reasoning could prove misleading (305).

There are still many prognostic models being developed in medical literature but often examining the same outcome as some already established models (306, 307). The recent technological advances and improvement of machine learning methods and artificial intelligence has led to development of more sophisticated and more “intelligent” data-driven models for more complex outcomes (308, 309). However, many published prognostic models have been developed using poor methods and others provide poor reporting, both of which can compromise the reliability and clinical relevance of models, prognostic variables, and risk groups derived from them (310).

2. MODEL DEVELOPMENT

2.1. Source of Data and Study Design

The participants used for model development should share a specific characteristic (predictor), suspected to be associated with a specific disease (outcome) (296). Prediction model development does not usually rely on primary data collection, since this would require a high amount of time and costs, considering that available data are usually already available in medical literature. The main study design that is suitable for model development is the cohort study design and specifically prospective cohort studies that allow optimal follow-up of predictors and outcomes. Randomized clinical trials (RCTs) and nested case-control studies are also included.

However, RCTs suffer also from some limitations that should be taken into consideration. First of all, there are usually eligibility criteria for participants and study centers, often excluding entire patient groups, and thus, there is uncertainty in extrapolating results to general population without validation studies (311, 312). Other limitations include missing consent of patients for data use in prognostic modelling, small sample size of RCTs, and relative short follow-up of participants (313).

Retrospective and nested case-control studies are also eligible designs but this does not apply for case-control studies that are only suitable for finding the independent predictors of a particular outcome and not for estimation of absolute risks (295). On the other hand, retrospective studies may have longer follow-up period than prospective studies but they also suffer more from sources of bias and confounding (314). Nested case-control studies are particularly useful for more rare diseases and outcomes and minimize biases compared to case-control studies, but suffer from reduced power due to sampling of controls, a fact that is also true for full cohort studies (315).

2.2. Outcomes

Outcomes should be clearly defined and be directly related to characteristics (predictors) of study participants. The duration of follow-up should also be defined, as long as the methods of outcome ascertainment. Since outcomes for prognostic studies often include mortality and disease incidence or recurrence, cohorts with an adequate follow-up period should be chosen (295). Ideally, outcome ascertainment should be blinded to predictors in order to avoid possible bias and maximize the validity of the results. This is even more necessary for prognostic modelling based on RCTs (316).

Ideally, prognostic studies should focus on clinical outcomes relevant to the patients, such as incidence, recurrence, or remission of disease, mortality, disease or treatment complications, pain, response to treatment, or quality of life. Intermediate and self-reported outcomes such as hospital stay, self-efficacy, emotion-scales, and social limitation, are usually not helpful. These outcomes should be measured without knowledge of the predictors under study to prevent bias. Blinding is also necessary for cause-specific mortality as knowledge of predictors might influence assessment of outcomes, but not for all-cause mortality (296).

2.3. Candidate Predictor Variables and Correction for Optimism

Candidate predictors are independent variables that are suspected to be linked to the study outcome. Initially, usually many such potential variables are chosen to be studied but that does not mean that all these predictors will be used in the final prediction model, since the most important variables are then narrowed down with various prediction selection methods. The initial candidate predictor list is generated a priori, usually based on systematic review of available medical literature and expert opinion. These can include clinical, laboratory and imaging tests, social/demographic, and disease characteristics (295).

The required number of patients is difficult to be estimated due to the multivariable character of prognostic research (296). Since the initial list with candidate predictors can be too large, there is a simple rule in statistics, that at least 10 events per variable (EPV) are required for one predictor to be fitted at the model. For example, if we have a cohort population sample with 30 outcomes (deaths/disease incidence) observed through follow-up then up to 3 risk factors (predictors) could be fitted in the multivariable model to avoid overfitting. However, many researchers do not support this hypothesis and propose that less than 10 EPV may be sufficient in many cases, and that other factors may play a more important role for model development than the total number of events per predictor (317-319).

When examining the predictive performance of a model in the same dataset used for its development, the estimates of calibration and discrimination are usually misleading (optimistic), primarily due to overfitting of predictor effects to the dataset at hand. Many of developed models in medical literature do not account for overfitting and usually have too small sample sizes relative to the number of predictors studied, do not use shrinkage methods, and do not provide optimism-correction statistics.

A large sample size is the best step in reducing potential for overfitting and optimism. The “events per variable” method discussed above is not always enough to avoid overfitting. To address

this Riley et al. suggested the introduction of a uniform shrinkage factor of ≥ 0.9 in the calculation of the desired sample size and provided a calculation formula (320). In addition, besides choosing an appropriate sample size, predictor effect estimates should also be corrected for optimism. This is achieved with penalization procedures where a slight bias is introduced to the model to reduce mean-square error in model's outcome predictions. This is usually described as Stein's paradox (321).

2.4. Final Model Development – Selection of Predictors

Unfortunately, it is not always obvious which predictors are suitable for the final prediction model. There is not a unanimous method for identifying the appropriate predictors. The two methods most widely used are the stepwise regression (including backward elimination and forward selection) and the full-model method.

The key concept behind the stepwise regression process is adding and removing candidate predictors in the final multivariable model, in a stepwise approach, until there is no reason to add or remove any other variable. This is often necessary when a large number of predictor variables are under investigation. There are two ways to achieve this. The backward elimination and the forward selection approach (295). In the backward elimination approach all candidate predictors (independent variables) are considered in the multivariable model and each one of them is then gradually eliminated based on some predefined significance cut-off levels (p-values), using some statistical tests for comparing regression models. Tests commonly used for this reason are the Likelihood Ratio and the F-test. These tests run a sequence of analyses removing or keeping predictors based on predefined p-values. For example, if for the multivariable model cut-off p-value is 0.05, and after the removal of a predictor in a sequential run the new value is 0.06, the variable is maintained into the model and not eliminated. In the forward selection approach, the multivariable prognostic model is built-up from an empty equation by adding predictors based on their theoretical importance. The independent variables can be added in the model one at a time or in groups (block-wise selection). The stepwise process means that in both methods (forward selection or backward elimination), the contribution of each variable in the final model is in every step, re-evaluated.

In full model approach all examined independent variables are forced into the model without eliminations. This aids in avoiding several biases and may be useful when there is a reasonable number of predictors, but cannot create viable models for every-day clinical practice when this number is too large. In any case, no matter which method is chosen, it is recommended to avoid removal of variables if they are not significantly associated to the outcome based only on univariate analyses, since these analyses do not take into consideration confounding of the independent predictors into the final multivariable model (322, 323). Furthermore, continuous variables should not be transformed into binary variables or into categories to avoid loss of information and residual confounding (288).

2.5. Weighing of Predictors

In the final multivariable analysis, each predictor in the equation is multiplied by a coefficient. This number estimates the change in the mean response per unit increase when all other predictors are kept constant. As a result, each predictor in the final model is mutually adjusted for the other predictors. These coefficients weigh the impact of each predictor on the estimated outcome probability. They are calculated from a set of samples (training set) for which both the predictors and the outcome are known. Equally important is the calculation of the baseline hazard, that is the probability of the outcome if all predictors equal to zero. For logistic regression the baseline hazard equals to the model's intercept (constant). On the other hand, Cox models have no intercept and calculating the baseline hazard is not necessary (295, 324).

2.6. Missing Data

Unfortunately, missing data are common in prognostic research. The larger the number of missing values, the larger the potential influence on final study results, since missing data are, to some extent, almost always related to other variables and to the outcome under investigation. Participants with missing data should not be excluded from the study, because in this way the effective sample is reduced, valuable information is discarded, and the predictive performance of the final model is also negatively affected. A systematic error can also be created as the final participants will not consist a random sample, but a sample of individuals without missing values. This could affect the predictor-outcome associations and limit the generalizability of the model (295, 324).

The issue of missing values is most commonly addressed using imputation techniques, and especially "multiple imputation". In the multiple imputation technique, using data from individuals without missing values, the so-called multivariable imputation models are created. These imputation models are then applied to every individual with a missing value and these values are estimated and filled-in based on the individual's other observed (not missing) values. In this way, a new full dataset is created containing both observed and calculated values, often called imputation dataset. This process is performed multiple times (e.g. 10 or 100), creating different imputed datasets. Then a prediction modelling analysis is performed for every dataset, and finally, using standard procedures, these multiple analysis results are averaged to an overall result with the corresponding standard errors or confidence intervals. However, if a variable is systematically missing for many participants it is better to omit this variable and not use it for the creation of the final prediction model (324-326).

3. ASSESSING MODEL PERFORMANCE

There are several methods available to assess the performance of risk prediction models. Traditional measures include the c-statistic for model discrimination, and the Homer-Lemeshow goodness-of-fit test, calibration-in-the-large, and calibration slope for model calibration. For overall model performance, the most common performance measures are the explained variation (R^2) and the Brier Score. In addition, new measures have been proposed for assessing model discrimination

and calibration after the addition of a new predictor, including the net reclassification improvement (NRI), and the integrated discrimination improvement (IDI) index (327).

3.1. Discrimination (c-index, AUC)

Discrimination refers to the ability of the risk prediction model to identify individuals who develop the outcome/event from those who do not, and rank them from low to high risk. Discrimination can be estimated for both, survival models using the c-statistic or c-index, and for logistic models using the similar area under the receiver operating characteristic curve (AUC or ROC) (295).

The c-statistic, c-index, or concordance statistic, is the probability that a random individual who experienced the event will get a higher score using the specific risk prediction model than another random individual who did not experience the outcome (328). The c-index for survival models equals to the AUC for logistic models and can take values from 0.5 to 1. A model with a c-index equal to 0.5 means that the model is no better than chance in predicting an outcome. Values near 0.5 describe poor model performance (discrimination power), while values above 0.7 or even better above 0.8, indicate a strong model (324). A value of 1 means that the model is capable to predict the event in every individual examined. The c-index is often paired with its confidence interval. When this interval includes the 0.5 the result is not significant.

The c-statistic is not used very often since the ROC curve gives also information on sensitivity, specificity and accuracy. The ROC curve is a plot of the true positive against the false positive rate. The accuracy of the prediction model is shown as the area under the curve. The larger the area the greater the accuracy of the model. Furthermore, we can estimate the model accuracy by the distance of the graph from the diagonal. The closer the graph to the diagonal the less its predictive accuracy. As a result, the AUC is also an easy method to compare two different prediction models built on the same setting (Figure 2) (329).

Other measures less commonly used for discrimination include the NRI and IDI (mainly used when a new predictor is added, discussed later), the D-statistic, SEP and PSEP, K-index, and the decision curve analysis. The Log-Rank test, although frequently used alongside a Kaplan-Meier survival curve, does not give an estimated of discrimination between risk groups, but is used to test the difference in survival between these groups. The use of p-values should generally be avoided as they are not useful for discrimination purposes (310, 330).

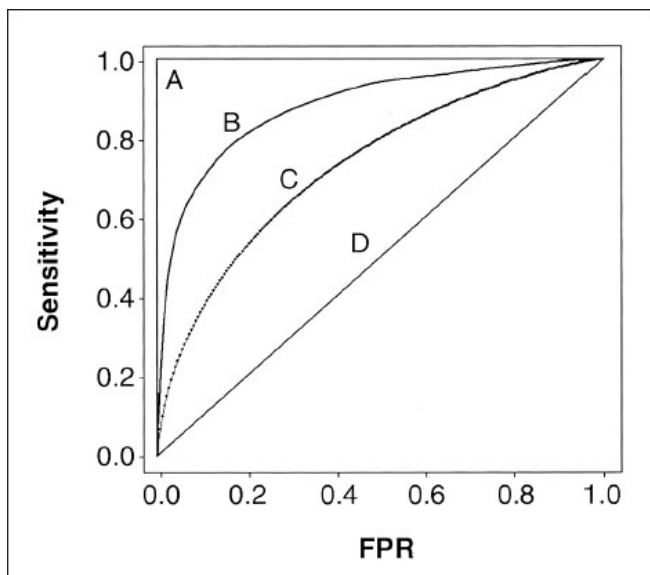


Figure 2. Four ROC curves with different values of the area under the ROC curve. A perfect test (A) has an area under the ROC curve of 1. The chance diagonal (D) has an area under the ROC curve of 0.5. ROC curves of tests with some ability to distinguish between those subjects with and those without a disease (B, C) lie between these two extremes. Test B with the higher area under the ROC curve has a better overall diagnostic performance than test C.

3.2. Calibration

Calibration refers to the agreement between the expected probability for an event as estimated by the model, and the observed event frequencies. As a result, calibration describes the absolute risk of an event. Calibration is usually reported using calibration plots of observed risk of an event against predicted risk using the model (295).

Calibration is commonly assessed using the Hosmer-Lemeshow goodness-of-fit test. It is computed by dividing the sample into arbitrary groups and using the chi-square test to compare the expected versus the observed events in every group. This results in a p-value that defines the calibration performance. Other methods to estimate the calibration of the model is the Calibration-in-the-large measure which is computed as the difference between the mean observed risk and the mean predicted risk, and the calibration plot which is calculated by regressing the observed outcome frequency on expected probabilities (Figure 3). Although less commonly used, the calibration plot is more valuable than the Hosmer-Lemeshow test, as the regression model provides more information (slope, confidence intervals) than the single p-value provided by the Hosmer-Lemeshow test and it does not depend on grouping of individuals (327, 331). For grouped data, a χ -squared test can also be used to compare observed and predicted numbers of events (332).

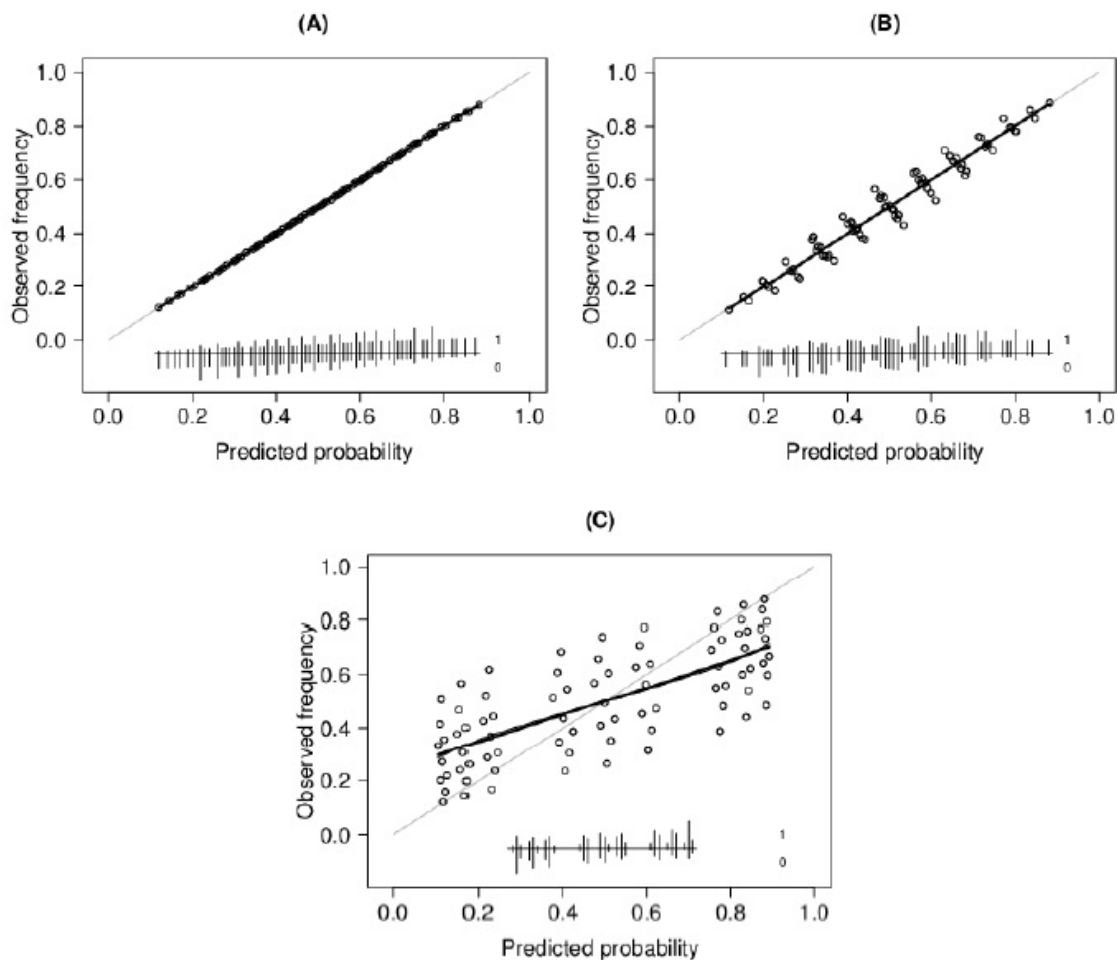


Figure 3. Calibration plots illustrating (A) strong calibration, (B) moderate but not strong calibration, (C) miscalibration.

3.3. Overall Model Performance

The overall model performance refers to the difference between the predicted and the actual outcome and as a result has both calibration and discrimination aspects. The explained variation (R^2) is the most common test for continuous outcomes since it is a logarithmic scoring rule. On the other hand, the Brier Score is used for binary outcomes and assesses the accuracy of a model. It takes values from 0 for a perfect model to 0.25 for a poor performing model with a 50% incidence of the outcome. However, these measures are less commonly used than the previously mentioned calibration and discrimination measures (327).

4. MODEL VALIDATION

4.1. Internal validation

After model development, the model may be used for predicting the examined outcome in new individuals. The generalizability of the model is assessed using validation techniques (333). In internal validation, the model performance is examined using the same dataset used also for the development of the model. There are two main methods of internal validation. In the simpler one, the original population sample is divided into two separate parts (often 2:1) and the first and usually larger part, often called ‘training set’, is used for model development, and the other part is used for model validation, that is for assessing the performance of the model in the validation sample. However, this method is not ideal since it wastes valuable data that could have been used for model development. Additionally, this approach tends to give optimistic results because the two datasets are very similar (332). On the other hand, the random split of the sample may create very different groups that can produce very different results (295).

On the other hand, bootstrapping is a statistical method in which many different random samples are computed based on the original study sample, using several random sampling techniques. These random samples have the same size as the original but with different patient characteristics. Usually 100 or 500 samples are created and for each model every step of the model development stage is repeated. In that way a new c-statistic is created for every new model. Comparing the average of all these new c-indexes with the original c-statistic provides an estimation of the optimism of the model and a measure of how it will perform in a different setting. In addition, with bootstrapping a shrinkage factor is created which can be used to adjust the regression coefficients to avoid overfitting of the final model (295, 334).

4.2. External validation

The performance of a prediction model is usually lower when applied to a population other than the population used for model development. The aim of external validation of a model is to demonstrate that the model performs equally well to similar but different individuals in a setting other than the model development one. The more different the new setting, the more generalizable the model to real life circumstances. On the other hand, internal validation offers only a small degree of generalization and transportability since it only uses data from individuals included in the model development sample (335).

Although more and more prediction models are constantly being developed, and especially in the fields of cancer and cardiovascular disease, without external validation studies the model rarely reaches a clinical application. In addition, even when available, poor conduction and reporting of external validation studies is also very common in medical literature. External validation refers to applying the model from the development study to a new population and assessing its performance, that is calibration and discrimination, to the new setting as well as comparing this performance to the model performance in the original model development study (336). The main types of external validation include temporal, geographical and setting validation.

In temporal external validation, new studied individuals come from the same setting, institution or hospital as the development study, but in a different time period. In general, the same inclusion and exclusion criteria apply. In some studies, a part of the population sample is not used for model development and is later (in some years) used as an external validation sample. In a way, this is the type of external validation closer to internal validation (splitting data method). However, temporal validation is a prospective evaluation of a model, independent of the original data and development process (332).

On the other hand, geographical external validation refers to a completely different institution, hospital or country where different inclusion and exclusion criteria apply for the population sample. This type of validation can also be performed using data from the original development study, especially in multicenter studies where data from a center or country can be used for model development and other data from a different country for external validation.

Setting validation refers to validation of the developed model in very different individuals than those for which the model was originally developed for. For example, a model for healthy individuals or general population may be used to predict the same outcome in coronary artery disease patients or cancer survivors (335).

In another classification, external classification techniques can be broken down according to investigators. In this classification, temporal validation refers to same investigators in a different time period, spatial validation to the same investigators in a different study center and fully external validation to different investigators and different centers (337). It has to be noted that external validation techniques can sometimes be combined. For example, an external validation study can be at the same time both geographical and temporal, increasing the degree of generalizability and transportability of the model.

5. ADJUSTING AND UPDATING A MODEL

5.1. Updating a Prediction Model

Most of the times, applying a risk prediction model to new individuals, outside the data development dataset, results in lower model performance. Usually, the more different the new population sample than the original one, the lower the performance of the model. For example, a risk prediction model developed for general population will perform lower in hypertensive patients in another country (setting and geographical validation), than using the same model in the same sample 3 years later (temporal external validation). When the performance is considerably lower,

researchers tend to develop a new model for the new individuals, than adjusting an already developed one. This leads to substantial loss of information data used in the original study.

However, there are many different statistical methods that can be used in order to update or adjust a risk prediction model, so that data from development and external validation study can be combined (335). These methods include:

- Adjustment only of the baseline hazard risk (intercept), for logistic models,
- Adjustment of all regression coefficients (weights) by one or more adjustment factors (predictors), in case one or more predictors perform much differently in the validation sample,
- Re-estimation of all weights of the model using only data from the validation sample,
- Stepwise selection of additional predictors, not included in the original model.

5.2. Adding a New Predictor

Described measures of discrimination such as the c-statistic and ROC curve, are not capable of detecting minor changes in predictive performance of a model when a new predictor or biomarker is added to an existing prediction model (338, 339). For this reason, some newer measures of discrimination have been created that include, the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI).

The NRI is an index that describes how a new model reclassifies individuals compared to an older model (340). The NRI quantifies individuals that are reclassified to higher or lower risk categories after the addition of the novel risk factor. This reclassification is based on predetermined risk groups. The correctly reclassified case moves to a higher risk category while the correctly reclassified non-case moves to a lower risk category after the addition of the new predictor (341). There is also a method for reclassifying individuals using NRI that does not require predefined categories (342).

The IDI describes also the capacity of a new marker to predict an outcome when added to an existing model (343). On the other hand, the IDI is not based on pre-specified groups like the NRI. It describes the improvement in the average sensitivity of the model after the addition of the new predictor (341).

6. MODEL APPLICATION

6.1. Model Reporting

The final model can take many different forms but the regression equation should always be available (risk factors with coefficients and intercept for logistic models), so that future researchers can easily apply the model to a new population sample. The model can be available as:

- The original regression equation,
- A simple risk score (87, 299),
- An online calculator (for example, riskcalc.sts.org/),
- Risk chart/table (297, 298),
- A nomogram,
- A scoring rule.

Interpretation according to cut-off levels should always be available, as long as guidelines for application of the achieved score in clinical practice. The original study of the model must be easily accessible with its respective reference. Sometimes, a simplified version of the model is available that is created from rounding of regression coefficients to absolute numbers. As a result, this simplified version has lower performance due to loss of valuable information and should always be accompanied by the original model and a comparison of their predictive performance. (e.g. AUC of the simplified vs the original model).

6.2. Impact Studies

The next step in developing, validating (internally and externally) and possibly updating a model, is assessing its impact in every day clinical practice. A simple and properly reported model can have an impact on behavior of physicians and other care-givers, on patient management and outcomes, and in cost-effectiveness of health-care systems. This impact can be studied in prediction model impact studies (344).

Impact studies require the presence both of an intervention and a control group, as a population for comparison. While the prediction model is available to doctors and individuals to guide treatment and clinical decision making, the control group is managed using usual care without guidance by the prognostic model or the relevant risk factors. In impact studies, there are two approaches available for presenting the prediction model in the intervention group. In the assistive approach, there are only probabilities of the outcome available to professionals and individuals, while in the directive approach there are also guidelines and recommendations for the treatment or decision plan.

There is a variety of different study designs for the conduction of an impact study. In *cluster randomized trial* design individuals or professionals are randomly assigned to intervention or control group and the outcomes are compared between the two groups. In *stepped-wedge randomized cluster trial* design, all clusters are introduced to the model at random time points after using conventional treatment for some time. In this way, all clusters (e.g. hospitals) perform both as intervention and control groups for some time and the outcomes are compared.

A similar, but non randomized design, is the *prospective impact study* design, where individuals are first treated under usual care and then the prognostic model is presented, and the change in clinical outcomes is assessed. In *decision analytic modeling*, data from well-conducted external validation studies on a prognostic model and data from randomized clinical trials and meta-analyses before and after publication of the model are used to assess the impact of the model on clinical decision making and outcomes.

In *cross-sectional impact studies*, physicians are randomly introduced (or not) to the model and their decisions are compared without follow-up for assessment of the outcome. Finally, in the simple *before and after* study approach, professionals are asked to offer treatment options to a specific individual, before and after introduction to model outcome probabilities (255, 335).

PREDICTORS OF TREATMENT EFFECT AND STRATIFIED MEDICINE (PROGRESS TYPE IV)

1. Definition and Application

Although, most treatments are expected to have beneficial effects on average, the possible harm and side effects should always be taken into account. Predictors of treatment effect and stratified medicine are two closely related terms. A predictor of treatment effect can be any type of factor (patient characteristic, symptom, biomarker, medical test) that is associated with the response (benefit or harm) to a specific intervention. The term stratified medicine refers to targeted treatment of specific patient groups (or strata), according to individual patient characteristics or established risk factors (predictors of treatment effect), guided by previous prognostic studies (256). A typical example of stratified medicine is the clinical practice guidelines published by several medical associations (e.g. European Society of Cardiology, American Diabetes Association etc.), where most clinical decisions and treatments are based on a benefit/harm ratio and on previous prognostic research and clinical trials. Even in cases where clinical trials are non-existent or unethical to be conducted, guidelines are based on expert opinions according to established medical literature and knowledge. Thus, stratified medicine categorizes individuals to groups and offers the best medical treatment for each group (345, 346).

Individuals at higher risk tend to gain more benefit from specific therapies. Using stratified medicine based on absolute risks for a disease, enables clinicians to offer these treatments to these high-risk groups. For example, the use of aspirin has shown a greater benefit in secondary prevention of patients with previous myocardial infarction or stroke than in asymptomatic individuals for primary prevention. In this lower risk group, the potential benefit is balanced to some degree by the bleeding risk related to aspirin use, and as a result it is not recommended for primary prevention in clinical practice guidelines (class III, harm). The impact of a predictor of treatment effect will generally vary depending on the baseline risk of the outcome (prognosis). People with the highest absolute risk tend to gain the largest benefit (or less harm) from a particular treatment.

On the other hand, stratified medicine may also be based on specific patient characteristics that have been linked with a positive response to treatment. A simple example is the lipid blood levels that guide the treatment with statins or the glucose levels for insulin treatment. In addition, in the last decades, many genes and receptors have been identified that predict the response to treatment and are targeted by special monoclonal antibodies. This approach has found many applications in cancer and other chronic diseases, but is also a key factor for research of future treatments (347-349).

2. Importance of Stratified Medicine

Stratified medicine is the cornerstone of well-documented, evidence-based, modern medicine. It is based on prognostic studies and as a result prognosis research plays a fundamental role for the stratification of patient groups and individualized treatment according to their characteristics. First of all, prognosis research highlights patient high-risk groups that are more likely to benefit from pharmacological or interventional treatment, in contrast to other lower-risk groups where a more conservative approach may be advisable. In this way, patient categories (strata) are created that make clinical decision making easier and evidence-based.

Secondly, by the identification of the above-mentioned high-risk groups, prognosis research also identifies the individual patient characteristics that act as risk factors and define the type of treatment strategy. This fact creates further research opportunities for better treatment strategies, discovery of more sensitive tests to identify these characteristics (e.g. blood tests, imaging tests), and finally approaches for individualized treatment according to DNA and mRNA-based research or by the use of monoclonal antibodies targeting specific cell or proteins (256).

When a factor predicting a different treatment response has been identified, the next step is its evaluation in primary, exploratory, randomized clinical trials or even more commonly in secondary analyses of other trials or in systematic reviews and meta-analyses based on this hypothesis. In this way, the outcome of individuals with the characteristic under study are compared to that of other patient groups under the same treatment. On the other hand, cost-effectiveness studies are also required for the assessment of these stratified treatment approaches, where prognosis estimation is also a prerequisite (339, 350).

3. Study designs

There are several study designs for the identification of predictors of treatment effect. However, the conduction of such studies is quite rare in medical literature. The treatment-only design is based on randomized trials where the effectiveness of a treatment is compared to no-treatment or another treatment. In test-positive only design the study is only conducted using individuals that test positive for a specific characteristic. However, whatever the result of a specific treatment it is uncertain what the benefit/harm ratio will be in individuals without this specific trait. Finally, in non-randomized comparative studies patients with the same startpoint are offered different therapies seeking predictors of treatment effect and followed-up for specific outcomes (257).

Unfortunately, most randomized clinical trials are not designed with sufficient power to detect treatment effects, since most such interaction are usually small and frequently missed (type II error). It has been estimated that clinical trials that could possibly identify small treatment effects, would require at least four times the sample size required to test the main outcome making trials even more costly and time consuming (351). As a result, the only really eligible study design to identify predictors of treatment effect remain the meta-analysis of large-scale observational data.

4. Limitations

Prognosis research and consequently stratified medicine suffers from several limitations also common in most fields of medical research. First of all, exploratory data may identify positive prognostic factor-outcome associations that may prove non-significant when assessed in different studies or in systematic reviews and meta-analyses. This is commonly referred as false positive finding or type I error. On the other hand, some truly predictive associations may be missed if the study is not designed with the appropriate statistical power to identify this interaction. This is the type II error or false negative finding (352, 353).

Both of these errors can be avoided by proper study design with adequate sample size, reporting of results regardless of significance, labelling exploratory studies as exploratory, assessment of the value of new factors over already established ones, avoiding dichotomization of continuous variables, and using meta-analyses, preferably of individual participant data and not of final results of the meta-analyzed studies, to increase power of results (256).

PART II

METHODOLOGY

AIMS OF THE STUDY

Our study focuses on systematically seeking, collecting, investigating and evaluating the quality of prognostic studies examining any kind of prognostic factors or prognostic models in relation to survival outcome. The main search base for these studies is the MEDLINE electronic science database. Each study, systematically searches for and records descriptive data and methodologies used and correlates the quality of the studies with the findings.

- Initially, our research focuses on the Framingham Risk Score, a major prognostic model in CVD risk prediction, and studies the extent of its validation and the range of phenotypes and outcomes for which it has been used in medical literature.
- Secondly, we perform a systematic review to identify studies which develop or validate prediction models to estimate adverse health outcomes in patients with already established cardiovascular disease (identify and classify risk models, summarize their performance, collect and summarize comparative information on their relative performance).
- Finally, a systematic review and meta-analysis of the relationship between hypertension, a widely used prognostic marker, and the outcome of cancer (as an example of chronic disease) is conducted.

AIM I

Mapping the expanded use of Framingham Risk Score in the medical literature.

1. INTRODUCTION

FRS is probably the most widely used and validated risk prediction model in medical literature of cardiovascular diseases (297, 354, 355). It calculates the 10-year risk of developing coronary heart disease (CHD) in healthy individuals (general population) without established cardiovascular disease (CVD). Its use is recommended in clinical practice guidelines and has been widely used in primary care practice to determine the indication for cholesterol lowering interventions, intensification of anti-hypertensive treatment, and the promotion of lifestyle changes, including smoking cessation, increased physical activity, and loss of body weight (356-359). However, at the same time, it has been extensively used in the medical literature in a variety of diverse populations and settings as an estimator of cardiovascular risk and as a predictor of future CHD. (354, 360). In the present study, we aimed to systematically map the expanded use of FRS in the medical literature, and to examine its extrapolation in different populations, settings and for the prediction of different phenotypes and outcomes than the ones originally developed for.

Prediction models are vital tools, which may guide clinical decision making, including treatment selection and patient counselling. Therefore, their role in personalized medicine and stratified healthcare is many times crucial (296). Prediction models require careful both internal and external validation in order to assess their performance characteristics (332). However, a model is expected to perform similarly only when used in study populations and for outcomes identical with those originally developed for and validated in (332, 361). Extrapolations of a predictive model performance in different settings is at least inaccurate. In reality, using any predictive model in a new population and/or for different outcomes requires *de novo* recalibration or update as well as revalidation. However, many studies using predictive models seem to perform such extrapolations routinely. The prevalence and characteristics of such extrapolations are not well known.

In this study, we tried to assess the extent of Framingham Risk Score validation, and the range of phenotypes and outcomes for which it has been used in biomedical literature. Based on the extended use of this widely used model, we aimed to obtain empirical evidence on extrapolations of predictive models to uses beyond their intended populations and outcomes.

2. METHODS

2.1. Search strategy

We used the ISI web of Science to identify all the citations to the Wilson et al. 1998 paper (297) where FRS was originally described (last update 1st April 2011, 2,413 citations). We then

limited results to ‘articles’ and to those including the word ‘Framingham’ in the abstract. We ended up with 592 citations that were assessed for eligibility.

2.2. Eligible Articles

Any epidemiological study, which calculated the FRS as a tool for risk assessment or in association to a disease outcome or disease risk factor, was considered eligible. We deemed eligible all study designs (cohort, case-control or cross-sectional) and populations and we used studies irrespective of whether they have actually calculated the FRS as originally described, or just claimed to have used FRS without use of the same coefficients or risk factors as originally proposed. We excluded studies assessing the FRS as an outcome after any kind of intervention, articles on ecological, cost-effectiveness or actuarial analyses, non-English studies, reviews, news and letters.

2.3. Extracted items

From each study we extracted information on publication date, the population studied, the study design (cohort, case-control, or cross-sectional), and the disease risk factor or the outcome with which FRS was associated with. For cohort studies we also recorded whether the aim of the study was to validate the FRS, to examine its predictive performance in relation to a specific outcome, to examine the added predictive value of another risk factor over and above the FRS or for any other reason described. When 2 or more outcomes or populations were examined in one study, those were captured separately.

2.4. Data analysis

We created 4 main different categories according to the study design and the research question of the studies: 1) cohort studies which associate FRS with an outcome or disease risk factor, 2) case-control studies which associate FRS with an outcome or disease risk factor, 3) cross-sectional studies which associate the FRS with a disease or risk factor, and 4) cross-sectional studies which simply calculate the FRS for risk assessment.

Cohort studies and case-control studies were further categorized into studies which examine: 1) both the same population as FRS was developed for (general or healthy) and same outcome as FRS was developed for (coronary heart disease (CHD), including ischemic heart disease, myocardial infarction, coronary artery disease mortality), 2) the same population only, 3) the same outcome only, and 4) both different populations and outcomes than FRS was developed for.

Cross-sectional studies were divided into those examining the same population as the one FRS was developed for and those examining different populations. We also grouped the outcomes or risk factors examined by cross-sectional studies into: 1) clinical cardiovascular outcomes (CHD, CVD or other), 2) non-cardiovascular outcomes, 3) measures of atherosclerotic disease (imaging or other subclinical disease physical measurements), 4) biomarkers (biomarkers of diet, metabolism or obesity, inflammatory biomarkers etc.), 5) components of the FRS, 6) other risk factors and 7) other prediction scores.

We calculated the percentage of studies, which examined the same population and/or the same outcome as FRS was developed for. We examined whether different study designs showed more frequent use of different outcomes to what FRS was developed for and different populations than FRS was developed for. We also investigated whether the proportion of studies that used different populations and/or outcomes changed with publication date. Categorical variables were compared with the chi-square test. To examine the association between publication date and use of outcomes and/or population as originally described for the FRS we used logistic regression.

3. RESULTS

Out of 592 citations, we found 375 articles eligible articles (Figure 1 - Flowchart). Of the 217 excluded, 93 (43%) did not actually use the FRS, 42 (20%) were review articles with no primary data, 28 (13%) were clinical trials assessing FRS as the outcome of interest, 27 (13%) were written in a language other than English, and 6 were cost-effectiveness or decision analyses (3%); the remaining 21 were excluded due to other diverse reasons (simulation studies, study protocols, survey on FRS use, ecological studies, case studies etc.).

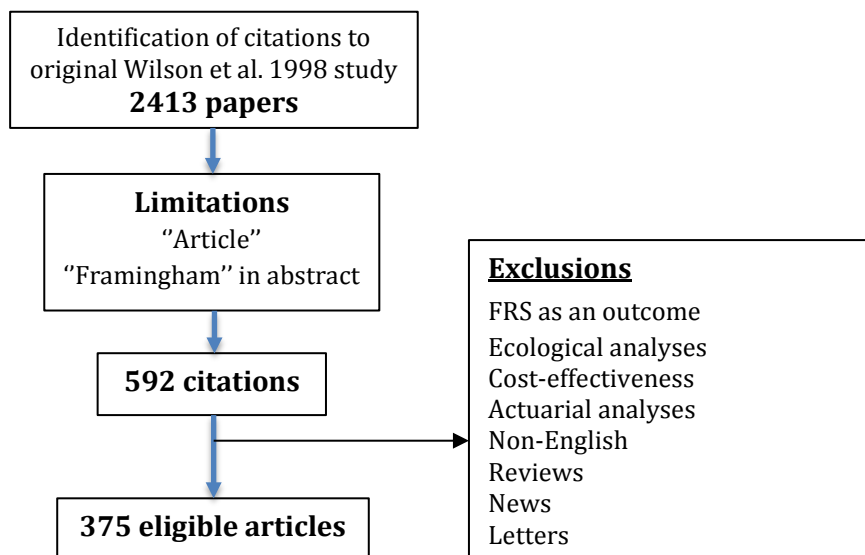


Fig. 1. Flowchart of studies assessed for eligibility.

We extracted 471 different meta-analyses out of 375 eligible papers involving the FRS (see references in Supplementary Appendix). Specifically, out of the 471 meta-analyses, 141 analyses examined associations between FRS and an outcome in cohort studies (30%). The remaining 330 were case-control analyses (N=16), cross-sectional analyses associating the FRS to an outcome or risk factor (N=252), or simply studies calculating the FRS (N=62) for risk assessment in a population.

32% of cohort analyses (N=45) had as a primary aim to externally validate the FRS or to examine its predictive value. The remaining analyses aimed to study the predictive value of another risk factor and calculated the FRS in order to adjust their final analyses (N=88, 62%), or calculated the FRS in order to compare it to other cardiovascular risk scores (N=8, 6%).

3.1. Cohort studies

The outcomes examined by cohort studies are listed in Figure 2. Less than half of the studies (N=62, 43%) examined the same outcome as FRS was developed for (CHD) while a total of 113 analyses (80%) examined outcomes closely related to CHD including CHD mortality and composite CVD outcomes. Other outcomes examined included all-cause mortality (N=18), FRS change (N=7), mitral or aortic valve calcium (N=2) and menopausal age (N=1). The characteristics of the examined populations in cohort studies are represented in Figure 3; 106 (75%) analyses examined the same population as FRS was initially developed for, that is general or healthy population. The rest of the analyses examined populations with CVD or at high risk for CVD (N=21) or populations with different non-CVD diseases (N=14).

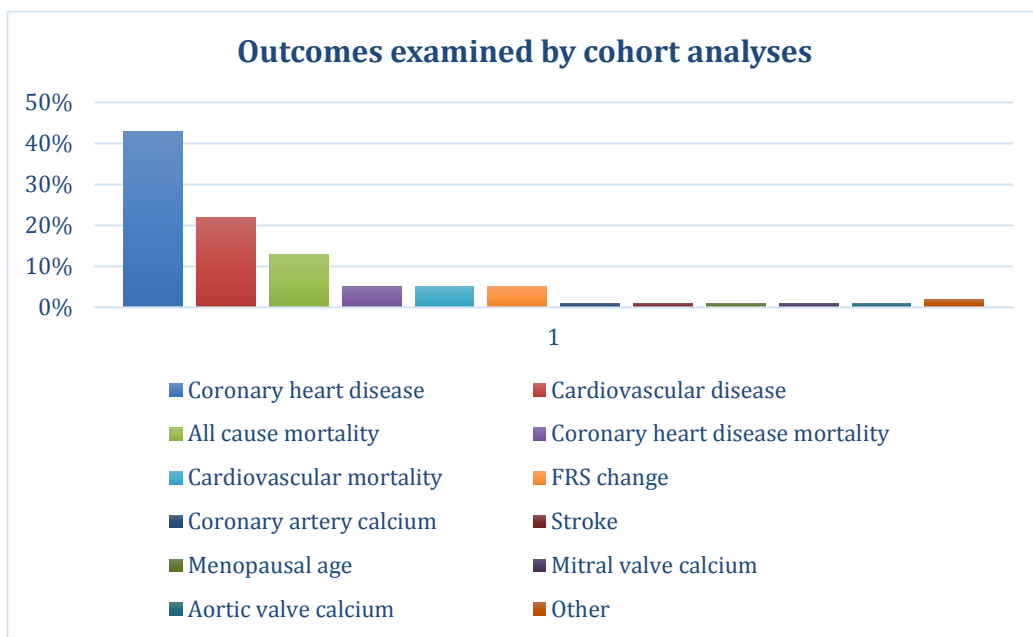


Fig. 2. Outcomes examined by cohort analyses.

Overall, 46 (32%) analyses, examined the same outcome and population as FRS was developed for, 60 (43%) analyses examined the same population only, 16 (11%) analyses examined the same outcome only, and 19 (13%) analyses examined both different outcome and population at the same time. The number of studies examining different outcomes and populations than FRS was developed did not change significantly over time since the original publication of FRS ($p=0.66$).

Among the 45 cohort analyses, which aimed to validate the FRS or test its predictive value, 28 (62%) examined CHD as the outcome of interest and 17 (38%) examined the FRS in general or healthy populations.

Table 1. Risk factors or disease phenotypes examined by 252 cross-sectional analyses that associated FRS with a disease or risk factor.

Disease	n (analyses)
CVD	
Cardiovascular or coronary heart disease	7
Peripheral arterial disease	2
Abdominal aortic aneurysm	1
Non-CVD	
HIV infection	4
Retinopathy	1
Chronic psoriasis	1
Chronic renal insufficiency	1
Nonalcoholic fatty liver disease	1
Depression	1
Osteoporosis	1
Atherosclerosis/subclinical disease	
Intima-media thickness	24
Coronary artery calcium	21
Arterial stiffness	17
Endothelial dysfunction	13
Carotid plaque	9
CT/CT angiography (coronary atherosclerosis)	6
MR/MR angiography (coronary atherosclerosis)	6
Friesinger index	2
Myocardial perfusion	2
Positron emission tomography (coronary flow reserve)	2
Other	6
FRS component	6
Other CVD risk scores	17
Biomarkers	
Diet/metabolism/obesity	42
Inflammation/hemostasis	17
Lipids	6
Liver function	5
Endothelial progenitor cells	1
Erectile dysfunction	1
Ferritin	1
Sphingomyelin	1
Thyroid function	1
Other risk factors	
Fitness	2
Occupational status	2
Caregiving	2
Cisplatin-based chemotherapy	1
Corticosteroid therapy	1
Antipsychotic medication	1
Cannabis use	1
Education level	1
Headache	1
Hysterectomy	1
Literacy skills	1
Parental longevity	1
Quality of parental emotional care	1
Risk perception	1
Shift work	1
Sleep disturbances	1
Smoking cessation program	1
Social mobility	1
Statin use	1
Aspirin resistance	1
Betel quid use	1
Birth size	1
Duration of diabetes	1

Abbreviations: CVD, cardiovascular disease; CT, computed tomography; MR, magnetic resonance; FRS, Framingham Risk Score.

Case-control studies

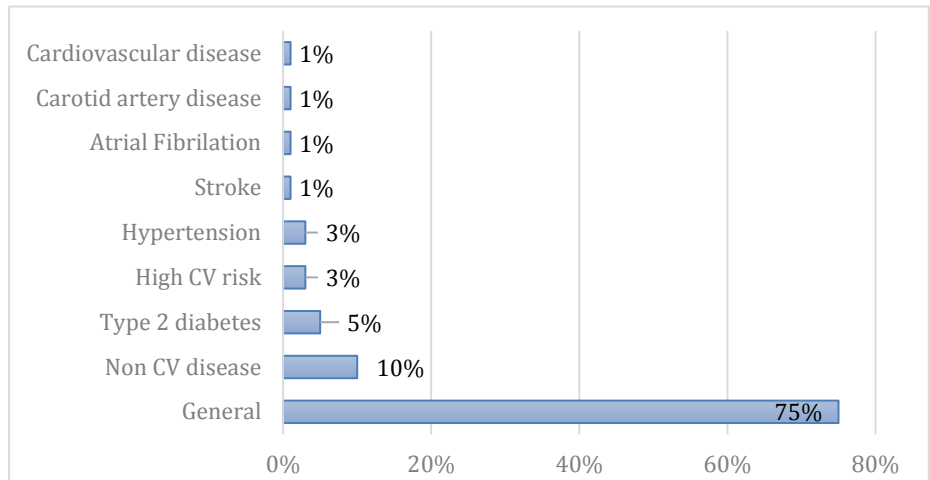
We derived data from only 16 available case-control analyses. Only 6 analyses (37%) compared CHD cases to healthy controls. Another 3 analyses compared HIV-infected patients vs. not infected. Other outcomes explored, all in single analyses, included composite CVD, stroke, acute coronary syndrome, schizophrenia, systemic lupus erythematosus, rheumatoid arthritis and dementia caregiving. There was no difference in the proportion of analyses examining outcomes different that FRS was developed for between cohort and case-control studies (63% vs. 56%, $p=0.62$). All case-control studies examined healthy controls.

3.3. Cross-sectional studies

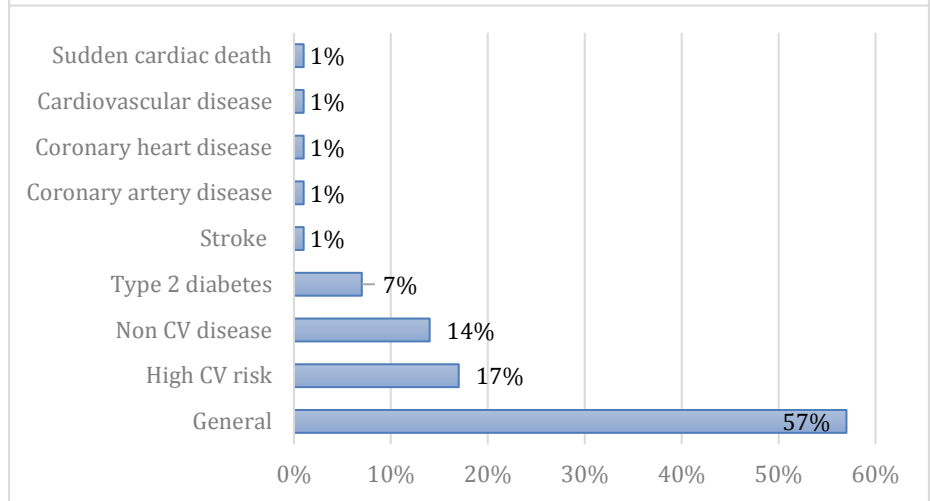
143 (57%) of all cross-sectional analyses ($N=252$), which associated FRS with a disease outcome or risk factor, examined general or healthy populations. The rest of the populations examined were participants at high-CVD risk ($N=44$, 17%), with a disease other than CVD ($N=34$, 13%) and with CVD or diabetes ($N=31$, 12%) (Figure 3). Similarly, the 62 cross-sectional analyses, which calculated FRS for risk assessment, examined general or healthy populations ($N=38$, 61%), populations with disease other than CVD ($N=10$, 16%), high CVD risk populations ($N=8$, 13%), and populations with CVD or diabetes ($N=6$, 10%) (Figure 3). Figure 4 depicts the range of populations with non-CVD disease examined by different study designs. Overall, cross-sectional analyses analyzed general or healthy populations less frequently than prospective studies (58% vs. 75%, $p<0.001$). Once more, use of the same population as FRS was developed for did not significantly change with time since publication of FRS in cross-sectional studies which associated FRS with an outcome ($p=0.49$) or in cross-sectional studies, which simply calculated FRS for risk assessment ($p=0.08$).

A wide range of different risk factors or disease endpoints was examined by the 252 analyses, which studied associations between FRS and a risk factor/disease endpoint in cross-sectional settings (Table 1).

A. Cohort analyses



B. Cross-sectional analyses associating FRS with risk factors or disease endpoints



C. Cross-sectional analyses calculating FRS for risk assessment

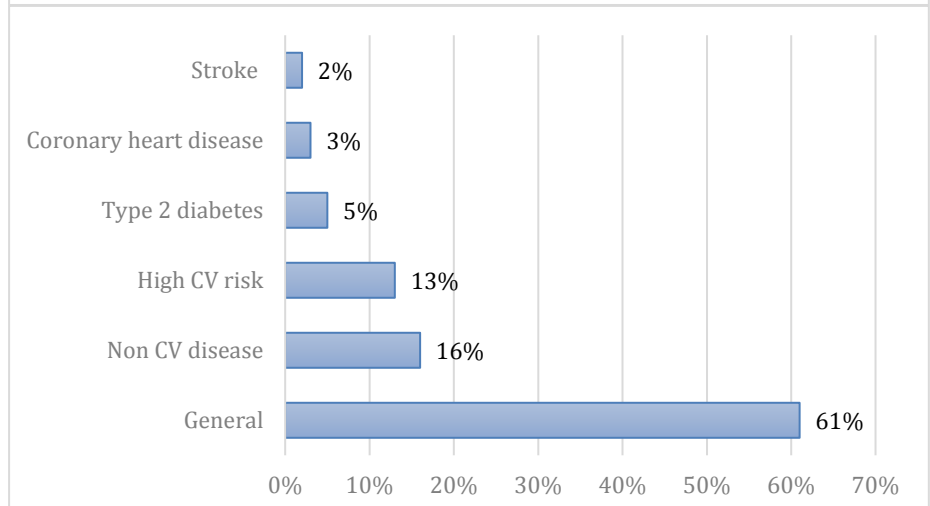


Fig. 3. Characteristics of examined populations in (A) cohorts, (B) cross-sectional analyses associating FRS with risk factors or disease endpoints, and (C) cross-sectional analyses calculating FRS for risk assessment. FRS, Framingham Risk Score.

4. DISCUSSION

Framingham risk score (FRS) is a gender-specific algorithm that was originally developed to estimate the 10-year coronary heart disease risk in healthy individuals. Our review shows that a large number of studies use the FRS in non-validated populations and outcomes. We found that FRS is calculated in populations with CVD or other non-CVD diseases. In addition, it is often used for a variety of outcomes ranging from coronary artery and valve calcium to age of menarche. The predictive performance of Framingham Risk Score in these settings is unknown and non-validated and the conclusions drawn from these studies are uncertain.

Prognostic models are developed and validated to assess risk of disease in a specific population, for a specific outcome and over a specific period of time (324). The prognostic ability of these models in different populations, outcomes and follow-up is unknown and requires recalibration or update in the new specific setting. The same applies also to FRS. Non-association between FRS and other specific phenotypes would not necessarily mean that these phenotypes are not associated with cardiovascular risk and vice-versa. FRS is a risk model which was developed to predict CHD, not necessarily any other phenotypes related or unrelated to CVD.

Similarly, the FRS was developed for healthy populations and is bound to have different prognostic performance in different patient groups and might require recalibration or updating in these different population settings but again the recalibrated/updated model would in essence be a new model requiring external validation. As a result, its predictive value on the range of populations described in our review remains uncertain. In fact, studies have shown the FRS underestimates the risk of CHD in high-CVD risk population (362). Moreover, there is no indication that FRS offers any considerable advantage in populations with non-CVD diseases over other prognostic tools based on biological reasoning or speculative plausibility considerations. As with non-validated outcomes, the presence or absence of association may reflect the different performance of the risk model in very distinct population groups. Consequently, the conclusions of studies using different populations than what FRS was developed for are questionable. We even documented that in a range of cross-sectional analyses, FRS is used as a surrogate of CHD, and is probed for association with wide range of putative risk factors - including even studies correlating FRS against its own components (363-365). Once more, the value of this information is unclear.

There are some limitations in our study that need to be mentioned. First of all, some of the studies might have calculated the FRS without citing the original Wilson 1998 paper (297). However, we do not expect these studies to use FRS more appropriately than the ones included in this review. Moreover, we did not capture whether authors indeed acknowledged the use of FRS in different settings and whether they identified the same potential problems as we have already discussed. However, even then, authors' stance to their own work is very difficult to categorize (366), and it is unclear whether it would offer any real difference if investigators publish doubtful analyses but at least admit in the text that these analyses may be problematic. Finally, we did not assess whether FRS was properly calculated when used, using the same risk factors and coefficients as proposed by Wilson et. al. It seems that the use of FRS in medical literature is suboptimal since even when studies claim to use specifically this specific prognostic tool, they frequently miscalculate it (360). Even when studies use FRS in different populations and/or outcomes than those it was originally developed for, it is difficult to differentiate which of these studies do this with a plan to eventually apply it in clinical practice, or simply to test and validate the its

performance in different settings. However, it is likely that in the end, all these studies may create also misunderstandings and spurious expectations of clinical applications.

To conclude, the FRS is commonly used in the medical literature to assess the cardiovascular risk of populations, to associate the cardiovascular risk with other risk factors and to predict diverse outcomes. However, only a minority of studies calculates the FRS in the same population and for the same outcome as originally proposed. Its performance in different settings is unknown, making the conclusion of many of these studies uncertain.

(The original study was published in the international scientific journal «Journal of Clinical Epidemiology», 2014 May. Epub 2014 Feb 7. PMID:24513280) (367).

AIM II

Risk prediction models for future events in patients with cardiovascular disease: a systematic review of methodology and reporting.

1. INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide. Prediction models are commonly used for the prevention of primary cardiovascular disease (CVD) outcomes. Several models are suggested by clinical guidelines and are used for pharmacological management or lifestyle modification in healthy individuals who are classified as high risk of developing CVD in future (297, 298, 368-379). Nonetheless, despite the fact that the number of people leaving with CVD is rapidly increasing, risk prediction for secondary prevention, in individuals with already known CVD, has received considerably smaller attention. Currently, no single model is recommended for use in clinical practice despite but many models have been proposed in the medical literature. Risk stratification is integral to the management of CVD patients and may significantly influence therapeutic decision-making.

We carried out a systematic evaluation of the methodology and reporting of multivariable prediction models developed to predict the risk of future cardiovascular events in patients presented with previously known cardiovascular disease. We aimed to describe the characteristics of such models including characteristics of those studies deriving risk models and on studies validating existing models.

2. METHODS

2.1. Search strategy

We conducted a broad systematic review following the recently published guidance from the Cochrane Prognosis Methods Group, using the CHARMS checklist, for reviews of studies of prediction model (380). Due to the volume of research in this area, we limited our systematic review on studies that were published within a 10-year time window, and specifically on studies published from January 2004 to June 2013. We selected these dates to capture recent research efforts and we used the same search strategy and pool of studies identified in a recent systematic review on risk prediction models for primary CVD prevention(306). Even though this strategy will not identify all available articles, it produces a systematic sample to be investigated. Also, validation studies published within this framework will capture any significant prediction models that have been developed prior to our search strategy but have been subsequently validated. Our literature search was performed in MEDLINE and EMBASE using search terms to identify primary articles reporting on the development, validation and/or incremental value of models predicting incident CVD, in patients with already established CVD.

2.2. Inclusion criteria

Articles were included if they met our inclusion criteria: primary aim had to be a) development or validation of multivariable risk prediction model or b) examination of incremental value of additional risk factor(s) over and above previously examined risk models for future mortality or CVD events in populations with existing CVD. Multivariable models were defined as including at least two predictors. Eligible outcomes were all cause mortality or any cardiovascular adverse event including CVD mortality, recurrent acute coronary syndrome (ACS), stroke and embolism, revascularization, heart failure (acute or hospitalization) as well as combined outcomes containing any of the above events. Eligible populations were patients admitted with established CVD consisting of known or suspected coronary artery disease (CAD) (e.g. chest pain, angina), ACS, heart failure, stroke and atrial fibrillation and specific groups such as patients with cardiac resynchronization therapy devices. Articles with models predicting in-hospital or short-term outcomes (≤ 30 days), cross-sectional studies and articles including patients undergoing surgery (e.g. patients undergoing cardiothoracic surgery) were excluded. Finally, eligible articles had to report original research (e.g., reviews and letters were excluded) on humans, and be written in English.

2.3. Data extraction, analysis and reporting

We followed the process outlined previously to identify potential eligible papers at the abstract level (306). Full text articles were retrieved and one reviewer screened the full text articles and

extracted data. In case of doubt, a second or third reviewer was involved. We categorized the eligible articles into three groups: development studies, external validation studies (with or without model recalibration) and studies of incremental value (added predictive value of one or more risk factors was examined). A single study could report the development of more than one model or the development and validation and added value of a risk models. In all these cases, we extracted information separately for each model development, validation and added value analyses that was reported. The list of extracted items was based on the recently issued Cochrane guidance for data extraction and critical appraisal for systematic reviews of prediction models (the CHARMS checklist)(380). The full list of extracted items is provided in the supplement.

The following items were extracted from development studies: study design (e.g., cohort, case-control), study population, cardiovascular condition at inclusion (e.g. ACS, stable CAD), geographical location, outcome, prediction horizon, modelling method (e.g., Cox proportional hazards model, logistic model), method, if any, of internal validation (e.g. bootstrapping, cross validation), number of study participants and CVD events, number and type of predictors, model presentation (e.g. full regression equation, risk chart), and predictive performance measures (e.g. calibration, discrimination).

For articles describing external validation of a prediction model we extracted information on the existing model (author, publication year, journal, acronym), the type of external validation (e.g. temporal, geographical), whether or not the validation was performed by the same investigators who developed the model, study population, geographical location, number of participants and events, and the model's performance and discrimination measures (e.g. calibration plot, c-statistic, AUC, etc.) before and (if conducted) after model recalibration.

For incremental value papers we recorded information on initial score (author, publication year, journal, acronym), study design, population and type of CVD, geographical location, outcome under investigation, prediction horizon, predictors in original model, number and type of new predictors, modeling method, whether internal, external validation and comparison with existing models was performed, sample size, model performance and discrimination measures (e.g. calibration plot, c-statistic, AUC etc.), model presentation and whether the same article also included development or external validation.

To accomplish consistent data extraction, a standardized data extraction form was used. All reviewers were extensively trained on how to use the form. When there was uncertainty on reporting or unexpected findings, a second reviewer checked the problematic extracted items. We did not explicitly perform a formal risk of bias assessment as no dedicated tool is currently available for studies of prediction models.

We synthesized the characteristics of interest, focusing on the populations in which the prediction models had been developed and validated, the types of predictors contained within the

prediction models, model discrimination, external validation and practical aspects of model implementation.

3. RESULTS

The search strategy identified 9965 unique articles through PubMed and EMBASE after removing duplicates. In total, 1388 full texts were screened, of which 79 articles met the eligibility criteria and were included in this review (Figure 1). Altogether, 46 articles concerned the development of one or more CVD risk prediction models, 47 articles described the external validation of one or more models and 24 were incremental value studies.

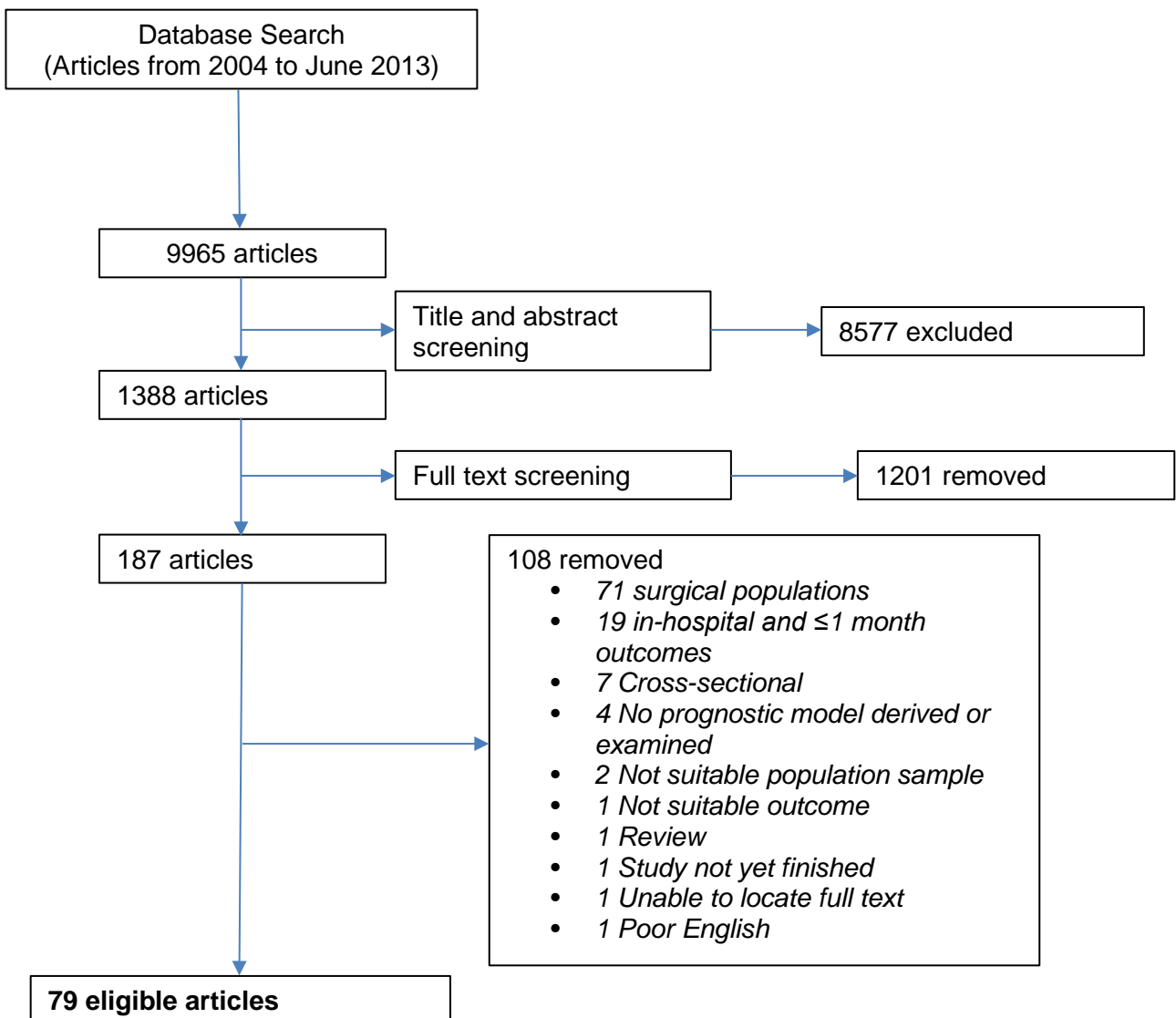


Figure 1. Flow diagram of studies identified and screened for eligibility.

Studies describing the development of risk prediction models

We identified 46 articles which described the development of 80 different models. Most studies developed up to 2 models (87%, n=40). Only 12 models (15%) were both internally and externally validated while over half of them (54%, n=44) were not validated at all. USA and Canada were the countries most frequently represented (35%, n=28), followed by Europe (28%, n=22). Other countries and regions (e.g. Africa, South America) were rarely represented. The development of the majority of models was based on Cox Proportional Hazards Regression analysis (68%, n=54), followed by Logistic Regression (23%, n=18). 2 models used a Weibull analysis, 4 used a combination of models (5%), while for 2 other models the modelling method was not mentioned at all. Finally, most models used a predictive horizon of more than 3 years (51%, n=41).

- *Populations and outcomes*

The mean population sample size per study was 4443, median 1142 and interquartile range (IR) 547 to 4951. We observed large variation in populations studied. Patients with ACS (34%) and patients with established or suspected CAD (33%) were the most studied patient groups. However, model for patients with peripheral artery disease (PAD), stroke, heart failure, atrial fibrillation (AF) or mixed conditions (e.g. CAD plus heart failure) represented almost 1/3 of the identified models. Most models were developed for people with ages ranging from 62 to 67 years (IR), with mean/median about 65 years. No model was sex specific, but men were more frequently represented than women, (men n=85694, 63%; women n= 50616, 37 %).

Notable variation and heterogeneity on the outcome level was also observed. 6 studies examined more than one outcome for the models developed, and we recorded 86 outcomes examined in relation to 46 developed models. All-cause mortality, major adverse cardiovascular events (MACE) and cardiovascular (CVD) mortality accounted for 70% of outcomes examined (n=60). We observed large heterogeneity in definitions of MACE; definitions included: death, myocardial infarction (MI), stroke, revascularization. Other outcomes examined such as MI and heart failure (HF) were responsible for the remaining 30%.

- *Predictors*

The majority of models used 5 to 7 predictors (36%, n=29) and included no more than 13 predictors. The 5 most widely used predictors were age and sex from demographics (used 55 and 32 times respectively), medical history of prior CAD (including prior MI, revascularization and artery bypass grafting) (n=35), history of diabetes (n=31) and smoking status (n=21). Other common factors (>10 times used) were comorbidities such as hypertension, stroke, HF and AF and other factors such as ventricular ejection fraction (EF), angina, circulating creatinine levels and statin use (Figure 2).

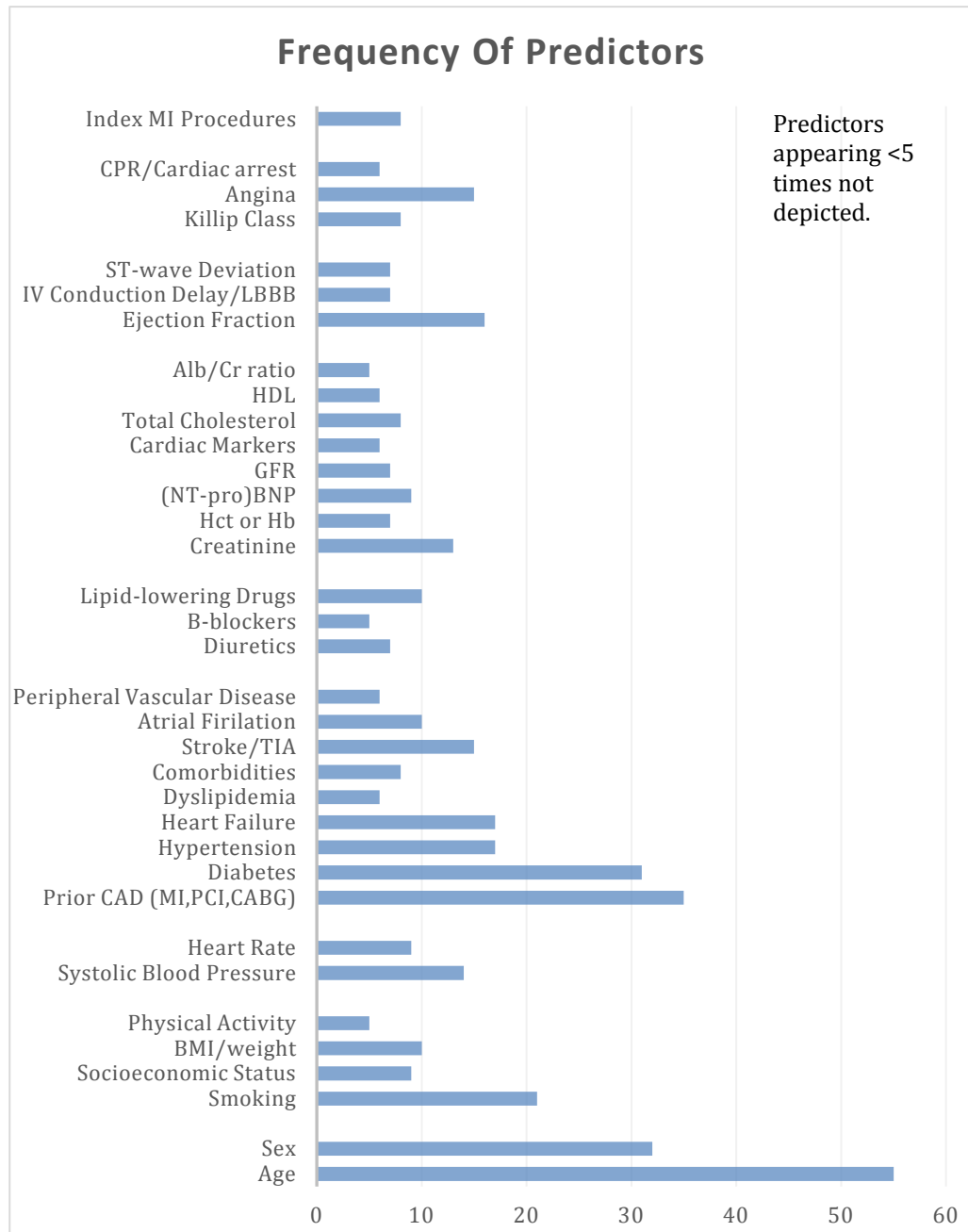


Figure 2. Development Studies, frequency of predictors in model derivation.

- *Measures of predictive performance*

The C-statistic and/or AUC was used to examine discrimination in 81% of models (n=65 out of 80 models), while the Hosmer-Lemeshow test was used to examine model calibration in 38% of models (n=30). Other performance measures like R-Squared and Likelihood Ratio were used less often (13% and 14% respectively). For 38 models (48%) both discrimination and calibration were reported. In total, 21 of the 80 developed models (26%) were internally validated, most often using bootstrapping (n=9), a random split of the dataset (n=8) or jack-knife (n=4). A summary of characteristics of development studies can be found in Figure 3.

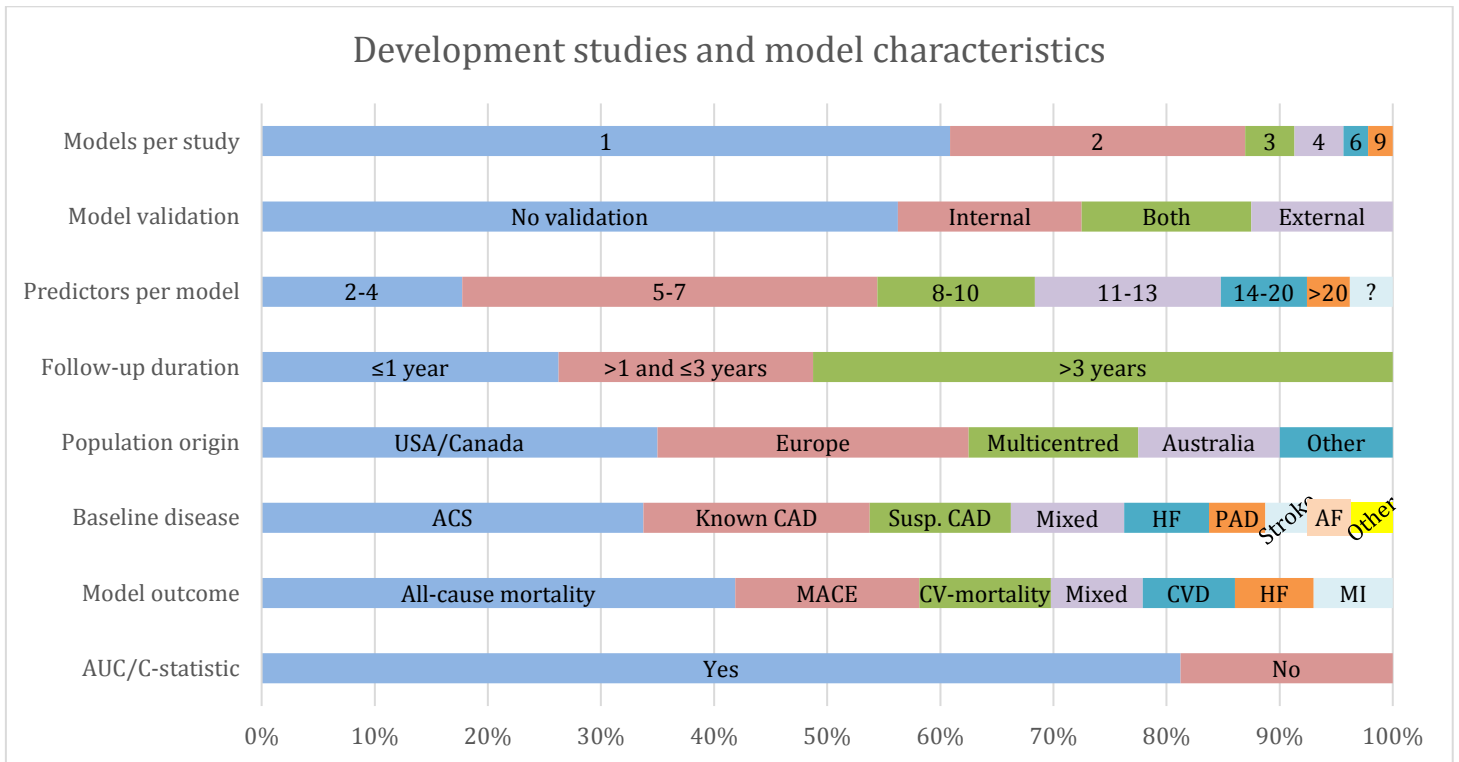


Figure 3. Development Studies Characteristics.

Studies describing the external validation of risk prediction models

We recorded 88 models out of 48 studies which examined external validation of risk prediction models. 10 out of 48 studies included the development and validation of risk scores and 38 were studies examining the validation of previously developed risk scores. Patients from Europe were represented in almost half of models (46%, n=40) and USA/Canada in 25% (n=22). Africa and South America were not represented at all.

Sample sizes of the validation studies ranged from small (161) to very large (51,807). 73% of the validation studies were performed in the same age range (mean age \pm 10 years) for which the model was originally developed, 62% were performed in the same CVD population for which the model was originally developed and 42% were performed for the same outcome as originally developed for. Validation studies examined models that had been developed from 1979 to 2012.

Out of the 88 models, the Framingham Risk Score (FRS) and its derivatives (FRS/updated FRS/FRS stroke) was the prognostic model most frequently validated with a total of 12 times (14%), followed by CHADS2 (9 times) (including CHA2DS2-VASc) and SYNTAX score 7 times (including clinical SYNTAX score). Other known scores validated more than once were: Global Registry of Acute Coronary Events score (GRACE), Systematic COronary Risk Evaluation (SCORE), Thrombolysis In Myocardial Infarction (TIMI), ABCD2 Score, Age, Creatinine and Ejection Fraction score (ACEF) and Seattle Heart Failure Model (SHFM).

Finally, in terms of type of external validation, most models were externally validated in a different setting than originally developed for (primary vs secondary prevention) with the exception of some models for recurrent stroke (e.g. ABCD2 score, “the ASPIRE approach” etc.). A large number (84%, n=67) of models were externally validated by different investigators than the ones who developed the model and 70% (n=61) were also geographically validated, meaning in a cohort from a different country than the one where the model was derived.

Discrimination metrics, AUC and C-statistic, were used by the vast majority of models (n=72, 82% of models) followed by log-rank (n=17, 35%). Calibration was examined in 19% of models by Hosmer-Lemeshow test (n=17) and 19% by Observed/Expected ratio and in 13% using calibration plots (n=11). 26 (30%) models presented both discrimination and calibration statistics. Characteristics of external validation studies are summarized on Figure 4.

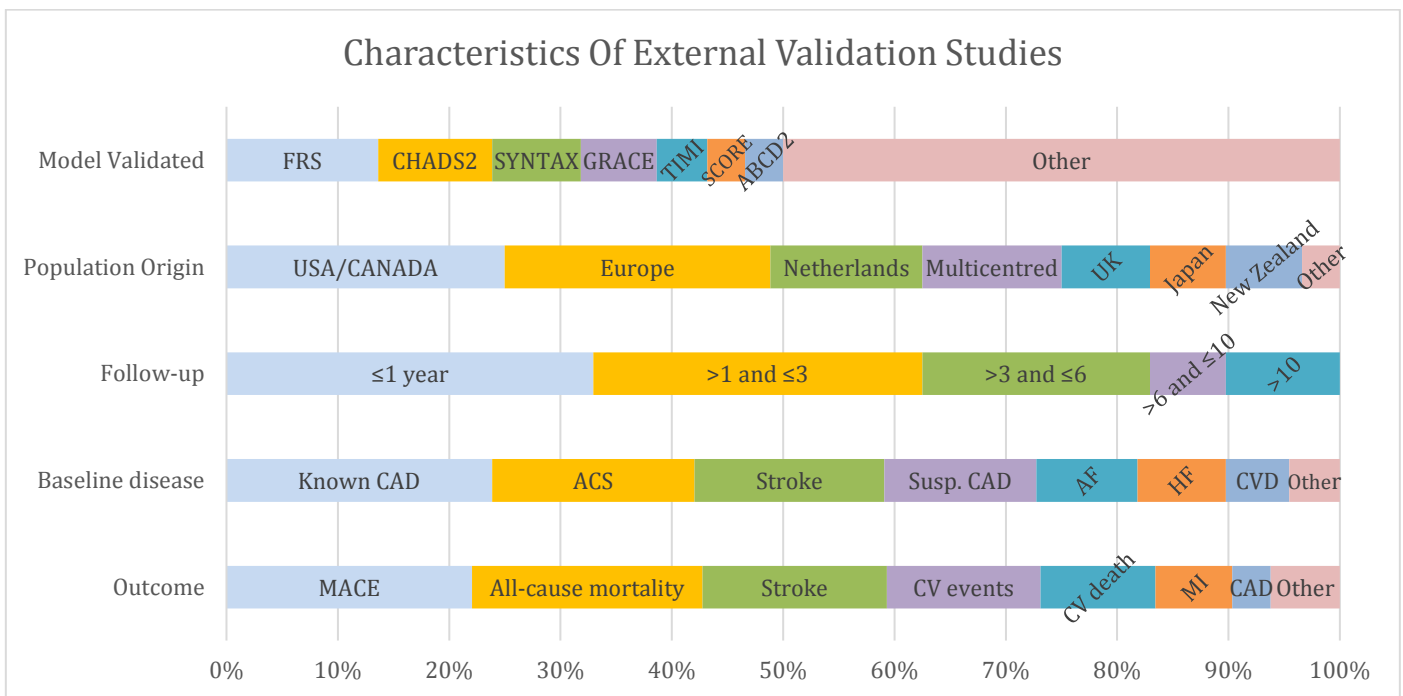


Figure 4. External Validation Studies characteristics.

Incremental value studies

We identified 25 studies which examined the incremental value of risk factors against 30 models. Altogether, the models studied were incremented a total of 75 times, since some models were incremented (new predictors added) 2 or more times in the same study. Over half of studies (n=13, 52%) were also external validation studies and 8 (32%) development studies. Most studies were conducted on European populations (n=12, 40%), 8 (27%) in USA and Canada samples, 7 (23%) were multi-centered and 3 on other countries.

ACS was the baseline CVD for 33% of models (n=10), followed by suspected and known CAD, AF, PAD and CVD in descending order. The follow-up period was mainly distributed between 1 and 10 years (80%). All-cause mortality and MACE were again the dominant outcomes (54%).

Sixteen times analyses tested the incremental value of risk factors against FRS (21%) followed by CHADS2, Mayo Clinic Risk Score and GRACE. Several (n=40) different predictors were added into the examined models; CRP and NT-proBNP (n=5, 9% each) were the most commonly examined ones.

Both discrimination and calibration were presented in 8 (32%) models, while no measures at all were available for 1 model. Regarding model improvement measures, AUC/C-statistic change was used in 87% (n=26) of models, model Chi-square change in 37%, integrated discrimination improvement (IDI) in 33%, net reclassification improvement (NRI) in 27% and reclassification ratio in 7% (some models used more than one improvement measures). Characteristics of incremental value studies are depicted on Figure 5.

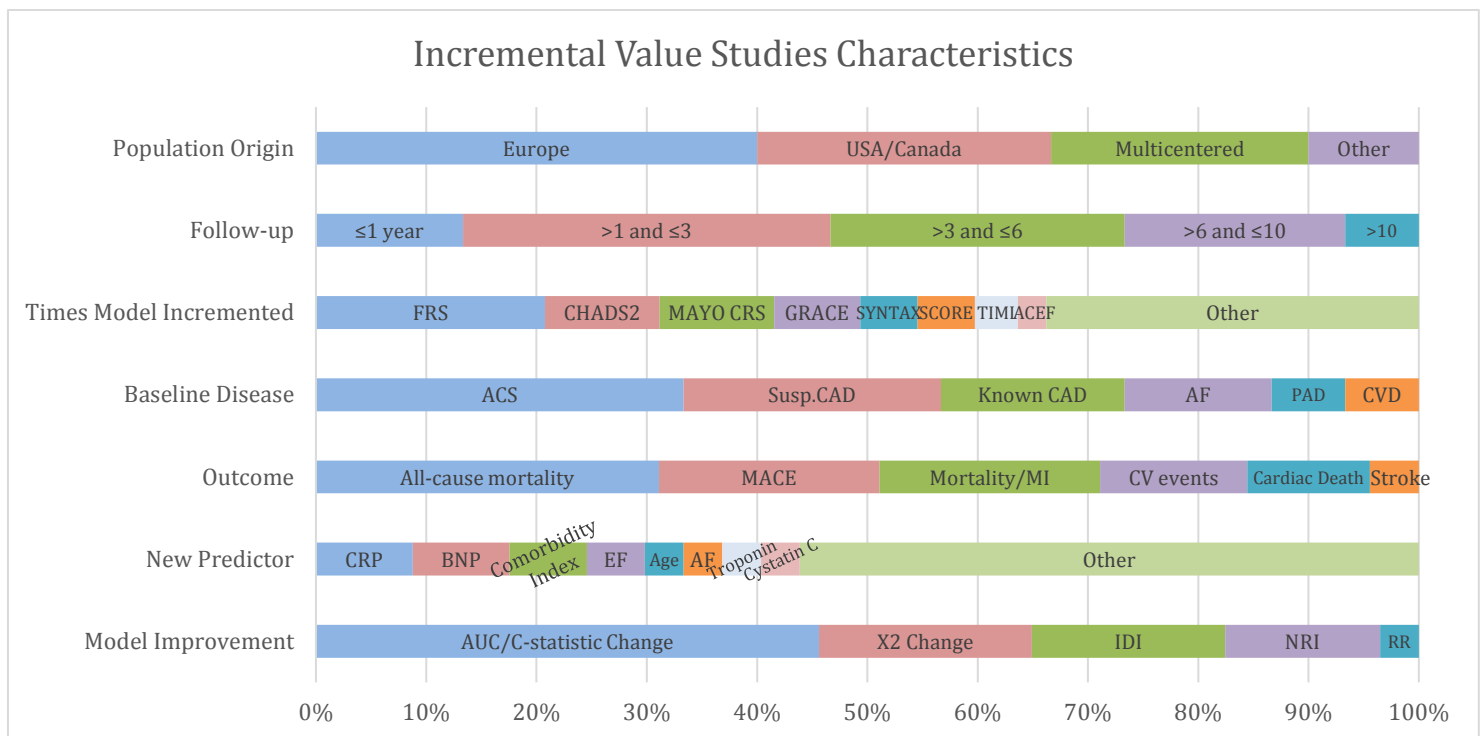


Figure 5. Incremental Value Studies Characteristics.

4. DISCUSSION

In this systematic review, we identified prediction models of recurrent cardiovascular disease (CVD) risk in patients with already established CVD, published over a decade (2004 to 2013). Compared to risk prediction models for apparently healthy individuals published within the same time period (306), we identified a much smaller number of articles (80 vs 212). This is to be expected, as most models in the medical literature are being developed for primary prevention and some of them are then validated in already established CVD (381), with the exception of models developed for recurrent stroke after transient ischemic attack (382, 383).

Current practice guidelines do not recommend the use of any particular prognostic model in secondary prevention of CVD but only in primary prevention. (384, 385) Both American and European guidelines suggest that patients with established CVD should be considered high-risk and medication as long as lifestyle intervention (quitting smoking, diet and physical activity) should be intensified and adjusted according to individual risk factors. From this systematic review, it appears that evidence is scarce on validity of available models and that efforts should be made to replicate findings in similar patient populations before any recommendation can be made as to which prognosis tool may be used.

We identified 46 development, 48 external validation and 25 incremental value papers, with some degree of duplication among the results, since some articles were used in more than one category. Altogether, we used 79 studies and although most of them presented some kind of assessment and performance measures for the models included, we did not observe a unanimous approach in data presentation. In addition, some level of poor reporting should be mentioned. First of all, a significant amount of studies (n=11, 14%) did not contain any performance measures but only Hazard Ratios or simple figures (e.g. nomograms) and almost 4 out of 10 studies did not include any calibration measures. In addition, half of studies did not state the use of specific prediction horizon but only mean follow-up period, and a large number of models used a period of ≤ 1 year (25% for development and 31% for external validation).

The data collected suggest that an ideal prediction model for secondary prevention would be a widely used and multiple times validated model, consisting of about 5 to 7 risk factors which are easy to measure and interpret and predicting all-cause mortality or MACE. As described, the factors most frequently used were: age, sex, smoking status, history of CAD, diabetes, hypertension and stroke or transient ischemic attack (TIA). In these factors we could also add dyslipidemia as it is represented in 3 different categories (history of, serum levels, statin use) and heart failure history or echocardiography-based ejection fraction.

The model that was most times externally validated (n=14) in the context of secondary prevention is the Framingham Risk Score (FRS) and its updates (297, 370, 386). FRS uses 7 risk factors including: age, sex, smoking, diabetes, systolic blood pressure or treated hypertension, total cholesterol and HDL levels. The second model (9 times validated) is the combination of CHADS2 and CHA2DS2-VASc scores, which consist of the following 7 risk factors: history of congestive

heart failure, hypertension, age, diabetes, previous stroke or TIA and vascular disease and sex (for CHA2DS2-VASc) (387, 388). Original FRS estimates the 10-year risk of developing coronary heart disease and CHA2DS2-VASc the risk of stroke in patients with non-rheumatic atrial fibrillation (AF) and not all-cause mortality. Despite being designed to predict respectively 10-year risk of developing coronary heart disease and risk of stroke in patients with non-rheumatic atrial fibrillation, these two models seem to be the most applicable to be used in secondary prevention but further research and validation is required.

- *Limitations*

There are several limitations in our study. First of all, we used only studies of the decade from 2004 to 2013, therefore important studies (particularly published from 2013 to 2017) are probably missing from our research. Our purpose was to give a general glance on risk models for secondary prevention and highlight the need for further research on this field. In addition, we noticed a lack of studies in populations of specific continents like Africa and South America but we also excluded studies not written in English, so this hypothesis may be biased. Furthermore, we used the mean follow-up period instead of prediction horizon in studies not clearly reporting the use of specific prediction horizon. We also tried to categorize our data for baseline disease and model outcome for better data presentation but some articles could be used in more than one category. However, we used only one to avoid duplication. Another point is that we grouped together some variants of the same model, although there are differences between them (e.g. CHADS2 and CHA2DS2-VASc, FRS and its updates etc.). Overall, we noticed a great variability in population samples, baseline disease and outcomes, follow-up period, and performance measures used, and despite our effort to synthesize these data as thoroughly as possible, we may draw a biased picture.

5. CONCLUSION

There is a large number of models in medical literature being used for recurrent cardiovascular outcomes in patients with established or suspected cardiovascular disease. While some of these models were initially developed for secondary prevention of CVD and are correctly being used in such populations (e.g. ABCD2 score), the majority of models used are newly derived models without proper external validation or models originally developed for general/healthy (e.g. FRS, SCORE) or other specific population (e.g. CHADS2, SYNTAX). Consequently, no specific prognostic model is incorporated in current practice guidelines. Most risk factors for CVD outcomes are already well established and share a lot in common with those for secondary prevention. Consequently, we advise to stop deriving more prediction models and to focus the effort on external validation and performance comparison of already existing models. Finally, the impact of such models in secondary prevention should be also investigated in impact studies, so that some of those models could be embedded in relevant guidelines and everyday clinical practice.

AIM III

Association between blood pressure and risk of cancer development: a systematic review and meta-analysis of observational studies.

1. INTRODUCTION

Hypertension and cancer are two multifactorial, severe and chronic conditions. Hypertension is a prognostic factor widely used in medical literature and, as a health condition, constitutes a major health problem worldwide, as it affects approximately 30% of adults over 20 years old, leading to high morbidity and mortality (389). A percentage of almost 50% of heart disease, stroke, and heart failure and about 14% of mortality was due to hypertension in 2015 (390). In addition, hypertension is of great economic impact for healthcare systems. Hypertension and its complications is responsible for about 10% of healthcare spending (391).

Cancer is one of the 4 major types of chronic diseases according to World Health Organization. It is the second leading cause of morbidity and mortality. Globally, there were approximately 18 million new cases and 9.6 million cancer-related deaths in 2018. Furthermore, in the next decades these numbers are expected to continue rising (163). As a consequence, if there is even a weak association between blood pressure and cancer risk, this could have a heavy impact on public health.

Kidney cancer is the only cancer consistently related to high blood pressure in medical literature (392, 393). However, it is not yet clear whether a reverse causation may explain part of this association (394). In addition, there is some evidence that hypertension may be also associated to breast, endometrial, prostate, and colorectal cancer (395-399). In the last years there has been a variety of new studies trying to investigate a possible association between metabolic syndrome, a part of which is hypertension, and risk of cancer (396, 400, 401). So, we conducted a meta-analysis trying to summarize relevant studies available in published medical literature.

2. METHODS

2.1. Data extraction and quality assessment

We searched for eligible studies, published in PubMed, from inception to November 2017 using the following algorithm: (*blood pressure OR hypertension OR “metabolic syndrome”*) AND (*cancer OR neoplas* OR malignan* OR tumor OR carcinoma*). We also hand-searched for potential missed studies in the references of eligible systematic or narrative reviews (396, 397, 402-411). We considered eligible all cohort and case-control studies conducted in humans assessing the association between systolic blood pressure (SBP) or diastolic blood pressure (DBP) or

hypertension and risk of any cancer development or cancer death. Hypertension was defined as any of the following: self-reported or measured SBP or DBP higher than predefined cut-off points (e.g. WHO or NCEP/ATP III criteria), self-reported medical history or drug-treated hypertension. In case of metabolic syndrome, we only used the component of hypertension. Criteria for exclusion were: any type of review, cross-sectional studies, case-reports, prognostic studies among patients with cancer diagnosis, studies in children, small-studies (defined as cohorts with less than 100 total individuals or case-control studies with less than 100 cancer cases, studies that did not provide enough information for calculating measures of association, non-English studies, and finally studies on pre-malignant outcomes (e.g., colorectal adenomas). When two different studies pertained to the same cohort, we retained the publication with the longer follow-up period.

From each eligible study we extracted information on author name, year and journal of publication, study design, sample size, population characteristics, definition of hypertension, relative risk (RR), 95% confidence interval (CI) and adjustments for confounders. When many different statistical models were reported, we always retained the most adjusted model. Two different investigators performed the literature search and data extraction and a third one re-checked the results for consistency.

The “Newcastle-Ottawa Scale” was used for the quality assessment of the included studies. This was performed also by two investigators, and any inconsistencies were resolved by a third author. Based on this tool, every study was judged on eight quality “questions”, grouped into three categories: i) selection, ii) comparability of study groups and iii) exposure or outcome ascertainment for case-control and cohort studies, respectively. A star was awarded for every quality item for a maximum of 9 stars for the highest quality studies (263).

2.2. Statistical analyses

Our primary analysis included only prospective studies (e.g., cohort or nested case-control designs). Analyses using case-control and cohort studies in combination are provided in the supplement. Separate meta-analyses were performed according to systolic or diastolic blood pressure and hypertension. Two different approaches were used for systolic and diastolic blood pressure. For the first one, we used a top to bottom category comparison, and for the second a dose-response per 10mmHg. Studies that reported a dose-response estimate were either pooled directly or after re-scaling to the corresponding increment unit using the generalized weighted least-squares regression model approach (412, 413). We summarized RRs and 95% CIs using fixed-effects and random-effects meta-analysis models. Three or more studies were required per exposure and outcome comparison (414). We used both the Cochran’s Q test and the I^2 statistic for the assessment of the heterogeneity between the studies in each analysis (415). 95% prediction intervals were also calculated to further assess heterogeneity, which represents the range in which the effect estimates of future studies will lie (416). Secondary subgroup meta-analyses were conducted according to sex, study design (prospective vs. case-control) and adjustment factors (at least age vs. age plus further multivariable adjustment). Small-study effects bias was assessed using the Egger’s regression asymmetry test (417). Analyses were performed in STATA 12 (College Station, Texas). All p-values were two-tailed. The study is reported according to the MOOSE checklist (418)

3. RESULTS

3.1. Study characteristics

We screened 39,891 study citations and after excluding ineligible studies using the aforementioned exclusion criteria, we ended up with a total of 148 individual studies (Figure 1). The characteristics of all included studies can be found in Supplemental Table 1. Specifically, we included 85 prospective studies (401, 419-502), 72 of which were cohort studies, 11 were nested case-control studies (419, 420, 422, 435, 436, 453, 454, 475, 480, 482, 497) and 2 were record-linkage studies (462, 465), and 63 case-control studies (400, 503-564). The majority (n=133; 90%) investigated cancer incidence. 48 (32%) studies were conducted only in men, whereas 57 (39%) only in women. Most studies (n=51; 34%) were conducted in the USA followed by Scandinavian countries (n=15; 10%), Italy, UK and Korea, and Japan. Out of the 128 studies that used hypertension as the exposure of interest, this was defined in 20 studies (16%) using the NCEP-ATPIII criteria ($\geq 130/85$ mmHg), 17 studies (13%) used the WHO definition ($\geq 140/90$ mmHg), 4 studies used $\geq 160/95$ mmHg, 38 pertained to self-reported hypertension, 16 studies used self-reported drug treatment for hypertension and 26 studies used a combination of self-reported disease and treatment, whereas 7 studies used other definitions.

Detailed information on the quality assessment, can be found On Supplementary Table 2. For prospective studies, the median number of stars per study was 7, and the interquartile range (IQR) was 1. In contrast, for case-control studies the median number of stars were 6 and the IQR was 2. Only a small minority of prospective (31%) and case-control studies (19%) performed extensive multivariable adjustments, that is, effect estimates adjusted for age and three of the following five potential confounders: body mass index, smoking, alcohol, physical activity and family history of cancer.

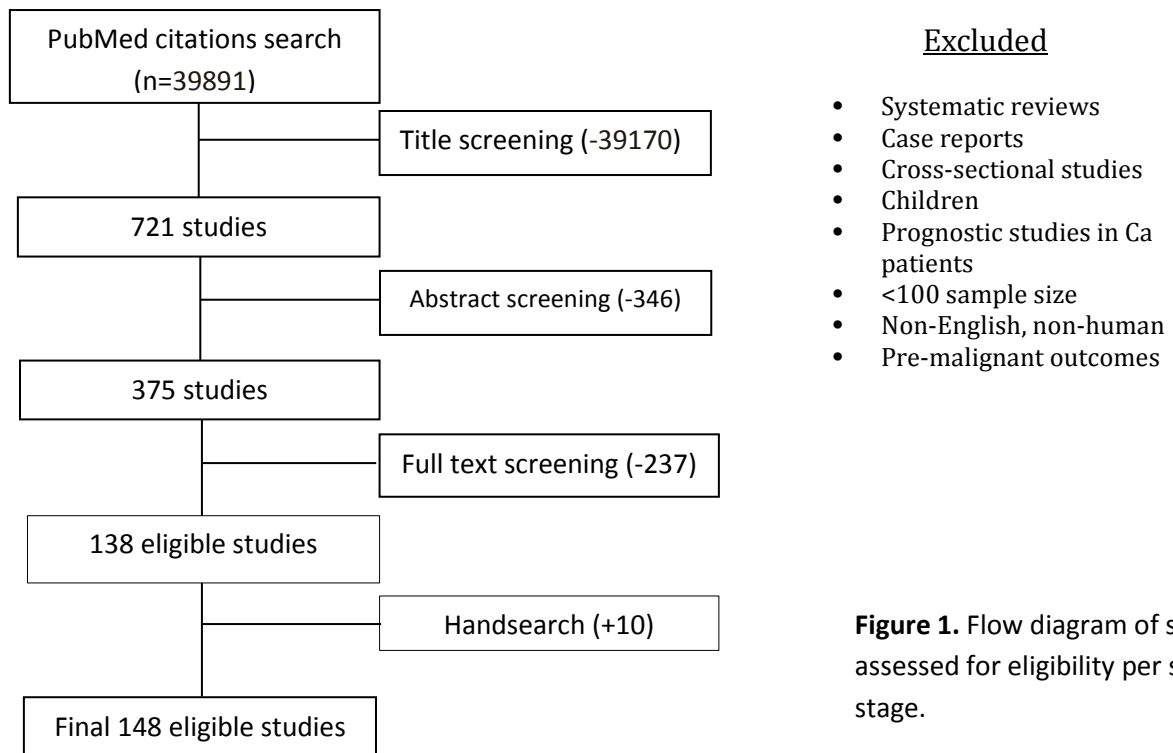


Figure 1. Flow diagram of studies assessed for eligibility per screening stage.

3.2. Meta-analysis

Our primary meta-analysis included only 85 prospective studies. We conducted 30 separate meta-analyses investigating the association between hypertension and 16 different cancers, and 29 meta-analyses between SBP or DBP and 11 cancers. Summary random effects relative risk estimates and 95% CIs per cancer site, number of studies used, I^2 statistic for heterogeneity, 95% prediction intervals and Egger's test of small-study effects for hypertension are summarized in Figure 2. In addition, in Supplemental Figure 1 the top/bottom approach for SBP and DBP is presented. Supplemental Table 3 there are extended information on the meta-analysis of prospective studies for the association between hypertension, SBP or DBP, and the risk of cancer. Finally, in Supplemental Table 4 we present our secondary sensitivity meta-analysis of both prospective and case-control studies combined. Supplemental Figures 2-60 depict all forest plots of cohort studies by cancer sites, and in Supplemental Figures 61-79 the forest-plots for both cohort and case-control studies.

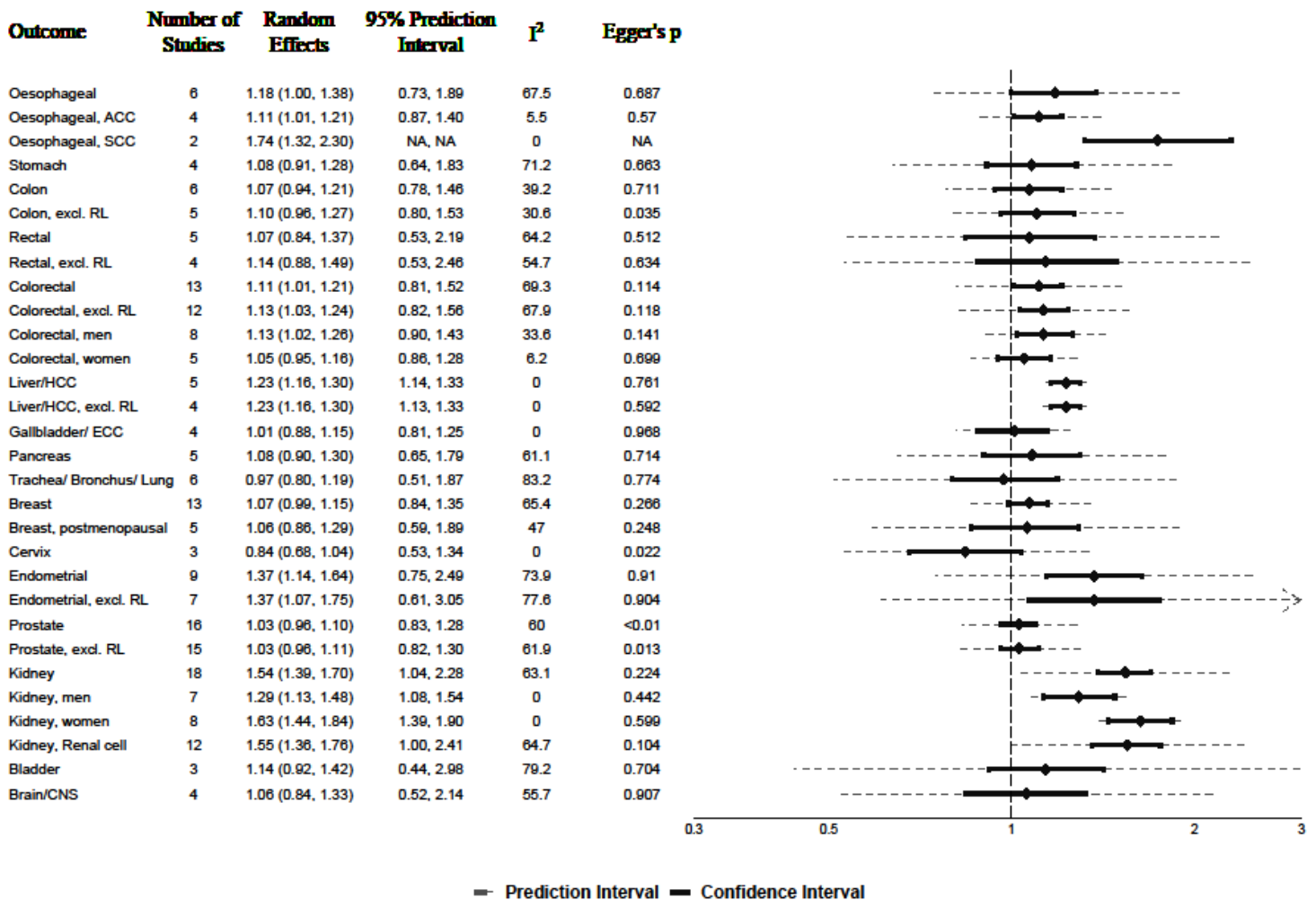


Figure 2. Summary relative risks and 95% confidence intervals of prospective studies for the association between hypertension and cancer risk.

Abbreviations: ACC, adenocarcinoma; SCC, squamous cell carcinoma; RL, record-linkage studies; HCC, hepatocellular carcinoma; ECC, extrahepatic cholangiocarcinoma; CNS, central nervous system, NA, Not applicable.

Based on 18 eligible prospective studies, we found a statistically significant association between hypertension and risk of kidney cancer (summary random effects RR, 1.54; 95% CI, 1.39-1.70), although with a large between-study heterogeneity (I^2 , 63.1%). However, no indication for small study effects was observed. When we considered only studies on renal cell carcinoma, we observed similar results (n=12 studies, RR, 1.55; 95% CI, 1.36-1.76; I^2 , 64.7%). This association remained statistically significant even when women (n=8 studies, RR, 1.63; 95% CI, 1.44-1.84; I^2 , 0%) or men (n=7 studies, RR, 1.29; 95% CI, 1.13-1.48; I^2 , 0%) were examined separately. Similar results were obtained in subgroup secondary meta-analyses of prospective studies that at least adjusted for age or studies with comprehensive multivariable adjustments, that is, as mentioned, age plus at least three of the following five risk factors: body mass index, smoking, alcohol, physical activity and family history of kidney cancer. When 14 case-control studies were meta-analysed together with the prospective studies, a summary RR of 1.60 (95% CI, 1.48-1.73; I^2 , 61.3%) was observed. We also observed statistically significant associations between SBP (RR per 10mmHg, 1.05; 95% CI 1.03-1.06; I^2 , 57%) and DBP (RR, 1.07; 95% CI, 1.04-1.10; I^2 , 55%) with kidney cancer, but these meta-analyses had evidence of small-study effects. All meta-analyses of kidney prospective studies are available in Table 1 and of prospective plus case-control studies on Supplementary Table 4)

Table 1. Meta-analysis of prospective studies for the association between hypertension and risk of kidney cancer.

Meta-analysis of prospective studies

ANALYSIS	SUMMARY FIXED EFFECTS RR (95% CI)	SUMMARY RANDOM EFFECTS RR (95% CI)	P-VALUE (Q TEST)	I^2 TEST	P-VALUE (EGGER'S TEST)	95% PREDICTION INTERVAL	No OF STUDIES USED
HTN (all)	1.60 (1.52-1.70)	1.54 (1.39-1.70)	0.000	63.1%	0.224	1.04-2.28	18
HTN (men)	1.29 (1.13-1.48)	1.29 (1.13-1.48)	0.492	0.00%	0.442	1.08-1.54	7
HTN (women)	1.63 (1.44-1.84)	1.63 (1.44-1.84)	0.658	0.00%	0.599	1.39-1.90	8
HTN (r. cell)	1.66 (1.55-1.78)	1.55 (1.36-1.76)	0.000	64.7%	0.104	1.00-2.41	12
SBP (per 10mmHg)	1.04 (1.03-1.05)	1.05 (1.03-1.06)	0.008	56.6%	0.036	1.00-1.09	9
DBP (per 10mmHg)	1.05 (1.03-1.06)	1.07 (1.04-1.10)	0.015	54.7%	0.029	0.99-1.14	9
T/B SBP	1.93 (1.64-2.26)	1.94 (1.60-2.36)	0.200	24.8%	0.711	1.26-3.00	9
T/B DBP	1.73 (1.46-2.05)	1.80 (1.36-2.38)	0.019	54.6%	0.703	0.81-4.01	8

Meta-analysis of prospective studies according to type of adjustments

Outcome	Age adjustment (at least)			Multivariate adjustment*		
	Studies	Random Effect	I^2	Studies	Random Effect	I^2
Kidney	14	1.54 (1.36-1.74)	70.5%	4	1.52 (1.32-1.75)	0%
Kidney, men	4	1.25 (1.01-1.55)	30.3%	3	1.40 (1.12-1.74)	0%
Kidney, women	6	1.65 (1.43-1.89)	0%	2	1.54 (1.17-2.04)	0%
Kidney, renal cell	9	1.56 (1.32-1.85)	72.0%	3	1.52 (1.31-1.75)	0%

Footnote

*Studies adjusted for age and at least 3 out of five 5 of the following risk factors: smoking, family history of cancer, BMI, alcohol and physical activity.

We also noted a positive association between hypertension and colorectal cancer using 13 prospective studies (RR 1.11; 95% CI, 1.01-1.21; I^2 , 69.3%). After the exclusion of one record-linkage study the association remained significant (RR 1.13; 95% CI, 1.03-1.24; I^2 , 67.9%). We also observed a significant association even after meta-analysing only the four studies that performed multivariable adjustments (RR 1.30; 95% CI, 1.03-1.66; I^2 , 66.6%). This association was statistically significant in men (RR 1.13; 95% CI, 1.02-1.26; I^2 , 33.6%), but not in women (RR 1.05; 95% CI, 0.95-1.16; I^2 , 6.2%) No significant associations were identified between SBP or DBP with colorectal cancer risk (Table 2). However, we have to mention that all meta-analyses for either hypertension or SBP/DBP separately on colon and rectal cancer risk did not yield any statistically significant findings (Figures 2).

Table 2. Meta-analysis of prospective studies for the association between hypertension and risk of colorectal cancer.

Meta-analysis of prospective studies

ANALYSIS	SUMMARY FIXED EFFECTS RR (95% CI)	SUMMARY RANDOM EFFECTS RR (95% CI)	P-VALUE (Q TEST)	I^2 TEST	P-VALUE (EGGER'S TEST)	95% PREDICTION INTERVAL	No OF STUDIES USED
HTN	1.06 (1.01-1.10)	1.11 (1.01-1.21)	0.000	69.3%	0.114	0.81-1.52	13
HTN (-RL)	1.07 (1.03-1.12)	1.13 (1.03-1.24)	0.000	67.9%	0.118	0.82-1.56	12
HTN men	1.11 (1.04-1.19)	1.13 (1.02-1.26)	0.160	33.6%	0.141	0.90-1.43	8
HTN women	1.05 (0.96-1.14)	1.05 (0.95-1.16)	0.372	6.2%	0.699	0.86-1.28	5
SBP (per 10mmHg)	1.01 (1.00-1.01)	1.01 (1.00-1.01)	0.396	4.0%	0.336	0.99-1.02	5
DBP (per 10mmHg)	1.01 (1.00-1.03)	1.01 (1.00-1.03)	0.757	0.0%	0.976	0.99-1.04	4
T/B SBP	1.19 (1.04-1.36)	1.19 (1.02-1.40)	0.268	20.3%	0.449	0.87-1.64	6
T/B DBP	1.21 (1.05-1.38)	1.23 (1.04-1.45)	0.397	1.7%	0.762	0.93-1.62	4

Meta-analysis of prospective studies according to type of adjustments

Outcome	Age adjustment (at least)			Multivariate adjustment*		
	Studies	Random Effect	I^2	Studies	Random Effect	I^2
Colorectal	9	1.07 (0.97-1.17)	68.2%	4	1.30 (1.03-1.66)	66.6%
Colorectal, excl. RL	8	1.09 (0.98-1.21)	67.3%	4	1.30 (1.03-1.66)	66.6%
Colorectal, men	5	1.10 (1.03-1.18)	0%	3	1.38 (0.92-2.06)	75.9%
Colorectal, women	4	1.02 (0.93-1.12)	0%	1	1.35 (1.01-1.80)	n/a

Abbreviations: n/a, not applicable; RL, record-linkage studies.

The meta-analysis yielded a borderline significant association between hypertension and risk of breast cancer (Figure 2; n=13 prospective studies; RR, 1.07; 95% CI, 0.99-1.15; I^2 , 65.4%). The association was not significant for post-menopausal breast cancer risk (RR, 1.06; 95% CI, 0.86-1.29; I^2 , 47%). However, statistically significant associations were observed for total (n=5; RR 1.10; 95% CI, 1.02-1.18; I^2 , 0%), and post-menopausal (n=2; RR 1.38; 95% CI, 1.03- 1.85; I^2 , 0%) breast cancer risk in prospective studies that performed multivariable adjustments (Table 3). The meta-analysis was also statistically significant for an increase of 10mmHg in systolic (RR 1.03; 95% CI, 1.01-1.04; I^2 , 0%), but not diastolic (RR 1.02; 95% CI, 1.00-1.05; I^2 , 44.3%) blood pressure. With the inclusion of case-control studies, the meta-analyses yielded statistically significant findings for both total (RR, 1.11; 95% CI, 1.04-1.19; I^2 , 70.2%) and post-menopausal disease (RR, 1.13; 95% CI, 1.02-1.25; I^2 , 37.5%) (Supplementary Table 4).

Table 3. Meta-analysis of prospective studies for the association between hypertension and risk of breast cancer.

Meta-analysis of prospective studies

ANALYSIS	SUMMARY FIXED EFFECTS RR (95% CI)	SUMMARY RANDOM EFFECTS RR (95% CI)	P-VALUE (Q TEST)	I^2 TEST	P-VALUE (EGGER'S TEST)	95% PREDICTION INTERVAL	No OF STUDIES USED
HTN (overall)	1.12 (1.08-1.15)	1.07 (0.99-1.15)	0.000	65.4%	0.266	0.84-1.35	13
HTN (postmen.)	1.01 (0.89-1.16)	1.06 (0.86-1.29)	0.110	47.0%	0.248	0.59-1.89	5
SBP (per 10mmHg)	1.03 (1.01-1.04)	1.03 (1.01-1.04)	0.684	0.0%	0.076	0.91-1.15	3
DBP (per 10mmHg)	1.01 (1.00-1.03)	1.02 (1.00-1.05)	0.166	44.3%	0.079	0.79-1.33	3

Meta-analysis of prospective studies according to type of adjustments

Outcome	Age adjustment (at least)			Multivariate adjustment*		
	Studies	Random Effect	I^2	Studies	Random Effect	I^2
Breast	8	1.03 (0.92-1.15)	76.6%	5	1.10 (1.02-1.18)	0%
Breast, postmenopausal	3	0.93 (0.80-1.09)	0%	2	1.38 (1.03-1.85)	0%

Our meta-analysis showed also a statistically significant association between hypertension and risk of endometrial cancer (Figure 2; n=9 prospective studies; RR, 1.37; 95% CI, 1.14-1.64), but with substantial heterogeneity (Supplemental Figure 22; I^2 , 73.9%). After the removal of two record linkage studies, we observed a significant RR of 1.37 (95% CI, 1.07-1.75) but again with substantial heterogeneity (Supplemental Figure 23; I^2 , 77.6%). Only two out of the nine prospective studies used multivariable adjusted models, and the meta-analysis among them yielded null results (RR, 1.05; 95% CI, 0.83-1.34; I^2 , 0%). When 13 case-control studies were meta-analysed together with the prospective studies, a statistically significant association was

found (Supplemental Table RR, 1.58; 95% CI, 1.35-1.85; I^2 , 88%). No analysis on SBP or DBP was performed, because there were not enough studies using continuous BP data.

5 prospective studies were available examining the association between hypertension and liver cancer. We found a significant association (Figure 2; RR, 1.23; 95% CI, 1.16-1.30; I^2 , 0%), but four out the five studies did not perform comprehensive multi-variable adjustments (Supplemental Table 1). After removing one record linkage study, the result remained identical. After adding two case control studies, no significant association was observed. (Supplemental Table 4; RR, 1.30; 95% CI, 0.99-1.71).

Very few eligible prospective studies were available on oesophageal cancer. The meta-analysis of 4 prospective studies between hypertension and esophageal adenocarcinoma yielded a statistically significant positive association (Figure 2; RR 1.11; 95% CI, 1.01-1.21; I^2 , 5.5%). We identified only 2 prospective studies on hypertension and esophageal squamous cell carcinoma, and the meta-analysis yielded a statistically significant estimate (RR, 1.74; 95% CI, 1.32-2.30; I^2 , 0%), but was based only on 248 cases. However, the meta-analysis of all 6 prospective studies on total oesophageal cancer yielded a statistically not significant estimate (RR, 1.18; 95% CI, 1.00-1.38; I^2 , 67.5%). Most of these studies however did not perform comprehensive multivariable adjustments.

We did not observe statistically significant associations between hypertension or SBP/DBP and cancer of stomach, gallbladder, pancreas, lung, cervix, prostate, bladder and brain (Figures 2).

4. DISCUSSION

Cancer is a multifactorial disease that shares many common risk factors with CVD, while other factors are cancer-specific, including radiation, immunosuppression, and infection by specific agents. Furthermore, there are many other factors, such as genes, proteins, and biomarkers that play a crucial part in cellular proliferation or apoptosis pathways. That is the main reason why most prognosis studies on cancer focus on prognostic factors, being either exploratory or confirmatory studies. There are not many prognostic models available for cancer, and the models described in medical literature usually refer to patients already diagnosed with cancer. Moreover, in cancer clinical practice guidelines, there are rarely any models recommended for use in everyday clinical practice.

The association between the risk of 18 cancers and hypertension is summarized in this meta-analysis of observational studies. The positive association between high blood pressure and kidney cancer risk that has already been described, was confirmed, and possible positive associations between hypertension and breast, liver, colorectal, endometrial and oesophageal cancers were also observed. On the other hand, statistically significant associations for gallbladder, stomach, lung, pancreas, cervix, breast, brain, and bladder cancers were absent.

The association between kidney cancer risk and hypertension has been investigated by many prospective observational studies over the past few decades and the vast majority of these studies

have showed a positive association. In our meta-analysis, this is translated to a 54% higher risk that was stronger in women compared to men (63% vs. 29%). A dose-response approach per every 10mmHg increase in SBP and DBP revealed also a 5% and 7% higher risk for kidney cancer, respectively. Similar associations have been reported in previous meta-analyses (193, 393, 407). However, both hypertension and cancer share many common risk factors including smoking, obesity, alcohol overconsumption and obesity (565). As a result, it still remains under question whether the reported association is causal. Most of the included studies in our meta-analysis have not adjusted for many of these potential confounders, but based on the four prospective studies that did follow a comprehensive adjustment approach we still observed positive associations, as outlined in the current and other meta-analyses (193). The causality of the observed association, however, requires large prospective studies and probably Mendelian randomization studies in order to be clarified (566). For example, a positive association between cancer risk and only diastolic blood pressure was recently demonstrated in a Mendelian randomization study of renal cell cancer (567). Possible pathophysiological mechanisms explaining a part of this association, may involve chronic renal hypoxia, lipid peroxidation, neurohormonal stress, and deregulation of renin-angiotensin system and specifically the overexpression of renin and cellular angiotensin receptors and the down-regulation of the angiotensin-converting enzyme (568-570).

Individuals with hypertension were also found to be at an 11% increased risk for colorectal cancer according to a meta-analysis of 13 prospective studies. Taking into account only 4 studies that performed comprehensive multivariable adjustments, the potential risk was even higher, at a level of 30%. A previous meta-analysis by Esposito et al. in 2013, including both prospective and case-control studies reported a 9% colorectal cancer risk (397). Hypertension may increase colorectal cancer risk by interfering in the apoptosis pathways, but to date, no well-documented mechanism exists (571). Consequently, our observations should be carefully approached, taking into account the scarcity of well-designed studies in medical literature.

Hypertension was found to be associated with a 7% higher risk of breast cancer in a meta-analysis of 13 prospective studies. Five of these studies that performed comprehensive multivariable adjustments, estimated this risk to be 10% in total, and 38% in post-menopausal women, observations in agreement with the findings of Han et al., in a meta-analysis of 12 prospective studies, that concluded to a 7% higher breast cancer risk, regardless of the adjustments performed (398). Apoptosis blocking, chronic inflammation that promotes the formation of reactive oxygen species and hypoxia due to adipose tissue may once more explain part of this association (572).

Although positive associations between hypertension and a number of cancers (namely endometrial, liver, oesophageal squamous cell carcinoma and adenocarcinoma) were also observed, the limited number of prospective studies included (ranging between 2 for squamous cell oesophageal carcinoma and 9 studies for endometrial cancer) and the absence of comprehensive multivariable adjustments in most of them, raise serious concern over the validity of the estimated associations. Previous meta-analyses investigating the potential association between hypertension and endometrial cancer, have in general shaped their conclusions without taking into consideration study design and quality (395, 396).

Hypertension (or blood pressure) was not found to be associated with gallbladder, stomach, cervix, lung, bladder, prostate and brain cancer. However, a recent meta-analysis of 21 cohort and case-control studies, regardless their quality and design of included studies, estimated the risk of

prostate cancer to be 8% higher in hypertensive individuals.(399).

The comprehensive search strategy and the large number of prospective studies included, the inclusion of “metabolic syndrome” in the search algorithm, the investigation of associations between hypertension and many individual cancers, and the detailed sensitivity and subgroup analyses, are the main strengths of this meta-analysis. There are also some limitations in our study. First, hypertension and malignancy share many common risk factors that may explain part of this association but unfortunately, the majority of the studies included did not perform comprehensive multivariable adjustments, which raises concerns over the study findings even for the well-described association between hypertension and kidney cancer. Second, most studies did not perform subgroup analyses by potential effect modifiers (e.g. anti-hypertensive medication use), which would have allowed a more accurate assessment of associations in different patient subgroups. Finally, as individuals treated for high blood pressure are usually under closer medical surveillance, cancer detection could be easier compared to untreated persons. As a result, detection bias may also account for some of the reported associations. The estimation of valid measures of association should be assisted by well-designed prospective, as well as Mendelian randomization studies.

In conclusion, the current meta-analysis across 18 cancer sites showed that hypertensive individuals were at higher risk of kidney, colorectal and breast cancer. However, careful interpretation is required as most meta-analyses included relatively small number of studies, several relative risks had weak or moderate magnitude and maybe affected by confounders. As a result, hypertension, one of the most widely used prognostic factors in medical literature seems to be associated with at least some sites of cancer, one of the main types of chronic diseases.

(The original study was published in the international scientific journal «Nature – Scientific Reports», 2019 June 12 PMID: 31189941) (573).

SUMMARY

Prognosis is defined as the likelihood of displaying a condition at a specific time period, based on clinical or non-clinical profile. *Prognostic factor* is any characteristic (variable) associated with the risk of a health outcome among people with a specific health condition. Finally, a *prognostic model* is a mathematical function that relates certain prognostic factors to the probability (risk) of a particular outcome happening in a well-defined population and within a specific time period.

Prognosis research and prognostic models is first of all crucial for patient counseling and clinical decision making. Modern medicine with personalized treatment and stratified healthcare is based upon these principles. Furthermore, it is important for the guidance of healthcare policies, insurance companies, as well as the design of clinical trials. However, for a prognostic model to be useful in clinical practice it shall be based upon biological reasoning, be simple, accurate, and offer a degree of generalization and clinical effectiveness.

There is no universal definition for chronic diseases but all of them share some common characteristics; they have a prolonged development period with an early asymptomatic stage and there is usually no definite cure. According to World Health Organization (WHO), the 4 main types of chronic diseases include the cardiovascular diseases (CVDs), cancer, chronic respiratory diseases, and diabetes. Our study focuses on the first 2 main types, CVDs and cancer.

Cardiovascular disease (CVD) is the disease of heart and blood vessels, that among others, includes coronary heart disease (e.g. myocardial infarction), cerebrovascular disease (e.g. stroke), hypertensive heart disease, heart failure and diseases of the arteries. It is the first cause of death globally with about 18 million deaths in 2016. 85% of these deaths were due to heart attack and stroke. Most CVDs can be prevented using primary prevention measures against well-established modifiable risk factors such as smoking, obesity, unhealthy diet, sedentary lifestyle and physical inactivity. People with other known risk factors like hypertension, diabetes, dyslipidemia, and metabolic syndrome or already suffering from cardiovascular disease need proper identification and management with lifestyle measures and appropriate medication such as anti-hypertensive treatment and statins. There are many prognostic models for CVD and some of them are also recommended by clinical practice guidelines (e.g. Framingham Risk Score, SCORE, GRACE and CHA2DS2-VASc Score).

Cancer is characterized by the abnormal growth and spread of cells due to mutations in the proliferation or apoptosis cellular pathways. It is the second leading cause of death worldwide with about 9.5 million deaths in 2018, with a high economic impact for diagnosis and treatment. The site responsible for most new cancer cases is the prostate for men (20%) and breast for women (30%). However, in both sexes, most deaths are attributable to lung cancer (about 25%). Cancer shares many common risk factors with CVD including smoking, physical inactivity, obesity, unhealthy diet, and diabetes. Other important risk factors include alcohol, radiation (UV, ionizing), immunosuppression, chronic inflammation, and infection with specific agents (e.g. EBV, HIV, HCV, Hel. Pylori). The major prognostic factors for cancer are divided into tumor-related (TNM stage, cancer biomarkers), patient-related (demographics, comorbidities, immune status), and environment-related (access to specialized technology and drugs). Since cancer is a multifactorial disease, prognosis research emphasizes mainly in the identification of primary risk factors. The use of prognostic models in cancer is more limited compared to CVD and they are rarely recommended in clinical practice guidelines. However, there are still some useful models including the

Nottingham Prognostic Index (NPI) predicting the 5-year survival after breast cancer surgery, the Bach Model, and Adjuvant!.

For many years, the field of prognosis lacked a unified taxonomy or a clear distinction between different types of prognosis research. However, in 2013 the PROGNosis RESEARCH Strategy (PROGRESS) partnership proposed a framework of 4 distinct but interrelated types.

Type I or overall prognosis research refers to the average outcome risk in the population under study in the context, time, and setting of current healthcare. It focuses on prospective study design and the main sources of bias are the selection bias and the information bias. The statistics used are different for continuous, binary, and time-to-event outcomes. For continuous outcomes (e.g. blood pressure), the main measures of association include the mean and median combined with the standard deviation (SD), interquartile range (IQR), and histograms. The statistical model used is the linear regression model. For binary outcomes (e.g. death at 5 years), the most important measures of association include the absolute risk, the risk difference, the risk ratio (RR), and the odds ratio (OR), while the model used is that of logistic regression. Finally, for time-to-event outcomes, the most important summary measures and functions are the incidence rate, the survival function and its visual representation (the Kaplan-Meier curve), the hazard function, and the hazard ratio (HR). In this case, the statistical model usually used is the Cox proportional hazards regression model.

Type II or prognostic factor research, refers to studies investigating the characteristics (prognostic factors), that are associated with a change in outcome risk. These studies are further divided into exploratory and confirmatory studies. Exploratory studies are hypothesis-free studies that are useful in identification of new prognostic factors associated with an outcome. However, these hypotheses require some degree of biological reasoning. On the other hand, confirmatory studies are useful for the evaluation and validation of newly identified factors (by exploratory studies), after adjustment for already established ones published in biomedical literature.

Type III or prognostic model research, aims in development, validation, assessment of the performance, and evaluation of the impact of models consisting of multiple prognostic factors. For prognostic model development we use data from prospective cohort studies and randomized clinical trials. The candidate predictors variables are chosen a priori based on systematic review and expert opinion and we usually use 1 predictor per 10 events (outcomes). For the selection of the final predictors we use either the full approach method where all predictors are forced into the model or the stepwise regression approach with either forward selection or backward elimination of predictors. The model performance is usually assessed using the performance measures of discrimination and calibration. Discrimination is usually assessed using the C-index statistic or the AUC/ROC curve, and calibration using the Hosmer-Lemeshow test, the observed/expected ratio, or calibration plots. Model validation is divided into internal (using a part of the same or computed dataset) and external validation, which is further subcategorized into temporal, geographical, and setting validation.

Furthermore, updating a model in a new setting is usually achieved by adjusting of the baseline hazard risk and/or adjusting of all regression coefficients by one or more risk factors. When a new factor is added in a model in incremental value studies the new model performance is usually assessed using indexes like the Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) index. The final model can take many forms such as a simple risk score, an online calculator or a risk chart. However, in any case the original regression equation should always be available for future researchers. Finally, impact studies assess the model impact in

clinical practice. This requires both an intervention group (where the model is available) and a control group for comparison.

Type IV or predictors of treatment effect research examines which characteristics predict a different response to a specific-treatment. A predictor of treatment effect is any factor associated with the response to a specific intervention. There are many different study designs including treatment-only design, non-randomized comparative studies, and meta-analyses of comparative data. The main sources of bias are the type-I and type-II errors.

The aims of our study were:

1. To assess the extent of validation and the range of phenotypes and outcomes for which a major prognostic model in CVD, the Framingham Risk Score, has been used in medical literature,
2. To identify studies which develop or validate prediction models to estimate adverse health outcomes in patients with already established cardiovascular disease (secondary prevention models), and
3. To study the relationship between hypertension, a widely used prognostic marker, and the outcome of cancer (a chronic disease).

AIM I

The Framingham Risk Score (FRS) is a gender-specific algorithm used to estimate the 10-year coronary heart disease risk of healthy individuals. It is probably the most well-known and most validated model in CVDs. Our first aim was to map the expanded use of the FRS in the medical literature. Specifically, our aim was to examine the use of FRS in different populations and settings and for different outcomes than the ones originally developed for.

For this reason, we identified all citations to the original Wilson et al.1998 paper where FRS was originally described through ISI Web of Science until April 2011 (n=2413 citations). We selected studies that stated in their abstract that they calculated or used the FRS for any reason and extracted information on publication date, population studied, outcome or disease risk factor with which FRS was associated and study design.

We identified 375 eligible papers corresponding to 471 analyses using the FRS in cohort (n=141), case-control (n=16) or cross-sectional (n=314) settings. Only a minority of the cohort studies had as a primary aim to externally validate the FRS (n=45). The studied population was different (from general or healthy) in 35 (25%), and 133 (42%) of the cohort and cross-sectional analyses. All case-control studies examined healthy controls. The studied outcome was different (from coronary heart disease) in 79 (56%) of the cohort analyses and in 10 (63%) of the case-control studies. Overall, only 46 (33%) of the 141 cohort analyses examined the same outcome and population as FRS was originally developed for.

In conclusion, we found that a large number of studies use FRS in populations and for outcomes other than the ones it has been developed for, and therefore for which its performance is unknown and non-validated. The presence or absence of associations in non-CVD populations may just reflect the different performance of the model in this setting. Before using prognostic models in different settings than originally developed recalibration/update and external validation is required.

AIM II

The majority of prognostic models in CVDs refer to primary prevention. Models for secondary prevention are lacking and are usually not validated. Our second objective was to provide

a systematic evaluation of the methodology and models developed to predict the risk of future cardiovascular (CVD) events in patients with already established cardiovascular disease. We conducted a systematic review using MEDLINE and EMBASE between January 2004 and June 2013. 79 articles were included out of 9965 potentially eligible ones, describing the development of 80 new models, external validation of 88 and incremental value of risk factors in 30 other models.

Most new models were developed in USA and Canada (35%, n=28) followed by Europe (28%, n=22), on patients with ACS (34%) and known or suspected CAD (33%) with a mean age of 65 years, predicting all-cause mortality or major adverse cardiovascular events (MACE) (59%), with a prediction horizon of over 3 years (51%). The majority of models used Cox (68%, n=54) or logistic (23%, n=18) regression and 5 to 7 predictors (36%, n=29) with age, sex, history of CAD, diabetes and smoking being the risk factors most frequently used. 81% of models (n=65) used C-statistic/AUC and 38% (n=30) the Hosmer-Lemeshow test for discrimination and calibration respectively, with only 21 models (26%) being internally validated.

88 models were externally validated with patients from Europe and USA being represented in 71% of cases. 73% were performed in the same age range, 62% on the same population sample and 42% for the same outcome as the original study. Framingham Risk Score (FRS), CHADS2, SYNTAX and GRACE were the scores more frequently validated (39%) with 70% of models being also geographically validated. AUC/C-statistic was available for 82% of models. 30 models were incremented with populations from Europe and USA/Canada in 67%. ACS was the dominant baseline CVD (33%) and all-cause mortality and MACE were responsible for 54% of outcomes.

FRS was the model mostly incremented (21%, n=16) and CRP and NT-proBNP the most commonly examined risk factors. AUC/C-statistic change was the most frequently used model improvement measure (87%, n=26). Internal validation was rarely performed and some regions like Africa or South America were inadequately represented.

In conclusion, the number of articles about models of recurrent cardiovascular disease (CVD) risk is substantially smaller compared to their counterparts for apparently healthy individuals published during the same period. The majority of models used are newly derived models without proper external validation or models originally developed for general (e.g. FRS, SCORE) or other specific population (e.g. CHADS2, SYNTAX). As a consequence, no specific prognostic model is incorporated in current practice guidelines. Most risk factors for CVD outcomes are already well established and share a lot in common with those for secondary prevention, so that future efforts should be focused on the external validation and performance evaluation of already existing models.

AIM III

Our third aim was to assess the association between hypertension, a widely used prognostic factor in medical literature and site-specific cancer, one of the 4 main types of chronic diseases. With the exception of renal cell carcinoma, studies assessing the association between hypertension and other cancers are inconsistent. We conducted a meta-analysis to assess this evidence.

We included observational studies investigating the association between any definition of hypertension or systolic and diastolic blood pressure and risk of any cancer, after searching PubMed until November 2017. We calculated summary relative risks (RR) and 95% confidence intervals (CI) using inverse-variance weighted random effects methods. A total of 148 eligible publications were identified out of 39,891 initially screened citations. Our primary analysis included only prospective studies. Separate analyses were performed for systolic, diastolic blood pressure, and

hypertension. The quality of the included studies was assessed using the Newcastle-Ottawa Scale. 90% of studies (n=133) investigated cancer incidence.

Considering only evidence from 85 prospective studies, we conducted 30 meta-analyses of hypertension and 16 different cancers. Positive associations were observed between hypertension and kidney, colorectal and breast cancer. Positive associations between hypertension and risk of oesophageal adenocarcinoma and squamous cell carcinoma, liver and endometrial cancer were also observed, but the majority of studies did not perform comprehensive multivariable adjustments. Systolic and diastolic blood pressure were only associated with higher risk of kidney cancer.

In addition to the previously well-described association between hypertension and risk of kidney cancer, the current meta-analysis suggested that hypertensive individuals may also be at higher risk of colorectal and breast cancer. However, careful interpretation is required as most meta-analyses included relatively small number of studies, several relative risks had weak or moderate magnitude and maybe affected by residual confounding.

ΠΕΡΙΛΗΨΗ ΣΤΗΝ ΕΛΛΗΝΙΚΗ

Ως *πρόγνωση* ορίζεται η πιθανότητα εμφάνισης μιας κατάστασης σε συγκεκριμένη χρονική περίοδο, με βάση το κλινικό ή μη-κλινικό προφίλ. *Προγνωστικός παράγοντας* είναι κάθε χαρακτηριστικό (μεταβλητή) που σχετίζεται με τον κίνδυνο μιας έκβασης υγείας, σε ανθρώπους με μία συγκεκριμένη πάθηση. Τέλος, ένα *προγνωστικό μοντέλο* είναι μια μαθηματική συνάρτηση που συσχετίζει συγκεκριμένους προγνωστικούς παράγοντες με την πιθανότητα (κίνδυνο) εμφάνισης μιας συγκεκριμένης έκβασης, σε έναν καλά ορισμένο πληθυσμό και σε συγκεκριμένη χρονική περίοδο.

Η έρευνα στην πρόγνωση και τα προγνωστικά μοντέλα είναι καίρια για τη συμβουλευτική των ασθενών και τη λήψη κλινικών αποφάσεων. Η σύγχρονη ιατρική, με την εξατομικευμένη αντιμετώπιση και τις διαβαθμισμένες παροχές υγείας, βασίζεται σε αυτές τις αρχές. Επιπλέον, η πρόγνωση είναι σημαντική για την καθοδήγηση πολιτικών υγείας, για τις ασφαλιστικές εταιρείες και για το σχεδιασμό κλινικών δοκιμών. Ωστόσο, για να είναι ένα μοντέλο χρήσιμο στην κάθε μέρα κλινική πράξη, χρειάζεται να βασίζεται σε βιολογικές αρχές, να είναι απλό, ακριβές και να προφέρει ένα βαθμό γενίκευσης και κλινικής αποτελεσματικότητας.

Δεν υπάρχει ένας κοινά αποδεκτός ορισμός για τις χρόνιες νόσους ώστοσο όλες έχουν κάποια κοινά χαρακτηριστικά: έχουν μια παρατεταμένη περίοδο ανάπτυξης με ένα πρώιμο ασυμπτωματικό στάδιο και συνήθως δεν έχουν οριστική θεραπεία. Σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας, στα 4 κύρια είδη χρόνιων νόσων περιλαμβάνονται η καρδιαγγειακή νόσος, ο καρκίνος, οι χρόνιες νόσοι του αναπνευστικού και ο διαβήτης. Η μελέτη μας επικεντρώνεται στους πρώτους 2 κύριους τύπους, τις καρδιαγγειακές νόσους και τον καρκίνο.

Η καρδιαγγειακή νόσος είναι η νόσος της καρδιάς και των αιμοφόρων αγγείων η οποία, ανάμεσα στα άλλα, περιλαμβάνει τη στεφανιαία νόσο (π.χ. το έμφραγμα του μυοκαρδίου), την εγκεφαλική αγγειακή νόσο, (π.χ. αγγειακό εγκεφαλικό επεισόδιο), την υπερτασική καρδιοπάθεια, την καρδιακή ανεπάρκεια και τις νόσους των περιφερικών αρτηριών. Είναι η πρώτη αιτία θανάτου παγκοσμίως με περίπου 18 εκατομμύρια θανάτους το 2016. Ποσοστό 85% αυτών των θανάτων οφείλονταν σε έμφραγμα ή εγκεφαλικό επεισόδιο. Τα περισσότερα καρδιαγγειακά νοσήματα μπορούν να αποφευχθούν με πρωτογενή προληπτικά μέτρα έναντι καλώς τεκμηριωμένων

παραγόντων κινδύνου όπως είναι το κάπνισμα, η παχυσαρκία, η ανθυγιεινή διατροφή, η καθιστική ζωή και η έλλειψη φυσικής άσκησης. Άτομα με άλλους γνωστούς παράγοντες κινδύνου, όπως η υπέρταση, ο διαβήτης, η δυσλιπιδαιμία και το μεταβολικό σύνδρομο ή άτομα που ήδη έχουν αναπτύξει καρδιαγγειακή νόσο, χρειάζονται έγκαιρη ανίχνευση και διαχείριση, τόσο με μέτρα που αφορούν την αλλαγή του τρόπου ζωής όσο και με κατάλληλη θεραπευτική αγωγή, όπως είναι τα αντιυπερτασικά φάρμακα και οι στατίνες. Υπάρχουν πολλά προγνωστικά μοντέλα καρδιαγγειακής νόσου και μερικά από αυτά συστήνονται από τις κατευθυντήριες οδηγίες. (π.χ. Framingham Risk Score, SCORE, GRACE and CHA2DS2-VASc Score).

Ο καρκίνος χαρακτηρίζεται από την ανώμαλη κυτταρική ανάπτυξη και διασπορά λόγω μεταλλάξεων στα κυτταρικά μονοπάτια που αφορούν τον κυτταρικό πολλαπλασιασμό ή την κυτταρική απόπτωση. Αποτελεί τη δεύτερη κύρια αιτία θανάτου παγκοσμίως, αριθμώντας περίπου 9,5 εκατομμύρια θανάτους το 2018, με μεγάλο οικονομικό αντίκτυπο για τη διάγνωση και τη θεραπεία του. Στους άνδρες, οι περισσότερες νέες περιπτώσεις καρκίνου (20%) αφορούν τον προστάτη, ενώ στις γυναίκες το μαστό (30%). Ωστόσο και στα δύο φύλα οι περισσότεροι θάνατοι οφείλονται σε καρκίνο του πνεύμονα (ποσοστό περίπου 25%). Ο καρκίνος και η καρδιαγγειακή νόσος έχουν πολλούς κοινούς παράγοντες κινδύνου όπως το κάπνισμα, η παχυσαρκία, η έλλειψη φυσικής άσκησης, η ανθυγιεινή διατροφή και ο διαβήτης. Άλλοι σημαντικοί παράγοντες κινδύνου περιλαμβάνουν τη λήψη αλκοόλ, την ακτινοβολία (UV ή ιονίζουσα), την ανοσοκαταστολή, τη χρόνια φλεγμονή και συγκεκριμένους λοιμώδεις παράγοντες (EBV, HIV, HCV, Hel. Pylori). Οι κύριοι προγνωστικοί παράγοντες για τον καρκίνο διαχωρίζονται σε όσους σχετίζονται με τον όγκο (στάδιο, βιοδείκτες καρκίνου), σε όσους σχετίζονται με τον ασθενή (δημογραφικά χαρακτηριστικά, συννοσηρότητα, κατάσταση ανοσοποιητικού συστήματος) και σε όσους σχετίζονται με το περιβάλλον (πρόσβαση σε εξειδικευμένη τεχνολογία και φάρμακα). Καθώς ο καρκίνος είναι μία πολυπαραγοντική νόσος, η προγνωστική έρευνα επικεντρώνεται κυρίως στην αναγνώριση των πρωταρχικών παραγόντων κινδύνου. Η χρήση των προγνωστικών μοντέλων στον καρκίνο είναι πιο περιορισμένη σε σχέση με την καρδιαγγειακή νόσο και σπάνια περιλαμβάνονται στις κατευθυντήριες οδηγίες. Ωστόσο, υπάρχουν κάποια χρήσιμα μοντέλα όπως το Nottingham Prognostic Index που προβλέπει την πενταετή επιβίωση ύστερα από επέμβαση για καρκίνο μαστού, το μοντέλο Bach και το μοντέλο Adjuvant!.

Για πολλά χρόνια στον τομέα της πρόγνωσης δεν υπήρχε μία ενοποιημένη ταξινόμηση ή ένας σαφής διαχωρισμός μεταξύ των διαφόρων ειδών προγνωστικής έρευνας. Ωστόσο, το 2013 δημιουργήθηκε μια σύμπραξη, η PROGNosis RESEARCH Strategy (PROGRESS), που πρότεινε τέσσερα διακριτά αλλά συγγενικά είδη.

Ο τύπος 1 ή γενική προγνωστική έρευνα αναφέρεται στο μέσο κίνδυνο έκβασης που διατρέχει ο πληθυσμός μελέτης, στο πλαίσιο, χρόνο και υπό τις συνθήκες του παρόντος συστήματος υγείας. Επικεντρώνεται κυρίως σε μελέτες προοπτικού σχεδιασμού και οι κύριες πηγές συστηματικού σφάλματος αφορούν το σφάλμα επιλογής και το σφάλμα πληροφορίας. Τα μέτρα σχέσης που χρησιμοποιούνται είναι διαφορετικά για συνεχείς, διχότομες και εκβάσεις που συμβαίνουν στο χρόνο. Για τις συνεχείς εκβάσεις, όπως παραδείγματος χάρη η αρτηριακή πίεση, τα κύρια μέτρα σχέσης περιλαμβάνουν τη μέση και διάμεση τιμή, σε συνδυασμό με την τυπική απόκλιση (SD), το ενδοτεταρτημοριακό εύρος (IQR) και τα ιστογράμματα. Το στατιστικό μοντέλο που χρησιμοποιείται είναι το μοντέλο γραμμικής παλινδρόμησης (linear regression). Για τις διχότομες εκβάσεις (π.χ. θάνατος σε 5 έτη) τα πιο σημαντικά μέτρα σχέσης περιλαμβάνουν τον απόλυτο κίνδυνο, τη διαφορά κινδύνου, το λόγο κινδύνων (RR) και το λόγο των πιθανοτήτων (OR), ενώ το μοντέλο που χρησιμοποιείται είναι αυτό της λογιστικής παλινδρόμησης (logistic regression). Τέλος, για τις εκβάσεις που συμβαίνουν στο χρόνο, τα πιο σημαντικά μέτρα σχέσης και συναρτήσεις είναι

το ποσοστό επίπτωσης, η συνάρτηση επιβίωσης και η γραφική αναπαράστασή της (η καμπύλη Kaplan-Meier), η συνάρτηση στιγμιαίου κινδύνου και ο λόγος στιγμιαίων κινδύνων (HR). Σε αυτή την περίπτωση το στατιστικό μοντέλο που συνήθως χρησιμοποιείται είναι το μοντέλο παλινδρόμησης αναλογικών στιγμιαίων κινδύνων κατά Cox (Cox proportional hazards regression).

Ο τύπος II ή έρευνα προγνωστικών παραγόντων αναφέρεται σε μελέτες που εξετάζουν τα χαρακτηριστικά (προγνωστικούς παράγοντες) που σχετίζονται με μεταβολή στον κίνδυνο της έκβασης. Αυτές οι έρευνες διαχωρίζονται επιπλέον σε διερευνητικές και μελέτες επικύρωσης. Οι διερευνητικές είναι μελέτες που χρησιμοποιούνται στην αναγνώριση νέων προγνωστικών παραγόντων που σχετίζονται με μία έκβαση, χωρίς περιορισμούς στη διαμόρφωση υποθέσεων (hypothesis-free studies). Το μόνο που απαιτείται στις υποθέσεις είναι κάποιος βαθμός βιολογικής λογικής. Από την άλλη οι επιβεβαιωτικές έρευνες ή έρευνες επικύρωσης, χρησιμοποιούνται στην εκτίμηση και επικύρωση νεοαναγνωρισθέντων παραγόντων, όπως προκύπτουν από τις ερευνητικές μελέτες, ύστερα από προσαρμογή (adjustment) για ήδη γνωστούς παράγοντες στην ιατρική βιβλιογραφία.

Ο τύπος III ή έρευνα των προγνωστικών μοντέλων, στοχεύει στην ανάπτυξη, επικύρωση, εκτίμηση της απόδοσης και αποτίμηση της επίπτωσης μοντέλων που αποτελούνται από πολλαπλούς προγνωστικούς παράγοντες. Για την ανάπτυξη ενός προγνωστικού μοντέλου χρησιμοποιούνται δεδομένα από προοπτικές μελέτες κοορτής και τυχαιοποιημένες κλινικές δοκιμές. Οι υποψήφιοι προγνωστικοί παράγοντες επιλέγονται εκ των προτέρων με βάση τη συστηματική ανασκόπηση της βιβλιογραφίας και τη γνώμη ειδικών και συνήθως χρησιμοποιείται ένας προγνωστικός παράγοντας ανά 10 γεγονότα-εκβάσεις. Για την επιλογή των τελικών προγνωστικών παραγόντων χρησιμοποιούμε είτε τη μέθοδο της ολικής προσέγγισης (full model approach), στην οποία όλοι οι παράγοντες εισάγονται στο μοντέλο είτε τη μέθοδο της σταδιακής παλινδρόμησης, επιλέγοντας τους παράγοντες σταδιακά στην πορεία (forward selection) ή περιορίζοντας τους προγνωστικούς παράγοντες ανάστροφα (backward elimination). Η απόδοση του μοντέλου συνήθως εκτιμάται με μέτρα όπως η διακριτική (discrimination) και η προσαρμοστική (calibration) ικανότητα. Η διακριτική ικανότητα εκτιμάται συνήθως με το C-index ή την καμπύλη ROC/AUC και η προσαρμοστική με το Hosmer-Lemeshow τεστ, το λόγο παρατηρούμενων/προσδοκώμενων εκβάσεων και τις καμπύλες προσαρμογής. Η επικύρωση του μοντέλου διαχωρίζεται σε εσωτερική (που χρησιμοποιεί ένα μέρος του αρχικού δείγματος πληθυσμού ή τεχνητά υπολογιστικά δεδομένα-bootstrapping) και εξωτερική η οποία κατηγοριοποιείται περαιτέρω σε χρονική, γεωγραφική και επικύρωση συνθηκών.

Η ανανέωση/εκσυγχρονισμός του μοντέλου σε νέες συνθήκες συνήθως επιτυγχάνεται είτε με προσαρμογή (adjustment) του βασικού στιγμιαίου κινδύνου είτε με προσαρμογή όλων των συντελεστών παλινδρόμησης με βάση έναν ή περισσότερους παράγοντες κινδύνου. Όταν ένας νέος παράγοντας προστίθεται σε ένα υπάρχον μοντέλο στις μελέτες αύξησης προγνωστικής αξίας, η νέα απόδοση του μοντέλου συνήθως εκτιμάται με δείκτες όπως ο NRI (Net Reclassification Index) και ο IDI (Integrated Improvement Index). Το τελικό μοντέλο μπορεί να πάρει πολλές μορφές όπως ένα απλό σκορ κινδύνου, ένας online υπολογιστής (calculator) ή ένα διάγραμμα κινδύνου. Ωστόσο, σε κάθε περίπτωση η αρχική συνάρτηση παλινδρόμησης πρέπει πάντα να είναι διαθέσιμη για τους μελλοντικούς ερευνητές. Τέλος, οι μελέτες επίπτωσης εκτιμούν τον αντίκτυπο του μοντέλου στην κλινική πράξη. Για αυτές τις μελέτες απαιτείται τόσο μια ομάδα παρέμβασης (όπου είναι διαθέσιμο το μοντέλο) όσο και μια ομάδα ελέγχου (control-group) για σύγκριση.

Ο τύπος IV ή έρευνα προγνωστικών παραγόντων απάντησης στη θεραπεία, εξετάζει ποια χαρακτηριστικά προβλέπουν τη διαφορετική ανταπόκριση σε μία συγκεκριμένη θεραπεία.

Προγνωστικός παράγοντας απάντησης στη θεραπεία αποτελεί κάθε παράγοντας που σχετίζεται με την ανταπόκριση σε συγκεκριμένη παρέμβαση. Υπάρχουν πολλοί διαφορετικοί σχεδιασμοί μελετών που περιλαμβάνουν το σχεδιασμό μονοθεραπείας (treatment-only), συγκριτικές μη τυχαιοποιημένες μελέτες και μετά-αναλύσεις συγκριτικών δεδομένων. Τα σφάλματα τύπου-I και τύπου-II αποτελούν τους κυριότερους περιορισμούς.

Οι στόχοι της παρούσας μελέτης ήταν οι εξής:

1. Η εκτίμηση της έκτασης επικύρωσης και της ποικιλίας των φαινότυπων και των εκβάσεων για τις οποίες, ένα από τα σημαντικότερα προγνωστικά μοντέλα καρδιαγγειακής νόσου, το Framingham Risk Score, έχει χρησιμοποιηθεί στην ιατρική βιβλιογραφία.
2. Η ταυτοποίηση μελετών οι οποίες αναπτύσσουν ή επικυρώνουν προγνωστικά μοντέλα για την εκτίμηση δυσμενών εκβάσεων υγείας σε ασθενείς με ήδη εγκατεστημένη καρδιαγγειακή νόσο (μοντέλα δευτερογενούς πρόληψης), και
3. Η μελέτη της σχέσης μεταξύ της υπέρτασης, ενός ευρέως χρησιμοποιούμενου προγνωστικού δείκτη, και της έκβασης του καρκίνου (μίας χρόνιας νόσου).

ΣΚΟΠΟΣ I

Το Framingham Risk Score (FRS) είναι ένας, διαφοροποιούμενος ανάλογα το φύλο, αλγόριθμος που χρησιμοποιείται για την εκτίμηση του 10-ετούς κινδύνου ανάπτυξης στεφανιαίας νόσου σε υγιή άτομα. Είναι ίσως το πιο γνωστό και περισσότερο επικυρωμένο μοντέλο στις καρδιαγγειακές παθήσεις. Ο πρώτος στόχος μας ήταν να χαρτογραφήσουμε τη χρήση του FRS στην ιατρική βιβλιογραφία. Συγκεκριμένα, σκοπός μας ήταν να εξετάσουμε τη χρήση του FRS σε διαφορετικούς πληθυσμούς και συνθήκες και για διαφορετικές εκβάσεις σε σχέση με αυτές για τις οποίες αρχικώς δημιουργήθηκε.

Για τον σκοπό αυτό εντοπίσαμε όλες τις παραπομπές στο άρθρο του Wilson και συν. (1998), όπου το FRS αρχικώς περιγράφηκε, μέσω της μηχανής αναζήτησης “ISI Web of Science” μέχρι τον Απρίλιο του 2011 (n=2413 αναφορές). Επιλέχθηκαν μελέτες που ανέφεραν στην περίληψή τους ότι υπολόγισαν ή χρησιμοποίησαν το FRS για οποιοδήποτε λόγο και εξαγάγαμε πληροφορίες για την ημερομηνία δημοσίευσης, τον υπό μελέτη πληθυσμό, την έκβαση ή τον παράγοντα κινδύνου με τον οποίο συσχετίστηκε το FRS, καθώς και για το σχεδιασμό της μελέτης.

Εντοπίσαμε 375 δόκιμα άρθρα που αντιστοιχούσαν σε 471 αναλύσεις και χρησιμοποίησαν το FRS σε προοπτικές μελέτες (n=141), ασθενών-μαρτύρων (n=16) ή μελέτες επιπολασμού (n=314). Μόνο μια μειοψηφία των προοπτικών μελετών είχε ως κύριο στόχο την εξωτερική επικύρωση του FRS (n=45). Ο πληθυσμός που μελετήθηκε ήταν διαφορετικός (από γενικό ή υγιή πληθυσμό) σε 35 (25%) και 133 (42%) από τις αναλύσεις κοόρτης και επιπολασμού αντίστοιχα. Όλες οι μελέτες ασθενών-μαρτύρων εξέτασαν υγιείς μάρτυρες. Η έκβαση υπό εξέταση ήταν διαφορετική (από στεφανιαία νόσο) σε 79 (56%) από τις προοπτικές αναλύσεις και σε 10 (63%) από τις μελέτες ασθενών-μαρτύρων. Συνολικά, μόνο 46 (33%) από τις 141 προοπτικές αναλύσεις εξέταζαν την ίδια έκβαση και πληθυσμό με την αρχική μελέτη για το FRS.

Συμπερασματικά, ένας μεγάλος αριθμός μελετών χρησιμοποιούν το FRS για διαφορετικούς πληθυσμούς και εκβάσεις από αυτές για τις οποίες αρχικά δημιουργήθηκε, όπου η απόδοσή του είναι άγνωστη και μη επικυρωμένη. Η παρουσία ή η απουσία συσχετίσεων σε μη καρδιαγγειακούς πληθυσμούς ίσως απλά αντανακλά τη διαφορετική απόδοση του μοντέλου σε αυτές τις συνθήκες. Πριν από την εφαρμογή προγνωστικών μοντέλων σε διαφορετικές συνθήκες σε σχέση με αυτές που αρχικώς δημιουργήθηκαν, χρειάζεται αναπροσαρμογή/ανανέωση και εξωτερική επικύρωση του μοντέλου.

ΣΚΟΠΟΣ II

Η πλειοψηφία των προγνωστικών μοντέλων στις καρδιαγγειακές παθήσεις αναφέρονται στην πρωτογενή πρόληψη. Τα μοντέλα που αναφέρονται στη δευτερογενή πρόληψη υπολείπονται σημαντικά και συνήθως δεν έχουν επικυρωθεί. Στόχος μας ήταν να παρέχουμε μια συστηματική αξιολόγηση της μεθοδολογίας και των μοντέλων που έχουν αναπτυχθεί για να προβλέψουν τον κίνδυνο εμφάνισης καρδιαγγειακών συμβαμάτων σε ασθενείς με ήδη εγκαταστημένη καρδιαγγειακή νόσο. Πραγματοποιήσαμε μια συστηματική ανασκόπηση χρησιμοποιώντας τις βάσεις δεδομένων MEDLINE και EMBASE μεταξύ Ιανουαρίου 2004 και Ιουνίου 2013. Περιλήφθηκαν 79 άρθρα από 9965 δυνητικά δόκιμων μελετών, που περιέγραφαν την ανάπτυξη 80 νέων μοντέλων, την εξωτερική επικύρωση 88 και την αυξητική αξία παραγόντων κινδύνου σε 30 άλλα μοντέλα.

Τα περισσότερα νέα μοντέλα αναπτύχθηκαν στις Ηνωμένες Πολιτείες και τον Καναδά (35%, $n=28$), ακολουθούμενα από την Ευρώπη (28%, $n=22$), σε ασθενείς με οξύ στεφανιαίο σύνδρομο (34%) και γνωστή ή υποψία στεφανιαίας νόσου (33%), με μέση ηλικία τα 65 έτη και με ορίζοντα πρόβλεψης άνω των 3 ετών (51%). Η πλειοψηφία των μοντέλων χρησιμοποίησε Cox (68%, $n=54$) ή λογιστική παλινδρόμηση (23%, $n=18$) και 5 έως 7 προγνωστικούς παράγοντες (36%, $n=29$), με την ηλικία, το φύλο, το ιστορικό στεφανιαίας νόσου, το διαβήτη και το κάπνισμα να αποτελούν τους πιο συχνά χρησιμοποιούμενους παράγοντες. Το 81% των μοντέλων ($n=65$) χρησιμοποίησαν το C-statistic/AUC και 38% ($n=30$) το Hosmer-Lemeshow τεστ για τη διακριτική ικανότητα (discrimination) και προσαρμογή του μοντέλου (calibration) αντίστοιχα, με μόνο 21 μοντέλα (26%) να έχουν εσωτερική επικύρωση.

Στα 88 μοντέλα που αφορούσαν εξωτερική επικύρωση, οι ασθενείς από την Ευρώπη και τις ΗΠΑ εκπροσωπήθηκαν στο 71% των περιπτώσεων. Ποσοστό 73% αφορούσαν την ίδια περίπου ηλικία, 62% το ίδιο δείγμα πληθυσμού και 42% το ίδιο αποτέλεσμα με την αρχική, πρότυπη μελέτη. Το Framingham Risk Score, το CHADS2, το SYNTAX και το GRACE ήταν τα πιο συχνά επικυρωμένα μοντέλα (39%), ενώ το 70% των μοντέλων επικυρώθηκε επίσης γεωγραφικά. Το AUC/C-statistic ήταν διαθέσιμο για το 82% των μοντέλων. Τριάντα μοντέλα προσαυξήθηκαν με πληθυσμούς από την Ευρώπη και ΗΠΑ/Καναδά στο 67%. Η στεφανιαία νόσος ήταν η κύρια αρχική καρδιαγγειακή νόσος (33%) και η θνησιμότητα από όλες τις αιτίες και τα μείζονα καρδιαγγειακά συμβαμάτα (MACE) ήταν υπεύθυνα για το 54% των εκβάσεων.

Το FRS ήταν το μοντέλο που πρωτίστως προσαυξήθηκε με νέους παράγοντες κινδύνου (21%, $n=16$), με το CRP και το NT-proBNP να αποτελούν τους πιο συχνά εξεταζόμενους παράγοντες. Το AUC/C-statistic ήταν το πιο συχνά χρησιμοποιούμενο μέτρο σύγκρισης της βελτίωσης του μοντέλου (87%, $n = 26$). Η εσωτερική επικύρωση πραγματοποιήθηκε σε ελάχιστες περιπτώσεις και ορισμένες περιοχές όπως η Αφρική ή η Νότια Αμερική εκπροσωπήθηκαν ανεπαρκώς.

Συμπερασματικά, ο αριθμός των άρθρων για τα μοντέλα επανεμφάνισης καρδιαγγειακών νοσημάτων (CVD) είναι σημαντικά μικρότερος σε σύγκριση με τον αντίστοιχο αριθμό για τα μοντέλα που αφορούν υγιή άτομα που δημοσιεύθηκαν κατά την ίδια περίοδο. Η πλειοψηφία των μοντέλων που χρησιμοποιούνται είναι νέα μοντέλα που δημιουργούνται χωρίς κατάλληλη εξωτερική επικύρωση ή μοντέλα που αναπτύχθηκαν αρχικά για το γενικό πληθυσμό (π.χ. FRS, SCORE) ή άλλο πληθυσμό με ιδιαίτερα χαρακτηριστικά (π.χ. CHADS2, SYNTAX). Συνεπώς, στις τρέχουσες κατευθυντήριες οδηγίες δεν προτείνεται κάποιο συγκεκριμένο μοντέλο για δευτερογενή πρόγνωση καρδιαγγειακών νοσημάτων. Ωστόσο, καθώς οι περισσότεροι παράγοντες κινδύνου καρδιαγγειακής νόσου έχουν ήδη καθιερωθεί και μοιράζονται πολλά κοινά με αυτά της δευτερογενούς πρόληψης, οι μελλοντικές προσπάθειες θα έπρεπε να επικεντρωθούν στην εξωτερική επικύρωση και την αξιολόγηση της απόδοσης των ήδη υπάρχοντων μοντέλων και όχι στη δημιουργία νέων.

ΣΚΟΠΟΣ ΙΙΙ

Ο τρίτος στόχος μας ήταν να εκτιμήσουμε την ύπαρξη πιθανής συσχέτισης μεταξύ της υπέρτασης, ενός ευρέως χρησιμοποιούμενου δείκτη στην ιατρική βιβλιογραφία και του καρκίνου, ενός από τα 4 κύρια ήδη χρονίων νόσων. Με την εξαίρεση του νεφροκυτταρικού καρκίνου, οι μελέτες που εκτιμούν τη συσχέτιση μεταξύ υπέρτασης και άλλων καρκίνων είναι συχνά αντιφατικές. Διεξήγαμε μια μετα-ανάλυση για να εκτιμήσουμε αυτή τη σχέση.

Συγκεκριμένα, συμπεριλάβαμε μελέτες παρατήρησης που ερευνούσαν τη συσχέτιση μεταξύ οποιουδήποτε ορισμού υπέρτασης ή συστολικής και διαστολικής πίεσης, και του κινδύνου ανάπτυξης οποιασδήποτε μορφής καρκίνου, αφού πρώτα εκτελέσαμε αναζήτηση στο PubMed μέχρι και το Νοέμβριο του 2017. Υπολογίσαμε τους συνολικούς σχετικούς κινδύνους (summary relative risks - RRs) και τα 95% διαστήματα εμπιστοσύνης (confidence intervals), χρησιμοποιώντας μεθόδους σταθμισμένων τυχαίων επιδράσεων αντίστροφης διακύμανσης (inverse-variance weighted random effects methods). Συνολικά εντοπίστηκαν 148 δόκιμες δημοσιεύσεις από τις 39,891 παραπομπές που αρχικώς εξετάστηκαν. Η πρωτογενής μας ανάλυση περιέλαβε μόνο προοπτικές μελέτες. Ξεχωριστές αναλύσεις διενεργήθηκαν για συστολική, διαστολική αρτηριακή πίεση και υπέρταση. Η ποιότητα των μελετών εκτιμήθηκε με την κλίμακα Newcastle-Ottawa. Το 90% των μελετών που χρησιμοποιήθηκαν μελέτησαν την επίπτωση καρκίνου.

Λαμβάνοντας υπόψη μόνο δεδομένα από τις 85 προοπτικές μελέτες διεξήγαμε 30 μετα-αναλύσεις για 16 διαφορετικά ήδη καρκίνου. Θετικές συσχετίσεις παρατηρήθηκαν μεταξύ υπέρτασης και νεφρικού, ορθοκολικού και καρκίνου του μαστού. Παρατηρήθηκαν επίσης θετικές συσχετίσεις μεταξύ υπέρτασης και κινδύνου για αδενοκαρκίνωμα και καρκίνωμα εκ πλακωδών κυττάρων του οισοφάγου, καρκίνου του ήπατος, καθώς και καρκίνου του ενδομητρίου. Ωστόσο, η πλειοψηφία των μελετών αυτών δεν είχε προβεί σε εκτεταμένες πολυπαραγοντικές προσαρμογές για συνήθεις συγχυτικούς παράγοντες. Η συστολική και διαστολική αρτηριακή πίεση συσχετίστηκαν μόνο με υψηλότερο κίνδυνο για νεφρικό καρκίνο.

Συμπερασματικά, επιπροσθέτως της ήδη γνωστής συσχέτισης μεταξύ υπέρτασης και καρκίνου του νεφρού, η τρέχουσα μετα-ανάλυση πρότεινε ότι οι ασθενείς με υπέρταση ίσως εμφανίζουν επίσης υψηλότερο κίνδυνο για εμφάνιση ορθοκολικού καρκίνου και καρκίνου του μαστού. Ωστόσο, απαιτείται προσεκτική ερμηνεία των αποτελεσμάτων καθώς οι περισσότερες μετα-αναλύσεις περιελάμβαναν ένα σχετικά μικρό αριθμό μελετών, αρκετοί σχετικοί κίνδυνοι είχαν αδύναμη ή μέτρια στατιστική ισχύ και ίσως επηρεάζονται από υπολειπόμενους συγχυτικούς παράγοντες.

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