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ARI VOUTILAINEN

STATISTICAL VALIDITY IN PROSPECTIVE COHORT STUDIES OF CORONARY HEART DISEASE AND ITS IMPACT ON STUDY RESULTS

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ABSTRACT

Prospective cohort studies of coronary heart disease have yielded results that are partly contradictory. The reasons behind this inconsistency are diverse. Some relate to inevitable differences across cohorts that may originate from cultural issues and different health care systems, for example. Some of the reasons, however, are because of the differences in data handling. Even closely related studies may produce contradictory results if they apply different techniques in the data preprocess and statistical analyses.

As its first research question, this thesis evaluated the current statistical validity in prospective cohort studies of coronary heart disease (CHD). The thesis introduced a systematic evaluation procedure that facilitates researchers in assessing the statistical validity of scientific journal articles that report prospective cohort studies of CHD and its risk factors. The procedure focuses on six statistical topics: the exclusion of study participants, time dependency and the interactions among study variables, the effect of follow-up time on study results, outcome sensitivity, competing risks, and missing data. Prospective CHD articles (n = 105) published in 2021 by scientific journals focusing mainly on epidemiology served as the study material for the evaluation.

Regarding the other research questions, this thesis demonstrated how the semisubjective statistical choices that researchers make before and during data handling affect the results of prospective CHD studies. The demonstrations assessed the advantages and disadvantages of data exclusions, compared continuous to categorical covariates, and analyzed different study outcomes (these related to the second research question on data preprocessing); investigated multiplicative, additive, and interactive associations (the third research question); and tested different risk factor–specific follow-up times (the fourth research question). Multiplicativity also covers time-dependency.

The subcohort of 2,682 middle-aged men from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) constituted the study material. Additional study material—a collection of 81 prospective cohort studies on the association of CHD with its behavior-related risk factors among men—was related specifically to detecting of the most appropriate risk factor–specific follow-up times. The articles belonging to the additional study material were discovered by reviewing meta-analyses published by May 2022 in scientific journals.

Several different statistical methods and tests were applied. The focus was on survival analysis, interactions, and time dependency. The Cox proportional hazards model was the core method.

The overall statistical validity of current prospective cohort studies of CHD and its risk factors was found to be poor. The mean validity score was 1.9 on a scale of zero to six. None of the articles reached the maximum score. One article scored 4.5 points, but 12% of the articles had not considered the evaluated statistical topics.

The demonstrations based on the KIHD data yielded three main results. The demonstrations did not find a statistical reason to exclude study participants who were not free from CHD at baseline; they detected mostly multiplicative but also additive and interactive associations across study variables; and they found the most appropriate follow-up time as being dependent on the risk factor and CHD manifestation in question. In most risk factor–outcome combinations the most appropriate follow-up time was 5–20 years.

To conclude, regarding the four research questions of this thesis, 1) it is evident that epidemiology does not value statistics enough. A widespread systematic procedure could help researchers and journals improve the overall statistical validity in the discipline, but it is hard to see this taking place without a simultaneous attitude change. 2) Study participants who are not free from the disease at baseline should not be excluded unless a sensitivity analysis suggests otherwise. Moreover, it is recommended to execute separate statistical analyses for different CHD manifestations. 3) Presenting the results of multiplicative and additive survival models together with covariate interactions in the same articles would facilitate researchers in recognizing the most important epidemiological relationships. 4) The length of follow-up time may affect the strength of the relationship between the outcome and covariate. This should especially be considered when comparing the results of survival analyses across cohorts, across different study outcomes, or across different covariates predicting the same outcome.

Keywords: Cohort study; Coronary heart disease; Epidemiology; Follow-up study; Prospective study; Statistical validity; Survival analysis

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Tilastotieteellinen oikeellisuus sepelvaltimotaudin etenevissä kohorttitutkimuksissa ja sen vaikutukset tutkimustuloksiin
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TIIVISTELMÄ

Sepelvaltimotaudin etenevät seurantatutkimukset tuottavat osittain toisistaan poikkeavia tuloksia. Tulosten epäjohdonmukaisuuden syyt ovat moninaisia. Osa syistä liittyy tutkimuskohorttien välisiin eroihin, jotka puolestaan ovat peräisin yhteiskuntien välisistä eroista. Nämä syyt eivät ole vältettävissä. Osa syistä sen sijaan liittyy eroihin aineiston tilastollisessa käsittelyssä ja näihin syihin on mahdollista vaikuttaa. Jopa hyvin samankaltaiset tutkimukset voivat tuottaa ristiriitaisia tuloksia, jos niiden aineistoja esikäsitellään eri tavoin ja analysoidaan erilaisilla tilastollisilla menetelmillä.

Väitöskirjatyön ensimmäisenä tutkimuskysymyksenä oli arvioida sepelvaltimotaudin etenevien seurantatutkimusten tilastotieteellinen oikeellisuus. Tätä varten väitöskirjassa esiteltiin menetelmä, jonka avulla tutkijat voivat järjestelmällisesti arvioida tieteellisissä artikkeleissa raportoitujen sepelvaltimotaudin ja sen riskitekijöiden etenevien seurantatutkimusten tilastotieteellistä oikeellisuutta. Esitelty menetelmä keskittyy kuuteen tilastotieteelliseen aiheeseen: aineiston rajaaminen, tutkimusmuuttujien vuorovaikutukset ja aikariippuvuus, seuranta-ajan vaikutus tutkimustuloksiin, päätemuuttujan herkkyys, kilpailevat riskit ja puuttuvat tiedot. Arvioinnin kohteena olivat epidemiologisesti

suuntautuneissa tiedelehdissä vuonna 2021 julkaistut sepelvaltimotaudin eteneviä tutkimuksia käsitelleet artikkelit (*n* = 105).

Väitöskirjan 2.–4. tutkimuskysymyksiin liittyen havainnollistettiin, miten tutkijan tekemät osittain subjektiiviset aineiston esikäsittelyyn ja tilastolliseen analysointiin liittyvät valinnat vaikuttavat sepelvaltimotaudin etenevän seurantatutkimuksen tuloksiin. Toinen tutkimuskysymys keskittyi aineiston esikäsittelyyn ja sen osatutkimuksissa arvioitiin aineiston rajaamisen hyötyjä ja haittoja, vertailtiin jatkuvia ja luokittelevia muuttujia ja analysoitiin eri päätemuuttujia. Kolmantena tutkimuskysymyksenä selvitettiin muuttujien välisiä multiplikatiivisia, additiivisia ja vuorovaikutteisia yhteyksiä. Neljäntenä tutkimuskysymyksenä testattiin useita riskitekijäkohtaisia seuranta-aikoja. Multiplikatiivisuus sisältää myös aikariippuvuuden.

Kuopiolaiseen sepelvaltimotaudin vaaratekijätutkimukseen osallistuneet 2682 keski-ikäistä miestä muodostivat tutkimusaineiston, jonka avulla havainnollistettiin aineiston esikäsittelyn ja tilastomenetelmällisten valintojen vaikutuksia tutkimustuloksiin. Lisätutkimusaineistoa, 81 miesten sepelvaltimotaudin ja sen elintapariskitekijöiden etenevää seurantatutkimusta, käytettiin erityisesti riskitekijäkohtaisten seuranta-aikojen testaamiseen. Lisätutkimusaineisto koottiin käymällä läpi toukokuuhun 2022 mennessä julkaistut aihetta käsittelevät meta-analyysit.

Väitöskirjatyössä sovellettiin monia tilastollisia menetelmiä. Useimmat niistä liittyivät elinaika-analyysiin sekä muuttujien vuorovaikutukseen ja aikariippuvuuteen. Coxin regressionanalyysi oli keskeisin menetelmä.

Kaiken kaikkiaan sepelvaltimotaudin ja sen riskitekijöiden etenevien vuonna 2021 julkaistujen seurantatutkimusten tilastotieteellinen oikeellisuus oli huono. Keskimääräinen oikeellisuuspistemäärä oli 1,9 asteikolla 0–6. Yksikään artikkeleista ei saavuttanut maksimipistemäärää. Yhden artikkelin pistemäärä oli 4,5, mutta 12 prosentissa artikkeleista ei ollut lainkaan käsitelty arvioituja tilastotieteellisiä aiheita.

Sepelvaltimotaudin vaaratekijätutkimuksen aineistoa hyödyntäneissä osatöissä ei havaittu tilastollista perustetta rajata aineiston ulkopuolelle tutkittavat, joilla oli sepelvaltimotauti jo tutkimuksen lähtötilanteessa. Tutkimusmuuttujien yhteydet olivat pääsääntöisesti multiplikatiivisia,

mutta myös additiivisia ja vuorovaikutuksellisia yhteyksiä havaittiin. Tarkoituksenmukaisin seuranta-aika oli jossain määrin riippuvainen sekä sepelvaltimotaudin ilmenemismuodosta että riskitekijästä. Useimmissa tapauksissa tarkoituksenmukaisin seuranta-aika oli 5–20 vuotta.

Johtopäätöksinä neljään tutkimuskysymykseen liittyen todetaan seuraavaa. 1) On selvää, että epidemiologiassa ei kiinnitetä riittävästi huomiota tutkimuksen tilastotieteelliseen oikeellisuuteen. Laajalevikkinen järjestelmällinen arviointimenetelmä voisi auttaa tutkijoita ja tiedelehtiä kohentamaan tilannetta, mutta ilman samanaikaista asennemuutosta myönteistä kehitystä lienee turha olettaa tapahtuvaksi. 2) Tutkittavia, joilla on kiinnostuksen kohteena oleva sairaus jo tutkimuksen lähtötilanteessa, ei tulisi rajata aineiston ulkopuolelle, ellei herkkyysanalyysin tulos anna siihen aihetta. Lisäksi on suositeltavaa analysoida sepelvaltimotaudin eri ilmenemismuodot erillisinä päätemuuttujina. 3) Multiplikatiivisten ja additiivisten elinaika-analyysien sekä muuttujien vuorovaikutusten esittäminen samassa tutkimusraportissa edesauttaisi tärkeimpien epidemiologisten yhteyksien tunnistamista. 4) Seuranta-ajan pituus voi vaikuttaa pääte- ja lähtömuuttujan välisen yhteyden voimakkuuteen ja se tulisi huomioida erityisesti silloin, kun tuloksia verrataan tutkimuskohorttien välillä, eri päätetapahtumien välillä ja samaa päätetapahtumaa ennustavien eri lähtömuuttujien välillä.

Avainsanat: Elinaika-analyysi; Epidemiologia; Etenevä tutkimus; Kohorttitutkimus; Sepelvaltimotauti; Seurantatutkimus; Tilastotieteellinen oikeellisuus

ACKNOWLEDGMENTS

This thesis is a deviation, a positive one, but a deviation anyway. After my first doctoral degree in 2009, I never thought I would carry out another. Not until I moved from the natural sciences to health sciences and realized that I need to again prove my competence if I wanted to build a career in a discipline novel to me. I started my journey in health sciences under the umbrella of nursing science, but already at that time, my interest was focused on methodological and statistical questions, as well as on health inequalities at the population level. (Here, I must remark that the old me, the biologist, will never completely accept how epidemiologists understand "population." From a biological perspective, all humans, practically speaking, belong to the same population.)

There is only one name on the cover of this thesis, but naturally, the thesis has arisen because of the contributions of more people. I wish to express my gratitude to my principal supervisor, Professor Tomi-Pekka Tuomainen. I will never cease admiring your wealth of research ideas; they have many times rescued me when I have been stuck in boring routines by pointing a new, often out-of-the-box, direction. I am also grateful to my supervisor, Professor Mikko Kolehmainen. During the past few decades, I have studied a lot—and I mean a lot—but the two data mining courses taught by Mikko are without a doubt among the most rewarding courses I have ever attended. Although data mining does not play a role in this thesis, Mikko's lessons have had a prominent effect on its style. I thank you, Mikko, for introducing me to the secrets of statistical modeling. Doctor Christina Brester has my sincere appreciation. Her contribution to the original publications of this thesis was of indispensable value. Christina, your level of dedication and deep understanding of statistics are hugely impressive!

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Professor Jonas Björk, receive my humble gratitude. Their professional suggestions enabled me to raise the overall quality of the thesis.

This thesis, as so many before it and hopefully many after, is based on the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). This thesis would not have become possible without KIHD. During my PhD process, Professor Jussi Kauhanen has acted as a principal investigator of KIHD. I thank you for our fluent cooperation with KIHD that, for its part, made this thesis possible.

I drafted this thesis, including its original publications, when I was working as a research manager in the institute of public health and clinical nutrition at the University of Eastern Finland. I warmly thank the institute, especially its head, Professor Pekka Mäntyselkä, for enabling this thesis. Pekka, your approbative attitude toward my PhD process has remarkably encouraged me, both practically and personally.

The phrase “last but not least” is overused and, thus, a bit corny. In the acknowledgments section of a PhD thesis, however, it has a point. Many of us, including myself, have a bad habit of taking for granted the most valuable people in our lives. This thesis is much more than a pile of papers, but it is absolutely nothing compared with my most valuable people. My dearests have not drawn a single letter or number to finish this thesis. Nevertheless, their overall contribution has been precious. Minna, Saga, and Isla, you are my constant inspiration, my source of happiness, my reason to exist. I love you.

In Kuopio, on November 7, 2023
Ari Voutilainen

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Voutilainen A, Brester C, Kolehmainen M and Tuomainen T-P. Effects of data preprocessing on results of the epidemiological analysis of coronary heart disease and behaviour-related risk factors. Annals of Medicine 53: 890-899, 2021.

II Voutilainen A, Brester C, Kolehmainen M and Tuomainen T-P. Epidemiological analysis of coronary heart disease and its main risk factors: are their associations multiplicative, additive, or interactive? Annals of Medicine 54: 1500-1510, 2022.

III Voutilainen A, Brester C, Kolehmainen M and Tuomainen T-P. What is the most appropriate follow-up time for detecting the epidemiological relationship between coronary artery disease and its main risk factors: novel findings from a 35-year follow-up study. Coronary Artery Disease 34: 320-331, 2023.

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ABBREVIATIONS

AMI	Acute myocardial infarction
AP	Attributable proportion
BEE	Basal energy expenditure
BMI	Body mass index
BRF	Behavioral risk factor
CASP	Critical Appraisal Skills Programme
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FAMI	Fatal acute myocardial infarction
FBG	Fasting blood glucose
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
ICD	International Classification of Diseases
ICR	Interaction contrast ratio
JBI	Joanna Briggs Institute
JCI	Journal citation indicator
JIF	Journal impact factor
KIHD	The Kuopio Ischaemic Heart Disease Risk Factor Study
LDL-C	Low-density lipoprotein cholesterol
LRT	Likelihood-ratio test
MET	Metabolic equivalent
MetS	Metabolic syndrome
MI	Myocardial infarction

NIH	National Institutes of Health
NOS	Newcastle-Ottawa Scale
NSTEMI	Non-ST-segment elevation myocardial infarction
OR	Odds ratio
OSQE	Observational Study Quality Evaluation
PAL	Physical activity level
RCT	Randomized controlled trial
RD	Risk difference
RERI	Relative excess risk due to interaction
ROBINS	Risk of Bias in Non-randomised Studies
RR	Risk ratio
S	The synergy index
SAP	Stable angina pectoris
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SD	Standard deviation
SE	Standard error
SEP	Socioeconomic position
SIGN	Scottish Intercollegiate Guidelines Network
STEMI	ST-segment elevation myocardial infarction
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVI	Statistical validity index
TEE	Total energy expenditure
TC	Total cholesterol
UA	Unstable angina
VLDL-C	Very low-density lipoprotein cholesterol

1 INTRODUCTION

In 1900, Karl Pearson, an English all-round mathematician, published a paper that established mathematical statistics. The paper introduced the concept of *p*-value that, according to Pearson, is the probability to detect the observed or a rarer count (Pearson, 1900). Since then, numerous statistical tests have been developed for scientific purposes and all those tests are brought together by one thing: their results are interpreted by means of the *p*-value. The interpretation of the *p*-value is straightforward. Values below 0.05 denote statistical significance, whereas values above 0.05 indicate statistical nonsignificance. This simplicity is engaging. At the same time, unfortunately, it makes it too easy for researchers to forget that the *p*-value can be arise from unsuitable statistical tests, or it can be falsely calculated.

In addition to statistical tests, the results of studies can be interpreted based on effect sizes that reflect the strength of association between variables. Typically, effect sizes are presented together with their confidence intervals which, in most cases, are generated from a normal distribution. This, in turn, links confidence intervals to the *p*-value and statistical significance. When the 95% confidence intervals of two effect sizes do not overlap, the effect sizes differs from each other, with the *p*-value being less than 0.05. Standardized mean difference, correlation coefficient, and ratios based on risks, odds, or hazards are common effect sizes.

Regarding the fact that most scientific studies nowadays draw their conclusions from statistical tests and effect sizes with confidence intervals, it is surprising how little science appreciates statistics. In 1993–1995, Steven N. Goodman and his colleagues surveyed scientific journals publishing medically related research and reported that only one-third of the journals guaranteed a statistical review for all papers (Goodman, Altman and George, 1998). The researchers repeated the survey in 2017 and found no positive change in the review policy across the over 20-year period. The proportion of journals using a specialized statistical review for

all accepted manuscripts had in fact declined to 23% (Hardwicke and Goodman, 2020).

The present thesis is interested in the study of health and diseases in human populations, a field known as epidemiology. Descriptive epidemiology quantifies how population health indicators, such as disease prevalence, vary with other population characteristics, including features that are related to space and time (Lash *et al*., 2021). Analytic epidemiology assesses how exposures are associated with the occurrence of diseases (Lash *et al*., 2021). In epidemiology, exposures are understood in a wider sense that covers all scales, from genetics to societal aspects.

Specifically, the current thesis inspects a prospective cohort study that is one of the main types of epidemiological research from the viewpoint of statistical validity. It is possible to categorize statistical issues that potentially affect the results of epidemiological studies into selection bias, information bias, and confounding bias (Delgado-Rodríguez and Llorca, 2004; Lash *et al*., 2021). Selection bias occurs when study participants differ from those who did not participate, and it affects the external validity of the study ("generalizability of the findings to a broader context") but also the internal validity ("the truth in the population") if the selection process distorts the relationship between the exposure and outcome. Information bias refers to errors and inaccuracy in measurements and outcome classification. Actual information biases arise because of systematic errors. Biases because of random errors are related to the question of adequate sample size and statistical power (Tripepi *et al*., 2010). Confounders are variables that create spurious (correlative) associations between exposures and outcomes, thus making it difficult to reveal actual associations.

Traditionally, in cohort studies, selection bias refers to the study-level baseline selection before the follow-up starts. However, from a broader perspective, selection bias can be classified according to the level of the selection (population vs. study specific), the type of the selection mechanism (in exposure vs. in population composition), and the timing of the selection (at study entry vs. during follow-up vs. postoutcome) (Björk *et al*., 2020). If the exposure causes an adverse outcome that precludes study participants from staying at the risk of the actual study outcome during the

entire follow-up period, the selection bias is because of competing risks. Death is an extreme example of a competing risk. When the (disease) outcome of the study (or its subclinical symptoms) causes changes in the exposure, the postoutcome selection bias is because of reverse causality. For instance, smokers may reduce the amount they smoke if they start to suffer from symptoms of asthma.

The present thesis does not aim at covering the entire statistical problematic concerning prospective cohort studies. Instead, it is focused on the following six topics: advantages and disadvantages of data exclusions, time dependency of and associations (multiplicative, additive, interactive) among study variables, the effect of follow-up time on study results, outcome sensitivity, competing risks, and missing data. The first four topics are also dealt with in the three original publications of the present thesis.

The current thesis belongs to applied epidemiology. Its eventual goal is to improve the application of statistics in epidemiological research practice. To reach this goal, the present thesis demonstrates how inadequate adherence to statistical principles and inadequate use of statistical techniques in data preprocessing and analyzing affect results of a typical prospective cohort study.

2 REVIEW OF THE LITERATURE

2.1 PROSPECTIVE COHORT STUDY

The main categories of epidemiological studies are cross-sectional, cohort, and case-control studies. Epidemiological studies, especially cohort and case-control studies, are often termed observational studies, and they can be retrospective or prospective. However, the present thesis deals with prospective cohort studies. In epidemiology, a cohort is a group of people who share at least one defining characteristic. People born the same year can be said to belong to the same birth cohort, for instance. A cohort study *per se* assumes a longitudinal study design, which means the study participants are followed over a certain period, and during that time, the same study variables are measured more than once. Prospective denotes a future follow-up period with respect to the date when the study was initiated. The length of period from baseline to the end of follow-up is called the follow-up time or just follow-up. Historically, the use of the terms "retrospective" and "prospective" has been confusing because of two different definitions (Vandenbroucke, 1991). Therefore, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, for example, recommends authors not to classify their studies as retrospective or prospective but rather describe exactly how the study was carried out (Vandenbroucke *et al*., 2007). The present thesis obeys the strict Harvard school definition with respect to "prospective": "an outcome is related to baseline characteristics that were originally collected according to a protocol with the particular follow-up in mind (Vandenbroucke, 1991)."

Observational studies rarely include a manipulation of study variables, which distinguishes them from research aiming at discovering the effect of an experiment on future events. Observational studies search for associations between variables, of which one typically serves as an outcome variable, that is, a dependent variable in statistical analyses, and the other variables act as explanatory variables, that is, independent variables in statistical analyses. Independent variables include the main

independent variables of which the study is interested with respect to its research questions, as well as the confounders that create spurious associations between the dependent and main independent variables. All independent variables can be termed covariates. Specifically, the term "outcome" is used in the present thesis when referring to the variable of which observed variation in the data is statistically explained by other (pre)selected variables. The outcome is coronary heart disease (CHD) unless otherwise informed. The term "event" would have been an alternative option, but it is more suitable for describing an incident with a definable point of time, such as death.

Whether an epidemiological study can verify causality is an endless debate. In 1965, Sir Austin Bradford Hill, a professor at the University of London, published the criteria for epidemiological associations that can be judged as causal relationships (Hill, 1965). Based on those criteria, the association is causal if it is strong, consistent, specific, dose-related (biologic gradient), plausible, and coherent (Hill, 1965; Lash *et al*., 2021). Moreover, the criteria call for experimental evidence, a delay between the cause and the result, and an analogy between the observed and other similar associations (Hill, 1965). Although the Bradford-Hill criteria have been widely understood as a checklist for an epidemiologically proved causal relation, Kenneth J. Rothman, a distinguished epidemiologist, criticizes them, and Hill himself also suggests that the points do not form a set of rigid criteria to be fulfilled (Hill, 1965; Lash *et al*., 2021). A modern approach emphasizes the biological bases of causal associations as developed measurement methods have enabled the direct observations of effects (Fedak *et al*., 2015). Rothman (2012) notes that the only valid criterion for causality is chronological order. The cause precedes the effect.

A randomized controlled trial (RCTs) provides the strongest evidence of causal relationships (effects of an exposure). An observational study that is longitudinal provides weaker evidence. If the observational study is cross-sectional, there is no time dimension, and the study cannot distinguish between causality, simultaneity, and reverse causality. In a causal relationship, *x* causes *y*. In a simultaneous relationship, *x* causes *y* and *vice versa*. In a reverse causality relationship, *y* causes *x*.

2.2 CORONARY HEART DISEASE

The honorable *Harrison's Principles of Internal Medicine* determines CHD as an inadequate supply of blood and oxygen to the myocardium, which causes myocardial ischemia (Antman and Loscalzo, 2018a). The most common reason behind the condition is the atherosclerosis of coronary arteries (Antman and Loscalzo, 2018a). Ischemic heart disease (IHD) and coronary artery disease (CAD) are very closely related terms of CHD (Sanchis-Gomar *et al*., 2016) but, in the present thesis, only CHD is used. CHD is a progressive disease of which various stages relate to different ischemic mechanisms from endothelial and microvascular dysfunction to systolic dysfunction (Antman and Loscalzo, 2018a). The different mechanisms represent the length of exposure to an inadequate supply of blood and oxygen.

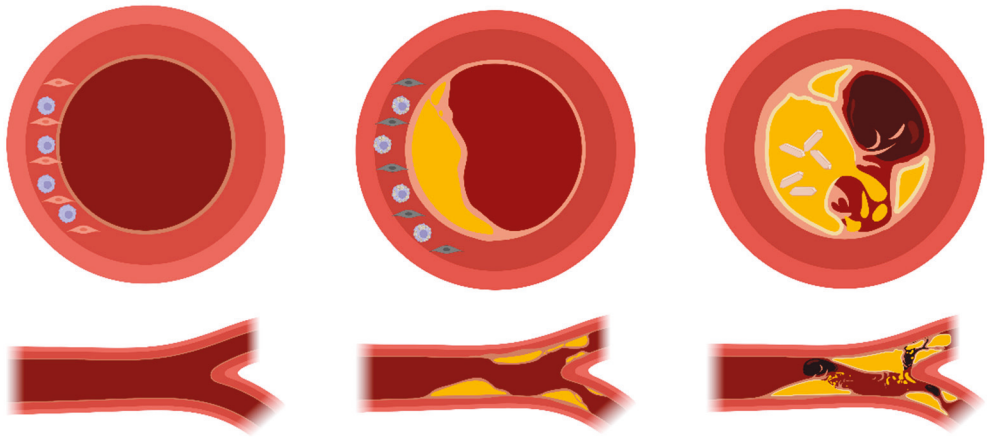

Figure 1. The pathogenesis of an atherosclerotic plaque. The upper subfigures illustrate a cross-section of an artery. The bottom subfigures illustrate a lengthwise cross-section of an artery. First, macrophages transform into foam cells, and vascular smooth muscle cells migrate to the innermost layer of artery. Second, foam and smooth muscle cells die and form the plaque's necrotic core. Third, the plaque containing cholesterol crystals ruptures and triggers the thrombus. The figure is not drawn to scale. The icons are from BioRender (License number: AN25X9SHPL).

Current understanding regards CHD as an inflammatory disease (Libby, Ridker and Hansson, 2011). The pathogenesis of an atherosclerotic lesion, that is, plaque begins with the activation of the innermost layer of arteries and the adhesion of white blood cells to it (Figure 1). The white blood cells maturate into macrophages that uptake lipids and transform into foam cells. In the next phase, vascular smooth muscle cells (SMCs) proliferate and migrate from the middle layer of an artery to the innermost layer. The synthesis of collagen and other extracellular matrix macromolecules is intensified. When foam cells and SMCs die, their lipid contents accumulate in the plaque and form the plaque's lipid necrotic core. At its advanced stage, the plaque also contains cholesterol crystals. If the plaque ruptures, blood coagulation components and tissue factors inside the plaque meet. This triggers thrombus: the ultimate complication of atherosclerosis. Biomechanical forces play a key role in the growth of plaque and can determine whether the plaque fractures or not (Brown *et al*., 2016).

Manifestations of CHD include stable angina pectoris (SAP), unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) (Antman and Loscalzo, 2018a, b; Giugliano, Cannon and Braunwald, 2018). SAP occurs because of transient myocardial ischemia at earlier stages of CHD; it can occur as a chronic condition with predictable symptoms. UA is characterized by prolonged symptoms with no evidence of damaged myocardium. NSTEMI is myocardial infarction (MI) based on cardiac biomarkers found in the blood but without electrocardiogram (ECG) findings that indicate transmural ischemia. STEMI is MI based on biomarker tests with the ECG findings. CHD may also lead to sudden cardiac death (SCD) (Albert and Stevenson, 2018).

Landmark studies on the natural history of CHD have discovered many factors that affect the prognosis of CHD. Already in the early 1960s, researchers were comparing the hearts of patients who died from CHD to those of patients who died accidentally, suggesting that atherosclerotic coronary artery lesions precede fatal CHD events (Strong and McGill, 1962). The natural history of CHD also comprises the development of coronary

collateral circulation following chronic conditions that reduce the supply of blood and oxygen to the myocardium (Gregg, 1974).

The history of CHD is long. People have suffered from reduced blood and oxygen supply to tissues because of arterial calcifications, including coronary arteries, at least since ancient Egypt (Leibowitz, 1970). Deaths from CHD started to grow in number in 1920s, and after that, the increase in the mortality rate in Western countries was rapid for decades (Ryle and Russell, 1949; Morris, 1951). The high CHD mortality was possible, at least in a small way, because there was no scientific interest in it. For instance, typically less than 10% of articles in the *British Heart Journal* (now published as *Heart*), one of the most traditional journals in cardiology, were on CHD in 1950s and 60s (Julian, 1987).

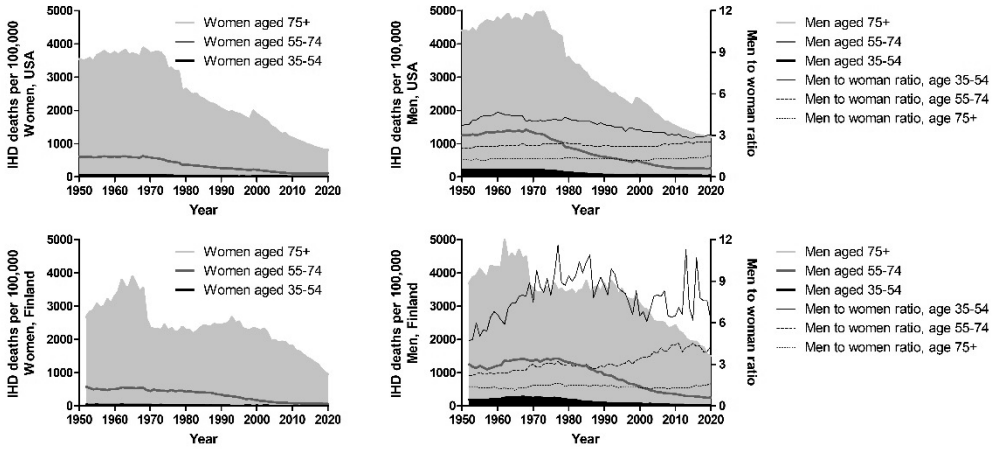

Figure 2. Annual CHD death rates in the USA and Finland by sex and age.

In Western countries, the CHD mortality rate slowly began to decrease in the 1970s or 1980s, depending on the country and age group (Figure 2). The reduction in mortality became possible after a verification of the relationship between MI and thrombotic occlusions of coronary arteries (Van de Werf, 2014) by animal testing, angiography investigations of patients, and experimental thrombolytic therapies (Chazov *et al*., 1976; Reimer *et al*., 1977; Reimer and Jennings, 1979; Rentrop *et al*., 1979; DeWood *et al*., 1980).

2.3 RISK FACTORS OF CORONARY HEART DISEASE

2.3.1 Traditional risk factors

From a Western world perspective, the CHD death rate in Finland is high among middle-aged and younger men compared with women (Figure 2). In Finland, the men-to-women rate ratio for CHD mortality varies annually between six and nine for persons younger than 55, whereas in the USA, the same ratio is around three. Correspondingly, the ratio is around four in Finland for persons aged 55 to 74 and below three in the USA. In the 1980s, the CHD death rate among Finnish middle-aged and younger men was high also compared with same-aged men in other countries, such as the USA (Figure 2). In eastern Finland, the rate was the highest in the world (Salomaa *et al*., 1996). After the 1980s, the CHD mortality among Finnish men has declined close to the level observed in the Western world on average (Figure 2) because of developed preventive actions, as well as improved acute care (Salomaa *et al*., 1996).

In the present thesis, the study outcome is CHD, and the associations between the risk factors and CHD are interpreted from a statistical viewpoint that does not editorialize the type of the association, either causal or noncausal. In prospective cohort studies, a risk factor is a covariate that is associated with an increased risk of the study outcome, that is, the condition of interest, during the follow-up. This denotes the risk factor may but does not necessarily cause the condition.

There are nine well-known main so-called traditional risk factors of CHD, of which three are nonmodifiable and six modifiable (Tsao *et al*., 2023). Here, modifiable means that the study participant can affect the risk factor during the follow-up, for example, by increasing physical activity. Nonmodifiable signifies the risk factors that will remain unchanged. Basically, the orthodox classification of CHD risk factors into modifiable and nonmodifiable by assuming a causal relationship between the modifiable risk factors and CHD because modifying noncausal factors do not affect the risk.

The nonmodifiable risk factors include male sex, age, and a family history of CHD (Tsao *et al*., 2023). The modifiable risk factors include diabetes, obesity, hypercholesterolemia, hypertension, smoking, and physical inactivity (Tsao *et al*., 2023). The risk factors are thought to mirror diet; thus, no foods are mentioned in the list. Overall, high insulinemic (sugar), high inflammatory (processed red meat), and diabetes-risk-increasing diets (processed carbohydrates) increase the risk of most chronic diseases, including cardiovascular diseases (CVD) (Wang *et al*., 2023). A systematic review and meta-analysis of 13 prospective cohort studies has found an association between the higher consumption of (processed) red meat and increased risk of CHD, but no association between poultry intake and CHD (Papier *et al*., 2023).

Male sex. The difference in the CHD risk between men and women especially refers to the risk of mortality. Men's CHD mortality is higher throughout adulthood but especially in middle age (Bots, Peters and Woodward, 2017). This finding is partly related to the fact that women develop CHD years later than men (Maas and Appelman, 2010). Traditionally, the sex difference in CHD has been explained by sex differences in CHD risk factors (Jousilahti *et al*., 1999), and most of those differences persist (Peters, Muntner and Woodward, 2019). Sex differences in body mass index (BMI) and total cholesterol (TC), however, have shown diminishing trends during the past couple of decades (Peters, Muntner and Woodward, 2019). In the USA, which provides the largest Western world population for the World Health Organization (WHO) statistics, the CHD death rate has smoothly declined since the mid-1970s in both sexes and in all age groups (WHO, 2023). At the same time, the men-to-women rate ratio for CHD death has lowered from four to three in the oldest WHO age group, that is, 75+ (Figure 2). In younger WHO age groups, the ratio is around two.

Age. Normal aging is characterized by structural and functional alterations of blood vessels, which increases the risk of developing CHD and other CVDs (Paneni *et al*., 2017). In addition, aging is typically associated with alterations in CVD risk factors. Among 15,000 Finnish men and women, age-related changes in the risk factors explained one-third of

the higher CHD risk in men and one-half in women aged 50–64 (Jousilahti *et al*., 1999). The CHD risk factors, such as a decreasing high-density lipoprotein cholesterol (HDL-C) to TC ratio and increasing systolic blood pressure (SBP), were studied in the 1980s, and a comparison was performed for men and women aged 25–49 (Jousilahti *et al*., 1999).

Family history of CHD. Based on longitudinal and case-control studies, individuals whose close relatives have CHD are at an increased risk for CHD death and MI. The adjusted risk ratio (RR) for CHD death is around 1.5 and that for MI around 2 when one relative is affected and around 4 if two or more relatives are affected (Leander *et al*., 2001; Bachmann *et al*., 2012). The family history of CHD is assumed to reflect both environmental and genetic components: socio-cultural factors, ethnic background, and inherited genetic variants. This assumption holds true, but in some cohorts, the family history of CHD is associated only weakly with conventional and genetic risk scores (Safarova, Bailey and Kullo, 2016). These inconsistent findings regarding the role of family history in the risk of CHD may partly be because of the distinct types of coronary plaques. Calcified (hard) plaques are determined by genetics, whereas noncalcified (soft) plaques are mostly influenced by environmental factors (Drobni *et al*., 2022). Moreover, some studies propose that the family history of premature MI increases the risk of CHD in family members because it provokes long-lasting distress among them (Nagel *et al*., 2021). Stressful life events are associated with an increased risk of future CHD (Wang *et al*., 2021).

Hypercholesterolemia. The specific cause of atherosclerotic CVDs is low-density lipoprotein cholesterol (LDL-C) (Ference *et al*., 2017). As a result, there is no exact threshold for an optimal LDL-C concentration, but the lower the circulating concentration, the lower the risk of CVD (Penson, Pirro and Banach, 2020). The causal relationship of LDL-C with atherosclerosis inevitably leads to associations between LDL-C and CVD/CHD risk factors. Indeed, LDL-C is tightly associated with metabolic syndrome (MetS), a combination of obesity, hypertension, dyslipidemia, and hyperglycemia (Fan *et al*., 2019). The cross-sectional association between LDL-C and MetS appears to not be mediated by inflammation (Fan *et al*., 2019). Despite the

key role of LDL-C in the development of atherosclerosis, many studies have applied TC to predict the risk of CHD and other CVDs. In the pooled data of tens of cohorts, for example, a 1-mmol/l increase in TC increased the risk of CHD by 1.2 in women within a follow-up time ranging from less than 10 to over 30 years (Peters *et al*., 2016).

Diabetes. Diabetes increases the risk of CHD and other CVDs because hyperglycemia damages blood vessels, for example, by decreasing their elasticity (Leon and Maddox, 2015). In the general population, the risk of CHD in men with diabetes is around 2.2 times the risk in men without (Peters, Huxley and Woodward, 2014). Among women, the corresponding RR is around 2.8 (Peters, Huxley and Woodward, 2014).

Obesity. Obesity increases the risk of CVDs through direct and indirect mechanisms. The former include systemic inflammation and endothelial dysfunction, whereas the latter refers to adverse changes in body composition that predispose the individual to hypercholesterolemia, hypertension, and diabetes (Powell-Wiley *et al*., 2021). Compared with normal weight adults, the age-adjusted risk of CHD is around 1.2 among overweight adults and around 1.6 among obese adults (Mongraw-Chaffin *et al*., 2015).

Hypertension. High blood pressure strains blood vessels in general and its relationship with CHD, specifically MI, is well-established (Mancia *et al*., 2023). In US epidemiological cohort studies, the risk of CHD was higher in hypertensive adults compared with their normotensive peers, but age, sex, and race affected the relationship between CHD and hypertension (Allen *et al*., 2012). The RR for CHD was the highest among Black women between the age of 55 and 65, 3.0 in stage 1 hypertension and 4.9 in stage 2 hypertension (Allen *et al*., 2012). The corresponding RR was the lowest among Black men between the ages of 55 and 65, 1.2 in stage 1 hypertension and 1.3 in stage 2 hypertension (Allen *et al*., 2012). Stage 1 hypertension denotes SBP 140–159 mmHg or diastolic blood pressure of (DBP) 90–99 mmHg, and stage 2 hypertension denotes SBP ≥160 mmHg, DBP ≥100 mmHg, or a condition treated with antihypertensive medication. Among Japanese urban residents, hypertension increased the lifetime risk of CHD multiplied by 1.8–2.0 in men and by 1.8–2.4 in women depending

on age (Turin *et al*., 2016). Based on a pooled analysis of UK health records, a 20 mmHg increase in SBP multiplies the risk of stable angina by 1.4 and that of UA and MI by 1.3 when adjusted for age and sex (Rapsomaniki *et al*., 2014). The corresponding multipliers for a 10 mmHg increase in DBP are 1.3 and 1.2 (Rapsomaniki *et al*., 2014). According to an individual participant data meta-analysis of 41 Asian, Australian, and New Zealand cohort studies and 600,000 individuals, SBP explains a greater proportion of the excess CHD death risk in people aged ≥55 years compared with triglycerides, TC, or diabetes (Asia Pacific Cohort Studies Collaboration, 2006). Hypertension is particularly frequent among older age groups, whereas the prevalence of other traditional risk factors is not as evidently dependent on age (Asia Pacific Cohort Studies Collaboration, 2006).

Smoking. The association between the risk of CHD and smoking is evident, and no safe level of smoking exists. Cigarette smoking is independently associated with lipid-rich coronary plaques (Soichiro *et al*., 2015). Among men who smoke one cigarette per day, compared with never smokers, the risk of CHD adjusted for multiple confounders is around 1.7 and among men who smoke 20 cigarettes per day, it is around 2.3 (Hackshaw *et al*., 2018). Among women, the corresponding RRs are 2.2 and 4.0, respectively (Hackshaw *et al*., 2018). It is possible that the association between CHD and smoking is partly because of poorer oral health among smokers (Batty *et al*., 2018) because both smoking and poor oral health sustain inflammation.

Physical inactivity. Overall, physical activity delays the development of atherosclerosis (Franklin *et al*., 2020), and the RR for CHD decreases with an increasing physical activity (Sattelmair *et al*., 2011). In a meta-analysis of prospective cohort studies, extreme physical activity reduced the risk of CHD multiplied by 0.8 among men but was even by 0.5 among women (Sattelmair *et al*., 2011). As a part of physical inactivity, sitting has been studied as an independent risk factor for CVD. The evidence suggests an association between sitting while watching TV and the risk of CVD (Henschel, Gorczyca and Chomistek, 2017). Other reasons for sitting, such as transportation-related or occupational sitting, do not result as evident associations with CVD risk (Henschel, Gorczyca and Chomistek, 2017).

Interactions across risk factors. Several studies have reported the interactions across the traditional CHD risk factors. The most convincing interactions have been detected between the genetic risk of CHD and age on a multiplicative scale (Ding *et al*., 2015), between the genetic risk and current smoking on an additive scale (Huang *et al*., 2022), and between the family history of CHD and obesity on an additive scale (Li *et al*., 2020). Additive interactions have also been observed between obesity and dyslipidemia (Li *et al*., 2020), as well as between diabetes and hypertension (Wang, Yang and Fu, 2021). Not all studies, however, have found interactions across CHD risk factors. Yiannakouris *et al*. (2014), for instance, reported no interactions of the genetic risk of CHD with smoking, hypertension, diabetes, physical activity, and BMI. Of the studies cited in this paragraph, Ding *et al*. (2015), Li *et al*. (2020), and Yiannakouris *et al*. (2014) are case-control studies, Huang *et al*. (2022) is an observational follow-up study, and Wang, Yang and Fu (2021) is a cross-sectional study.

2.3.2 Nontraditional risk factors

In addition to the traditional risk factors of CHD, prospective cohort studies have recognized other factors that, in some populations predict but do not necessarily cause CHD (Roeters van Lennep *et al*., 2002). These nontraditional risk factors include, for example, homocysteine, C-reactive protein, fibrinogen, iron, lipoprotein (a), proteinuria, and oral health (Altamura *et al*., 2023; Roeters van Lennep *et al*., 2002; Perkovic *et al*., 2008; Emerging Risk Factors Collaboration *et al*., 2010; Lp-PLA(2) Studies Collaboration *et al*., 2010; C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) *et al*., 2011; Das De, Krishna and Jethwa, 2015). Many of the nontraditional CHD risk factors are related to inflammation, and they mediate the effect of traditional risk factors. The nontraditional risk factors of CHD were not included as covariates in the statistical analyses of the present thesis, so they are not dealt with in the Results, Discussion, or Conclusion sections.

Socioeconomic position. The epidemiological relationships of a low socioeconomic position (SEP) with CVD/CHD and poorer prognostic

outcomes in CHD have been well established, and up-to-date meta-analyses confirm them (Anand *et al*., 2023; Wang, Li and Zheng, 2023). The relationship is independent of the outcome type (incidence or mortality), as well as on the indicator of SEP (income, education, or deprivation) (Wang, Li and Zheng, 2023). Because SEP covers multiple areas of life, it shows associations with a wide variety of specific factors. For instance, height is associated both with overall welfare and the risk of CHD (Steckel, 2009; Paajanen *et al*., 2010). A recent study combining Finnish population-based health surveys concluded that the associations are related more strongly to the impact of childhood living conditions on height than to genetically determined expected height (Silventoinen *et al*., 2023).

Psychological factors. The main psychological factors that have been associated with an increased risk of CHD are depression and anxiety *sensu lato* and work stress, including physical, emotional, and mental strain (Sara *et al*., 2018; Wang *et al*., 2021; Xu *et al*., 2023). Psychological factors also include components that decrease the risk of CHD. Of them, social support covering emotional, informational, and practical dimensions is the most convincing one (Xu *et al*., 2023). In addition, psychological interventions improve prognostic outcomes in patients with CHD (Xu *et al*., 2023).

Sleep disturbances. The newest heart disease and stroke statistics report from the American Heart Association considers nonoptimal sleep as one of the main risk factors of CVD (Tsao *et al*., 2023). A prospective cohort study of over 60,000 Taiwan residents associated sleep problems with an increased risk of CHD (Lao *et al*., 2018). In the study by Lao *et al*. (2018), sleep problems refer to short sleep (<6 h/d), dreamy sleep, difficulties in falling asleep, and the use of sleep medication. A study with animal and human experiments suggests that plasma exosomes (lipid nanovesicles released from cells) may induce endothelial inflammation and atherosclerosis in sleep-deprived subjects (Li *et al*., 2023).

Alcohol consumption. Alcohol consumption has shown a J-shaped association with the risk of CHD: light-to-moderate drinking decreases the risk, whereas heavy drinking increases it (Ronksley *et al*., 2011). Broadly, alcohol increases all-cause mortality, but regarding CVD, the association between the disease risk and alcohol consumption depends on the CVD

manifestation in question (Wood *et al*., 2018). Regarding CHD, except for MI, the risk is the lowest when the consumption is about 100 grams of pure alcohol per week, but differences in the risk across different consumption categories are minor (Wood *et al*., 2018). Any alcohol consumption is associated with a decreased risk of MI, but after 100 g/week, the increased consumption does not lower the risk anymore (Wood *et al*., 2018). An additional aspect to the association between the risk of CHD and alcohol consumption relates to differences across lifelong teetotalers, ex-drinkers, and drinkers. Overall, current drinkers, both moderate and heavy drinkers, are associated with the lowest risk of CHD compared with nondrinkers, former drinkers, and occasional drinkers (Bell *et al*., 2017). However, based on poststratification demonstrations, it is probable that the lack of data representativeness distorts the epidemiological association between alcohol consumption and mortality. In the UK Biobank sample, when the bias because of the lack of representativeness is controlled for, the "protective nature" of alcohol consumption in respect of CVD mortality disappears (Stamatakis *et al*., 2021). In the present thesis, alcohol consumption was used as a covariate in the statistical analyses reported in Original Publication I.

2.3.3 Acute and subacute triggers

An observation that MIs are the most frequent in the morning between 6:00 a.m. and 12:00 p.m. raised interest among clinicians in the 1980s (Muller, Tofler and Stone, 1989). The recognition of the circadian variation of acute coronary events recreated the question concerning a triggering onset of coronary thrombosis. Initially, the triggering onset was hypothesized in 1910 (Obraztsov and Strazhesko, 1910), but in the following decades, no evidence was found to support it (Master, 1960). Since the 1980s, however, the triggering onset of MI, SCD, and stroke has been proven correct by numerous empirical studies (Tofler and Muller, 2006; Mittleman and Mostofsky, 2011; Schwartz, Kloner and Naghavi, 2018). The triggers are commonly classified as physical, psychological, chemical, and environmental ones (Mittleman and Mostofsky, 2011). Most

of the triggers are part of normal life, such as lifting heavy objects or having a respiratory infection, being angry or mentally stressed, drinking coffee or alcohol, and being exposed to traffic-related air pollution or temperature changes (Mittleman and Mostofsky, 2011). Mainly high-risk atherosclerotic patients are vulnerable to the triggering onset of MI, SCD, and stroke (Schwartz, Kloner and Naghavi, 2018; Franklin *et al*., 2020).

2.4 STATISTICAL VALIDITY AND ITS EVALUATION

There are many methods that can be used to assess the methodological quality of studies. These methods are known as assessment tools, and they have been designed to gather, evaluate, and interpret evidence. Jarde, Losilla and Vives (2012a) systematically review the assessment tools of nonexperimental studies, finding that, out of 74, 61 are applicable to the cohort design. The domain of statistics and data analysis was included in 68% of the tools, also with respect to the cohort design tools. Correspondingly, Ma *et al*. (2020) list 27 tools for medical studies, of which five focus on cohort studies. These five tools are the CASP checklist by the Critical Appraisal Skills Programme, the NIH quality assessment tool by the National Institutes of Health, the SIGN methodology checklist by the Scottish Intercollegiate Guidelines Network, the JBI critical appraisal checklist by the Joanna Briggs Institute, and the Newcastle-Ottawa Scale (NOS) by Wells *et al*. (2021) (Table 1).

The CASP checklist comprises 12 major items, of which none specifically assess the statistical validity and only one question relates to statistical analyses (Critical Appraisal Skills Programme, 2023). The NIH quality assessment tool includes 14 major items, and again, only one question relates to statistical analyses (National Heart, Lung, and Blood Institute, 2021). In addition to this one question, the NIH tool asks for statistical power descriptions. In both the CASP checklist and NIH tool, a specific statistical question asks the following: Are potential confounding variables considered in the statistical analyses? The SIGN methodology checklist comprises two sections and their statements (Scottish Intercollegiate Guidelines Network, 2012). The SIGN checklist also includes a question

regarding the adjustment for potential confounders and requests the reviewer to consider the statistical power of the study. Moreover, in the subsection of statistical analysis, the SIGN checklist asks the following: Have confidence intervals been provided? The JBI critical appraisal checklist consists of 11 major items, and one of them assesses statistical validity (Joanna Briggs Institute, 2020). The question in the items, however, is presented on a very general level: Was an appropriate statistical analysis used? The NOS comprises eight major items and each of them includes two to four questions (Wells *et al*., 2021). None of the items assesses the statistical validity, and the word statistic is totally missing from the scale.

Table 1. Tools to assess the methodological quality of cohort studies.

Name of the tool	Developer	Items	Areas of statistics
The CASP checklist	Critical Appraisal Skills Programme	12	Confidence intervals, confounders, effect estimates, lost to follow-up
The NIH quality assessment tool	National Institutes of Health	14	Confounders, effect estimates, lost to follow-up, power, sample size
The SIGN methodology checklist	Scottish Intercollegiate Guidelines Network	18	Confidence intervals, confounders, lost to follow-up, power
The JBI critical appraisal checklist	Joanna Briggs Institute	11	Confounders, lost to follow-up, statistical analysis[1]
The NOS scale	Universities of Newcastle (AUS) and Ottawa (CAN)	8	Confounders[2], lost to follow-up[2]

Notes. There are more assessment tools available, but these five tools are all recommended. Regarding confounders and lost to follow-up the statistical aspect refers to sensitivity analyses and/or statistical adjustments. [1]A general appraisal. [2]The statistical aspect is unclear.

All these five assessment tools are recommended nowadays, and the NOS is the most used (Ma *et al*., 2020). However, because the assessment tools in general have been developed from the perspective of systematic review and meta-analysis, they aim at assessing each domain of the study process. The statistical validity constitutes only a part of the overall evaluation at its best.

In addition to their systematic review, Jarde, Losilla and Vives (2012b) analyze the psychometric properties of three comprehensive tools. The tools have been developed to assess the methodological quality in *ex post facto* studies. The tools by Fowkes and Fulton (1991) and Downs and Black (1998) are suitable for assessing prospective cohort studies. These tools are old, and they do not belong to the present-day assessment methods. The analysis by Jarde, Losilla and Vives (2012b) shows that the domain of statistics and data analysis reaches statistically nonsignificant agreement between the tools, which means the tools are not measuring the same construct. In Fowkes and Fulton (1991), the domain includes two aspects: the adjustment for confounding and adjustment for incomplete data. In Downs and Black (1998), the domain includes the adjustment for time lengths in addition to the two aspects observed in Fowkes and Fulton (1991). After the review and psychometric evaluation of assessment tools, Jarde *et al*. have designed their own tool to screen the methodological quality of cohort studies. This tool, Q-Coh, has a moderate to good domain-specific inter-rater agreement (Jarde *et al*., 2013). In Q-Coh, the statistical validity of studies is assessed by only one very generalized—or even vague—question: Do the results of the statistical analysis reflect the true situation? Consequently, Q-Coh does not truly improve the assessment procedure of cohort studies' methodological quality from a statistical viewpoint.

Observational Study Quality Evaluation (OSQE). A more recent attempt to develop the methodological quality assessment of observational studies has been published by Drukker *et al*. in 2021. Drukker *et al*. (2021) merge criteria proposed in three checklists into a new quality assessment tool called the Observational Study Quality Evaluation (OSQE). The reviewed checklists include the NOS, STROBE by Vandenbroucke *et al*., (2007) and

von Elm *et al*., (2007), along with a criteria list for RCTs by De Brouwer et al. (2012). The cohort version of the developed new tool, the OSQE cohort, includes one mandatory question concerning statistics: Does statistical analysis control the relevant confounders? The OSQE cohort also ascertains how missing data are dealt with. Furthermore, the OSQE cohort consists of two optional questions. The first one asks the following: Are effect modifiers analyzed correctly? The second one asks the following: Is the sample size sufficient, looking at calculations/explanations? Compared with other assessment tools introduced in this chapter so far, the OSQE cohort is most focused on statistical validity.

Risk of Bias in Non-randomised Studies – of Exposure (ROBINS-E). Yet another tool to evaluate epidemiological studies is the Risk of Bias in Non-randomised Studies – of Exposure (ROBINS-E) by ROBINS-E Development Group (2022). ROBINS-E is designed to serve the needs of systematic reviews, and it aims at assessing the strength of evidence with respect to a relationship of an exposure with an outcome. ROBINS-E asks for the appropriate analysis methods and suggests inverse probability weighting (Kaufman, 2010), if time-varying confounders are present. This suggestion excludes the standard Cox proportional hazards model (Cox, 1972), for instance. Moreover, ROBINS-E assesses the exposure window: Does it include the beginning of the exposure, and is it wide enough for the outcome to occur? If the exposure has started before the beginning of the follow-up, ROBINS-E requires the outcome events to occur soon after the beginning of the follow-up to be removed from statistical analyses. This requirement in general relates to the control of reverse causality (Sattar and Preiss, 2017). ROBINS-E also states that the strength of the association between an exposure and outcome varies over time and across different outcomes. The latency period is an example of this type of time dependency because the time that passes between an exposure and a disease is related both to the exposure and disease. ROBINS-E emphasizes the importance of dealing with missing data; it includes 10 signaling questions concerning missing data and, for example, demands for the recognition of “missing at random.” In general, ROBINS-E calls for sensitivity analyses to demonstrate the impacts of potential biases. The

biases can be originated from the selection of participants into the study and statistical analysis, as well as from missing data. From the viewpoint of statistical validity, ROBINS-E is much more detailed and comprehensive than the other assessment tools introduced in this chapter. It is the only tool that distinctly instructs the evaluator about the correct statistical choices and methods. Other tools blindly rely on the evaluator's statistical expertise, and they cannot answer the question about statistical validity raised in the present thesis.

To summarize, statistical validity in this thesis denotes adequate use of data and statistical analysis methods. The requirements of adequate use are fulfilled if a study controls for the following six sources of biases and errors: 1) Are there differences between disease-free study participants and those who are not free from the disease of interest at baseline? 2) Are model assumptions regarding the time dependency of variables violated, or are there uncontrolled interactions across covariates? 3) Are follow-up times inappropriate? 4) Are study outcomes vague? 5) Do competing risks exist? 6) Are there differences between study participants whose data includes missing values and those whose data do not?

The question concerning the types of associations (Berrington de González and Cox, 2007)—multiplicative or additive—receives special attention because it is related to both time-dependent variables and variable interactions. In general, a multiplicative function refers to the product of the effects, and an additive function refers to the sum of the effects. Competing risks are events that remove study participants from the population at the risk of the actual study outcome, thus competing with the condition of interest (Lash *et al*., 2021). Because the prevention of all competing risks, such as deaths from other diseases than the disease of interest, is practically impossible, competing risks are typically ignored or statistically removed (Lash *et al*., 2021). In the present thesis, the dealing with competing risks refers to any descriptive or analytic statistical handling. The various procedures to statistically consider competing risks yield estimates that are not necessarily comparable with each other as such (Young *et al*., 2020), which, for its part, stresses scrutiny when handling competing risks. In general, focusing on the unconditional risk,

that is, the probability of the outcome of interest without statistically eliminating competing risks may sometimes be a more practical and interpretable approach (Lash *et al*., 2021). On the other hand, biased estimates because of competing risks are an indisputable phenomenon, which is true also in the main study material of the present thesis: the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study (Brester *et al*., 2023). The six topics of statistical validity introduced in this paragraph are dealt with in more detail in Chapter 4.1.1.

3 AIMS OF THE STUDY

The present thesis had two main aims. First, it evaluated the statistical validity of the prospective studies on CHD. Second, it demonstrated the effects of partially subjective choices with respect to data preprocessing and statistical analyzing on the results of prospective cohort studies. All demonstrations were related to the epidemiological association of CHD with its main well-known risk factors (Tsao *et al*., 2023) and they applied the KIHD data as a study material.

The specific research questions were as follows:

1) How frequently and comprehensively do recent prospective studies of CHD and its potential and known risk factors use and report data preprocessing and statistical analyses? This topic is not dealt with in original publications, only in the present thesis.

2) How do study participant exclusions, covariate manipulations, and outcome variable selection affect the results of the epidemiological analysis of CHD and its risk factors? This topic is dealt with in Original Publication I.

3) Are the epidemiological associations across CHD and its main risk factors multiplicative, additive, or interactive? Multiplicativity also covers time dependency. This topic is dealt with in Original Publication II.

4) What is the most appropriate follow-up time for detecting the epidemiological association between CHD and its main risk factors? This topic is dealt with in Original Publication III.

4 SUBJECTS AND METHODS

4.1 EVALUATION OF STATISTICAL VALIDITY

The research evidence concerning the interests of the present study is scarce or even nonexistent when the literature search is targeted specifically to the expressed study questions pertaining to prospective cohort studies. As a result, the current thesis presents an evaluation of statistical validity, in addition to an ordinary review of the literature. The evaluation was directed to recent peer-reviewed journal articles that report one or more epidemiological (prospective) relationships of CHD with its known or potential risk factors.

Analyzing a period from 1924 to 2021, the word “coronary” results in five and a half million documents in Google Scholar. The starting year of this period, 1924, refers to the foundation of the American Heart Association (AHA) that launched scientific research on heart diseases. The first percentage of those documents were published by the end of 1966. The first 10 percentages were published by the end of 1995. Half of the documents are from the last 11-year period of 2011–2021 (Figure 3). Because of the vast number of coronary documents, the present evaluation of statistical validity focused on 2021, the last complete year available at the time of the evaluation. Google Scholar web pages (https://scholar.google.com/) were last visited on February 21, 2023.

The number of coronary documents peaked in 2013, with CHD research has passing its most intensive phase. For instance, no similar recent decreasing trend in the number of documents regarding another prominent public health diseases, such as Alzheimer’s, can be seen (Figure 3). On the other hand, the number of documents concerning lung cancer, another disease with a strong impact on public health, has also declined during the past few years. The number of lung cancer documents peaked in 2017, four years after the peak of CHD documents (Figure 3).

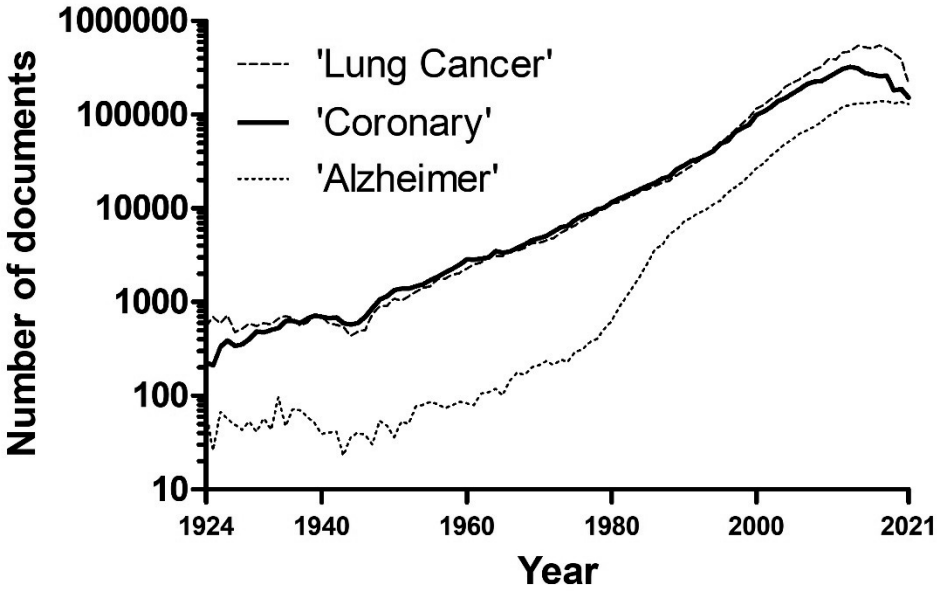

Figure 3. Number of documents in Google Scholar by words representing three public diseases: lung cancer, CHD, and Alzheimer's disease. Note the logarithmic scale of the y-axis.

The goal of the present evaluation of statistical validity was to find out how frequently and with what quality the statistical domains demonstrated in the present thesis have been considered in recent epidemiological studies of CHD and its risk factors. Moreover, the evaluation compared the statistical validity of CHD research between articles published by journals with a particular focus on epidemiology and those published by journals with a more general and/or clinical focus.

Because the ROBINS-E assessment tool covers most of the statistical domains dealt with in the current thesis, it would have been possible to apply it in the evaluation of statistical validity. However, ROBINS-E does not consider interactions across covariates nor different manifestations of the outcome. Therefore, new assessment criteria that concentrate specifically on the statistical questions disclosed in the present thesis were generated. ROBINS-E served as a valuable guideline.

4.1.1 The evaluation process

As a prerequisite, journals having no Web of Science status were not included in the evaluation. The omitted epidemiology journals were as follows: *Asian Journal of Epidemiology*, *Environmental Epidemiology*, *Epidemiologia*, and *Frontiers in Epidemiology*.

In the first phase of the evaluation process, Web of Science by Clarivate was applied to list the scientific journals categorized as public health journals in Journal Citation Reports. Then, journals that have the word "epidemiology" or a corresponding term in their names were extracted. These journals were presumed to represent the core of epidemiology literature because of their focus. All articles published in those journals in 2021 were inspected to discover papers dealing with the epidemiological relationship of CHD with its known or potential risk factors. Later in the text, these articles are referred to as epidemiology journal articles. The Web of Science web page was last visited on September 14, 2022.

In the second phase of the evaluation process between September 16 and 23, 2022, the article search was completed using PubMed and Scopus. Again, the aim was to find scientific journal articles dealing with the epidemiological relationship of CHD with its risk factors. Searches were targeted on article titles and abstracts. In PubMed, the search terms included "coronary" and "heart" and the search was restricted to observational studies. In Scopus, the search terms included "coronary," "isch*," "myocardial," "follow*," "prospective," and "cohort" with the exclusion terms of "bypass" and "percutaneous." The search terms were selected based on preliminary searches that recognized the terms that yielded the most of the correct and incorrect hits. Both PubMed and Scopus searches were limited to articles published in 2021. Later in the text, these articles have been referred to as the articles published in nonepidemiology journals to distinguish them from the articles found in the first phase of the evaluation. The term "nonepidemiology" is merely for the present classification. It does not aim at describing the journals' typical contents as such. Supplements, conference abstracts, errata, and writings

without scientific content, such as obituaries and acknowledgments to reviewers, were excluded in the first and second phases of the evaluation.

In the third phase of the evaluation process, full texts of articles discovered in the first and second phases were scanned, and if the article fulfilled the inclusion criteria, it was forwarded into the next phase of the evaluation. The inclusion criteria required CHD or MI as a dependent variable in a survival analysis. The article was excluded if the dependent variable combined CHD or MI with other outcome(s), such as stroke, or if the study did not include a prospective follow-up period. Angina, coronary artery interventions, and SCD alone were unacceptable dependent variables because they do not enable distinguishing between fatal and nonfatal outcomes. Based on preliminary literature searches, cohort studies of CHD commonly combines different conditions into CHD, such as silent myocardial ischemia, angina, nonfatal MI, and fatal MI. These manifestations refer to different stages of the disease progression; thus, they should at least partly be associated with different risk factors. Because the purpose of the present thesis was to specifically distinguish between different CHD manifestations, only studies that had classified themselves as CHD studies were included in the evaluation process.

In the fourth phase of the evaluation process, the methods and results sections of the articles were read to investigate the following domains: 1) Had the study tested the effect of participant exclusions (not free from the disease at baseline excluded vs. included) on its results? 2) Had the study considered multiplicative, additive, and interactive associations across the dependent variable and covariates? Here, multiplicativity also covers time dependency. 3) Had the study tested the effect of follow-up time on its results? 4) Had the study considered outcome sensitivity from the viewpoint of different CHD manifestations? The handling of 5) competing risks and 6) missing values was also investigated, although the topics have not been dealt with in the original publications of this thesis. The second domain referred to the consideration of time-varying effects in time-to-event analyses. In the Cox proportional hazards model, this consideration denotes the investigation of model assumptions, as well as the fit of time-varying covariates, if the assumptions are not met. In the third domain, the

exclusion of events that had occurred during the first years of follow-up were approved as a control for the follow-up time.

In the fifth and final phase of the evaluation process, points were given to the findings in the fourth phase, as described in Table 2. The total possible sum of points per journal article ranged from 0 to 6. This total sum was termed the Statistical Validity Index (SVI).

Table 2. Domains to evaluate the statistical validity of cohort studies.

Statistical domain	Finding (and points)
1) Study participant exclusions	A sensitivity analysis (1) Descriptive statistics, no analysis (0.5) Not considered (0)
2) Associations across variables	Time-dependency (1) Interactions but no time-dependency (0.5) Not considered (0)
3) Follow-up time	A sensitivity analysis[1] (1) Descriptive statistics, no analysis (0.5) Not considered (0)
4) Outcome sensitivity	A sensitivity analysis[1] (1) Descriptive statistics, no analysis (0.5) Not considered (0)
5) Competing risk	A competing risk analysis (1) Descriptive statistics, no analysis (0.5) Not considered (0)
6) Missing values	Imputed or excluded with a reasoning[2] (1) Excluded without a reasoning (0.5) Not considered (0)

Notes. [1]At least two follow-up periods (Domain 1) or CHD manifestations (Domain 2). [2]At least covariate-specific frequencies or proportions.

4.2 THE KUOPIO ISCHAEMIC HEART DISEASE RISK FACTOR STUDY

4.2.1 Study design

The present thesis used the male cohort of KIHD as the study material (Figure 4). The aims of the current thesis for their part complete the ultimate goal of KIHD: to provide new information about the etiology of CHD by detecting previously unknown risk factors of CHD specifically in eastern Finnish men (Salonen, 1988).

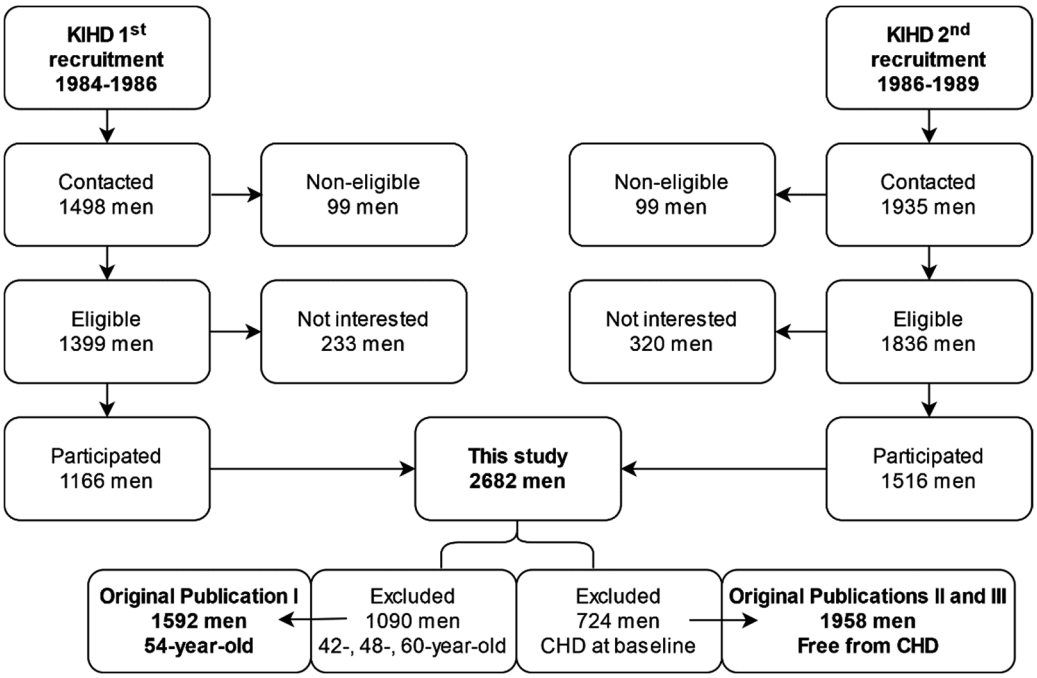

Figure 4. Flowchart of the first two KIHD recruitment rounds that provided study material for the present thesis.

In its first recruitment round from March 1984 to December 1986, KIHD contacted 1,498 men. They were 54 years old and lived in the city of Kuopio or in its surrounding rural municipalities: Karttula, Lapinlahti, Leppävirta, Maaninka, Siilinjärvi, Suonenjoki, Tuusniemi, and Vehmersalmi. Of those contacted men, 1,399 (93.4%) were eligible, and of the eligible men, 1,166 (83.3%) were willing to participate in KIHD.

In its second recruitment round from August 1986 to December 1989, KIHD contacted 1,935 men. They were 42, 48, 54, or 60 years old and, again, lived in the city of Kuopio or in its surrounding municipalities, except for Lapinlahti and Tuusniemi, which were dropped. Of those contacted men, 1,836 (94.9%) were eligible for the study. Of the eligible men, 1,516 (82.6%) were willing to participate.

All KIHD study subjects who participated in the KIHD baseline examinations between March 1984 and December 1989—altogether 2,682 men—were included in the present thesis (Figure 4). In its third recruitment round from June 1988 to January 2001, the KIHD study involved 920 54-, 60-, 66-, and 72-year-old eastern Finnish women. The present thesis, however, did not include women, because only men performed the exercise tolerance test that was useful in addressing the present research questions.

4.2.2 Coronary heart disease at baseline

To identify study participants who were not free of CHD when recruited in the KIHD study, the KIHD baseline examinations included a maximal symptom-limited exercise tolerance test (Lakka *et al*., 1994). The test was carried out at the Kuopio Research Institute of Exercise Medicine. Bicycle ergometers with a linear (Medical Fitness Equipment 400 L, Mearn, the Netherlands) or a step-by-step (Tunturi EL 400, Turku, Finland) increase in the workload by 20W per minute served as devices for assessing physical work. Measurements of oxygen uptake were based on a breath-by-breath method (MGC 2001, Medical Graphics, St. Paul, MN) or a mixing-chamber method (Mijnhardt Oxycon 4, Odijk, the Netherlands). The former method represented 76% out of the 2,682 KIHD study participants (n = 2,044), whereas the latter method represented 24% (n = 638). The test procedure also consisted of standard 12-lead ECG recordings (Kone, Turku, Finland) before, during, and after the ergometer test. The recordings before the ergometer test corresponded to the resting ECG.

Moreover, because the exercise stress testing in general may not recognize all CHD patients (Banerjee *et al*., 2012), the KIHD baseline

questionnaires included the following CHD-related questions: Has your physician told you that you have had a MI? Has your physician told you that you suffer from angina? Have you taken medicine for angina over the past 7 days? Do you take sublingual nitroglycerine once per week or more frequently? Have you undergone a coronary bypass operation? Based on a Norwegian cohort of CHD patients, the self-reported use of CHD medication shows substantial agreement with the prescription data (Pedersen *et al*., 2021).

Based on the ergometer test, ECG recordings, and answers to the CHD-related questions, the KIHD study participant was diagnosed as having CHD if he was unable to complete the ergometer test because of angina-type chest pain, if Q waves on the ECG recordings indicated a MI, if horizontal or downsloping ST depressions on the ECG recordings were ≥1 mm in aVF or V5 leads, or if he answered "yes" to at least one of the questions.

4.2.3 Study covariates

The main risk factors of CHD (Tsao *et al*., 2023) served as the covariates in statistical analyses of the present thesis. They were the following: age at KIHD baseline, family history of CHD, glycemic status, BMI, cholesterol status, blood pressure status, smoking status, and physical activity. Some analyses also included alcohol consumption as a covariate. The statistical analyses did not consider sex because all study participants were males.

As a part of KIHD baseline examinations, the study participants answered questions about their family history of CHD, the use of medication, smoking habits, and alcohol consumption. In addition, they filled out a form concerning physical activity over a typical 24-hour day and gave blood samples. Before the blood sampling between 8 a.m. and 10 a.m., the study participants had abstained from alcohol for 3 days and from smoking and eating for 12 hours. A research nurse drew blood using a vacuum without a tourniquet (Terumo Venoject VT-100PX, Terumo Corp., Tokyo, Japan).

Family history of CHD. Regarding the family history, the KIHD inquiry questions were as follows: Did your biological father have CHD? Did your biological mother have CHD? Did your biological sibling have CHD? Consequently, the family history of CHD in KIHD focused on the heritability of CHD, not necessarily on the environment in which one grew up.

Glycemic status. A glucose dehydrogenase method (Merck, Darmstadt, Federal Republic of Germany) was applied to measure fasting blood glucose (FBG). In addition, the study participants answered the following questions: Do you have diet-controlled diabetes? Do you use oral diabetes medications? Do you use insulin? For the present thesis, the study participants were categorized as having no diabetes (FBG <5.6 mmol/l), having prediabetes (FBG 5.6–6.9 mmol/l or following a diet), or having diabetes (FBG ≥7.0 mmol/l or using glucose-lowering medications). This categorization applies universal standards of diabetes care (Cosentino *et al*., 2020; ADA, 2021).

Body mass index. As a part of the KIHD baseline examinations, a research nurse measured study participants' height and weight. BMI was defined as the weight in kilograms divided by the square of height in meters, which categorized study participants as normal weight (BMI <25.0 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥30.0 kg/m^2). This categorization corresponds to the widely accepted cut-offs (Global BMI Mortality Collaboration *et al*., 2016).

Cholesterol status. The fasting serum TC was measured enzymatically (CHOD-PAP, Boehringer, Mannheim, Federal Republic of Germany). In the KIHD lipid analyses, very low-density lipoprotein cholesterol (VLDL-C) referred to the top serum lipoprotein fraction, LDL-C referred to a computational difference between the bottom and HDL-C fractions, and HDL-C referred to the supernatant after precipitation of the bottom fraction (Salonen *et al*., 1991). Serum cholesterol levels were considered normal, when LDL-C concentration was <3.4 mmol/l and high, when LDL-C concentration was >4.1 mmol/l. If LDL-C measurements were missing, serum cholesterol levels were considered normal, when TC concentration was <5.2 mmol/l and high, when TC concentration was >6.2 mmol/l. These cut-offs do not strictly follow standard clinical guidelines (Mach *et al*., 2020),

but they can be seen as a compromise between the guidelines and data-oriented statistical requirements. In the KIHD male cohort, only 15% of study participants had a desirable cholesterol level—serum LDL-C <3.0 mmol/l—at baseline which, from the viewpoint of statistical analyses' plausibility, is a small proportion of subjects to serve as a reference group. As a result, the study participants with desirable cholesterol levels were combined with those having below borderline levels. Only 17 (0.6%) study participants reported the use of cholesterol-lowering medications, and they were categorized as having hypercholesterolemia.

Blood pressure status. There are different blood pressure measurements available in KIHD. The present thesis, as most previous KIHD studies, applied the mean value of six measurements with a random-zero mercury sphygmomanometer. Of those measurements three relate to a supine position, two to a sitting position, and one to a standing position. The study participants were categorized as normotensive (SBP <120 and DBP <80 mmHg), prehypertensive (SBP 120–139 or DBP 80–89 mmHg), or hypertensive subjects (SBP >139 or DBP >89 mmHg). These cut-off values follow the criteria applied in the famous Framingham Heart Study that in many ways resembles KIHD (Franco *et al*., 2005). Thus, the cut-offs are not necessarily equal to suggestions based on other studies or standard guidelines (Atasoy *et al*., 2019; Antza *et al*., 2020). Nearly one-fourth of the study participants, 608 (22.7%), reported the use of blood pressure–lowering medications, and they were classified as hypertensive subjects.

Smoking status. The study participant was categorized as a never smoker if he had never smoked regularly and a smoker if he had smoked regularly within the past 30 days based on self-reports. Those who had smoked but not in the past 30 days were categorized as former smokers.

Physical activity. KIHD study participants filled out a 24-hour exercise diary. The semistructured diary form consisted of 10 exercise types with respect to different metabolic equivalent (MET) levels. To assess total energy expenditure (TEE), the study participants were asked to select the type that best describes their physical activity for every 30 minutes. A MET is the amount of oxygen consumed at rest, such as sitting, and typically, it is expressed as O_2/kg/min (Jetté, Sidney and Blümchen, 1990). Body weight,

body height, and age were entered into the Mifflin-St Jeor equation to calculate basal energy expenditure (BEE) (Mifflin *et al*., 1990). Then, TEE was divided by BEE to create physical activity level (PAL) categories as follows: TEE/BEE <2.00 denoted moderate physical activity, TEE/BEE 2.00–2.40 denoted vigorous physical activity, and TEE/BEE >2.40 denoted extreme physical activity (FAO/WHO/UNU, 2001). In KIHD, only 74 (2.8%) study participants reported PAL of <1.70, which can be considered reflecting a sedentary lifestyle (FAO/WHO/UNU, 2001). For the present thesis, sedentary subjects were classified into the same category as moderately active subjects. Because it is likely that PALs in KIHD are overestimations, because of self-report questionnaires being a measurement method (Prince *et al*., 2008; Groothuis *et al*., 2022), the PALs were considered as relative rather than absolute values. In general, PALs 1.40–2.40 can be sustained for a long time (FAO/WHO/UNU, 2001).

Alcohol consumption. KIHD study participants answered questions about their drinking frequency, drinking intensity, and drinking preferences. Based on those answers, the amount of alcohol consumed per week was estimated. The study participants were classified into three categories: low risk of health harms because of alcohol consumption (≤1 portion per week), moderate risk (≤3 portions per day), and high risk (>3 portions per day). According to Finnish standards, a portion corresponds to 12 grams of pure alcohol. This categorization is data specific, though it tries to match the current understanding of low-risk drinking. In the KIHD male cohort, the proportion of nondrinkers was 13.6% and the proportion of men who consumed approximately 100 grams of pure alcohol per week (90–110 g) was 4.6%. This 5% should be at the lowest risk for CHD (Wood *et al*., 2018).

4.3 REFERENCE MATERIAL

To answer the fourth research question concerning the epidemiologically most appropriate follow-up times for different outcome covariate pairs, the present thesis applied material from meta-analyses. This additional material was not published in Original Publications I–III. It provides study-level references to individual-level within-cohort findings from the KIHD

study. The material was gathered by means of PubMed and Google Scholar in May 2022. The aim was to find prospective cohort studies on the association of CHD with behavioral risk factors (BRFs) in men. The search terms included “meta-analysis,” “review,” “prospective,” “follow-up,” “CAD,” “CHD,” “diabetes,” “obesity,” “hypercholesterolemia,” “dyslipidemia,” “hypertension,” “smoking,” “physical inactivity”, and “sedentary.”

The searches resulted in seven meta-analyses. The meta-analyses reported study-level RRs or hazard ratios (HR) to risk factor-specific comparisons between men who were diagnosed with CHD or died from CHD during the follow-up and those who stayed free of CHD until the end of the follow-up. The meta-analyses included 81 separate prospective cohort studies (Appendix 1). Of the 81 studies, 26 compared men with and without diabetes, 17 compared obese to normal weight, 26 compared smokers to never smokers, 13 compared physically lowly active to highly active, and 30 studies provided RRs or HRs for CHD with respect to a 1-mmol/l increase in TC. None of the studies compared hypertensive to normotensive men. One study did not inform the follow-up time. To simplify the interpretation of results, HRs were considered RRs.

The study by Allen *et al*. (2012) pools USA cohorts and reports the risk of CHD in normotensive, prehypertensive, stage 1 hypertensive, and stage 2 hypertensive adults by sex, race, and age. The study by Allen *et al*. (2012) has been excluded from the reference material because it does not provide RRs or HRs. Moreover, it does not perform a systematic review to gather data. In Chapter 2.3.1, the paragraph dealing with hypertension as a CHD risk factor describes the results of Allen *et al*. (2012) in detail.

4.4 STATISTICAL METHODS

R was the principal statistical software (R Core Team, 2022). The main R packages included “ggplot2” (Wickham, 2016), “interactionR” (Babatunde, 2021), “survival” (Therneau and Grambsch, 2000; Therneau, 2022), “survminer” (Kassambara, Kosinski and Biecek, 2021), and “timereg” (Scheike and Martinussen, 2006; Scheike and Zhang, 2011). Other statistical software used were IBM SPSS Statistics 27 and GraphPad Prism 5.

Microsoft Excel was applied in solving equations. Simple directed acyclic graphs (DAG) were drawn to illustrate the link between theoretical reasoning and empirical findings. They were not used to produce actual results. The R package "ggdag" by Barrett (2023) was applied to DAGs.

4.4.1 Cox proportional hazards model: hazard function

The main statistical method applied was the Cox proportional hazards model. The model was first proposed by a British statistician, Sir David Roxbee Cox in 1972 (Cox, 1972). In this chapter, the introduction to the Cox model is derived from the following textbooks: *Analysis of Survival Data* (Cox and Oakes, 1984), *Applied Survival Analysis. Regression Modeling of Time to Event Data* (Hosmer and Lemeshow, 1999), and *Modeling Survival Data. Extending the Cox model* (Therneau and Grambsch, 2000).

The Cox model describes the relationship of covariates to a censored outcome, such as survival, by specifying the hazard function. A regression model for the function (1) is the product of two other functions. In them, $h_0(t)$ characterizes, how $h(t, x, \beta)$ changes as a function of time, and $r(x, \beta)$ characterizes, how $h(t, x, \beta)$ changes as a function of a covariate.

$$h(t, x, \beta) = h_0(t) r(x, \beta) \tag{1}$$

The Cox model's results are expressed as HR, that is, the ratio of the hazard function for subject 1 to the hazard function for subject 2 (2). As seen in (2), HR depends only on $r(x, \beta)$ because both the function for subject 1 and that for subject 2 include $h_0(t)$. Cox (1972) suggests using $r(x, \beta) = \exp(x\beta)$; thus, the explicit HR in the Cox model is (3):

$$\mathrm{HR}(t, x_1, x_0) = \frac{h_0(t) r(x_1, \beta)}{h_0(t) r(x_0, \beta)} \tag{2}$$

$$\mathrm{HR}(t, x_1, x_0) = e^{\beta(x_1 - x_0)} \tag{3}$$

In (3), β is estimated based on the partial likelihood function (Cox, 1972; Therneau and Grambsch, 2000, pp. 40–41).

4.4.2 Cox proportional hazards model: proportionality and time

Because HR is not dependent on time (2), the Cox model assumes $\beta(t) = c$. "Proportional hazards," the term in the model's name, refers to the multiplicative relationship between the hazard function for subject 1 and that for subject 2. The combination of these assumptions—$\beta(t) = c$ and multiplicativity—leads to an inevitable conclusion that the Cox model HR must be constant over time. Later in the text of the present thesis, the assumption of proportional hazards (PH) is termed as the PH assumption.

It is important to distinguish the time dependency of a coefficient $\beta(t)$ that violates the PH assumption from the time dependency of a covariate $X(t)$ that can be dealt with by distributing the data into time intervals and then considering them in the Cox model. For example, if FBG is associated with the risk of CHD with a constant β, but the FBG level measured frequently during the follow-up shows a fluctuating pattern, the PH assumption is not violated, though the covariate depends on time.

Despite the dominance of the Cox model in epidemiology, the epidemiological relationships between outcomes and covariates are generally supposed to be more frequently additive than multiplicative (Lefebvre and Giorgi, 2021). As a result, the Cox model should not be used without performing tests on the PH assumption *a priori*. One way to assess the PH assumption is to inspect the scaled Schoenfeld residuals plotted over time (Grambsch and Therneau, 1994). The Schoenfeld residuals are independent of time and, thus, any nonrandom residual pattern against time signifies violations of the PH assumption, as well as statistically significant relationships between the residuals and time.

To demonstrate the use of Schoenfeld residuals as an indicator of time dependency, a Cox model on the incident CHD in the KIHD male cohort of 2,682 study participants as an outcome and the main CHD risk factors as covariates was performed. In the methodological demonstrations reported in this and the following chapters, the term "incident CHD" refers to CHD diagnoses assigned between the KIHD study's baseline and December 31, 2019. The outcome does not consider the CHD status at baseline, so the incident CHDs are not exactly *de novo* CHDs. To simplify the interpretation

of Schoenfeld residuals, seven covariates including age, the family history of CHD, glycemic status, BMI, cholesterol status, blood pressure status, and smoking status were dichotomized as in Original Publication II. In addition to these categorical variables, physical activity and alcohol consumption served as continuous covariates. This dataset used for the present methodological demonstrations is hereinafter called Demo Data. The results based on Demo Data are not actual study results; they just support the text describing the Cox proportional hazards model (Chapters 4.4.2, 4.4.3, and 4.4.4), Aalen's additive regression model (Chapter 4.4.5), and covariate interactions (Chapter 4.4.6).

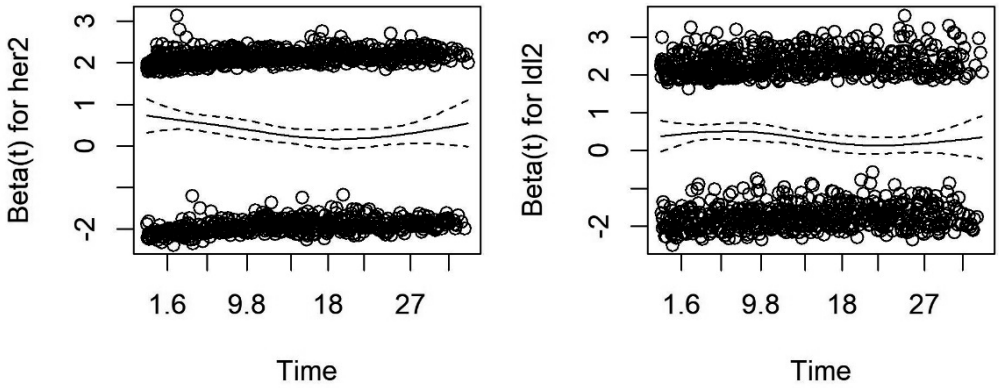

Figure 5. Relationships between the scaled Schoenfeld residuals and follow-up time regarding the effect of the family history of CHD (her2) and that of the cholesterol status (ldl2) on the risk of CHD in Demo Data. In the figures, the solid line represents a spline fit and dashed line a ±2-standard-error band for it. This figure does not report actual study results; it just supports the text that describes the Cox proportional hazards model.

The global statistical test did not indicate a violation of the PH assumption (p = 0.095), and only one coefficient showed time-dependency according to individual tests (p = 0.026) (Figure 5, Table 3, Appendix 2).

Although the idea in the scaled Schoenfeld residuals is to visually judge whether they are randomly distributed and unrelated to time, the task becomes challenging if the relationship between the residuals and time is weak. In Demo Data, the effect of the family history of CHD on the risk of

incident CHD was statistically significantly related to time (p = 0.026), whereas the corresponding effect of cholesterol status was not (p = 0.067) (Table 3). In practice, it would have been impossible to notice this difference using only a visual inspection of the Schoenfeld plots (Figure 5).

Table 3. Covariate-specific HRs for the incident CHD in Demo Data from Cox models without and with consideration of time-dependent coefficients. This table does not report actual study results; it just supports the text that describes the Cox proportional hazards model.

Covariate	**Cox model Crude**	**Cox model Time interval**	**Cox model Time function**
Age HR (95% CI) Dichotomous	2.07 (1.77–2.43) p for $\beta(t)$ 0.484	2.08 (1.77–2.43)	2.08 (1.77–2.43)
Family history Dichotomous	1.46 (1.30–1.64) p for $\beta(t)$ 0.026	<10 yrs.: 1.96 (1.61–2.39) 10–20: 1.14 (0.93–1.40) 20–30: 1.36 (1.07–1.72) >30 yrs.: 1.10 (0.60–2.02)	1.79 (1.43–2.23) with tX
Glycemic status Dichotomous	2.00 (1.67–2.40) p for $\beta(t)$ 0.804	2.00 (1.67–2.40)	2.00 (1.67–2.40)
Body mass index Dichotomous	1.19 (1.02–1.39) p for $\beta(t)$ 0.257	1.19 (1.02–1.38)	1.19 (1.02–1.38)
Cholesterol Dichotomous	1.39 (1.24–1.57) p for $\beta(t)$ 0.067	1.39 (1.24–1.57)	1.39 (1.24–1.57)
Blood pressure Dichotomous	1.71 (1.50–1.95) p for $\beta(t)$ 0.165	1.71 (1.50–1.95)	1.71 (1.50–1.95)
Smoking status Dichotomous	1.50 (1.31–1.71) p for $\beta(t)$ 0.572	1.50 (1.31–1.71)	1.50 (1.31–1.71)
Physical activity Continuous	0.89 (0.79–1.00) p for $\beta(t)$ 0.116	0.89 (0.79–1.00)	0.89 (0.79–1.00)
Alcohol Continuous	1.00 (1.00–1.00) p for $\beta(t)$ 0.713	1.00 (1.00–1.00)	1.00 (1.00–1.00)

If the PH assumption is not met—that is, the model coefficients (β) depend on time—it is possible to expand the Cox model with different βs for different time intervals. In Demo Data, only β of the family history of CHD showed time dependency. To address this violation of the PH assumption, Demo Data were distributed into four epochs: <10, 10–20, 20–30, and >30 years of follow-up. This procedure statistically removed the time dependency (p = 0.335 for the global test and 0.504 for the family history covariate) and revealed the family history being a significant predictor of CHD during the first 10 years of follow-up with the HR [95% confidence interval (CI), p-value] of 1.96 (1.77–2.16, <0.001) and again from 20 to 30 years of follow-up with the HR of 1.36 (1.12–1.59, 0.011). It also is possible to add covariate-specific time functions in the Cox model. In the simple Demo Data example, a product of time and variable of interest, the family history of CHD, served as the time function. As seen in Table 3, applying time intervals or a time function in the Cox model affected HRs solely with respect to the modified covariate in question.

4.4.3 Cox proportional hazards model: linearity

In addition to the proportional hazards, the Cox model assumes a linear relationship between the hazard function and covariates. This assumption is known as the log-linearity assumption (Lefebvre and Giorgi, 2021), and it can be verified, for example, by plotting martingale residuals against the covariates. The martingale residual is calculated at the end of follow-up for each subject, and the expected value of each residual is 0. Negative martingale residuals indicate subjects, who lived or stayed disease-free longer than expected, whereas positive martingale residuals denote subjects who died or got the disease sooner than expected. The residual can range from $-\infty$ to +1. In Demo Data, the martingale residuals raised some concerns regarding the linearity of the relationship between the hazard function and continuous covariates, that is, physical activity and alcohol consumption (Appendix 3). A simple procedure to try to solve the nonlinearity problem is to replace the covariate in question, x, with a function of x, such as $log_{10}x$ or $\sqrt{x}$. In Demo Data, these common

transformations did not entirely fix the issue, although the $\log_{10}$-transformed alcohol consumption resulted in more linear relationship compared with the original alcohol consumption variable that caused the most concern (Appendix 3).

Yet another way to assess the relationship between the hazard function and covariates is to plot deviance residuals. The deviance residual is a normalized transform of the martingale residual that is highly skewed particularly for right censored data. In prospective follow-up data, subjects are typically categorized as completed and censored. Among the former, the outcome of interest is observed during the follow-up, whereas, among the latter, the follow-up terminates because of a random factor, such as another outcome or the end of the follow-up before the outcome is observed. Because most of the incomplete observations occur at or near the end of the follow-up, this kind of prospective data are called right censored. If the deviance residuals are nonsymmetrically distributed around zero in the residual plot, the follow-up times depend on the order of subjects in the dataset, which, naturally, is an unwanted situation. Moreover, large standard deviations (SDs) of the residuals should be considered as influential observations, that is, outliers. In Demo Data, the deviance residuals were symmetrically distributed around zero, but several subjects related to higher SDs than $|3|$ (Appendix 4).

4.4.4 Cox proportional hazards model: additional aspects

The standard Cox model assumes continuous data and uses the ranks of event times to fit the model, meaning that it does not consider ties. Because real data often contain tied events, additional algorithms are used to address the issue of ties. In follow-up studies, if two or more subjects encounter the outcome of interest at the same time, which means the length of time from the beginning point t_0 to the observation of the outcome t_1 is the same for both subjects, they are considered ties. Technically, ties are possible, if event time measures are discrete, such as days, or continuous event times are used as intervals. The Breslow

approximation is the simplest and most-used algorithm to deal with ties in the Cox model. Another frequent method is the Efron approximation.

Along with HRs, Cox model results can be interpreted based on statistical tests on covariate coefficients (β). Statistical textbooks usually introduce at least the likelihood-ratio test (LRT) and Wald test to analyze the chi-square distributed null hypothesis $H_0: \beta = \beta^{(0)}$, in which $\beta^{(0)}$ is the initial value for β, with zero being the default value in most cases. Statistically, zero is an adequate default value, but this might not be true from a biological perspective, at least when considering age, which inevitably increases the risk of mortality, as well as that of most illnesses. The LRT is considered the most and Wald test the least reliable test of β.

For the end user of statistical software, the resulting Cox model HRs are easy to understand and interpret. On the contrary, a deep understanding of the partial likelihood function that estimates βs and, thus, forms the heart of the Cox model is unreachable for most researchers in practice. As a result, a simpler method to estimate HRs would bring the statistical methodology closer to the end users. A quantity to assess HR is the ratio of the mean follow-up time in the reference group to the mean follow-up time in the exposed group.

In Demo Data, the method based on mean follow-up times systematically underestimated the HRs, expect for physical activity and alcohol consumption, which had no effect on the CHD risk in the Cox model (Figure 6). Specifically, the HR related to high-risk alcohol consumption was difficult to assess by means of follow-up times because it increased the risk of all-cause mortality in Demo Data but not that of CHD. The mean estimation method was indeed more appropriate for assessing the HRs for all-cause mortality. The method systematically underestimated the HRs, except for the dichotomized PAL, but it well described ranks in the HRs (Figure 6). The main drawback of the mean estimation method is that it only allows to assess one covariate at a time. That is, the method is unable to estimate a covariate-specific HR adjusted for other covariates. Moreover, the method cannot control competing risks.

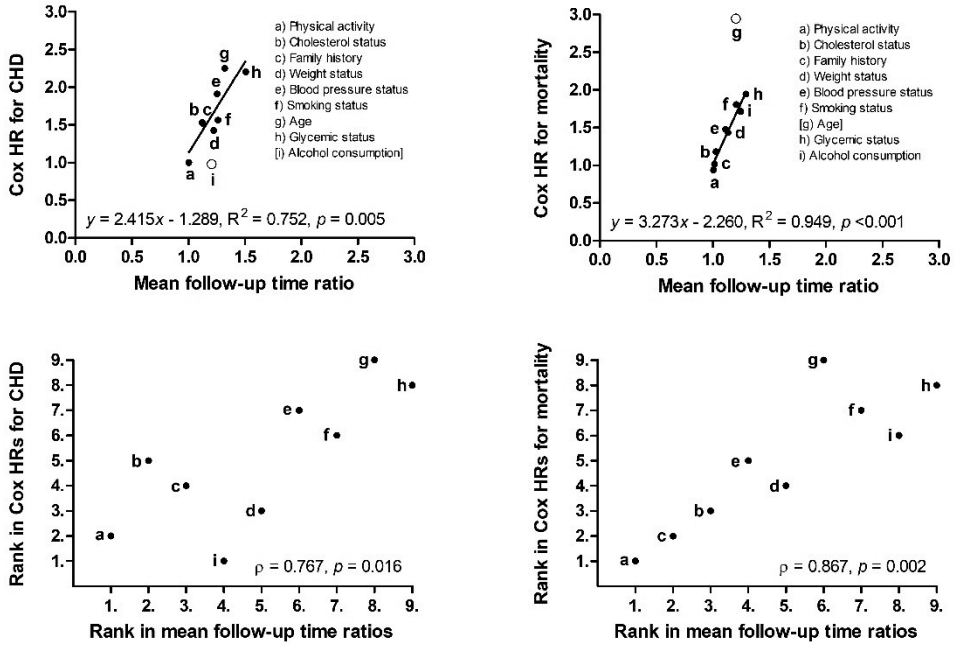

Figure 6. Relationships between the Cox model HRs and HR estimations based on the ratio of the mean follow-up time in the reference group to the mean follow-up time in the exposed group in Demo Data. The left panel presents the HRs for CHD and the right panel the HRs for all-cause mortality. Lower case letters indicate different risk factors. This figure does not report actual study results; it just supports the text that describes the Cox proportional hazards model.

4.4.5 Aalen's additive regression model

The multiplicative Cox model is not the only statistical technique that can be used to analyze survival data. If the time dependency of βs is a major issue, additive methods should be considered instead of the Cox model. To investigate the covariate-specific additive hazards of the incident CHD in Demo Data, Aalen's additive regression model was performed. The Aalen model (4) expresses the cumulative hazard $\mathrm{H}(t)$ by means of a time-dependent intercept $\mathrm{a}(t)$ that represents the time-dependent reference hazard, a vector of covariates X that can also depend on time and a time-dependent matrix of βs $\mathrm{B}(t)$ (Aalen, 1989; 1993).

$$\mathrm{H}(t) = \mathrm{a}(t) + \mathrm{X}\,\mathrm{B}(t) \tag{4}$$

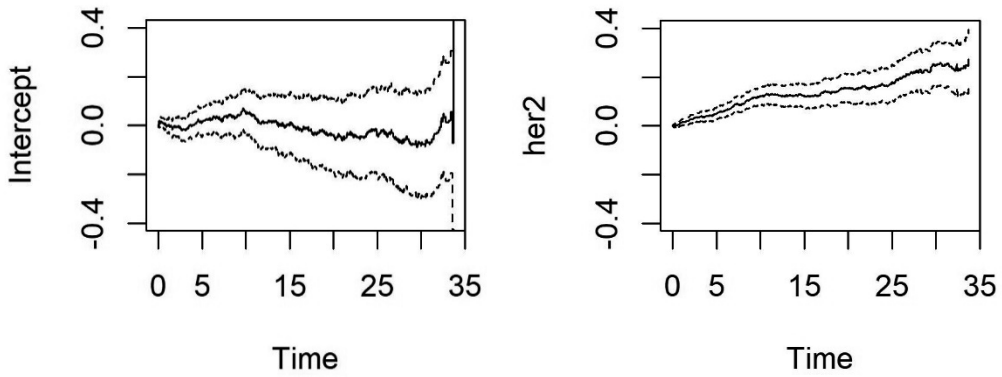

Figure 7. The reference hazard of the incident CHD (on the left) and the cumulative additive effect of the family history of CHD on the hazard of the incident CHD in Demo Data (on the right). The family history of CHD was the only time-dependent covariate in the Cox model. Bands indicate ±SE. This figure does not report actual study results; it just supports the text that describes the Aalen's additive regression model.

Physical activity and alcohol consumption were the only covariates that did not show statistically significant additive effects on the hazard of incident CHD in Demo Data according to Aalen's additive regression model. Physical activity and alcohol consumption were the only covariates with negative mean coefficients (Appendix 5). Glycemic status was associated with the largest covariate followed by age, blood pressure status, smoking status, the family history of CHD, cholesterol status, and BMI. The intercept of the model was statistically not significant (p = 0.871, Figure 7), indicating that the covariates included in the model captured the additional hazard in its entirety. In the Cox model, β of the family history of CHD was dependent on time. In Aalen's model, the cumulative additive effect of the family history on the hazard of incident CHD revealed a similar temporal pattern as the time intervals applied in the Cox model. In Demo Data, the family history of CHD affected the hazard of CHD, particularly during the first 10 years of follow-up and then again after 25 years (Figure 7).

4.4.6 Covariate interactions

The present thesis mostly followed the works by Rothman and his colleagues with respect to the definitions and measures of interaction and referred to a statistical interaction instead of a biological interaction (Lash *et al*., 2021). When the effect of an exposure on an outcome depends on another exposure, the exposures interact with each other. The interaction between two or more covariates can also be linked to the epidemiological theory of causation (Lash *et al*., 2021). According to it, the covariates can interact with each other only when they are the components of the same causal mechanism that inevitable leads to the disease. The thought behind the theory is that a disease is usually a consequence of a concurrent existence of more than one "risk factors," of which none solely cause the disease. For example, the theory could argue that CHD is necessarily caused by hypercholesterolemia when it occurs together with at least two other risk factors, including obesity, hypertension, and diabetes.

In its simplest form, a multiplicative interaction between two exposures can be assessed by means of RRs and an additive interaction by risk differences (RD). If both exposures affect the outcome in question, there will be either a multiplicative or additive interaction between them. As a result, the presence of an interaction is uninteresting, but there should be an additional reason for the investigation of interactions. The present thesis aimed at demonstrating how the results of the Cox model can be altered if statistically significant interactions between exposures, as well as between exposures and confounders, are included in it. Thus, the reason for the investigation of interactions was statistical. From a statistical perspective, exposures correspond to model covariates.

To demonstrate how an interaction can be detected based on RRs and RDs, all nine covariates in Demo Data (Table 3 on page 64) were dichotomized as in Original Publication II. The number of covariate combinations was $\frac{9!}{(9-2)!2!} = 36$ and each combination was analyzed separately. First, the risk of the incident CHD in the absence of both exposures p_{00}, in the presence of one exposure p_{01} and p_{10}, and in the presence of both exposures p_{11} was calculated. Second, 95% CI estimates

for p_{00}, p_{01}, p_{10}, and p_{11} were generated using Wilson's method (5), which has been recommended instead of the standard Wald interval (Wilson, 1927; Brown, Cai and DasGupta, 2001) (Tables 4 and 5). For example, among men who were over 50 years old and whose cholesterol levels were high (serum LDL-C concentration >4.1 mmol/l or taking cholesterol-lowering medications), the p_{11} was $\frac{483}{920} = 0.53$, with the 95% Wilson CI of 0.50–0.55 (5).

$$p = \frac{\hat{p} + \frac{z_{\alpha/2}^2}{2n} \pm z_{\alpha/2}\sqrt{\frac{\hat{p}\hat{q}}{n} + \frac{z_{\alpha/2}^2}{4n^2}}}{1 + \frac{z_{\alpha/2}^2}{n}} \cong \frac{0.526 \pm 1.96 \times 0.013}{1.003} \cong 0.499, 0.550 \qquad (5)$$

Age and cholesterol status were used as the exposure variables in the Demo Data calculations of RRs and RDs (Tables 4 and 5). To detect statistically significant interactions, CIs were calculated for RRs and RDs (Altman, 1991, pp. 266–268; Newcombe and Altman, 2000, pp. 45–56). The RR for CHD in <50-year-old men with the serum LDL-C >4.1 mmol/l compared with <50-year-old men with the serum LDL-C ≤4.1 mmol/l was $\frac{0.42}{0.22} = 1.91$. Correspondingly, the RR for CHD in >50-year-old men with the serum LDL-C >4.1 mmol/l compared with >50-year-old men with the serum LDL-C ≤4.1 mmol/l was 1.20. The 95% CIs for the RRs were calculated based on standard errors (SE). The respective SEs for the $\ln(\mathrm{RR})$ were $\sqrt{\frac{1}{98} + \frac{1}{99} - \frac{1}{98+138} - \frac{1}{99+345}} \cong 0.118$ and 0.047. Finally, the respective 95% CIs for the RRs were $e^{\ln(1.91) \pm 1.96 \times 0.118} \cong 1.52 - 2.41$ and 1.09−1.32. The RD for CHD among <50-year-old men with the serum LDL-C >4.1 mmol/l compared with <50-year-old men with the serum LDL-C ≤4.1 mmol/l was 0.42–0.22 = 0.22. The corresponding RD in >50-year-old men was 0.09. The 95% CIs for the RDs were calculated based on the 95% Wilson CIs for p_{00}, p_{01}, p_{10}, and p_{11} (Tables 4 and 5). Among >50-year-old men, the lower 95% confidence limit for the RD was $0.20 - \sqrt{(0.42 - 0.35)^2 + (0.26 - 0.22)^2} \cong 0.12$ and the upper limit was $0.20 + \sqrt{(0.22 - 0.19)^2 + (0.48 - 0.42)^2} \cong 0.27$. Among >50-year-old men, the 95% CI for the RD was 0.05–0.13.

Table 4. CHD in <50-year-old men based on the cholesterol status in Demo Data. This table does not report actual study results; it just supports the text that describes covariate interactions.

Cholesterol status	CHD	No CHD	*n*	Risk of CHD
LDL-C >4.1 mmol/l or medication	a: 98	b: 138	a + b = 236	p_{01}: a / (a + b) = 0.42 95% CI: 0.35–0.48
LDL-C ≤4.1 mmol/l	c: 99	d: 345	c + d = 444	p_{00}: c / (c + d) = 0.22 95% CI: 0.19–0.26

Table 5. CHD in >50-year-old men based on the cholesterol status in Demo Data. This table does not report actual study results; it just supports the text that describes covariate interactions.

Cholesterol status	CHD	No CHD	*n*	Risk of CHD
LDL-C >4.1 mmol/l or medication	a: 483	b: 437	a + b = 920	p_{11}: a / (a + b) = 0.53 95% CI: 0.50–0.55
LDL-C ≤4.1 mmol/l	c: 451	d: 582	c + d = 1033	p_{10}: c / (c + d) = 0.44 95% CI: 0.41–0.47

In summary, because the 95% CIs for the RRs did not overlap with each other (1.32 < 1.52), there was a multiplicative interaction between age and cholesterol status. Analogously, because the 95% CIs for the RDs did overlap with each other (0.13 > 0.12), there was no additive interaction between age and cholesterol status. Nonoverlapping CIs can be considered a sign of statistical significance.

In addition to RDs, the interaction contrast ratio (ICR), that is, relative excess risk due to interaction (RERI), the synergy index (*S*), and attributable proportion (AP), were used to assess additive interactions (6–8). ICR reports the relative excess (ICR >0) or deficit risk (ICR <0) because of the interaction, *S* is the ratio of the relative risk in the doubly exposed group to

the sum of relative risks in the singly exposed groups, and AP is the proportion of ICR in the doubly exposed group. If the additive interaction is positive, ICR >0, *S* >1, and AP >0. In addition, consistently, if the additive interaction is negative, ICR <0, *S* <1, and AP <0.

$$\mathrm{ICR} = \mathrm{RR}_{11} - \mathrm{RR}_{10} - \mathrm{RR}_{01} + 1 \tag{6}$$

$$S = \frac{\mathrm{RR}_{11}-1}{(\mathrm{RR}_{10}-1)+(\mathrm{RR}_{01}-1)} \tag{7}$$

$$\mathrm{AP} = \frac{\mathrm{ICR}}{\mathrm{RR}_{11}} \tag{8}$$

For the interaction between age and cholesterol status in Demo Data (Tables 4 and 5), $\mathrm{RR}_{11} = \frac{0.53}{0.22} \cong 2.41$, $\mathrm{RR}_{10} = \frac{0.44}{0.22} = 2.00$, $\mathrm{RR}_{01} = \frac{0.42}{0.22} \cong 1.91$, so ICR was $2.41 - 2.00 - 1.91 + 1 = -0.5$, *S* was $\frac{2.41-1}{(2.00-1)+(1.91-1)} \cong 0.74$, AP was $\frac{-0.5}{2.41} \cong -0.21$, and they all indicated a negative additive interaction, which, in this case, meant the combined effect of age >50 and serum LDL-C >4.1 mmol/l was smaller than the sum of the individual effects.

Concerning multiplicative interactions, the measure introduced in equation (9) was applied in addition to RRs. The measure is the ratio of the relative risk in the doubly exposed group to the product of relative risks in the singly exposed groups; therefore, it is a multiplicative scale version of *S*. If the measure >1, the multiplicative interaction between the exposures is positive, and if it is <1, the interaction is negative. For the interactive effect of age and cholesterol status on the risk of incident CHD in Demo Data, the measure resulted in $\frac{2.41}{2.00 \times 1.91} \cong 0.63$, thus indicating a negative multiplicative interaction.

$$\text{Multiplicative interaction} = \frac{\mathrm{RR}_{11}}{\mathrm{RR}_{10}\mathrm{RR}_{01}} \tag{9}$$

It would have been possible to use odds ratios (ORs) instead of RRs in all the calculations described in this chapter, but it would not have affected the conclusions concerning the interactions.

To sharpen the statistical evaluation of interactions in the actual study data (see also Original Publication II), 95% CIs for ICR, *S*, and AP were calculated based on the variance recovery method MOVER (Zou, 2008), and *p*-values for multiplicative interactions were derived from logistic regressions and Cox models. Assessing the statistical significance of the interactions simply based on the overlap of CIs is vague.

4.4.7 The most appropriate follow-up time

In the present thesis, the epidemiologically most appropriate follow-up time meant the length of follow-up relating to the point estimate that most indicated the association between the outcome and covariate in question. The starting point for the definition of the epidemiologically most appropriate follow-up time was the epidemiological relationship between CHD and its BRFs (see Chapter 2.3.1 along with Original Publications I and II). Because the BRFs factually explain the risk of CHD, the follow-up time associated with the largest statistically significant effect size should be the follow-up time that most correctly and accurately describes the relationship between CHD and the BRF in question.

In KIHD, the follow-up began on the day the subject participated in the baseline examinations (T_0). In the present thesis, the follow-up ended on the day when the subject died or had a CHD diagnosis or on December 31, 2019, if the subject was then still alive with no known CHD diagnoses (T^*_{max}). The subjects whose follow-up ended on December 31, 2019, or who died before that from non-CHD causes were censored. Among the subjects who had a CHD diagnosis or who died from CHD before December 31, 2019, the follow-up time refers to the time from baseline to the event. However, because diagnoses were assigned during hospitalizations and postmortem examinations, the time-to-event data, in this case, do not represent the onset of the disease but rather the manifestation of (severe) CHD symptoms.

Two datasets were prepared to study the epidemiologically most appropriate follow-up time: the KIHD male cohort and the reference study-level data from published meta-analyses (see Chapters 4.2 and 4.3). With

respect to the study material from KIHD, the Cox model served as the main statistical analysis method. The models were constructed separately for different clinical CHD manifestations [(CHD, MI/UA, and fatal acute myocardial infarction (FAMI)] as the outcome variables, with age, the family history of CHD, glycemic status, BMI, cholesterol status, blood pressure status, smoking status, and physical activity as the covariates. All possible multiplicative covariate interactions were tested, and the PH assumption was assessed by means of Schoenfeld residuals. So far, the analysis procedure resembled those applied in Original Publications I and II. To find the epidemiologically most appropriate follow-up time for all outcome covariate pairs, separate Cox models were performed on annual cumulative incidences from 1 to 35 years of follow-up. In the Cox models, each CHD manifestation served as the outcome with age, the family history of CHD, glycemic status, BMI, cholesterol status, blood pressure status, smoking status, and physical activity as covariates. Moreover, to see the difference between CHD risk factors manifesting within years and those manifesting within decades a sliding window procedure with a subarray of 5 years was carried out. In practice, this denoted modeling the HR for CHD diagnosed within time frames $T_0 - T_5, T_1 - T_6, \dots, T_{25} - T_{30}$. Diagnose codes assigned after 30 years of follow-up were excluded from the sliding window procedure because of the small number of new CHD diagnoses, which were 7.4 per year on average.

A prospective cohort study included in a published meta-analysis was used as a statistical unit in the analyses of the study-level data. To reveal the associations of CHD with its risk factors, quadratic and cubic curves were fitted to the risk factor-specific relationships between the RR for CHD (y) and the length of follow-up time in years (x). The coefficient of determination (r^2) was chosen as a measure of goodness-of-fit mainly because it is so widely known. By and large, r^2 should be used with caution because it is a valid measure only when model parameters are linear (Spiess and Neumeyer, 2010). The CHD outcome included both fatal and nonfatal events because many meta-analyses had pooled them. Three study-specific RRs, one with respect to the association between CHD and glycemic status and two with respect to the association between CHD and

BMI, were excluded from the analyses because they related to follow-up times longer than 35 years, that is, T^*_{max} in the KIHD male cohort. HRs were considered RRs.

The results derived from the study-level material were compared with those from the KIHD male cohort to assess ecological fallacy that may arise when conclusions based on group-level analyses are extended to individuals. In epidemiology, the term ecological refers to using a group of individuals as a statistical unit in analyses instead of an individual, and the ecological fallacy originates from the grouping as such because it typically affects the relationship between the dependent and independent variables (Piantadosi, Byar and Green, 1988). The ecological fallacy exists if the slope β_g of a regression model that is based on group-level data (g) ≠ the slope β_i of a regression model that is based on individual-level data (i).

5 RESULTS

5.1 STATISTICAL VALIDITY IN REVIEWED JOURNAL ARTICLES

Web of Science provided information of 45 scientific journals of which the names include the word "epidemiology." Out of those journals, nine did not belong to the public health category (*Epidemiologie Mikrobiologie Imunologie*, *Epidemiology and Psychiatric Sciences, Genetic Epidemiology*, *Health Services Research and Managerial Epidemiology*, *Journal of Cancer Epidemiology*, *Journal of Oral Health and Oral Epidemiology*, *Ophthalmic Epidemiology*, *Revista de Epidemiologia e Controle de Infeccao*, and *Social Psychiatry and Psychiatric Epidemiology*), four had not published papers in 2021 (*Epidemiologia e Psichiatria Sociale*, *Epidemiology Biostatistics and Public Health*, *Journal of Exposure Analysis and Environmental Epidemiology*, and *Microbial Drug Resistance-Mechanisms Epidemiology and Disease*), and two had published only review articles (*Current Epidemiology Reports* and *Epidemiologic Reviews*) (Figure 8).

The final number of epidemiology journals included in this evaluation of statistical validity was 30. In 2021, these 30 journals had published altogether 4,183 articles, of which 18 (0.4%) dealt with the epidemiological relationship of CHD with its known or potential risk factors (Figure 8). In comparison, 875 (20.9%) articles dealt with COVID-19. Out of the 30 journals, 15 were from Europe, nine from United States, four from Asia, one from Oceania, and one from South America. Appendix 6 describes the 30 journals and number of articles published by them in more detail.

The PubMed search resulted in 2,059 documents, and 75 of them were selected for the full-text scan based on titles and abstracts. The Scopus search resulted in 520 documents, of which 61, after excluding two PubMed duplicates, were forwarded into the full text scan. Out of the 136 journal articles, 49 were excluded because of the below reasons, and 87 fulfilled the inclusion criteria (Figure 8). The reasons for exclusion were in the following order: The journal had no Web of Science status (3 articles). The study was a meta-analysis (5 articles). The study did not include an

actual prospective follow-up period (14 articles). The dependent variable was something other than CHD or MI (2 articles). The dependent variable combined CHD with non-CHD outcome(s) (25 articles).

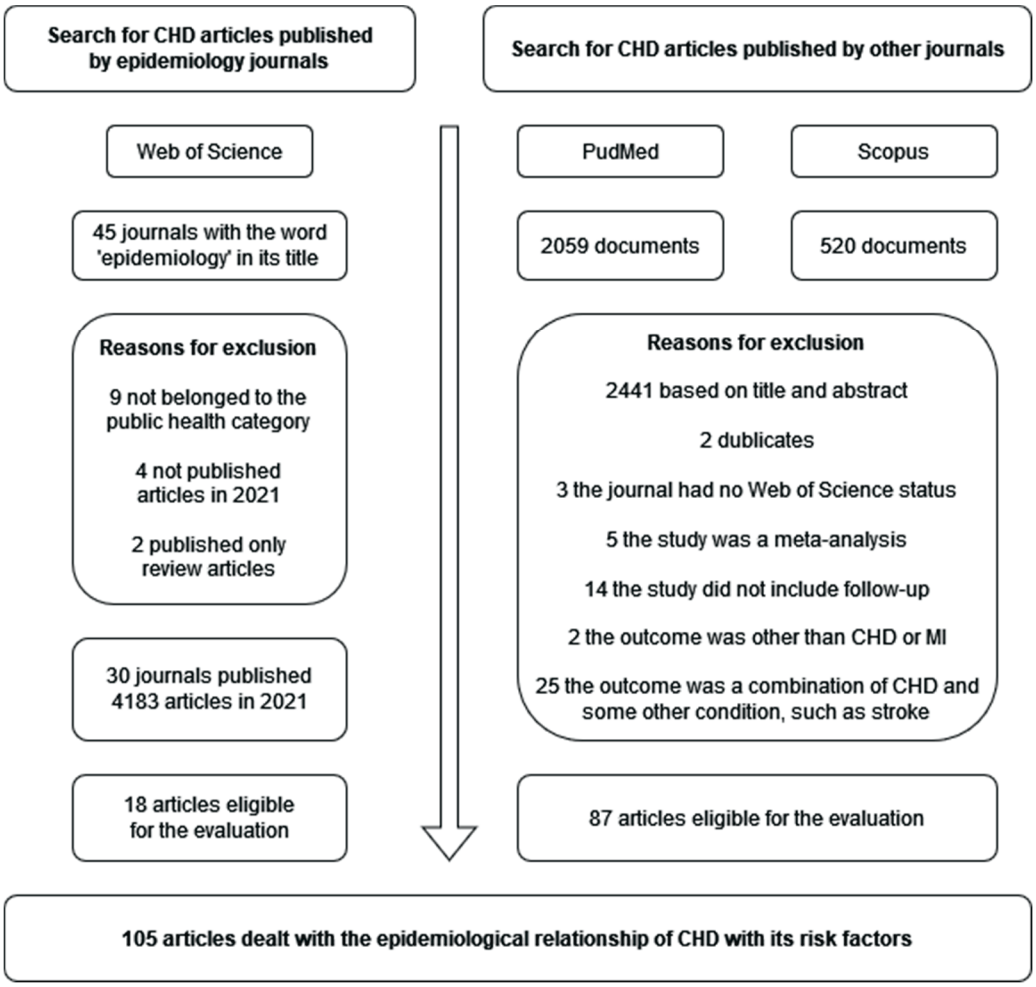

Figure 8. Flow of the search for journal articles dealing with the epidemiological relationship of coronary heart disease (CHD) with its risk factors. The arrow indicates the direction of the flow.

The maximum observed SVI was 4.5. Only one article published in *Diabetes, Obesity & Metabolism* reached this value. The most frequent SVI category was 1.5 followed by 2 (Figure 9). One-third of the articles belonged to these two categories (*n* = 32, 30.5% out of 105 articles). The

distribution of articles by SVI did not differ between the 18 articles published in six epidemiology journals and 87 articles published in 60 nonepidemiology journals ($\chi 2$ = 8.620, df = 9, exact p = 0.490).

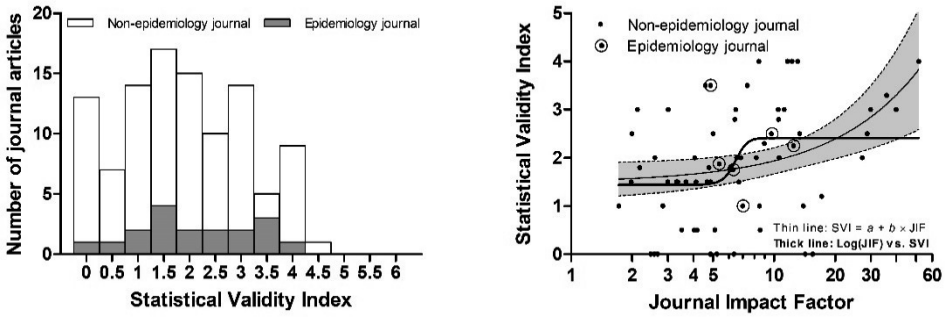

Figure 9. On the left: the distribution of journals articles by Statistical Validity Index (SVI); the y-axis informs the number of articles published in 2021. On the right: the relationship between SVI and Journal Impact Factor (JFI); note the logarithmic scale of the x-axis that curves the linear relationship between SVI and JIF.

SVI increased linearly with Journal Impact Factor (JIF) and the transition point from the basic SVI level of 1.5 to the higher level of 2.5 took place between the JFIs of 5 and 8 (Figure 9). In detail, the association of SVI with JIF was 0.046 × JIF + 1.481 (R^2 = 0.14, p = 002), and the JIF value relating to the halfway SVI was 6.4 with a 95% CI of 5.0–7.9. Web of Science did not report JIF to *Open Heart*, but it was estimated based on Journal Citation Indicator (JCI) as follows: JIF = 5.622 × JCI – 0.683 (R^2 = 0.87, p <0.001).

The mean (SD) SVI of 105 articles was 1.9 (1.2). Regarding the six statistical domains of SVI, different association types (multiplicative, additive, and interactive) and missing values were best considered with the respective mean (SD) domain-specific values of 0.5 (0.5) and 0.5 (0.4).

The mean (95% CI) SVI of the articles published in epidemiology journals was 2.1 (1.6–2.6), and that of articles published in nonepidemiology journals was 1.8 (1.6–2.1). The mean SVI did not differ between the articles published in epidemiology journals and those published in nonepidemiology journals (Table 6). However, there was a difference

between the epidemiology and nonepidemiology journal articles with respect to competing risks. The articles published in epidemiology journals had considered competing risks in their statistical analyses with lower quality compared with the articles published in nonepidemiology journals (Table 6).

Table 6. Statistical validity of journal articles per statistical domain.

Statistical domain	**All articles (*n* = 105)**	**Epidemiology journals' articles (*n* = 18)**	**Other articles (*n* = 87)**	**P-value**
Participant exclusions	0.14 (0.01–0.27)	0.14 (0.01–0.27)	0.08 (0.03–0.13)	0.365
Association types	0.55 (0.46–0.64)	0.67 (0.46–0.88)	0.52 (0.42–0.62)	0.237
Length of follow-up	0.26 (0.18–0.35)	0.33 (0.11–0.56)	0.25 (0.16–0.33)	0.439
Outcome sensitivity	0.25 (0.16–0.33)	0.25 (0.05–0.45)	0.25 (0.16–0.34)	0.979
Competing risks	0.20 (0.12–0.28)	0.06 (0[1]–0.16)	0.23 (0.14–0.32)	0.019[2]
Missing values	0.53 (0.45–0.61)	0.61 (0.44–0.78)	0.51 (0.42–0.60)	0.350
Statistical Validity Index (Min–max: 0–6)	1.89 (1.65–2.12)	2.11 (1.58–2.64)	1.84 (1.58–2.10)	0.392

Notes. Values indicate mean (95% CI). P-value is from a t-test for the difference between articles published in epidemiology journals and articles published in other journals. [1]The negative lower bound of 95% CI marked as zero. [2]P-value for unequal variances. Because of the low number of epidemiology journals (*n* = 18) their SVI should have been around 3 to reach a statistically significant difference between the journal groups.

The most common statistical method applied was the Cox model in 89 out of 105 journal articles (84.8%). In 28 articles (26.7%), the Cox model was combined with the Kaplan–Meier method. The Kaplan–Meier method was much less common in articles published in epidemiology than nonepidemiology journals. Only one article published in epidemiology journals had used the Kaplan–Meier method. The avoidance of Kaplan–Meier may be related to limitations of the method, and epidemiology journals may be better aware of them. Particularly, when competing risks are present, the Kaplan–Meier method tends to overestimate cumulative incidences (Verduijn *et al*., 2011; Schuster *et al*., 2020). We have demonstrated the Kaplan–Meier problem in the KIHD cohort, that is, the main study material of this thesis, with respect to CVD mortality (Brester *et al*., 2023). Methods other than the Cox and Kaplan–Meier were rare. The logistic model was applied in eight, the Poisson model in six, a linear model in two, a flexible parametric survival model in two, and an additive hazards regression model in one article. Moreover, one article was purely descriptive without any statistical models.

Participants exclusions. Most articles (*n* = 74, 70.5%) had without reason excluded study participants not free from the disease at baseline. Only five articles (4.8%) had executed subgroup survival analyses of study participants free versus not free from the disease at baseline. Two articles detected differences between the subgroups. In one article, the hazard of the outcome was lower in the subgroup of study participants free from the disease at baseline, and in the other article, it was higher. Moreover, nine articles (8.6%) provided the results of baseline differences between the study participants free and not free from the disease at baseline, and 17 articles (16.2%) had included all study participants without any information regarding the baseline disease status.

Association types. Altogether 64 articles (61.0%) had paid attention to diverse types of associations across variables. Only 20 of them (19.0%) had considered both the time dependency (multiplicative vs. additive) and interactions. In addition to those 20 articles, 31 articles had considered the time dependency without paying attention to interactions, and 13 articles showed the opposite scenario. In most of the 51 articles, the time

dependency aspect meant a visual and/or statistical examination of the PH assumption to justify the use of the Cox proportional hazards model.

Length of follow-up. Less than one-third of the articles (*n* = 30, 28.6%) had applied more than one follow-up times and/or excluded outcomes detected during the first years of follow-up. The procedure to exclude outcomes detected during the first years is explained as a method to control the reverse causality (Sattar and Preiss, 2017), similar to the exclusion of study participants not free from the disease at baseline. Out of the 30 articles, five had considered different follow-up times but did not report their associations with survival analysis results. The mean (95% CI) follow-up time of the prospective studies introduced in the articles was 18.1 (15.9–20.3) years. One article did not inform the follow-up period.

Outcome sensitivity. Subgroup survival analyses by different CHD manifestations and/or by fatal versus nonfatal events were performed in one-fourth of the articles (*n* = 27, 25.7%). The study outcome was MI or AMI (acute myocardial infarction) in 31 articles (29.5%), MI combined with something else, such as UA, in 15 articles (14.3%), and CHD in 59 articles (56.2%). Whether the outcome included both fatal and nonfatal cases was unclearly stated in many articles. However, most articles without a doubt had combined fatal with nonfatal events (approximately 70%).

Competing risks. Less than one-fifth of the articles had executed a competing risk analysis (*n* = 20, 19.0%), and two articles had paid attention to competing risks but not analyzed them in the survival context.

Missing values. Over one-third of the articles (*n* = 38, 36.2%) dealt with missing values. Here, dealing with missing values refers to an imputation procedure, to excluding study participants with missing values after reporting their variable-specific frequencies and/or proportions, or to a statistical comparison between the study participants with and without missing values.

5.2 THE KUOPIO ISCHAEMIC HEART DISEASE RISK FACTOR STUDY

5.2.1 Baseline characteristics

The mean age of study participants was 53.1 years, and 59.4% of them belonged to the age group of 54 years. About half of them had at least one close relative, including biological father, mother, and siblings, diagnosed with CHD. The mean FBG of the study participants was 4.8 mmol/, and only 9.6% of them lived with prediabetes or diabetes. By contrast, the mean TC of them was high: 5.9 mmol/l. On average, the study participants were slightly overweight former smokers and suffered from prehypertension. Study participants' baseline characteristics are presented in Tables 7 and 8.

Altogether, 724 study participants were not free of CHD at baseline. Of those participants, 424 (58.6%) answered "yes" to the question about angina, 254 (35.1%) to the question about the use of medicines for angina, 219 (30.2%) to the question about MI, 173 (23.9%) to the question about the use of sublingual nitroglycerine, and 21 (2.9%) to the question about a coronary bypass operation. Moreover, 200 (27.6%) out of the 724 study participants were diagnosed as having CHD based on ST segment depressions on the ECG recordings, 117 (16.2%) were diagnosed based on Q waves on the ECG recordings, and 88 (12.2%) were diagnosed based on angina-type chest pain in the ergometer test.

Those study participants who had CHD at baseline were older, had more often at least one close relative with CHD, more often lived with diabetes and hypertension, had higher serum TC and LDL-C levels, were more often smokers, and consumed less energy per day (Tables 7 and 8). Those study participants not free of CHD also had a slightly lower mean DBP (Table 7), but when the blood pressure–lowering medication users were excluded, the statistical difference in DBP disappeared (87.4 vs. 88.4 mmHg, p = 0.104). This, however, was not because of an increased mean DBP level in the study participants not free of CHD, although the frequency of blood pressure–lowering medication users among them was higher (45.3 vs. 14.3%, p <0.001), but because of a decreased mean DBP level in the study participants free of CHD.

Table 7. Baseline characteristics as continuous variables by CHD status.

Variable	Total	No CHD	CHD	P-value
Number	2682	1958	724	N/A
Age in years	53.1 (5.1)	52.6 (5.3)	54.4 (4.5)	<0.001
FBG in mmol/l missing data (*n*)	4.8 (1.2) 41	4.7 (1.0) 29	5.0 (1.7) 12	<0.001
BMI in kg/m^2 missing data (*n*)	26.9 (3.6) 12	26.8 (3.6) 9	27.0 (3.7) 3	0.261
TC in mmol/l missing data (*n*)	5.9 (1.1) 50	5.9 (1.1) 36	6.0 (1.1) 14	0.002
LDL-C in mmol/l missing data (*n*)	4.0 (1.0) 66	4.0 (1.0) 47	4.1 (1.1) 19	0.005
SBP in mmHg missing data (*n*)	134.2 (17.1) 14	134.4 (16.7) 12	133.8 (18.2) 2	0.432
DBP in mmHg missing data (*n*)	88.7 (10.5) 16	89.2 (10.6) 13	87.4 (10.4) 3	<0.001
Pack-years missing data (*n*)	8.7 (17.1) 63	8.2 (16.4) 40	9.8 (18.7) 13	0.054
TEE in kcal/day missing data (*n*)	3956 (958) 18	3996 (968) 13	3850 (925) 5	<0.001
Alcohol g/week missing data (*n*)	76.3 (137.0) 4	76.2 (119.9) 4	76.5 (175.2) 0	0.955

Notes. Values indicate mean (SD). P-value is from a t-test for the difference between CHD and non-CHD subjects. TC and LDL-C are serum values. A pack-year is the number of cigarette packs (20 cigarettes per pack) smoked per day times the duration of smoking in years. N/A signifies not assessed.

With respect to BMI, SBP, PAL, and alcohol consumption, the study participants who were not free of CHD were like those who were free of CHD at baseline (Tables 7 and 8).

Table 8. Baseline characteristics as categorical variables by CHD status.

Variable	Total	No CHD	CHD	P-value
Number	2682	1958	724	N/A
Age 42 years	334 (12.5)	294 (15.0)	40 (5.5)	<0.001
Age 48 years	358 (13.3)	274 (14.0)	84 (11.6)	
Age 54 years	1592 (59.4)	1148 (58.6)	444 (61.3)	
Age 60 years	398 (14.8)	242 (12.4)	156 (21.5)	
No CHD relatives	1351 (50.8)	1061 (54.6)	290 (40.3)	<0.001
One CHD relative	898 (33.7)	638 (32.8)	260 (36.2)	
Two CHD relatives	347 (13.0)	213 (11.0)	134 (18.6)	
Three CHD relatives	66 (2.5)	31 (1.6)	35 (4.9)	
missing data (*n*)	20	15	5	
No diabetes	2425 (90.4)	1800 (91.9)	625 (86.3)	<0.001
Prediabetes	159 (5.9)	102 (5.2)	57 (7.9)	
Diabetes	98 (3.7)	56 (2.9)	42 (5.8)	
Normal weight	843 (31.6)	622 (31.9)	221 (30.7)	0.225
Overweight	1351 (50.6)	993 (50.9)	358 (49.7)	
Obese	476 (17.8)	334 (17.1)	142 (19.7)	
missing data (*n*)	12	9	3	
Normal cholesterol level	705 (26.8)	539 (28.0)	166 (23.4)	0.005
Borderline level	772 (29.3)	568 (29.5)	204 (28.7)	
Hypercholesterolemia	1156 (43.9)	816 (42.4)	340 (47.9)	
missing data (*n*)	49	35	14	
Normotension	257 (9.6)	205 (10.5)	52 (7.2)	<0.001
Prehypertension	799 (29.9)	645 (33.1)	154 (21.3)	
Hypertension	1614 (60.4)	1098 (56.4)	516 (71.5)	
missing data (*n*)	12	10	2	

Table 8. Continues.

Variable	Total	No CHD	CHD	P-value
Never smoker	861 (32.1)	672 (34.3)	189 (26.1)	<0.001
Former smoker	955 (35.6)	675 (34.5)	280 (38.7)	
Current smoker	866 (32.3)	611 (31.2)	255 (35.2)	
Moderately active	540 (20.3)	385 (19.9)	155 (21.6)	0.271
Vigorously active	913 (34.4)	665 (34.3)	248 (34.6)	
Extremely active	1202 (45.3)	888 (45.8)	314 (43.8)	
missing (*n*)	27	20	7	
Alcohol ≤1 portion/week	957 (35.7)	677 (34.6)	280 (38.7)	0.102
Alcohol ≤3 portions/day	1545 (57.7)	1150 (58.9)	395 (54.6)	
Alcohol >3 portions/day	176 (6.6)	127 (6.5)	49 (6.8)	
missing (*n*)	4	4	0	

Notes. Values indicate *n* (%). P-value is from the Mann–Whitney U test for the difference between CHD and non-CHD subjects. Cholesterol status refers to serum LDL-C, or if it was missing, to serum TC together with the use of cholesterol-lowering medications. According to Finnish standards, one portion contains 12 grams of pure alcohol. N/A signifies not assessed.

5.2.2 Coronary heart disease after baseline

In the KIHD study, those conditions diagnosed after baseline are based on annual linkages to national registries. In the present thesis, CVD refers to International Classification of Diseases 10th Revision (ICD-10) codes of I00–I99, CHD to I20–I25, and MI or UA to I20.0 and I21–I22 assigned during hospitalizations. The codes were retrieved from the Care Register for Health Care based on data permission THL/93/5.05.00/2013 by the Finnish Institute for Health and Welfare. The FAMI manifestation refers to ICD-10 codes of I21 with respect to the underlying causes of death from the Causes of Death Register based on data permission TK/782/07.03.00/2021 by Statistics Finland. In the ICD-10, the block of I00–I99 contains diseases of the circulatory system and that of I20–I25 CHD (THL, 2011, pp. 349–386). In the latter, I20.0 indicates UA, I21 AMI, and I22 subsequent MI (THL, 2011,

pp. 354–360). Before 1996, diagnoses were assigned based on the ICD-9 coding system, and those older codes were converted to ICD-10 codes for this thesis. The transition from the ICD-9 to the ICD-10 was not expected to cause changes in the classification of CHD conditions (Hsu *et al*., 2021). In the big picture, the quality of the Care Register for Health Care is and has been satisfactory at worst and good at best (Sund, 2012).

By the end of 2019, 1,929 (71.9%) participants of the KIHD male cohort had a CVD diagnosis, 1,152 (43.0%) a CHD diagnosis, and 776 (28.9%) a MI or UA diagnosis. For every thirteenth participant, 209 (7.8%) have died from AMI. In all, the KIHD male study participants have been followed until death or the end of 2019 for 24.3 years on average, with a minimum duration of 8 days and the maximum duration of 35.8 years.

5.3 PARTICIPANT EXCLUSIONS, COVARIATES, AND OUTCOME

The current thesis views the impact of participants exclusions and outcome sensitivity on results of prospective cohort studies from a frequentist perspective that relies on statistics and empirical data. However, it is possible to assess the impact in respect of causal thinking, for example, by DAGs (Tennant *et al*., 2021). The following results from KIHD are presented to illustrate the link between theoretical reasoning and empirical findings.

Based on genetic, epidemiologic, and clinical studies, CHD arises because of atherosclerosis of coronary arteries (Antman and Loscalzo, 2018a), and the ultimate cause of atherosclerosis is LDL-C (Ference *et al*., 2017). Consequently, it is reasonable to expect that hypercholesterolemia is a necessary cause in the causal pathway that leads to CHD. Other risk factors would then be a component that completes the multifactorial sufficient cause of CHD (Lash *et al*., 2021).

In KIHD, the main CHD risk factors are weakly correlated with each other in a cross-sectional examination. LDL-C is correlated only with age (r = 0.079, p <0.001) and smoking (r = 0.53, p = 0.008). These correlations correspond to ORs of around 1.2 (95% CI 1.1–1.4, 60 vs. 42 years old, current vs. never smokers) (Figure 10). The correlations and ORs are independent of whether the study participants not free from CHD at

baseline are excluded. In a Cox model that predicts CHD diagnoses assigned during the follow-up, the hazard of CHD in men with hypercholesterolemic LDL-C levels is around 1.8 (95% CI 1.5–2.1) compared with men with normal LDL-C levels (Figure 10).

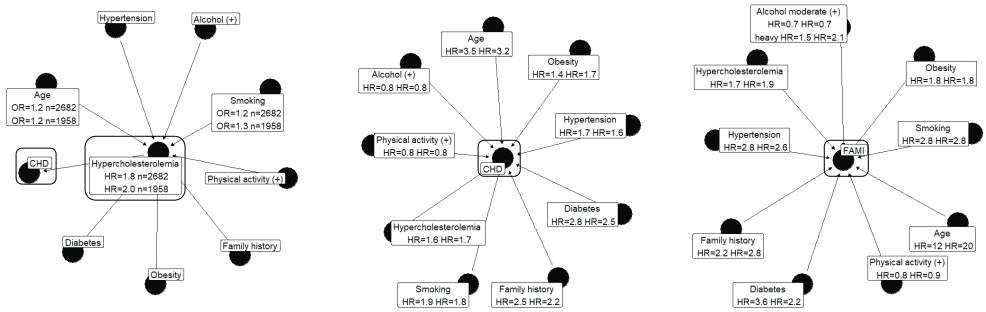

Figure 10. Simple directed acyclic graphs to illustrate the association of CHD with its risk factors in the KIHD study. The left subfigure shows cross-sectional associations of LDL-C with other CHD risk factors, together with a predictive association of LDL-C with CHD. The centermost subfigure shows predictive associations of the risk factors with CHD. The right subfigure shows predictive associations of the risk factors with FAMI. In each subfigure, the first HRs refers to data without exclusions (*n* = 2682) and the second HRs to data excluding study participants who were not free of CHD at baseline (*n* = 1958). Physical activity and moderate alcohol consumption appear as protective factors, and they are marked with a plus.

When baseline risk factors are associated with the CHD diagnoses without the intermediating role by LDL-C, all of them predict CHD, here with the 95% CIs for fully adjusted HRs being either above or below 1 (Figure 10). Physical activity and alcohol consumption appear as protective factors. In this scenario, the exclusion of study participants not free from CHD at baseline does not strongly affect the HRs, whereas the change of the outcome from CHD to FAMI alters the general view. In the FAMI model, age is a dominant risk factor; moderate alcohol consumption remains as a protective factor, but heavy consumption is transformed into a risk factor; smoking and hypertension become more evident.

The HRs reported in Figure 10 do not exactly correspond to the HRs presented in the forthcoming Tables 9–11 because the latter were focused solely on BRFs, not adjusted for age and family history of CHD.

The results presented in Chapters 5.3.1–5.3.3 are based on a subcohort of 1,592 54-year-old KIHD study participants. The restriction was applied to simplify statistical analyses by excluding age, which is the strongest predictor of CHD *per se*. Out of those 1,592 men, 672 (42%) had a CVD, excluding hypertension at baseline. Over the follow-up, by the end of 2017, 1,181 (74%), 703 (44%), and 502 (32%) received a CVD, CHD, and/or MI/UA diagnosis, respectively, and 136 died from AMI (9%). Original Publication I of the present thesis reports baseline characteristics in the subcohort.

5.3.1 Study participant exclusions

Original Publication I presented three different criteria for study participant exclusions: excluding those with any CVD, diabetes, or high TC at baseline (n = 794), excluding those with any CVD except for hypertension (n = 920), and no exclusions (n = 1592). Each criterion yielded reasonable results; the risk factors were associated with HRs >1, so they increased the risk of CHD in the follow-up. The results differed across the criteria with respect to statistical significance (p-value below or above 0.05). The criterion with no exclusions most often resulted in statistically significant HRs (Table 9).

Original Publication I reported two different scenarios to exclude study participants retrospectively based on their CHD status at the end of the follow-up (Table 10). In the first scenario, men who were not free from CHD at the end of the follow-up were excluded if they had any CVD, diabetes, or high TC at baseline, but all men who were free of CHD at the end of the follow-up were included, regardless their baseline statuses. This scenario resulted in 957 study participants being eligible for statistical analysis. In the second scenario, a reciprocal exclusion procedure was applied so that all men with CHD at the end of the follow-up were included but the men free from CHD at the end of follow-up were excluded, here according to their baseline statuses considering any CVD, diabetes, and high TC. The second scenario resulted in 1,430 eligible study participants.

Table 9. Fully adjusted HRs and *p*-values from Cox models of CHD.

Covariate	Criterion	Continuous HR per 1 SD	Categorical HR 3rd vs. 1st
Blood glucose	Full exclusions	1.26 (p <0.01)	7.21 (p <0.01)
	Partial exclusions	1.15 (p <0.01)	3.64 (p <0.01)
	No exclusions	1.12 (p <0.01)	2.61 (p <0.01)
Body mass index	Full exclusions	1.13 (NS)	1.51 (p = 0.03)
	Partial exclusions	1.19 (p <0.01)	1.64 (p = 0.01)
	No exclusions	1.20 (p <0.01)	1.79 (p <0.01)
Total cholesterol	Full exclusions	1.18 (p = 0.01)	1.47 (p = 0.02)
	Partial exclusions	1.17 (p = 0.01)	1.27 (NS)
	No exclusions	1.20 (p <0.01)	1.39 (p <0.01)
Blood pressure	Full exclusions	1.05 (NS)	1.17 (NS)
	Partial exclusions	1.09 (NS)	1.20 (NS)
	No exclusions	1.10 (p = 0.02)	1.13 (NS)
Smoking	Full exclusions	1.26 (p <0.01)	1.78 (p <0.01)
	Partial exclusions	1.23 (p <0.01)	1.64 (p <0.01)
	No exclusions	1.22 (p <0.01)	1.69 (p <0.01)
Physical activity	Full exclusions	0.95 (NS)	0.89 (NS)
	Partial exclusions	0.93 (NS)	0.87 (NS)
	No exclusions	0.90 (p = 0.02)	0.78 (p = 0.01)
Alcohol consumption	Full exclusions	1.01 (NS)	1.13 (NS)
	Partial exclusions	1.00 (NS)	0.94 (NS)
	No exclusions	0.94 (NS)	0.91 (NS)

Notes. In the first Cox model, all covariates were in a continuous form, and in the second model, they were in predetermined categories. When all study participants were included, *n* was 1,592, and the number of CHDs in the follow-up 730 (45.9%). Partial exclusions reduced *n* to 920 and the number of CHDs to 355 (38.6%). Full exclusions reduced *n* to 794 and the number of CHDs to 293 (36.9%). NS signifies not statistically significant (p ≥0.05).

Table 10. Fully adjusted HRs and *p*-values from the Cox models of CHD.

Covariate	Scenario	Categorical HR 3rd vs. 1st
Smoking	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	1.56 (p <0.01) 1.79 (p <0.01)
Alcohol consumption	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	1.13 (NS) 1.13 (NS)
Body mass index	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	1.23 (NS) 1.94 (p <0.01)
Physical activity	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	0.87 (NS) 0.79 (p = 0.02)
Blood pressure	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	1.19 (NS) 1.14 (NS)
Blood glucose	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	2.86 (p <0.01) 3.27 (p <0.01)
Total cholesterol	No exclusions in no CHD, fully in CHD Full exclusion in no CHD, no in CHD	1.48 (p = 0.02) 1.43 (p <0.01)

Notes. In the first scenario, baseline exclusions were targeted to study participants who had CHD and no exclusions were targeted to those who had no CHD at the end of the follow-up. Then, *n* was 1,155, and the number of CHDs in the follow-up 293 (25.4%). The second scenario was a reciprocal procedure. Then, *n* was 1,231, and the number of CHDs 730 (59.3%). NS signifies not statistically significant ($p \geq 0.05$).

The two retrospective scenarios aimed to discover if the end-of-study status would affect the importance of study participant exclusions. With respect to the CHD outcome, only the second scenario was able to detect statistically significant associations of it with BMI and physical activity (Table 10). Both scenarios detected the associations of CHD with smoking, FBG, and TC and found no associations of CHD and with blood pressure and alcohol consumption.

5.3.2 Continuous and categorical covariates

In respect to the Cox model's ability to recognize the expected associations of CHD with its risk factors, there were only minor differences between the types of covariates (Tables 7–9). That is, whether the covariates were in continuous or categorical forms had negligible effects on the Cox model's results from a practical point of view.

5.3.3 Outcome sensitivity

The results reported in this chapter are based on the most conventional study participant exclusion criterion: participants not free from CHD at baseline. Furthermore, concerning the categorical covariates only comparisons between the reference and highest risk category were considered. These choices were made to ease and clarify interpretation.

The main differences across the outcomes studied were related to blood pressure and TC. The former was associated with any CVD but not with CHD, whereas the latter was particularly associated with the actual CHD manifestations but not with CVD or FAMI (Table 11).

Table 11. Fully adjusted HRs and *p*-values for the Cox models of diverse outcomes.

Covariate	CVD	CHD	MI/UA	FAMI
n	920	355	242	53
Smoking	1.17 (p <0.01) 1.49 (p <0.01)	1.23 (p <0.01) 1.64 (p <0.01)	1.32 (p <0.01) 2.05 (p <0.01)	1.18 (NS) 2.00 (p = 0.04)
Alcohol consumption	1.05 (NS) 1.20 (NS)	1.00 (NS) 0.94 (NS)	0.97 (NS) 0.86 (NS)	1.11 (NS) 1.19 (NS)
Body mass index	1.14 (p <0.01) 1.54 (p <0.01)	1.19 (p <0.01) 1.64 (p = 0.01)	1.19 (p = 0.01) 1.70 (p = 0.02)	1.31 (p = 0.04) 2.51 (p = 0.02)
Physical activity	0.98 (NS) 1.03 (NS)	0.93 (NS) 0.87 (NS)	0.94 (NS) 0.89 (NS)	1.15 (NS) 1.31 (NS)

Table 11. Continues.

Covariate	CVD	CHD	MI/UA	FAMI
Blood pressure	1.17 (p <0.01) 1.50 (p <0.01)	1.09 (NS) 1.20 (NS)	1.09 (NS) 1.06 (NS)	1.24 (NS) 2.71 (NS)
Blood glucose	1.19 (p <0.01) 3.03 (p <0.01)	1.15 (p <0.01) 3.64 (p <0.01)	1.20 (p <0.01) 3.90 (p <0.01)	1.27 (p = 0.01) 2.73 (NS)
Total cholesterol	1.04 (NS) 1.07 (NS)	1.17 (p = 0.01) 1.27 (NS)	1.24 (p <0.01) 1.41 (p = 0.04)	1.24 (NS) 1.48 (NS)

Notes. The upper value per cell indicates the covariate as a continuous variable (HR and p per 1 SD increase), and the lower value indicates it as a categorical one (HR and p per 1 category increase). NS signifies not statistically significant (p ≥0.05).

5.4 ASSOCIATIONS ACROSS VARIABLES

The results presented in Chapter 5.4 are based on a subcohort of 1,958 KIHD study participants who were free from CHD at baseline. After this restriction, no sensitivity analyses by the baseline CHD status were required. Out of those 1,958 men, 717 (37%) received a CHD diagnosis by the end of 2019, and 301 (15%) died from CHD. Original Publications II and III, together with Tables 7 and 8 on pages 84–86 of the present thesis, report baseline characteristics among the subcohort of 1,958 men in detail.

In general, the type of association, multiplicative or additive, was assessed based on more than one method. The present thesis utilized statistical models and interaction measures as the primary methods. The Cox proportional hazards model was used to identify multiplicative and the Aalen's additive regression model additive associations. The Cox model assumes associations that are independent of time, whereas the Aalen's model allows time-dependent covariates. This fundamental difference between the Cox and Aalen's models can be applied to distribute associations into multiplicative and additive ones. The main interaction

measures were RR and RD. In principle, RRs identify multiplicative and RDs additive associations. Moreover, a linear regression was used to assess the type of association. In a multiplicative association, $y = x \times c$. In an additive association, $y = x + c$.

5.4.1 Associations between the outcome and covariates

A score for the absolute risk of future CHD was constructed to illustrate the nature of the association between CHD and its traditional risk factors. Original Publication II explains the scoring in detail. Briefly, it considered age, the family history of CHD, diabetes, smoking, obesity, cholesterol (LDL-C), and hypertension as CHD risk factors and distributed them into severity classes according to clinical guidelines and previous research findings (see Chapter 4.2.3).

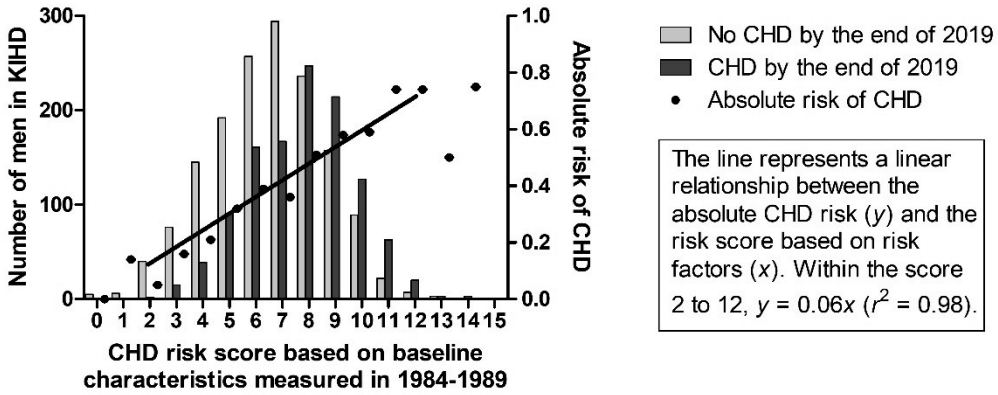

Figure 11. The relationship between the absolute risk of future CHD and the risk score constructed on study subjects' baseline characteristics.

The potential CHD risk score ranged from 0, indicating the lowest expected risk of CHD, to 15, denoting the highest expected risk. Men with a risk score of 0 were 42 years old, had no close relatives with CHD, FBG <5.6 mmol/l, BMI <25 kg/m^2, S-LDL-C <3.4 mmol/, SBP <120 mmHg, DBP <80 mmHg, and had never smoked. Correspondingly, men with a risk score of 15 were 60 years old, had two or more close relatives with CHD, FBG >6.9

mmol/l or took medications for diabetes, BMI ≥30 kg/m^2, S-LDL-C >4.1 mmol/ or took medications for high cholesterol, SBP >139 mmHg or DBP >89 mmHg or took medications for high blood pressure, and currently smoked. Among KIHD men, the observed score ranged from 0 to 14; that is, none of the men belonged to the class of the most severe risk of future CHD (Figure 11).

The score for the absolute risk of the future CHD illustrates the multiplicative nature of the association between CHD and its risk factors. Within the score from 2 to 12, the relationship between the risk of CHD (y) and the risk score (x) was $y = 0.06x$ ($r^2 = 0.977$, $p < 0.001$). Men with the risk scores 0, 1, 13, or 14 were excluded from the regression model because, in those risk classes, n was ≤7, whereas in other classes, it was ≥27. The corresponding additive relationship would have been $y = x/100 + 0.06$, which results in a CHD risk of 20% at its peak, when the observed maximum in the KIHD male cohort was about 70%.

Every risk factor tested—age, family history, smoking, obesity, hypertension, diabetes, and LDL-cholesterol—was a statistically significant predictor of CHD on the multiplicative (Cox model) and additive scales (Aalen's model) (Figure 12, Appendix 7). To some extent, the association between CHD and LDL-C was dependent on time (Table 12). Thus, as a covariate, LDL-C violated the Cox model's PH assumption. Also, the age-covariate showed a minor sign of time dependency. When these two time-dependencies were fixed by interacting the coefficients in question with time, the HR for CHD with respect to LDL-C increased from 1.30 to 1.49, whereas that regarding age decreased from 1.48 to 1.29 (Table 12). These fixes did not affect other covariate-specific HRs.

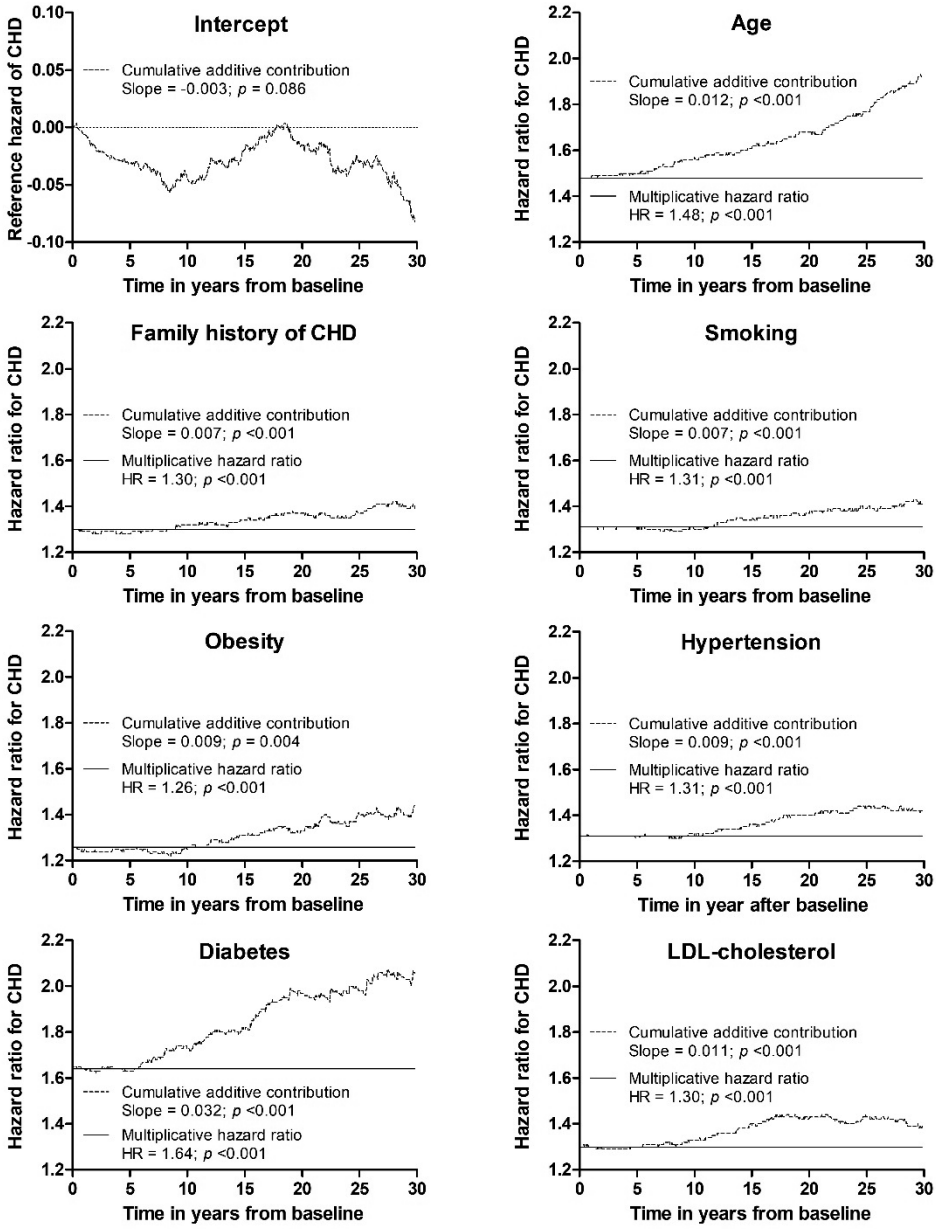

Figure 12. Hazard ratios for CHD based on seven risk factors. The risk factors were dichotomized (absent vs. present) to clarify the results. The upper left figure illustrates a cumulative additive intercept term that can be interpreted as the hazard of future CHD when all risk factors are absent. Slopes of the cumulative additive contributions ranged from 0.0068 for smoking (p <0.001) to 0.0315 for diabetes (p <0.001).

Table 12. Results of tests on the time dependence of CHD risk factors together with fully adjusted covariate-specific HRs for CHD before and after considering the time dependence.

Risk factor	Statistical tests' *p*-values for time-dependence		HR (95% CI) for CHD: No fixing	HR (95% CI) for CHD: Coefficient interacted with time
	Test 1	Test 2		
Age	0.12	1/10 times <0.05	1.48 (1.35–1.63)	1.29 (1.07–1.57)
Family history of CHD	0.53	0/10 times <0.05	1.30 (1.17–1.44)	1.30 (1.17–1.43)
Smoking	0.72	0/10 times <0.05	1.31 (1.19–1.45)	1.32 (1.20–1.45)
Obesity	0.95	0/10 times <0.05	1.26 (1.13–1.42)	1.27 (1.13–1.42)
Hypertension	0.83	0/10 times <0.05	1.31 (1.16–1.49)	1.32 (1.16–1.49)
Diabetes	0.67	0/10 times <0.05	1.64 (1.39–1.92)	1.64 (1.40–1.93)
LDL-cholesterol	0.13	4/10 times <0.05	1.30 (1.18–1.42)	1.49 (1.23–1.81)

Notes. Covariates were in the same categorical forms as in the CHD risk scoring. Test 1 is from Grambsch and Therneau (1994), and it tests H0: slope = 0. Test 2 is from Lin, Wei and Ying (1993), and it compares the observed residual pattern with simulated realizations and assesses its unusuality. In both tests, *p*-values <0.05 are considered a sign of a statistically significant interaction with time. Test 2 was repeated 10 times. Interactions between coefficients and time concern age and LDL-cholesterol only.

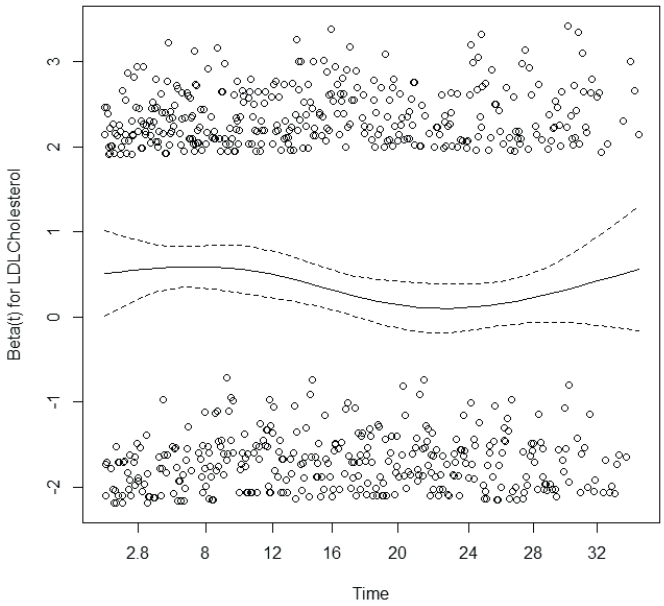

Figure 13. Time dependency of $\beta(t)$ for LDL-C as a predictor of CHD.

Distributing the data into time intervals, <10, 10–20, 20–30, and >30 years of follow-up, statistically improved the validity of the PH assumption. Also, it revealed that LDL-C, the covariate being most strongly dependent on time, was an evident multiplicative predictor of CHD from baseline to 10 years of follow-up (HR by a 3-class LDL-variable: 1.48, 95% CI: 1.31–1.66, *p* <0.001; HR by a dichotomized LDL-variable: 1.76, 95% CI: 1.49–2.03, *p* <0.001) but not thereafter (Figure 13).

5.4.2 Associations across covariates

Out of the 21 interactions between the seven CHD risk factors tested, three showed statistical significance (Table 13). Obesity interacted negatively with smoking on the multiplicative and additive scales. It increased the risk of CHD in nonsmokers but not in smokers. Furthermore, obesity and LDL-cholesterol interacted negatively with age on a multiplicative scale. They both increased the risk of CHD in men <50 years old but not in men >50 years old. Original Publication II reports the interaction measures' values for statistically nonsignificant interactions in its supplementary material.

Table 13. Statistically significant interactions between CHD risk factors.

Interaction measure	LDL-cholesterol × Age	Obesity × Age	Obesity × Smoking
Multiplicative: RR (95% CI)	2.11 (1.59–2.79) * 1.22 (1.07–1.38) *	1.72 (1.27–2.33) 1.11 (0.95–1.30)	1.35 (1.15–1.57) 0.92 (0.66–1.28)
Multiplicative: OR (95% CI)	2.81 (1.89–4.17) * 1.40 (1.13–1.74) *	2.18 (1.36–3.50) 1.20 (0.91–1.58)	1.64 (1.25–2.16) 0.88 (0.53–1.46)
Multiplicative: S (95% CI)	0.50 (0.32–0.78) *	0.55 (0.32–0.95) *	0.54 (0.30–0.96) *
Additive: RD (95% CI)	0.20 (0.12–0.28) 0.08 (0.03–0.13)	0.16 (0.06–0.27) 0.04 (-0.02–0.11)	0.12 (0.05–0.18) -0.03 (-014–0.09)
Additive: ICR (95% CI)	-0.74 (-2.24–0.29)	-0.72 (-2.22–0.42)	-0.78 [-1.50-(-0.01)] *
Additive: S (95% CI)	0.79 (0.56–1.11)	0.71 (0.41–1.23)	0.06 (0.00–>>1.00)
Additive: AP (95% CI)	-0.19 (-0.57–0.08)	-0.26 (-0.87–0.11)	-0.75 [-2.20-(-0.19)] *

Notes. S, ICR, and AP were computed using the R package “interactionR” (Babatunde, 2021), so the numbers may slightly differ from hand calculations. Asterisks indicate statistically significant interactions.

5.5 THE MOST APPROPRIATE FOLLOW-UP TIME

The results presented in Chapter 5.5 are based on the same subcohort of 1,958 KIHD study participants as the results presented in Chapter 5.4 (see Tables 7 and 8 on pages 84–86 for baseline characteristics). These KIHD study participants were free from CHD at baseline, 717 (37%) of them received a CHD diagnosis, and 109 (6%) died from AMI by the end of 2019. When CHD diagnoses from the Care Register for Health Care and FAMIs from the Causes of Death Register were combined, the number of men with CHD at the end of follow-up was 750 (38%).

In the current thesis, the most appropriate follow-up time was determined as the length of follow-up that relates to the largest statistically significant HR (point estimate) for as many CHD risk factors as possible.

5.5.1 Individual-level results based on the KIHD study

Based on the cumulative hazards, smoking was the strongest predictor of CHD over the first 6 years of follow-up (Figures 14, 15, Original Publication III). For the next 4 years, prediabetes and high LDL-C overcame smoking. Starting from year 11, diabetes became the strongest predictor, and it remained as such until the end of the follow-up. The sliding window procedure with a subarray of 5 years also emphasizes the importance of smoking as a predictor of CHD over the first years of follow-up. Onward from the 4–9 years of follow-up, diabetes was the strongest predictor of CHD, disregarding the period 14–27 years of follow-up when hypertension took its place as the strongest predictor. In most of the time windows up to year 18 of follow-up, LDL-C acted as the second strongest predictor of CHD.

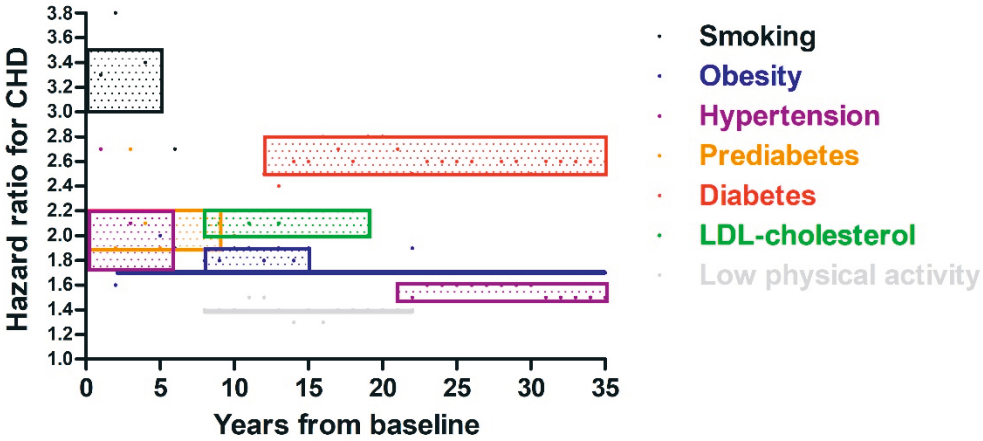

Figure 14. Fully adjusted cumulative HRs for CHD based on six traditional risk factors. Colored quadrangles highlight time periods during which the risk factor in question showed its most plausible association with CHD.

From the perspective of follow-up times, the most obvious differences between CHD and FAMI with respect to their risk factors were related to

LDL-C and hypertension. The former was mainly associated with CHD and the latter with FAMI (Figures 14, 15). Moreover, physical activity showed notable associations only with FAMI.

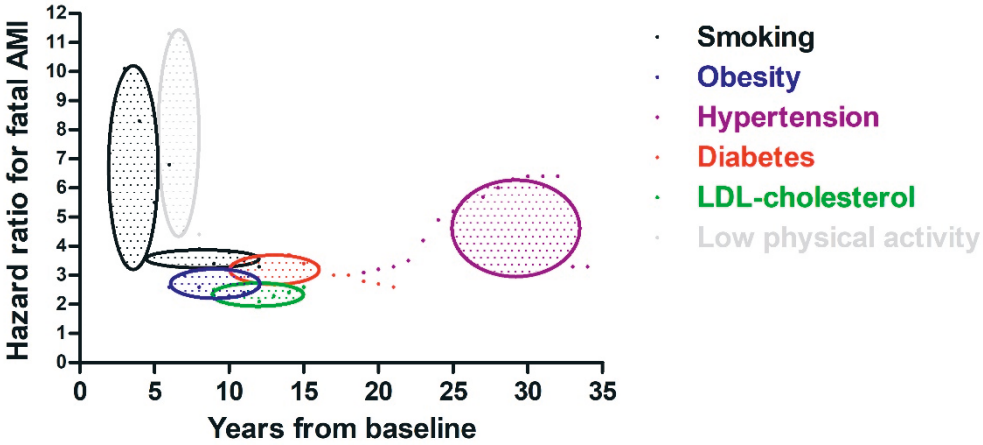

Figure 15. Fully adjusted cumulative HRs for FAMI based on six traditional risk factors. Colored ovals highlight time periods during which the risk factor in question showed its most plausible association with FAMI.

5.5.2 Study-level results based on the reference material

This chapter describes the findings from seven meta-analyses that were used as the reference material for the individual-level KIHD data. The individual- and study-level findings are compared with each other in the Discussion section. The meta-analyses reported study-level RRs or HRs for the association of CHD with its traditional modifiable risk factors among men (Appendix 1). Altogether, these meta-analyses comprised 81 prospective cohort studies of which one did not inform the follow-up time.

Two meta-analyses reported a multiple-adjusted pooled RR for CHD in diabetic men compared with nondiabetic men being 1.85 and 2.16 (Lee *et al*., 2000; Peters, Huxley and Woodward, 2014). In total, these meta-analyses consisted of 25 primary studies. The curve of best fit on those studies explained 15% of the variation in the RR, and it obviously peaked after approximately 10 years of follow-up (Figure 16).

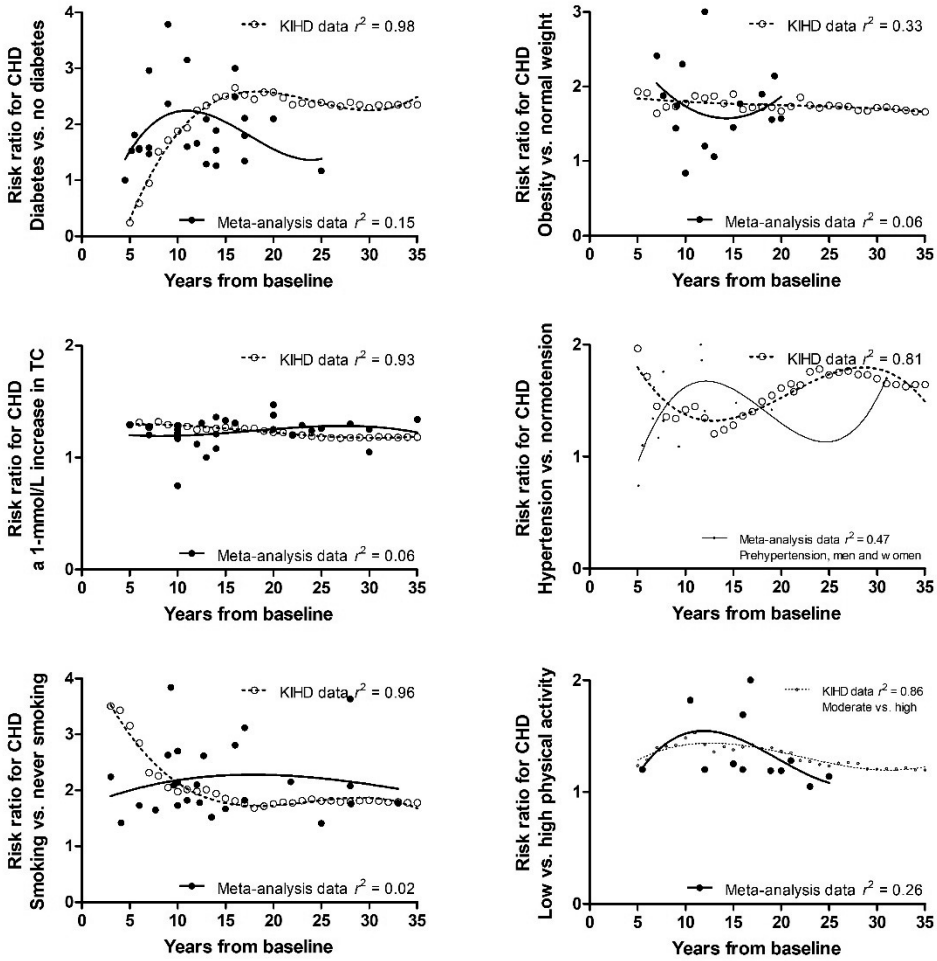

Figure 16. Associations between the RR for CHD and follow-up time by six traditional modifiable CHD risk factors. The dashed line represents the KIHD study with 1,958 study participants as statistical units. The solid line represents seven published meta-analyses with 80 original prospective cohort studies as statistical units.

One meta-analysis of the 17 primary studies reported RRs for CHD in obese versus normal weight men (Mongraw-Chaffin *et al*., 2015). The age-adjusted pooled HR for CHD was 1.60. To better enable a comparison between the study-level and individual-level results, two studies with follow-up times longer than 35 years were excluded. The curve of best fit

on the rest of the 15 studies explained 6% of the variation in the RR and showed no association of the RR with the follow-up time (Figure 16).

Two meta-analyses reported the following RRs for CHD per 1-mmol/L increase in TC: 1.24 in a general male population, 1.28 in men aged ≥65 years (1.22 for CHD mortality), and 1.24 in elderly men (Anum and Adera, 2004; Peters *et al*., 2016). Altogether, these meta-analyses included 30 primary studies, of which one did not inform the follow-up time. The curve of best fit on the rest of the 29 studies explained 6% of the variation in the RR (Figure 16).

One meta-analysis of 26 primary cohort studies reported a pooled RR for CHD of 2.05 among men who smoke 20 cigarettes per day compared with never smokers (Hackshaw *et al*., 2018). After excluding one primary study with an exceptionally long follow-up time of 50 years, the curve of best fit explained only 2% of the variation in the RR (Figure 16).

One meta-analysis combined 13 studies investigating the association of CHD with physical activity in men (Sofi *et al*., 2008). One of the primary studies was the KIHD study. The pooled RR for CHD was 0.73 in high versus low or zero and 0.88 for moderate versus low or zero physical activity (Sofi *et al*., 2008). For the curve fitting the KIHD study was excluded, and the high physical activity group was converted to the reference group by $e^{-1\times\ln(\mathrm{RR})}$. The curve of best fit on the rest of the 12 studies explained 26% of the variation in the RR for CHD and expressed an inverse U-shaped relationship between the RR and follow-up time (Figure 16).

The literature search revealed no meta-analyses on cohort studies comparing the risk of CHD in hypertensive versus normotensive men. One meta-analysis of 17 United States cohort studies reported the cumulative risk for CHD in hypertensive versus normotensive men being 1.5–1.9 for the first 30 years (Allen *et al*., 2012). Two meta-analyses compared the risk of CHD in prehypertensive versus normotensive individuals and concluded a RR of 1.13 in men with SBP of 130–139 or DBP of 85–89 and 1.20 in men with SBP of 120–129 or DBP of 80–84 mmHg (Guo *et al*., 2013; Huang *et al*., 2015). In the dataset of 17 primary studies with Asian and Western subjects (Huang *et al*., 2015), the RR for CHD correlated positively with the follow-up time (r = 0.592, p = 0.012) (Figure 16).

6 DISCUSSION

The present thesis has presented four research questions. The Discussion section is organized according to those questions (Figure 17). The first question aimed at solving how frequently and comprehensively recent prospective studies of CHD and its risk factors use and report data preprocessing and statistical analyses. To reach this aim, a systematic procedure to evaluate statistical validity of scientific journal articles reporting prospective cohort studies was developed. The statistical validity of 105 prospective CHD articles published in 2021 was evaluated using the procedure. The first research question was not dealt with in original publications, only in the present thesis.

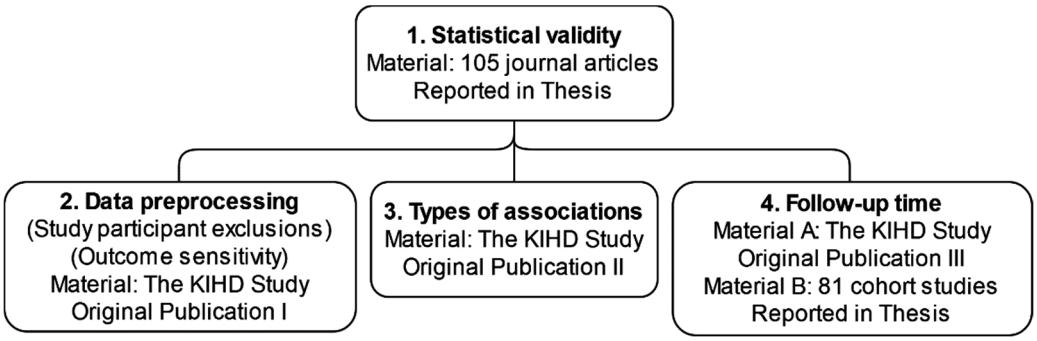

Figure 17. The main themes dealt with in the Discussion. The themes are connected to the four research questions, three of which were initially reported in journal articles (Original Publications I–III). The figure also informs study materials related to each theme. In the evolution of this thesis, statistical validity served as a starting point for the other themes.

The second research question focused on data preprocessing and aimed at revealing how study participant exclusions, covariate manipulations, and outcome sensitivity affect the results of the epidemiological analysis of CHD and its BRFs. Specifically, three different exclusion strategies were applied. 1) Study participants were excluded if they had CHD, diabetes, or cholesterol medication at baseline. This

strategy excluded study participants with CHD and those being at the highest risk of developing CHD. 2) Study participants were excluded if they had CHD at baseline. 3) All study participants were included. Covariate manipulations referred to the use of the same covariates as categorical or continuous independent variables in statistical analyses. Regarding outcome sensitivity, different clinical CHD manifestations (CVD, CHD, MI/UA, and FAMI) were compared. Original Publication I reports the results concerning the second research question.

The third research question focused on the associations between CHD and its main risk factors as well as on those across the main risk factors. It aimed at discovering the following association types: multiplicative, additive, and interactive. In the present thesis, multiplicative refers mainly to the Cox proportional hazards model that assumes multiplicative relationships between hazards functions and coefficients that are constant over time. In the Cox proportional hazards model, the concepts of "multiplicative" and "time independent" are closely linked to each other. Correspondingly, additive refers mainly to the Aalen's additive hazard model that uses a time-dependent reference hazard and a time-dependent coefficient matrix. Both an outcome-covariate association and covariate-covariate interaction can be multiplicative or additive. Multiplicative and additive associations *per se* require different statistical techniques to be properly analyzed (Lefebvre and Giorgi, 2021). Original Publication II reports the results concerning the third research question.

The fourth research question focused on the epidemiologically most appropriate follow-up times for different outcome–covariate pairs. The studied outcomes (clinical CHD manifestations) included CHD, MI/UA, and FAMI, and the covariates covered the main CHD risk factors. In the present thesis, the epidemiologically most appropriate follow-up time refers to the length of follow-up relating to the point estimate that most indicates the association between the outcome and covariate in question. Assumably, the relationship between an outcome and a risk factor weakens over the follow-up because factors not included in the list of independent variables and changes in the study participants' lifestyle, such as quitting smoking, start to affect the risk of the outcome of interest. The modification of risk

factors may also lead to a trade-off between the critical period when the exposure has its strongest effect on the outcome. In general, the repeated assessment of exposure measures is a method to control for the exposure misclassification because of the modification of risk factors, even though it may increase the number of dropouts and, thus, complicate the problem of missing data (Karahalios *et al*., 2012). Statistically, a risk factor may even transform into a protective factor if, after a long follow-up period, only a few of study participants with the risk factor in question are alive. The phenomenon is known as depletion of the susceptible or collider stratification bias (Stovitz, Banack and Kaufman, 2018). Original Publication III reports the results that answer the fourth research question.

6.1 STATISTICAL VALIDITY OF JOURNAL ARTICLES

Compared with COVID-19, for instance, CHD is currently not a hot topic in epidemiology. This finding is not a surprise regarding the decreasing trend in the number of Google Scholar documents on CHD over the past 10 years. The finding concerning the low statistical validity of epidemiological CHD papers, on the contrary, is surprising. None of the evaluated 105 CHD papers had dealt with all six statistical domains included in SVI, and 13 papers had not even touched any of them. Although SVI does not cover all aspects of statistical validity, the overview it draws is worrying.

Goodman and his colleagues have addressed that medical scientific journals do not appreciate statistics, despite the general academic concern regarding research validity. Based on their surveys, the unsatisfactory situation has existed at least since the early 1990s (Goodman, Altman and George, 1998; Hardwicke and Goodman, 2020) and no arguments suggest the situation would have been better before that (George, 1985). Hence, the undervaluation of statistics in medical scientific journals appears to be an established policy, although journals with higher impact factors appear to take statistics more seriously (Goodman, Altman and George, 1998; Katz *et al*., 2004; Hardwicke and Goodman, 2020).

Despite the undervaluation of statistics in medical journals, the reporting quality of journal articles with regarding statistical aspects has

shown some improvement. Abraira *et al*. (2013) compare clinical research articles that had used survival analyses and been published by medical journals in 1991 to those published in 2007. The authors show a statistically significant improvement in the reporting of sample size, the precision of survival curve and effect size estimates, and the PH assumption check (Abraira *et al*., 2013). The improvements in the reporting of follow-up time and the validity of regression models are also close to statistical significance (Abraira *et al*., 2013). Interestingly, there are differences in the improvement across specialties. Cardiology increases the risk of not reporting sample size, and the risk of not reporting the precision of survival curve estimates decreased from 1991 to 2007 in oncology and internal medicine but increased in cardiology (Abraira *et al*., 2013). The risk of not reporting the PH assumption check, on the other hand, is found to have been the lowest in cardiology both in 1991 and 2007 (Abraira *et al*., 2013). In the quality assessment tool developed by Abraira *et al*., (2013), the precision of survival curve estimates refers to confidence intervals and the number of subjects at risk.

The evaluation of statistical validity carried out in the present thesis concludes no major differences in the statistical validity between articles published in epidemiological and other medical journals. Minor differences exist. Epidemiology journals had more rarely considered competing risks in their statistical analyses but avoided the Kaplan–Meier method, which may relate to its tendency to overestimate cumulative incidences when the follow-up time is long and competing risks are present (Verduijn *et al*., 2011; Schuster *et al*., 2020; Brester *et al*., 2023).

The low statistical validity does not characterize only epidemiological CHD papers; the phenomenon is widespread. Most previous reviews of the statistical reporting quality in medical papers have been interested in RCTs, particularly clinical trials, with a narrow focus on a certain specialty. Based on reviews including not only RCTs or clinical trials, the reporting of survival analysis is poor irrespective of the context. Among articles published by leading Chinese oncology journals in 2013 (n = 242), the Cox model was used in 112, but the PH assumption check was reported in none of them (Zhu *et al*., 2017). Among 76 survival analysis articles reporting tuberculosis

in Africa and published between 2010 and 2020, the Cox model was applied in 67 (88%) and the PH assumption check was reported in 32 (42%) (Ngari *et al*., 2021). In those articles, competing risks were analyzed in three but not in combination with the Cox model (Ngari *et al*., 2021). Among the total joint arthroplasty articles that had applied the Cox model and been published before September 2019 (n = 318), the reporting was adequate in 63 (20%) (Kuitunen *et al*., 2021). In the review by Kuitunen *et al*. (2021), adequate reporting required testing of the PH assumption, informing the test method and its results, and correcting the Cox model, if needed.

Groenwold *et al*. (2008) have found the reporting of confounding bias being poor or moderate in 174 observational studies with a median quality score of four on an 8-point scale. They show no major differences in the reporting quality across the years from 2004 to 2007 nor between epidemiological and general medical journals (Groenwold *et al*., 2008). After eight years, the authors repeated their study, comparing the years from 2010 to 2012 to their previous results (Groenwold *et al*., 2008) and finding only minor improvements in the reporting of confounding bias (Pouwels *et al*., 2016).

Typically, reviews of survival analysis articles' quality have relied on the series of survival analysis papers published by *British Journal of Cancer* in 2003 (Bradburn *et al*., 2003a, b; Clark *et al*., 2003a, b). The starting point for this series is the review by the English statistician Douglas G. Altman and his fellow workers. In their review, Altman and colleagues conclude that reporting of study design, data handling, statistical analysis, and their results was of low quality in 132 survival analysis articles published by cancer journals in 1991 (Altman *et al*., 1995).

The most frequent tool to assess the reporting quality of observational studies is STROBE. STROBE was launched in 2007 (Vandenbroucke *et al*., 2007; von Elm *et al*., 2007), and since then, it has been extended and tailored to different fields. Sharp *et al*. (2019) investigate the use of STROBE and its extensions in journals publishing observational studies and report that only 12 out of 257 journals (5%) without exception required STROBE, whereas 139 journals (54%) did not even mention it. The relevant STROBE extension was required only by two journals (Sharp *et al*., 2019). The

STROBE checklist for cohort studies includes several items that are related to statistical validity, so from this perspective, STROBE is the second-best quality assessment tool available, if we state that ROBINS-E is the best one. The tool developed by Abraira *et al*., (2013) is also detailed and comprehensive, but unfortunately, it has not reached a wider audience. After the launch of STROBE, many researchers expected it to have a positive impact on the reporting quality of observational studies in epidemiology. However, based on comparisons between the pre- and post-STROBE eras no significant improvement in most of the STROBE items has occurred (Pouwels *et al*., 2016; Rao *et al*., 2016; Cheng *et al*., 2021). Evaluations applying STROBE have detected differences in the guideline adherence between disciplines, with general medical journals showing higher adherence than ear, nose, and throat journals (Hendriksma *et al*., 2017), as well as between cohort and other observational studies, with the former being more adherent (Langan *et al*., 2010; Zhang J. *et al*., 2021).

To summarize, the findings of the present thesis concerning the statistical validity of journal articles with prospective cohort studies of CHD are in accordance with the earlier broader findings wrapped up in the previous paragraphs. The overall statistical validity is poor. In many cases, when the authors had assessed the PH assumption, they had not interpreted the results of the assessment. Typically, the violation of the PH assumption was not detected or reported, but nonetheless, the authors had used time-dependent covariates in the statistical model. Although it most probably is appropriate to use an additive model when the PH assumption is met (Abadi *et al*., 2011), the authors have not rationalized their choice. In addition, authors of one article mix up the PH and log-linearity assumptions. Another example relates to missing values. SVI does not require the recognition of missing at random; thus, it treats the articles much gentler than ROBINS-E, for instance. Fortunately, both the findings based on the SVI launched in the present thesis and those from previous investigations of reporting quality conclude that statistical validity and overall reporting quality increase together with JIF (Goodman, Altman and George, 1998; Katz *et al*., 2004; Hardwicke and Goodman, 2020; Zhang J. *et al*., 2021; Held *et al*., 2022; Ziemann *et al*., 2022). This is important from the

viewpoint of the impact factor system's plausibility. The statistician's contribution also is associated with a better adherence to reporting guidelines (Zhang J. *et al*., 2021; Held *et al*., 2022; Ziemann *et al*., 2022).

6.2 MAIN FINDINGS COMPARED WITH PREVIOUS RESEARCH

Based on the material included in the present evaluation of statistical validity, the results of the epidemiological CHD studies are almost without exception interpreted based on *p*-values, that is, statistical significance. Broadly, the lack of effect size estimation seriously weakens the interpretation of the results (Sullivan and Feinn, 2012). As opposed to *p*-values, effect sizes (measures of the magnitude of the difference between groups) are not influenced by sample size, and they can provide information concerning the strength and direction of the association between variables (Berben, Sereika and Engberg, 2012). In addition to the estimation of effect sizes, epidemiological studies should more often consider causal thinking to theoretically reason their statistical analyses. This aspect was also disregarded in the prospective cohort studies of CHD included in the present evaluation of statistical validity.

The current thesis analyzed data and concluded findings from the viewpoint of statistical significance to bring the findings close to the prevailing practice of reporting. Although effect estimations and causal reasoning are unquestionably important—in some cases even crucial parts of epidemiological research—frequentist inference is also needed to complete the picture. Hence, the present thesis was focused specifically on emphasizing the valid use of statistics in the epidemiological research of CHD with its risk factors.

6.2.1 Exclusions of study participants

The approach to exclude study participants not free from the disease, which was the outcome of interest, at baseline relates to the control of reverse causality (Sattar and Preiss, 2017). Typically, the approach is accepted without question, even though the issue of reverse causality *ipso*

facto is vacuous from the viewpoint of prospective cohort studies. Epidemiological relationships, in practice, cannot ever be interpreted as evident signs of causations because of the lack of randomization. Furthermore, the epidemiological relationship between the outcome (disease) and predictor (risk) may be because of causality, simultaneity, or reverse causality, and then, the exclusion of study participants unnecessarily lowers *n* and leads to statistically nonsignificant *p*-values. That is, the exclusion of study participants not free from the disease at baseline does not solve simultaneity and reverse causality biases. Let us assume that researchers want to study if physical inactivity predicts CHD. They exclude CHD patients and start the follow-up. If the relationship is causal, physically inactive study participants develop CHD sooner and more frequently than their physically active peers. If the relationship is simultaneous, physically inactive study participants again develop CHD, but the researchers should have also excluded participants who were physically inactive at baseline to ensure no CHD patients were included. If the relationship is reversed, by excluding CHD patients, the researchers exclude physically inactive study participants.

Previous prospective cohort studies have, almost as a rule, excluded the study participants not free from the disease at baseline (e.g., 70% of the articles included in the present evaluation of statistical validity). Those few of them who have included all study participants and executed an appropriate sensitivity analysis (e.g., 5% of the articles included in the present evaluation) have (Lee *et al*., 2021a) and have not (Fu *et al*., 2021; Kristófi *et al*., 2021; Patel *et al*., 2021; Perez-Cornago *et al*., 2021) found the effects of the exclusion on the study results. Here, the effect means that the epidemiological relationship between CHD and risk factor is observed among study participants not free from the disease at baseline but not among study participants free from the disease.

Based on the findings reported in Original Publication I and partly in Original Publication II the study participant exclusion has only minor effects on the study results in the KIHD male cohort regarding the epidemiological relationship between CHD and its traditional risk factors. In all the tested associations, the risk factors increased the hazard of CHD

as expected. The exclusion procedure affected statistical significance so that the observed *p*-values were more rarely <0.05 when the study participants not free from the disease at baseline were excluded. From the viewpoint of effect sizes—HRs in this case—the impact of the study participant exclusion did not show a clear pattern. Regarding the CHD outcome, the deviation toward the null (HR = 1) seemed to be more frequent, whereas, regarding the FAMI outcome, the deviations toward and away from the null were equally frequent.

Interestingly, the exclusion of study participants not free from the disease at baseline from the group of participants who did not develop CHD over the follow-up made it easier to detect statistically significant associations regarding some risk factors (obesity and low physical activity). This finding suggests that, from a statistical viewpoint, it is more important for "a control" than "a case" to be free from the disease at baseline. However, this type of selection of study participants after the start of the exposure window may produce bias (see, e.g., ROBINS-E Development Group, 2022); therefore, it serves only methodological interests. It cannot be applied to investigations of epidemiological relationships as such.

In principle, including study participants not free from the disease at baseline can cause bias if it affects the distribution of study participants into exposed and unexposed. Concerning CHD, the inclusion of those who are already diseased at baseline increases the number of those who have the main CHD risk factors, particularly dyslipidemia, diabetes, obesity, and hypertension. If the main risk factors are considered as exposure, the inclusion inevitably decreases sensitivity because all of those already diseased at baseline are not rediagnosed during the follow-up. This scenario should lead to biases toward the null (Lash *et al*., 2021), which can be seen in the results of the present thesis by looking at the trends in the HRs referring to actual study results (Tables 9 and 10 on pages 90–91), as well as in those that were calculated for DAGs to illustrate the link between theoretical reasoning and empirical findings (Figure 10 on page 88).

Moreover, because it is mainly high-risk atherosclerotic patients who are vulnerable to the triggering onset of MI (Schwartz, Kloner and Naghavi, 2018), the association between MI and triggering risk factor should be the

most detectable when only study participants who were not free of CHD at baseline are included in the statistical analyses. In the KIHD male cohort, that kind of result can be seen with respect to alcohol consumption, which is a typical trigger for MI (Mittleman and Mostofsky, 2011). Heavy alcohol consumption increased the risk of FAMI more clearly among KIHD men with the highest CHD risk score of ≥8 (HR 1.88, 95% CI 1.03–3.44, *n* = 1189, events = 143) compared with men with a risk score of 6–8 (HR 1.12, 95% CI 0.43–2.88, n = 871, events = 56). Among men with the lowest CHD risk score of <6, there were only 10 FAMIs. The CHD risk score has been introduced in Original Publication II and on pages 94–95 of the current thesis.

The present thesis has not enabled a univocal recommendation concerning the exclusion of study participants not free from the disease at baseline. The role of exclusion depends on the outcome and risk factors in question, and it appears to differ across cohorts. A sensitivity analysis to test the effect of exclusion on study results should be a mandatory part of every prospective cohort study. As an additional perspective, it is worth noting that the adjustment for baseline status of the study outcome, that is, the dependent variable in the statistical model, may lead to biased effect estimates and spurious statistical associations between the dependent and independent variables (Glymour *et al*., 2005).

6.2.2 Outcome sensitivity

In prospective cohort studies of CHD, it is typical to merge different manifestations of the disease into one outcome. Regarding the present evaluation of statistical validity, only 24% of the articles included performed a sensitivity analysis to discover if the epidemiological relationship between CHD and risk factors of interest were equal between different CHD manifestations, such as AMI and angina. Of those articles that had executed a sensitivity analysis, up to 72% reported at least minor differences between the manifestations. Here, a minor difference denotes the epidemiological relationship between CHD and the risk factor pointing to the same direction in the same order of magnitude across the

manifestations tested but being statistically significant only for some of them. Correspondingly, a major difference denotes the direction of the relationship being obviously opposite between the manifestations. Among the articles included in the present evaluation of statistical validity, the differences were frequent particularly between fatal and nonfatal manifestations. For example, high education level increased the risk of incident CHD (HR 95% CI's lower bound >1) but reduced the risk of fatal CHD (HR 95% CI's upper bound <1) in a cohort of a half a million Chinese adults (Chen *et al*., 2021).

According to the demonstrations reported in Original Publication I, CHD manifestations differed from each other regarding their epidemiological relationships with risk factors in the KIHD male cohort. The finding supports earlier findings from other cohorts (MacKenzie *et al*., 2017). In KIHD, current tobacco smoking, obesity, and diabetes were associated with an increased risk of any tested manifestation. Hypercholesterolemia was associated specifically with the CHD manifestation (ICD-10: I20–I25). Smoking, when considering both present and past smoking, was particularly associated with MI or UA (ICD-10: I20.0 and I21–I22). Hypertension was associated more strongly with CVD than CHD. In Original Publication I, the CVD outcome included strokes, which may, for its part, explain the finding. The etiology of stroke differs from that of CHD, and hypertension is the number one risk factor for stroke (O'Donnell *et al*., 2010). In Original Publication I, alcohol consumption and low physical activity were weakly associated with CHD manifestations. Based on HRs calculated for the simple DAGs presented on page 88, however, they appeared as protective factors. Regarding FAMI, moderate alcohol consumption was a protective factor and heavy consumption a risk factor. The differences between the CHD manifestations regarding their relationships with risk factors may reflect the possible triggering onset of MI (Tofler and Muller, 2006; Mittleman and Mostofsky, 2011; Schwartz, Kloner and Naghavi, 2018). Cigarette smoking and alcohol consumption are common triggers (Mittleman and Mostofsky, 2011).

The present results suggest that CHD manifestations should not be combined without question with each other into a single outcome. In meta-

analyses of the epidemiological relationship between CHD and its risk factors, however, it is common to merge different manifestations, even without performing sensitivity analyses. Those meta-analyses that have performed sensitivity analyses have typically reported no statistically significant differences between incident and fatal CHDs but have not considered other types of CHD manifestations (Anum and Adera, 2004; Peters, Huxley and Woodward, 2014; Mongraw-Chaffin *et al*., 2015; Peters *et al*., 2016).

6.2.3 Multiplicative, additive, and interactive associations

The epidemiological relationships between diseases and their risk factors can be assessed by applying additive or multiplicative techniques. The latter ones—the Cox proportional hazards model especially—are more popular mainly because their results can be interpreted as HRs instead of cumulative hazards. This popularity has created a situation in which the problem with respect to multiplicative techniques—their strong statistical assumptions—is too often overlooked.

From a statistical viewpoint, analyses of epidemiological relationships would benefit from using additive and multiplicative techniques together (Lim and Zhang, 2009; Stevens *et al*., 2012; Nordahl *et al*., 2013; Lefebvre and Giorgi, 2021). Additive and multiplicative techniques do not rule out but instead supplement each other because their results should *per se* lead to similar conclusions (Girerd *et al*., 2016).

Regarding CHD, its epidemiological relationships with risk factors are broadly multiplicative and interactive (Poulter, 1999), although additive relationships also exist (Silberberg, 1990; Yin and Cai, 2004). In the Framingham Heart Study, for instance, an additive hazards model of CHD results in narrower confidence intervals than a corresponding multiplicative hazards model (Yin and Cai, 2004). In addition, in the Framingham Heart Study, additive and multiplicative models emphasize the importance of partly different risk factors. Smoking is a statistically significant predictor of CHD in the multiplicative but not in the additive model, whereas BMI and SBP are significant predictors only in the additive

model (Yin and Cai, 2004). Male sex and cholesterol are significant predictors in both models (Yin and Cai, 2004). In general, when multiplicative and additive models yield partially different results, researchers should underline the associations detected at both scales and interpret the other associations with caution.

In accordance with the general view, most of the associations of CHD with its traditional risk factors were multiplicative in the KIHD male cohort (see Original Publication II). Cholesterol measured as LDL-C seemed to be the only truly additive BRF of CHD in KIHD when the interactions across the risk factors were considered. The time-dependency of the relationship between the risk of CHD and cholesterol has been observed in cohort studies and RCTs already decades ago (Law, Wald and Thompson, 1994). Serum cholesterol concentration predicts CHD particularly in middle-aged men (Law, Wald and Thompson, 1994; Original Publication II), which, in prospective cohort studies, typically means that the relationship between CHD and cholesterol weakens over time because the study participants had passed middle age. The additive nature of LDL-C is of particular importance because LDL-C can be accounted for as the pivotal risk factor for CHD in general.[1] Moreover, when additive associations are included in a survival model, it does affect not just the covariate in question, but the effect sizes related to other covariates may change as well. In KIHD, the time-fixing for LDL-C increased its effect size but decreased that of age (Original Publication II).

Out of the articles included in the present evaluation of statistical validity, the Cox proportional hazards model was applied in 85% and out of those, the PH assumption was assessed in less than 50% of the articles. The violation of the PH assumption was reported in 17% of the articles in which the assessment was performed. This proportion was twice as high in relation to that found in cancer genetics cohorts (Zeng *et al*., 2022).

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[1] In KIHD, the CHD risk score presented in Original Publication II suggested no major differences in the importance across the traditional risk factors of CHD when they were regarded as stand-alone factors, but each of them increased the risk by approximately 6%.

Because of nonsystematic reporting of the evaluation of PH assumption, it is challenging to compare the proportion of studies in which the assumption is violated across disciplines or cohorts. Journals may assume the evaluation of PH assumption, but instead, they should oblige a valid interpretation of it.

The traditional presumption concerning the main CHD risk factors is that they cluster in individuals (Poulter, 1999), often in the form of MetS (Hu, Qiao and Tuomilehto, 2005). This coexistence of risk factors intrinsically raises the possibility that they do interact. In prospective studies of CHD, however, risk factors have commonly been viewed separately, with the focus being on a single risk factor at a time. In the articles of the present evaluation of statistical validity, interactions across risk factors were assessed in 32% of the studies. Most of those articles did not recognize statistically significant interactions across the risk factors in terms of their associations with the future risk of CHD. The reported interactions were between the triglyceride-glucose index and sex in a Chinese cohort of circa 100,000 adults (Tian *et al*., 2021), between severe hypoglycemia and microvascular complications in patients with type 1 diabetes (Fahrmann, Adkins and Driscoll, 2021), between the MetS and age among middle-aged or older Swedish men (Lind *et al*., 2021), and between the exposure to fine particulate air pollution and age in a cohort of over 800,000 Canadians (Zhang Z. *et al*., 2021). Among United States community-dwelling middle-age or older adults, the degree of ambulatory care fragmentation interacted with self-rated health (Kern *et al*., 2021), lipoprotein (a) interacted with inflammation, coagulation, and race/ethnicity (Ong *et al*., 2021), and the interaction between income and the density of walking destinations in the area interacted with sex (Gullon *et al*., 2021). The level of education interacted with age, sex, and region (rural or urban) in a large Chinese cohort (Chen *et al*., 2021). In a harmonized data of 21 European cohorts, the epidemiological relationship between CHD and educational status was mediated by allostatic load and the role of mediation differed between sexes (Hicks *et al*., 2021). Two articles belonging to the present evaluation of statistical validity had

mistakenly reported interactions between risk factors, although there was variation only in one of the factors.

Based on the demonstrations reported in Original Publication II, age interacted with LDL-C and BMI and BMI interacted with smoking regarding the risk of future CHD diagnosis in the KIHD male cohort. The role of age as a modifier in the association between CHD and cholesterol has been known for decades (Jacobsen *et al*., 1992). In fact, the epidemiological relationship between CHD and cholesterol is so evidently affected by age that studies could routinely stratify it by age. The other interactions observed in the KIHD male cohort—age × BMI and BMI × smoking—are not as fundamental as that between age and cholesterol, but their presence varies from cohort to cohort (Jousilahti *et al*., 1996; Chouraki *et al*., 2008; Asia Pacific Cohort Studies Collaboration, 2009).

Out of the three interactions between the CHD risk factors in the KIHD male cohort, age × LDL-C and age × BMI were solely multiplicative, whereas BMI interacted with smoking at both scales: multiplicative and additive (see Original Publication II). Because the scale of the interaction is hardly ever considered in prospective studies of CHD and its risk factors, it is difficult to compare the findings from KIHD to other findings. However, because most prospective cohort studies of CHD apply multiplicate survival analyses, it is expected that the interactions reported are at the multiplicative scale. Interactions across covariates in general should be assessed based on more than one interaction measure, which would make it possible to distinguish between multiplicative and additive interactions. Statistically speaking, an interaction can be either additive or multiplicative, not both. Additive and multiplicative refer to different scales, that is, sum and product, respectively, and they preclude each other. In research practice, however, it is possible to observe an interaction that is simultaneously on both scales mainly because the interpretation is based on statistical significance that, in turn, depends on *n*. Consequently, if the *n* is high enough, an interaction can be statistically significant on both scales.

6.2.4 The most appropriate follow-up time

In the KIHD male cohort, the most appropriate follow-up time to detect the epidemiological relationship between CHD and cholesterol—the number one risk factor for CHD—was 5–20 years (see Original Publication III). Of the other traditional BRFs, BMI and glycemic status suggested the same follow-up window. Smoking and physical activity favored follow-up times shorter than 10 years, and blood pressure favored follow-up times longer than 20 years. Smoking, physical activity, and blood pressure were associated specifically with FAMI. The association of physical activity and smoking with shorter follow-up times and MI may partly be explained by their role as triggers of acute coronary events (Mittleman and Mostofsky, 2011). The triggering onset of coronary thrombosis is not dependent on the follow-up time, but patients with CHD are constantly vulnerable to it.

In NIPPON DATA80, a cohort of over 10,000 ≥30-year-old Japanese, the most appropriate risk factor -specific follow-up times correspond to those observed in KIHD (Okami *et al*., 2021). Particularly, the importance of smoking during the first decade of the follow-up and that of blood pressure during the third decade of the follow-up were characteristic of both KIHD and NIPPON DATA80.

Of the articles included in the present evaluation of statistical validity, in their survival analyses, 24% had regarded the effects of follow-up time on the detected epidemiological relationship between CHD and its risk factors. In most cases, this denoted sensitivity analyses after excluding the first years of follow-up. The few long-term follow-up studies that had executed separate analyses for more than two follow-up times reported statistically significant associations most often when the follow-up time was 5–20 years (Jarrick *et al*., 2021). In some cases, the studied association was stronger when the follow-up time was closer to 5 years (Pagano *et al*., 2021), but in some other cases, a follow-up time closer to 20 years appeared to be more appropriate (Hallum *et al*., 2021).

The study-level results that are presented as reference material in the present thesis allow for only directional conclusions. The results suggest follow-up times around 10 years for the epidemiological relationship of

CHD with glycemic status, blood pressure, and physical activity. Regarding this reference material, it would have been a more sophisticated choice to use a cohort as a statistical unit in the analyses instead of a study. There are probable differences in the risk factor-specific, most appropriate follow-up times across cohorts.

Here, the most appropriate follow-up time refers to the length of follow-up when the epidemiological relationship between CHD and a risk factor reaches its statistically most convincing point estimate. In other words, the present definition of the most appropriate follow-up time should not be linked to the natural history of CHD as such, although the progression speed of CHD intrinsically affects the most appropriate follow-up time.

6.3 ADDITIONAL STATISTICAL TOPICS TO BE NOTED

The list of potential statistical issues that should be noticed in prospective cohort studies is endless. Chapter 6.3 discusses some of those that were not scrutinized in Original Publications I–III.

Log-linearity assumption. There are two statistical assumptions concerning the Cox proportional hazards model. The first assumption—the PH assumption—is the primary theme of the present thesis. The second assumption, which is known as the log-linearity assumption, is explained in Chapter 4.4.3, but it was not included in the evaluation of statistical validity or Original Publications I–III. The choice to exclude the log-linearity assumption from the statistical topics was made because the assumption was not analyzed in most of the evaluated journal articles.

Competing risks. The main reason for why competing risks were not demonstrated in Original Publications I–III is that the importance of the topic in epidemiologic CHD studies has been dealt with in at least one other recent PhD thesis (Ghosh, 2019) and stressed in many journal articles (e.g., MacKenzie *et al*., 2017; Puddu, Amaduzzi and Ricci, 2017). Also, the KIHD research group has already studied competing risks in terms of CVD and cancer (Voutilainen *et al*., 2022; Brester *et al*., 2023)

Missing data. How to treat missing data is one of the most intensively studied methodological questions in epidemiology (Hunt *et al*., 2021). In

recent years, the topic has been visible, for example, in the *Journal of Clinical Epidemiology* (Lee *et al*., 2021b; van Smeden *et al*., 2021).

Statistical power. *A priori* power analysis to estimate the required sample size is a crucial phase in the planning of RCTs. In cohort studies, statistical power usually refers to a retrospective power analysis, that is, calculating the power after the study has been completed that *per se* is useless because it provides the same information as *p*-values of the statistical analyses that have already been conducted. In principle, CIs show the ultimate statistical precision obtained in the study, and they are stressed, for example, in the STROBE statement (Vandenbroucke *et al*., 2007; von Elm *et al*., 2007). In the appendix of Original Publication I, a post-hoc power analysis was reported to illustrate how many cases there should have been to yield statistically significant results.

Discriminatory power. The statistical techniques introduced in the present thesis do not answer the crucial question of how well the statistical model can distinguish the study participants meeting the outcome of interest during the follow-up from those who do not. The Cox model's HRs and *p*-values indicate which covariates are statistically significant in the selected covariate combination. They do not reveal if the model *per se* is good at classifying the study participants. To bring model validation closer to the prevailing practice in epidemiology, researchers could, for instance, report concordance probability estimates (CPEs) in their papers together with statistical significance. Based on CPEs, it is simple to decide which covariates constitute the most predictive statistical model (Gönen and Heller, 2005; Heller and Mo, 2016). In Original Publication II, the negative log-likelihood function was used to evaluate model fit. Doctor Christina Brester has actively worked in the KIHD research group to develop epidemiological predictive modeling (Brester *et al*., 2018, 2021, 2022, 2023). In general, discriminatory power refers to predictive, not to descriptive, data science tasks. Predictive models apply data that include both input (e.g., coronary risk scores at baseline) and output variables (e.g., coronary events during the follow-up period), whereas descriptive models use data that provide only inputs (Hernán, Hsu and Healy, 2019).

6.4 STRENGTHS, LIMITATIONS, AND FUTURE PERSPECTIVES

The present thesis has two main strengths. First, the performed systematic evaluation concerning the state of statistical validity in scientific journal articles that deal with the epidemiological relationship between CHD and its risk factors creates a plausible starting point for the thesis. Second, the study cohort—KIHD—has features that made the present exploration possible. KIHD includes information from all capital modifiable and nonmodifiable risk factors of CHD, and it is long enough to enable the investigation of the association between follow-up time and study results. KIHD provides the results of ECG recordings, exercise stress tests, and detailed health interviews at baseline to reliably indicate study participants who had CHD before the start of the follow-up.

The main limitation with respect to the findings reported in Original Publications I–III is their debatable generalizability. Those findings are from one cohort—KIHD—, which has some unique characteristics. Based on answers to self-assessment physical activity questionnaires applied in KIHD, there are no inactive study participants in the cohort, and some participants are more than extremely physically active. This does not reflect reality but is a probable consequence of the assessment method. Self-assessment physical activity questionnaires in general are low in validity and reliability, so their results should be used to rank study participants within cohorts, not to direct comparisons across cohorts (Shephard, 2003; Westerterp, 2009). Furthermore, the KIHD cohort used in the present thesis is homogeneous in terms of sex and race.

An additional limitation is the lack of clinical severity evaluations in respect to the CHD manifestations during the KIHD follow-up. The manifestations were based solely on ICD-10 codes.

In the future, the demonstrations presented in Original Publications I–III should be repeated in cohorts other than KIHD to better evaluate the generalizability of the findings. Future demonstrations should also include topics other than those dealt with in Original Publications I–III. The most urgent topic is model optimization, a step that needs to be taken to find out which CHD risk factors truly distinguish those study participants who

have and have not CHD during the follow-up period (see Brester *et al*., 2018, 2021, 2022, 2023). Furthermore, an investigation regarding the effect of the order of data handling procedures on the study results is recommended. This investigation should ask if it makes a difference in which order the data handling procedures, such as the replacement of missing data, the manipulation of covariates, and the exclusion of study participants, are carried out. Moreover, broad detailed evaluations of statistical validity of epidemiological journal articles are required, and the results of those evaluations must be intensively reported to reform the custom of how epidemiology values statistics.

7 CONCLUSIONS

The present thesis has evoked the following main conclusions with respect to its four research questions:

1) The overall statistical validity of current prospective cohort studies of CHD and its risk factors is poor. Many studies are not at all concerned about statistical validity, or at least they do not disclose it in their study reports.

2A) From a statistical viewpoint, there is no reason to exclude patients who are not free from the disease of interest at study baseline from statistical analyses unless a sensitivity analysis suggests otherwise. The present evaluation of statistical validity and findings from the KIHD study show that, in many cases, the exclusion does not affect the associations across dependent and independent variables. It only reduces *n*, thus decreasing the number of statistically significant associations. 2B) Combining different CHD manifestations into a single outcome may yield results that are difficult to compare with the results of other studies because the combination of the outcome variable is not—and cannot ever be—constant over studies. It is more recommendable to perform separate analyses for different CHD manifestations. Particularly, fatal manifestations appear to differ from nonfatal manifestations in respect to their associations with risk factors.

3) Prospective cohort studies of CHD and its risk factors would benefit from presenting the results of multiplicative and additive survival models in the same articles. In doing this, distinguishing between multiplicative and additive covariates would become easier. Moreover, because multiplicative models and additive models should lead to similar conclusions, their concurrent use would make it easier to notice the most convincing results. Including additive covariates in multiplicative survival models without considering their time dependency may, for example, distort the order of importance across covariates.

4) In the KIHD study and based of the reference material of 81 other prospective cohort studies, the recommended most appropriate follow-up

time to detect the epidemiological relationship of CHD with its risk factors is 5–20 years. The CHD manifestation, risk factor, and cohort in question affect the recommendation.

To summarize, there are two take-home messages from the present thesis. First, scientific journals whose contents focus mainly on epidemiology should pay more attention to statistics in general and require statistical validity from their authors. Second, the semisubjective statistical choices that researchers make before and during data handling affect the results of prospective cohort studies. As a result, justifiable choices based on sensitivity analyses should be preferred instead of choices that are made blindly following a tradition.

REFERENCES

Aalen, O. O. (1989) 'A linear regression model for the analysis of life times', *Statistics in Medicine*, 8(8), pp. 907–925. doi: 10.1002/sim.4780080803

Aalen, O. O. (1993) 'Further results on the non-parametric linear regression model in survival analysis', *Statistics in Medicine*, 12(17), pp. 1569–1588. doi: 10.1002/sim.4780121705

Abadi, A. *et al*. (2011) 'Comparison of Aalen's additive and Cox proportional hazards model for breast cancer survival: analysis of population-based data from British Columbia, Canada', *Asian Pacific Journal of Cancer Prevention*, 12(11), pp. 3113–3116. PMID: 22393999

Abraira, V. *et al*. (2013) 'Reporting quality of survival analyses in medical journals still needs improvement. A minimal requirements proposal', *Journal of Clinical Epidemiology*, 66(12), pp. 1340–1346.e5. doi: 10.1016/j.jclinepi.2013.06.009

ADA (2021) '2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021', *Diabetes Care*, 44(Suppl 1), pp. S15–S33. doi: 10.2337/dc21-S002

Albert, C. M. and Stevenson, W. G. (2018) 'Cardiovascular collapse, cardiac arrest, and sudden cardiac death' in Jameson, J. L. *et al*. (eds.) *Harrison's Principles of Internal Medicine*. 20th edn. New York: McGraw-Hill Education, pp. 2059–2068.

Allen, N. *et al*. (2012) 'Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: The Cardiovascular Lifetime Risk Pooling Project', *Circulation*, 125(1), pp. 37–44. doi: 10.1161/CIRCULATIONAHA.110.002774

Altamura, S. *et al*. (2023) 'Oral health as a modifiable risk factor for cardiovascular disease', *Trends in Cardiovascular Medicine*, online: 23 March 2023. doi: 10.1016/j.tcm.2023.03.003

Altman, D. G. (1991) *Practical Statistics for Medical Research*. London: Chapman & Hall.

Altman, D. G. *et al*. (1995) 'Review of survival analyses published in cancer journals', *British Journal of Cancer*, 72(2), pp. 511–518. doi: 10.1038/bjc.1995.364

Anand, V. V. *et al*. (2023) 'Socioeconomic deprivation and prognostic outcomes in acute coronary syndrome: a meta-analysis using multidimensional socioeconomic status indices', *International Journal of Cardiology*, 383, pp. 140–150. doi: 10.1016/j.ijcard.2023.04.042

Antman, E. M. and Loscalzo, J. (2018a) 'Ischemic heart disease' in Jameson, J. L. *et al*. (eds.) *Harrison's Principles of Internal Medicine*. 20th edn. New York: McGraw-Hill Education, pp. 1850–1866.

Antman, E. M. and Loscalzo, J. (2018b) 'ST-segment elevation myocardial infarction' in Jameson, J. L. *et al*. (eds.) *Harrison's Principles of Internal Medicine*. 20th edn. New York: McGraw-Hill Education, pp. 1872–1885.

Antza, C. *et al*. (2020) 'American, European and international hypertension guidelines: time to shake hands?', *International Journal of Cardiology Hypertension*, 8:100075. doi: 10.1016/j.ijchy.2020.100075

Anum, E. A. and Adera, T. (2004) 'Hypercholesterolemia and coronary heart disease in the elderly: a meta-analysis', *Annals of Epidemiology*, 14(9), pp. 705–721. doi: 10.1016/j.annepidem.2003.10.009

Asia Pacific Cohort Studies Collaboration (2006) 'The impact of cardiovascular risk factors on the age-related excess risk of coronary heart disease', *International Journal of Epidemiology*, 35(4), pp. 1025–1033. doi: 10.1093/ije/dyl058

Asia Pacific Cohort Studies Collaboration (2009) 'Impact of cigarette smoking on the relationship between body mass index and coronary heart disease: a pooled analysis of 3264 stroke and 2706 CHD events in 378579 individuals in the Asia Pacific region', *BMC Public Health*, 9:294. doi: 10.1186/1471-2458-9-294

Atasoy. S. *et al*. (2019) 'Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/KORA study', *European Heart Journal*, 40(9), pp. 732–738. doi: 10.1093/eurheartj/ehy694

Babatunde, Y. A. (2021). 'InteractionR: an R package for full reporting of effect modification and interaction', *Software Impacts*, 10:100147. doi: 10.1016/j.simpa.2021.100147

Bachmann, J. M. *et al*. (2012) 'Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study', *Circulation*, 125(25), pp. 3092–3098. doi: 10.1161/CIRCULATIONAHA.111.065490

Banerjee, A. *et al*. (2012) 'Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies', *International journal of clinical practice*, 66(5), pp. 477–492. doi: 10.1111/j.1742-1241.2012.02900.x

Barrett, M. (2023) '*ggdag: Analyze and Create Elegant Directed Acyclic Graphs*. Available at: https://CRAN.R-project.org/package=ggdag (Accessed: 30 October 2023.

Batty, G. D. *et al*. (2018) 'Oral health and later coronary heart disease: cohort study of one million people', *European Journal of Preventive Cardiology*, 25(6), pp. 598–605. doi: 10.1177/2047487318759112

Bell, S. *et al*. (2017) 'Association between clinically recorded alcohol consumption and initial presentation of 12 cardiovascular diseases: population based cohort study using linked health records', *The BMJ*, 356:j909. doi: 10.1136/bmj.j909

Berben, L., Sereika, S. M. and Engberg, S. (2012) 'Effect size estimation: methods and examples', *International Journal of Nursing Studies*, 49(8), pp. 1039–1047. doi: 10.1016/j.ijnurstu.2012.01.015

Berrington de González, A. and Cox, D. R. (2007) 'Interpretation of interaction: a review', *The Annals of Applied Statistics*, 1(2), pp. 371–385. doi: 10.1214/07-AOAS124

Björk, J. *et al*. (2020) 'A novel framework for classification of selection processes in epidemiological research', *BMC Medical Research Methodology*, 20:155. doi: 10.1186/s12874-020-01015-w

Bots, S. H., Peters, S. A. E. and Woodward, M. (2017) 'Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010', *BMJ Global Health*, 2(2):e000298. doi: 10.1136/bmjgh-2017-000298

Bradburn, M. J. *et al*. (2003a) 'Survival analysis part II: multivariate data analysis – an introduction to concepts and methods', *British Journal of Cancer*, 89(3), pp. 431–436. doi: 10.1038/sj.bjc.6601119

Bradburn, M. J. *et al*. (2003b) 'Survival analysis part III: multivariate data analysis – choosing a model and assessing its adequacy and fit', *British Journal of Cancer*, 89(4), pp. 605–611. doi: 10.1038/sj.bjc.6601120

Brester, C. *et al*. (2018) 'Evolutionary methods for variable selection in the epidemiological modeling of cardiovascular diseases', *BioData Mining*, 11:18. doi: 10.1186/s13040-018-0180-x

Brester, C. *et al*. (2021) 'Post-analysis of predictive modeling with an epidemiological example', *Healthcare*, 9(7):792. doi: 10.3390/healthcare9070792

Brester, C. *et al*. (2022) 'Epidemiological predictive modeling: lessons learned from the Kuopio ischemic heart disease risk factor study', *Annals of Epidemiology*, 70, pp. 1–8. doi: 10.1016/j.annepidem.2022.03.010

Brester, C. *et al*. (2023) 'Predicting risk of cardiovascular death in the high-dimensional cohort follow-up data in the presence of competing events: a guide for building a modeling pipeline', *Biostatistics & Epidemiology*, 7(1):e2084704. doi: 10.1080/24709360.2022.2084704

Brown, A. J. *et al*. (2016) 'Role of biomechanical forces in the natural history of coronary atherosclerosis', *Nature Reviews Cardiology*, 13(4), pp. 210–220. doi: 10.1038/nrcardio.2015.203

Brown, L. D., Cai, T. T. and DasGupta, A. (2001) 'Interval estimation for a binomial proportion', *Statistical Science*, 16(2), pp. 101–133. doi: 10.1214/ss/1009213286

Chazov, E. I. *et al*. (1976) 'Intracoronary administration of fibrinolysin in acute myocardial infarct (in Russian)', *Terapevticheskii Arkhiv*, 48(4), pp. 8–19. PMID: 136054

Chen, L. *et al*. (2021) 'Educational disparities in ischaemic heart disease among 0.5 million Chinese adults: a cohort study', *Journal of Epidemiology and Community Health*, 75(11), pp. 1033–1043. doi: 10.1136/jech-2020-216314

Cheng, B. *et al*. (2021) 'Reporting practices for genomic epidemiology of tuberculosis: a systematic review of the literature using STROME-ID

guidelines as a benchmark', *The Lancet Microbe*, 2(3), pp. e115–e129. doi: 10.1016/s2666-5247(20)30201-9

Chouraki, V. *et al*. (2008) 'Smoking habits, waist circumference and coronary artery disease risk relationship: the PRIME study', *European Journal of Cardiovascular Prevention and Rehabilitation*, 15(6), pp. 625–630. doi: 10.1097/HJR.0b013e32830fe479

Clark, T. G. *et al*. (2003a) 'Survival analysis part I: basic concepts and first analyses', *British Journal of Cancer*, 89(2), pp. 232–238. doi: 10.1038/sj.bjc.6601118

Clark, T. G. *et al*. (2003b) 'Survival analysis part IV: further concepts and methods in survival analysis', *British Journal of Cancer*, 89(5), pp. 781–786. doi: 10.1038/sj.bjc.6601117

Cosentino, F. *et al*. (2020) '2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD', *European Heart Journal*, 41(2), pp. 255–323. doi: 10.1093/eurheartj/ehz486

Cox, D. R. (1972) 'Regression models and life-tables', *Journal of the Royal Statistical Society: Series B (Methodological)*, 34(2), pp. 187–202. doi: 10.1111/j.2517-6161.1972.tb00899.x

Cox, D. R. and Oakes, D. (1984) *Analysis of Survival Data*. Cambridge: Chapman and Hall.

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) *et al*. (2011) 'Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data', *The BMJ*, 342:d548. doi: 10.1136/bmj.d548

Critical Appraisal Skills Programme (2023) *CASP Cohort Study Checklist*. Available at: https://casp-uk.net/casp-tools-checklists/ (Accessed: 28 February 2023).

Das De, S., Krishna, S. and Jethwa, A. (2015) 'Iron status and its association with coronary heart disease: systematic review and meta-analysis of prospective studies', *Atherosclerosis*, 238(2), pp. 296–303. doi: 10.1016/j.atherosclerosis.2014.12.018

De Brouwer, C. P. M. *et al*. (2012) *Training Critical Appraisal of a Topic; an Indispensable Manual in the Area of Evidence Based Medicine*. Maastricht: Mediview.

Delgado-Rodríguez, M. and Llorca, J. (2004) 'Bias', *Journal of Epidemiology and Community Health*, 58(8), pp. 635–641. doi: 10.1136/jech.2003.008466

DeWood, M. A. *et al*. (1980) 'Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction', *The New England Journal of Medicine*', 303(16), pp. 897–902. doi: 10.1056/NEJM198010163031601

Ding, X. Q. *et al*. (2015) 'Interaction between microRNA expression and classical risk factors in the risk of coronary heart disease', *Scientific Reports*, 5:14925. doi: 10.1038/srep14925

Downs, S. H. and Black, N. (1998) 'The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions', *Journal of Epidemiology and Community Health*, 52(6), pp. 377–384. doi: 10.1136/jech.52.6.377

Drobni, Z. D. *et al*. (2022) 'Heritability of coronary artery disease: insights from a classical twin study', *Circulation: Cardiovascular Imaging*, 15(3):e013348. doi: 10.1161/CIRCIMAGING.121.013348

Drukker, M. *et al*. (2021) 'Development of a methodological quality criteria list for observational studies: the observational study quality evaluation', *Frontiers in Research Metrics and Analytics*, 6:675071. doi: 10.3389/frma.2021.675071

Emerging Risk Factors Collaboration *et al*. (2010) 'C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis', *The Lancet*, 375(9709), pp. 132–140. doi: 10.1016/S0140-6736(09)61717-7

Fahrmann, E. R., Adkins, L. and Driscoll, H. K. (2021) 'Modification of the association between severe hypoglycemia and ischemic heart disease by surrogates of vascular damage severity in type 1 diabetes during ~30 years of follow-up in the DCCT/EDIC study', *Diabetes Care*, 44(9), pp. 2132–2139. doi: 10.2337/dc20-2757

Fan, J. *et al*. (2019) 'Small dense LDL cholesterol is associated with metabolic syndrome traits independently of obesity and inflammation', *Nutrition & Metabolism*, 16:7. doi: 10.1186/s12986-019-0334-y

FAO/WHO/UNU (2001) 'Human energy requirements. Report of a joint FAO/WHO/UNU expert consultation', *FAO Food and Nutrition Technical Report Series*, 1, pp. 1–96.

Fedak, K. M. *et al*. (2015) 'Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology', *Emerging Themes in Epidemiology*, 12:14. doi: 10.1186/s12982-015-0037-4

Ference, B. A. *et al*. (2017) 'Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel', *European Heart Journal*, 38(32), pp. 2459–2472. doi: 10.1093/eurheartj/ehx144

Fowkes, F. G. and Fulton, P. M. (1991) 'Critical appraisal of published research: introductory guidelines', *The BMJ*, 302(6785), pp. 1136–1140. doi: 10.1136/bmj.302.6785.1136

Franco, O. H. *et al*. (2005) 'Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis', *Hypertension*, 46(2), pp. 280–286. doi: 10.1161/01.HYP.0000173433.67426.9b

Franklin, B. A. *et al*. (2020) 'Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risk into perspective–an update: a scientific statement from the American Heart Association', *Circulation*, 141(13), pp. e705–e736. doi: 10.1161/CIR.0000000000000749

Fu, L. *et al*. (2021) 'Atherogenic index of plasma is associated with major adverse cardiovascular events in patients with type 2 diabetes mellitus', *Cardiovascular Diabetology*, 20(1):201. doi: 10.1186/s12933-021-01393-5

George, S. L. (1985) 'Statistics in medical journals: a survey of current policies and proposals for editors', *Medical and Pediatric Oncology*, 13(2), pp. 109–112. doi: 10.1002/mpo.2950130215

Ghosh, A. (2019) *A dynamic competing risk model for multi-type recurrent events with dependent termination*. PhD thesis. University of Texas.

Girerd, N. *et al*. (2016) 'Quantification of treatment effect modification on both an additive and multiplicative scale', *PLoS One*, 11(4):e0153010. doi: 10.1371/journal.pone.0153010

Giugliano, R. P., Cannon, C. P. and Braunwald, E. (2018) 'Non-ST-segment elevation acute coronary syndrome (non-ST-segment elevation myocardial infraction and unstable angina)' in Jameson, J. L. *et al*. (eds.) *Harrison's Principles of Internal Medicine*. 20th edn. New York: McGraw-Hill Education, pp. 1866–1872.

Global BMI Mortality Collaboration *et al*. (2016) 'Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents', *The Lancet*, 388(10046), pp. 776–786. doi: 10.1016/S0140-6736(16)30175-1

Glymour, M. M. *et al*. (2005) 'When is baseline adjustment useful in analyses of change? An example with education and cognitive change', *American Journal of Epidemiology*, 162(3), pp. 267–278. doi: 10.1093/aje/kwi187

Goodman, S. N., Altman, D. G. and George, S. L. (1998) 'Statistical reviewing policies of medical journals: caveat lector?', *Journal of General Internal Medicine*, 13(11), pp. 753–756. doi: 10.1046/j.1525-1497.1998.00227.x

Grambsch, P. M. and Therneau, T. M. (1994) 'Proportional hazards tests and diagnostics based on weighted residuals', *Biometrika*, 81(3), pp. 515–526. doi: 10.1093/biomet/81.3.515

Gregg, D. E. (1974) 'The natural history of coronary collateral development', *Circulation Research*, 35(3), pp. 335–344. doi: 10.1161/01.res.35.3.335

Groenwold, H. H. *et al*. (2008) 'Poor quality of reporting confounding bias in observational intervention studies: a systematic review', *Annals of Epidemiology*, 18(10), pp. 746–751. doi: 10.1016/j.annepidem.2008.05.007

Groothuis, R. J. *et al*. (2022) 'Self-report versus measured physical activity levels during outpatient cardiac rehabilitation', *Journal of Cardiopulmonary Rehabilitation and Prevention*, 42(3), pp. 172–177. doi: 10.1097/HCR.0000000000000642

Gullon, P. *et al*. (2021) 'Does a physical activity supportive environment ameliorate or exacerbate socioeconomic inequities in incident coronary heart disease?', *Journal of Epidemiology and Community Health*, 75(7), pp. 637–642. doi: 10.1136/jech-2020-215239

Guo, X. *et al*. (2013) 'Association between pre-hypertension and cardiovascular outcomes: a systematic review and meta-analysis of prospective studies', *Current Hypertension Reports*, 15(6), pp. 703–716. doi: 10.1007/s11906-013-0403-y

Gönen, M. and Heller, G. (2005) 'Concordance probability and discriminatory power in proportional hazards regression', *Biometrika*, 92(4), pp. 965–970. doi: 10.1093/biomet/92.4.965

Hackshaw, A. *et al*. (2018) 'Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports', *The BMJ*, 360:j5855. doi: 10.1136/bmj.j5855

Hallum, S. *et al*. (2021) 'Impact of male-origin microchimerism on cardiovascular disease in women: a prospective cohort study', *American Journal of Epidemiology*, 190(5), pp. 853–863. doi: 10.1093/aje/kwaa250

Hardwicke, T. E. and Goodman, S. N. (2020) 'How often do leading biomedical journals use statistical experts to evaluate statistical methods? The results of a survey', *PLoS ONE*, 15(10):e0239598. doi: 10.1371/journal.pone.0239598

Held, U. *et al*. (2022) 'The incremental value of the contribution of a biostatistician to the reporting quality in health research – a retrospective, single center, observational study', *PLoS One*, 17(3):e0264819. doi: 10.1371/journal.pone.0264819

Heller, G. and Mo, Q. (2016) 'Estimating the concordance probability in a survival analysis with a discrete number of risk groups', *Lifetime Data Analysis*, 22(2), pp. 263–279. doi: 10.1007/s10985-015-9330-3

Hendriksma, M. *et al*. (2017) 'Evaluation of the quality of reporting of observational studies in otorhinolaryngology – based on the STROBE statement', *PLos One*, 12(1):e0169316. doi: 10.1371/journal.pone.0169316

Henschel, B., Gorczyca, A. M. and Chomistek, A. K. (2017) 'Time spent sitting as an independent risk factor for cardiovascular disease', *American*

Journal of Lifestyle Medicine, 14(2), pp. 204–215. doi: 10.1177/1559827617728482

Hernán, M. A., Hsu, J. and Healy, B. (2019) 'A second chance to get causal inference right: a classification of data science tasks', *CHANCE*, 32(1), pp. 42–49. doi: 10.1080/09332480.2019.1579578

Hicks, B. *et al*. (2021) 'Roles of allostatic load, lifestyle and clinical risk factors in mediating the association between education and coronary heart disease risk in Europe', *Journal of Epidemiology and Community Health*, 75(12), pp. 1147–1154. doi: 10.1136/jech-2020-215394

Hill, A. B. (1965) 'The environment and disease: association or causation?', *Proceedings of the Royal Society of Medicine*, 58(5), pp. 295–300. PMID: 14283879

Hosmer, D. W., Jr. and Lemeshow, S. (1999) *Applied Survival Analysis. Regression Modeling of Time to Event Data*. New York, N.Y.: John Wiley & Sons, Inc.

Hsu, M.-C. *et al*. (2021) 'Effect of ICD-9-CM to ICD-10-CM coding system transition on identification of common conditions: an interrupted time series analysis', *Pharmacoepidemiology & Drug Safety*, 30(12), pp. 1653–1674. doi: 10.1002/pds.5330

Hu, G., Qiao, Q. and Tuomilehto, J. (2005) 'Metabolic syndrome, diabetes, and coronary heart disease', in Marmot, M. and Elliott, P. (eds.) *Coronary Heart Disease Epidemiology: From Aetiology to Public Health*. 2nd edn. New York: Oxford University Press, pp. 311–330.

Huang, Y. *et al*. (2015) 'Prehypertension and the risk of coronary heart disease in Asian and Wester populations: a meta-analysis', *Journal of the American Heart Association*, 4:e001519. doi: 10.1161/JAHA.114.001519

Huang, Y. *et al*. (2022) 'Interaction between genetics and smoking in determining risk of coronary artery diseases', *Genetic Epidemiology*, 46(3–4), pp. 199–212. doi: 10.1002/gepi.22446

Hunt, N. B. *et al*. (2021) 'A systematic review of how missing data are handled and reported in multi-database pharmacoepidemiologic studies', *Pharmacoepidemiology and Drug Safety*, 30(7), pp. 819–826. doi: 10.1002/pds.5245

Jacobsen, S. J. *et al*. (1992) 'Cholesterol and coronary artery disease: age as an effect modifier', *Journal of Clinical Epidemiology*, 45(10), pp. 1053–1059. doi: 10.1016/0895-4356(92)90145-D

Jarde, A., Losilla, J.-M. and Vives, J. (2012a) 'Methodological quality assessment tools of non-experimental studies: a systematic review', *Anales de Psicologia*, 28(2), pp. 617–628. doi: 10.6018/analesps.28.2.148911

Jarde, A., Losilla, J. M. and Vives, J. (2012b) 'Suitability of three different tools for the assessment of methodological quality in ex post facto studies', *International Journal of Clinical and Health Psychology*, 12(1), pp. 97–108. ISSN: 1697-2600

Jarde, A. *et al*. (2013) 'Q-Coh: a tool to screen the methodological quality of cohort studies in systematic reviews and meta-analyses', *International Journal of Clinical and Health Psychology*, 13(2), pp. 138–146. doi: 10.1016/S1697-2600(13)70017-6

Jarrick, S. *et al*. (2021) 'Immunoglobulin A nephropathy and ischemic heart disease: a nationwide population-based cohort study', *BMC Nephrology*, 22(1):165. doi: 10.1186/s12882-021-02353-7

Jetté, M., Sidney, K. and Blümchen, G. (1990) 'Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity', *Clinical Cardiology*, 13(8), pp. 555–565. doi: 10.1002/clc.4960130809

Joanna Briggs Institute (2020) *Checklist for Cohort Studies. Critical Appraisal Tools for Use in JBI Systematic Reviews*. Available at: https://jbi.global/critical-appraisal-tools (Accessed: 28 February 2023).

Jousilahti, P. *et al.* (1996) 'Body weight, cardiovascular risk factors, and coronary mortality: 15-year follow-up of middle-aged men and women in Eastern Finland', *Circulation*, 93(7), pp. 1372–1379. doi: 10.1161/01.CIR.93.7.1372

Jousilahti, P. *et al*. (1999) 'Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland', *Circulation*, 99(9), pp. 1165–1172. doi: 10.1161/01.cir.99.9.1165

Julian, D. G. (1987) 'The history of coronary care units', *British Heart Journal*, 57(6), pp. 497–502. doi: 10.1136/hrt.57.6.497

Karahalios, A. *et al*. (2012) 'A review of the reporting and handling of missing data in cohort studies with repeated assessment of exposure measures', *BMC Medical Research Methodology*, 12:96. doi: 10.1186/1471-2288-12-96

Kassambara, A., Kosinski, M. and Biecek, P. (2021) *Survminer: Drawing Survival Curves Using 'ggplot2'*. Available at: https://CRAN.R-project.org/package=survminer (Accessed: 8 September 2022).

Katz, K. A. *et al*. (2004) 'Statistical reviewing policies in dermatology journals: results of a questionnaire survey of editors', *Journal of the American Academy of Dermatology*, 51(2), pp. 234–240. doi: 10.1016/j.jaad.2004.02.015

Kaufman, J. S. (2010) 'Marginalia: comparing adjusted effect measures', *Epidemiology*, 21(4), pp. 490–493. doi: 10.1097/EDE.0b013e3181e00730

Kern, L. M. *et al*. (2021) 'Healthcare fragmentation and incident acute coronary heart disease events: a cohort study', *Journal of General Internal Medicine*, 36(2), pp. 422–429. doi: 10.1007/s11606-020-06305-z

Kristófi, R. *et al*. (2021) 'Cardiovascular and renal disease burden in type 1 compared with type 2 diabetes: a two-country nationwide observational study', *Diabetes Care*, 44(5), pp. 1211–1218. doi: 10.2337/dc20-2839

Kuitunen, I. *et al.* (2021) 'Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review', *BMC Musculoskeletal Disorders*, 22(1):489. doi: 10.1186/s12891-021-04379-2

Lakka, T. A. *et al*. (1994) 'Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction', *The New England journal of medicine*, 330(22), pp. 1549–1554. doi: 10.1056/NEJM199406023302201

Langan, S. *et al*. (2010) 'The reporting of observational research studies in dermatology journals: a literature-based study', *Archives of Dermatology*, 146(5), pp. 534–541. doi: 10.1001/archdermatol.2010.87

Lao, X. Q. *et al*. (2018) 'Sleep quality, sleep duration, and the risk of coronary heart disease: a prospective cohort study with 60,586 adults', *Journal of Clinical Sleep Medicine*, 14(1), pp. 109–117. doi: 10.5664/jcsm.6894

Lash, T. L. *et al*. (2021) *Modern Epidemiology*. 4th edn. Philadelphia, P.A.: Wolters Kluwer.

Law, M. R., Wald, N. J. and Thompson, S. G. (1994) 'By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease', *BMJ*, 308(6925), pp. 367–372. doi: 10.1136/bmj.308.6925.367

Leander, K. *et al*. (2001) 'Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEEP)', *Epidemiology*, 12(2): 215–221. doi: 10.1097/00001648-200103000-00014

Lee, K.-J. *et al*. (2021a) 'Five-year risk of acute myocardial infarction after acute ischemic stroke in Korea', *Journal of the American Heart Association*, 10(1):e018807. doi: 10.1161/JAHA.120.018807

Lee, K. J. *et al*. (2021b) 'Framework for the treatment and reporting of missing data in observational studies: the Treatment And Reporting of Missing data in Observational Studies framework', *Journal of Clinical Epidemiology*, 134, pp. 79–88. doi: 10.1016/j.jclinepi.2021.01.008

Lee, W. L. *et al*. (2000) 'Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies', *Diabetes Care*, 23(7), pp. 962–968. doi: 10.2337/diacare.23.7.962

Lefebvre, F. and Giorgi, R. (2021) 'A strategy for optimal fitting of multiplicative and additive hazards regression models', *BMC Medical Research Methodology*, 21(1):100. doi: 10.1186/s12874-021-01273-2

Leibowitz, J. O. (1970) *The History of Coronary Heart Disease*. London: Wellcome Institute of the History of Medicine.

Leon, B. M. and Maddox, T. M. (2015) 'Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research', *World Journal of Diabetes*, 6(13), pp. 1246–1258. doi: 10.4239/wjd.v6.i13.1246

Li, C. *et al*. (2020) 'Risk of coronary heart disease in the rural population in Xinjiang: a nested case-control study in China', *PLoS ONE*, 15(3):e0229598. doi: 10.1371/journal.pone.0229598

Li, X. *et al*. (2023) 'Sleep deprivation promotes endothelial inflammation and atherogenesis by reducing exosomal miR-182-5p', *Arteriosclerosis, Thrombosis, and Vascular Biology*, 43(6), pp. 995–1014. doi: 10.1161/ATVBAHA.123.319026

Libby, P., Ridker, P. M. and Hansson, G. K. (2011) 'Progress and challenges in translating the biology of atherosclerosis', *Nature*, 473(7347), pp. 317–325. doi: 10.1038/nature10146

Lim, H. J. and Zhang, X. (2009) 'Semi-parametric additive risk models: application to injury duration study', *Accident Analysis & Prevention*, 41(2), pp. 211–206. doi: 10.1016/j.aap.2008.07.015

Lin, D. Y., Wei, L. J. and Ying. Z. (1993) 'Checking the Cox model with cumulative sums of martingale-based residuals', *Biometrika*, 80(3), pp. 557–572. doi: 10.2307/2337177

Lind, L. *et al*. (2021) 'A longitudinal study over 40 years to study the metabolic syndrome as a risk factor for cardiovascular diseases', *Scientific Reports*, 11:2978. doi: 10.1038/s41598-021-82398-8

Lp-PLA(2) Studies Collaboration *et al*. (2010) 'Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies', *The Lancet*, 375(9725), pp. 1536–1544. doi: 10.1016/S0140-6736(10)60319-4

Ma, L. L. *et al*. (2020) 'Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better?', *Military Medical Research*, 7:7. doi: 10.1186/s40779-020-00238-8

Maas, A. H. and Appelman, Y. E. (2010) 'Gender differences in coronary heart disease', *Netherlands Heart Journal*, 18(12), pp. 598–602. doi: 10.1007/s12471-010-0841-y

Mach, F. *et al*. (2020) '2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk', *European Heart Journal*, 41(1), pp. 111–188. doi: 10.1093/eurheartj/ehz455

MacKenzie, G. *et al*. (2017) 'Competing risk analysis of factors related to long-term incidence of CHD', *Journal of Epidemiology and Community Health*, 71(1), pp. 33-36. doi: 10.1136/jech-2016-207347

Mancia, G. *et al*. (2023) '2023 ESH guidelines for the management of arterial hypertension *The Task Force for the management of arterial hypertension of the European Society of Hypertension*: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)', *Journal of Hypertension*, 41(12), pp. 1874–2071. doi: 10.1097/HJH.0000000000003480

Master, A. M. (1960) 'The role of effort and occupation (including physicians) in coronary occlusion', *The Journal of the American Medical Association*, 174(8), pp. 942-948. doi: 10.1001/jama.1960.03030080004002

Mifflin, M. D. *et al*. (1990) 'A new predictive equation for resting energy expenditure in healthy individuals', *The American Journal of Clinical Nutrition*, 51(2), pp. 241-247. doi: 10.1093/ajcn/51.2.241

Mittleman, M. A. and Mostofsky, E. (2011) 'Physical, psychological and chemical triggers of acute cardiovascular events: preventive strategies', *Circulation*, 124(3), pp. 346–354. doi: 10.1161/CIRCULATIONAHA.110.968776

Mongraw-Chaffin, M. L. *et al*. (2015) 'The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1.2 million participants', *The Lancet Diabetes & Endocrinology*, 3(6), pp. 437–449. doi: 10.1016/S2213-8587(15)00086-8

Morris, J. N. (1951) 'Recent history of coronary disease', *The Lancet*, 1(6646), pp. 69–73. doi: 10.1016/s0140-6736(51)91163-4

Muller, J. E., Tofler, G. H. and Stone, P. H. (1989) 'Circadian variation and triggers of onset of acute cardiovascular disease', *Circulation*, 79(4), pp. 733–743. doi: 10.1161/01.CIR.79.4.733

Nagel, J. *et al*. (2021) 'How family history of premature myocardial infarction affects patients at cardiovascular risk', *Health Psychology*, 40(11), pp. 754–763. doi: 10.1037/hea0001128

National Heart, Lung, and Blood Institute (2021) *NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*. Available at:

https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools (Accessed: 28 February 2023).

Newcombe, R. G. and Altman, D. G. (2000) 'Proportions and their differences' in Altman, D. G. *et al*. (eds.) *Statistics with Confidence*. 2nd edn. London: BMJ Publishing Group, pp. 45–56.

Ngari, M. M. *et al*. (2021) 'A systematic review of the quality of conduct and reporting of survival analyses of tuberculosis outcomes in Africa', *BMC Medical Research Methodology*, 21(1):89. doi: 10.1186/s12874-021-01280-3

Nordahl, H. *et al*. (2013) 'Education and risk of coronary heart disease: assessment of mediation by behavioral risk factors using the additive hazards model', *European Journal of Epidemiology*, 28(2), pp. 149–157. doi: 10.1007/s10654-012-9745-z

Obraztsov, V. P. and Strazhesko, N. D. (1910) 'The symptomatology and diagnosis of coronary thrombosis' in Vorobeva, V. A. and Konchalovski, M. P. (eds.) *Works of the First Congress of Russian Therapist*. Moscow, Russia: Comradeship Typography of AE Moscow: Mamontov, pp. 26–43.

O'Donnell, M. J. *et al*. (2010) 'Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study', *The Lancet*, pp. 112–123. doi: 10.1016/S0140-6736(10)60834-3

Okami, Y. *et al.* (2021) 'Risk factors that most accurately predict coronary artery disease based on the duration of follow-up – NIPPON DATA80', *Circulation Journal*, 85(6), pp. 908–913. doi: 10.1253/circj.CJ-20-0739

Ong, K. L. *et al*. (2021) 'Lipoprotein (a) and coronary artery calcification: prospective study assessing interactions with other risk factors', *Metabolism: Clinical and Experimental*, 116:154706. doi: 10.1016/j.metabol.2021.154706

Paajanen, T. A. *et al*. (2010) 'Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis', *European Heart Journal*, 31(14), pp. 1802–1809. doi: 10.1093/eurheartj/ehq155

Pagano, E. *et al*. (2021) 'Prediction of mortality and major cardiovascular complications in type 2 diabetes: external validation of UK Prospective

Diabetes Study outcomes model version 2 in two European observational cohorts', *Diabetes, Obesity & Metabolism*, 23(5), pp. 1084–1091. doi: 10.1111/dom.14311

Paneni, F. *et al*. (2017) 'The aging cardiovascular system: understanding it at the cellular and clinical levels', *Journal of the American College of Cardiology*, 69(15), pp. 1952–1967. doi: 10.1016/j.jacc.2017.01.064

Papier, K. *et al*. (2023) 'Meat consumption and risk of ischemic heart disease: a systematic review and meta-analysis', *Critical Reviews in Food Science and Nutrition*, 63(3), pp. 426–437. doi: 10.1080/10408398.2021.1949575

Patel, A. P. *et al*. (2021) 'Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank', *Arteriosclerosis, Thrombosis, and Vascular Biology*, 41(1), pp. 465–474. doi: 10.1161/ATVBAHA.120.315291

Pearson, K. (1900) 'On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling', *Philosophical Magazine Series 5*, 50(302), pp. 157–175. doi: 10.1080/14786440009463897

Pedersen, E. *et al*. (2021) 'Self-reported medication use among coronary heart disease patients showed high validity compared with dispensing data', *Journal of Clinical Epidemiology*, 135, pp. 115–124. doi: 10.1016/j.jclinepi.2021.02.015

Penson, P. E., Pirro, M. and Banach, M. (2020) 'LDL-C: lower is better for longer—even at low risk', *BMC Medicine*, 18(1):320. doi: 10.1186/s12916-020-01792-7

Perez-Cornago *et al*. (2021) 'Plant foods, dietary fibre and risk of ischaemic heart disease in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort', *International Journal of Epidemiology*, 50(1), pp. 212–222. doi: 10.1093/ije/dyaa155

Perkovic, V. *et al*. (2008) 'The relationship between proteinuria and coronary risk: a systematic review and meta-analysis', *PLoS Medicine*, 5(10):e207. doi: 10.1371/journal.pmed.0050207

Peters, S. A. E., Huxley, R. R. and Woodward, M. (2014) 'Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events', *Diabetologia*, 57(8), pp. 1542–1551. doi: 10.1007/s00125-014-3260-6

Peters, S. A. E. *et al*. (2016) 'Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: a systematic review and meta-analysis', *Atherosclerosis*, 248, pp. 123–131. doi: 10.1016/j.atherosclerosis.2016.03.016

Peters, S. A. E., Muntner, P. and Woodward, M. (2019) 'Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016', *Circulation*, 139(8), pp. 1025–1035. doi: 10.1161/CIRCULATIONAHA.118.035550

Piantadosi, S., Byar, D. P. and Green, S. B. (1988) 'The ecological fallacy', *American Journal of Epidemiology*, 127(5), pp. 893–904. doi: 10.1093/oxfordjournals.aje.a114892

Poulter, N. (1999) 'Coronary heart disease is a multifactorial disease', *American Journal of Hypertension*, 12(10 Pt 2), pp. 92S–95S. doi: 10.1016/s0895-7061(99)00163-6

Pouwels, K. B. *et al*. (2016) 'Quality of reporting of confounding remained suboptimal after the STROBE guideline' *Journal of Clinical Epidemiology*, 69, pp. 217–224. doi: 10.1016/j.jclinepi.2015.08.009

Powell-Wiley, T. M. *et al*. (2021) 'Obesity and cardiovascular disease: a scientific statement from the American Heart Association', *Circulation*, 143(21), pp. e984–e1010. doi: 10.1161/CIR.0000000000000973

Prince, S. A. *et al*. (2008) 'A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review', *International Journal of Behavioral Nutrition and Physical Activity*, 5:56. doi: 10.1186/1479-5868-5-56

Puddu, P. E., Amaduzzi, P. L. and Ricci, B. (2017) 'Coronary heart disease incidence and competing risks: an important issue', *Journal of Geriatric Cardiology*, 14(7), pp. 425–429. doi: 10.11909/j.issn.1671-5411.2017.07.007

Rao, A. *et al*. (2016) 'Quality of reporting and study design of CKD cohort studies assessing mortality in the elderly before and after STROBE: a systematic review', *PLos One*, 11(5):e0155078. doi: 10.1371/journal.pone.0155078

Rapsomaniki, E. *et al*. (2014) 'Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people', *The Lancet*, 383(9932), pp. 1899–1911. doi: 10.1016/S0140-6736(14)60685-1

R Core Team (2022) *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Reimer, K. A. and Jennings, R. B. (1979) 'The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow', *Laboratory Investigation*, 40(6), pp. 633–644. PMID: 449273

Reimer, K. A. *et al*. (1977) 'The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs', *Circulation*, 56(5), pp. 786–794. doi: 10.1161/01.cir.56.5.786

Rentrop, K. P. *et al*. (1979) 'Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase', *Clinical Cardiology*, 2(5), pp. 354–363. doi: 10.1002/clc.4960020507

ROBINS-E Development Group (2022) *Risk Of Bias In Non-randomized Studies – of Exposure (ROBINS-E)*. Launch version, 1 June 2022. Available at: https://www.riskofbias.info/welcome/robins-e-tool (Accessed: 26 May 2023).

Roeters van Lennep *et al*. (2002) 'Risk factors for coronary heart disease: implications of gender', *Cardiovascular Research*, 53(3), pp. 538–549. doi: 10.1016/s0008-6363(01)00388-1

Ronksley, P. E. *et al*. (2011) 'Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis', *The BMJ*, 342:d671. doi: 10.1136/bmj.d671

Rothman, K. J. (2012) *Epidemiology: An Introduction.* 2nd edn. New York, N.Y.: Oxford University Press, Inc.

Ryle, J. A. and Russell, W. T. (1949) 'The natural history of coronary disease; a clinical and epidemiological study', *British Heart Journal*, 11(4), pp. 370–389. doi: 10.1136/hrt.11.4.370

Safarova, M. S., Bailey, K. R. and Kullo, I. J. (2016) 'Association of a family history of coronary heart disease with initiation of statin therapy in individuals at intermediate risk', *JAMA Cardiology*, 1(3), pp. 364–366. doi: 10.1001/jamacardio.2016.0227

Salomaa, V. *et al*. (1996) 'Decline of coronary heart disease mortality in Finland during 1983 to 1992: roles of incidence, recurrence, and case-fatality', *Circulation*, 94(12), pp. 3130–3137. doi: 10.1161/01.CIR.94.12.3130

Salonen, J. T. (1988) 'Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study', *Annals of Clinical Research*, 20(1–2), pp. 46–50. PMID: 3408213

Salonen, J. T. *et al*. (1991) 'HDL, HDL2, and HDL3 subfractions, and the risk of acute myocardial infarction. A prospective population study in eastern Finnish men', *Circulation*, 84(1), pp. 129–139. doi: 10.1161/01.cir.84.1.129

Sanchis-Gomar, F. *et al*. (2016) 'Epidemiology of coronary heart disease and acute coronary syndrome', *Annals of Translational Medicine*, 4(13):256. doi: 10.21037/atm.2016.06.33

Sara, J. D. *et al*. (2018) 'Association between work-related stress and coronary heart disease: a review of prospective studies through the job strain, effort-reward balance, and organizational justice models', *Journal of the American Heart Association*, 7(9):e008073. doi: 10.1161/JAHA.117.008073

Sattar, N. and Preiss, D. (2017) 'Reverse causality in cardiovascular epidemiological research: more common than imagined?', *Circulation*, 135(24), pp. 2369–2372. doi: 10.1161/CIRCULATIONAHA.117.028307

Sattelmair, J. *et al*. (2011) 'Dose response between physical activity and risk of coronary heart disease: a meta-analysis', *Circulation*, 124(7), pp. 789–795. doi: 10.1161/CIRCULATIONAHA.110.010710

Scheike, T. H. and Martinussen, T. (2006) *Dynamic Regression Models for Survival Data*. New York, N.Y.: Springer.

Scheike, T. H. and Zhang, M.-J. (2011) 'Analyzing competing risk data using the R timereg package', *Journal of Statistical Software*, 38(2), pp. 1–15.

Schuster, N. A. *et al*. (2020) 'Ignoring competing events in the analysis of survival data may lead to biased results: a nonmathematical illustration of competing risk analysis', *Journal of Clinical Epidemiology*, 122, pp. 42–48. doi: 10.1016/j.jclinepi.2020.03.004

Schwartz, B. G., Kloner, R. A. and Naghavi, M. (2018) 'Acute and subacute triggers of cardiovascular events', *The American Journal of Cardiology*, 122(12), pp. 2157–2165. doi: 10.1016/j.amjcard.2018.08.049

Scottish Intercollegiate Guidelines Network (2012) *SIGN Methodology Checklist 3: Cohort Studies*. Available at: https://www.sign.ac.uk/what-we-do/methodology/checklists/ (Accessed: 28 February 2023).

Sharp, M. K. *et al*. (2019) 'A cross-sectional bibliometric study showed suboptimal journal endorsement rates of STROBE and its extensions', *Journal of Clinical Epidemiology*, 107, pp. 42–50. doi: 10.1016/j.jclinepi.2018.11.006

Shephard, R. J. (2003) 'Limits to the measurement of habitual physical activity by questionnaires', *British Journal of Sports Medicine*, 37(3), pp. 197–206. doi: 10.1136/bjsm.37.3.197

Silberberg, J. S. (1990) 'Estimating the benefits of cholesterol lowering: are risk factors for coronary heart disease multiplicative?', *Journal of Clinical Epidemiology*, 43(9), pp. 875–879. doi: 10.1016/0895-4356(90)90071-v

Silventoinen, K. *et al*. (2023) 'Height, social position and coronary heart disease incidence: the contribution of genetic and environmental factors', *Journal of Epidemiology and Community Health*, 77(6), pp. 384–390. doi: 10.1136/jech-2022-219907

Sofi, F. *et al*. (2008) 'Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies', *The European Journal of Cardiovascular Prevention & Rehabilitation*, 15(3), pp. 247–257. doi: 10.1097/HJR.0b013e3282f232ac

Soichiro, K. *et al*. (2015) 'Impact of cigarette smoking on coronary plaque composition', *Coronary Artery Disease*, 26(1), pp. 60–65. doi: 10.1097/MCA.0000000000000168

Spiess, A.-N. and Neumeyer, N. (2010) 'An evaluation of R2 as an inadequate measure for nonlinear models in pharmacological and biochemical research: a Monte Carlo approach', *BMC Pharmacology*, 10:6. doi: 10.1186/1471-2210-10-6

Stamatakis, E. *et al*. (2021) 'Is cohort representativeness *passé*? Poststratified associations of lifestyle risk factors with mortality in the UK Biobank', *Epidemiology*, 32(2), pp. 179–188. doi: 10.1097/EDE.0000000000001316

Steckel, R. H. (2009), 'Heights and human welfare: recent developments and new directions', *Explorations in Economic History*, 46(1), pp. 1–23. doi: 10.1016/j.eeh.2008.12.001

Stevens, J. *et al*. (2012) 'Body mass index at age 25 and all-cause mortality in Whites and African Americans: The Atherosclerosis Risk in Communities study', *Journal of Adolescent Health*, 50(3), pp. 221–227. doi: 10.1016/j.jadohealth.2011.06.006

Stovitz, S. D., Banack, H. R. and Kaufman, J. S. (2018) "Depletion of the susceptibles' taught through a story, a table and basic arithmetic', *BMJ Evidence-Based Medicine*, 23:199. doi: 10.1136/bmjebm-2018-110972

Strong, J. P. and McGill, Jr., H. C. (1962) 'The natural history of coronary atherosclerosis', *The American Journal of Pathology*, 40(1), pp. 37–49. PMID: 13917861

Sullivan, G. M. and Feinn, R. (2012) 'Using effect size—or why the *P* value is not enough', *Journal of Graduate Medical Education*, 4(3), pp. 279–282. doi: 10.4300/JGME-D-12-00156.1

Sund, R. (2012) 'Quality of the Finnish Hospital Discharge Register: a systematic review', *Scandinavian Journal of Public Health*, 40(6), pp. 505–515. doi: 10.1177/1403494812456637

Tennant, P. W. G. *et al*. (2021) 'Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations', *International Journal of Epidemiology*, 50(2), pp. 620–632. doi: 10.1093/ije/dyaa213

Therneau, T. (2022). *A Package for Survival Analysis in R. R Package Version 3.3-1*. Available at: https://CRAN.R-project.org/package=survival (Accessed: 8 September 2022).

Therneau, T. M. and Grambsch, P. M. (2000) *Modeling Survival Data. Extending the Cox Model*. New York, N.Y.: Springer.

THL (2011) *The Finnish Version of the International Statistical Classification of Diseases and Related Health Problems*. 3rd edn. Mikkeli: Finnish Institute for Health and Welfare (THL).

Tian, X. *et al*. (2021) 'Triglyceride-glucose index is associated with the risk of myocardial infarction: an 11-year prospective study in the Kailuan cohort', *Cardiovascular Diabetology*, 20(1):19. doi: 10.1186/s12933-020-01210-5

Tofler, G. H. and Muller, J. E. (2006) 'Triggering of acute cardiovascular disease and potential preventive strategies', *Circulation*, 114(17), pp. 1863–1872. doi: 10.1161/CIRCULATIONAHA.105.596189

Tripepi, G. *et al*. (2010) 'Selection bias and information bias in clinical research', *Nephron Clinical Practice*, 115(2), pp. c94–c99. doi: 10.1159/000312871

Tsao, C. W. *et al*. (2023) 'Heart disease and stroke statistics—2023 update: a report from the American Heart Association', *Circulation*, 147(8), pp. e93–e621. doi: 10.1161/CIR.0000000000001123

Turin, T. C. *et al*. (2016) 'Impact of hypertension on the lifetime risk of coronary heart disease', *Hypertension Research*, 39(7), pp. 548–551. doi: 10.1038/hr.2016.23

Vandenbroucke, J. P. (1991) 'Prospective or retrospective: what's in a name?', *BMJ*, 302(6771), pp. 249–250. doi: 10.1136/bmj.302.6771.249

Vandenbroucke, J. P. *et al*. (2007) 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration', *PLoS Medicine*, 4(10):e297. doi: 10.1371/journal.pmed.0040297

Van de Werf, F. (2014) 'The history of coronary reperfusion', *European Heart Journal*, 35(37), pp. 2510–2515. doi: 10.1093/eurheartj/ehu268

van Smeden, M. *et al*. (2021) 'Approaches to addressing missing values, measurement error, and confounding in epidemiologic studies', *Journal of Clinical Epidemiology*, 131, pp. 89–100. doi: 10.1016/j.jclinepi.2020.11.006

Verduijn, M. *et al*. (2011) 'The analysis of competing events like cause-specific mortality—beware of the Kaplan-Meier method', *Nephrology Dialysis Transplantation*, 26(1), pp. 56–61. doi: 10.1093/ndt/gfq661

von Elm, E. *et al*. (2007) 'The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies', *PLoS Medicine*, 4(10):e296. doi: 10.1371/journal.pmed.0040296

Voutilainen, A. *et al*. (2022) 'How competing risks affect the epidemiological relationship between vitamin D and prostate cancer incidence? A population-based study', *Andrologia*, 54(6):e14410. doi: 10.1111/and.14410

Wang, C. *et al*. (2021) 'Associations of job strain, stressful life events, and social strain with coronary heart disease in the Women's Health Initiative Observational Study', *Journal of the American Heart Association*, 10(5):e017780. doi: 10.1161/JAHA.120.017780

Wang, Z., Yang, T. and Fu, H. (2021) 'Prevalence of diabetes and hypertension and their interaction ffects on cardio-cerebrovascular diseases: a cross-sectional study', *BMC Public Health*, 21(1):1224. doi: 10.1186/s12889-021-11122-y

Wang, P. *et al*. (2023) 'Optimal dietary patterns for prevention of chronic disease', *Nature Medicine*, 29(3), pp. 719–728. doi: 10.1038/s41591-023-02235-5

Wang, T., Li, Y. and Zheng, X. (2023) 'Association of socioeconomic status with cardiovascular disease and cardiovascular risk factors: a systematic review and meta-analysis', *Journal of Public Health*, online: 21 January 2023. doi: 10.1007/s10389-023-01825-4

Wells, G. A. *et al*. (2021) *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses*. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed: 28 February 2023).

Westerterp, K. R. (2009) 'Assessment of physical activity: a critical appraisal', *European Journal of Applied Physiology*, 105(6), pp. 823–828. doi: 10.1007/s00421-009-1000-2

WHO (2023) *WHO Mortality Database: Ischaemic Heart Disease*. Available at: https://platform.who.int/mortality/themes/theme-details/topics/indicator-groups/indicator-group-details/MDB/ischaemic-heart-disease (Accessed: 6 June 2023).

Wickham, H. (2016) *ggplot2: Elegant Graphics for Data Analysis*. New York, N.Y.: Springer-Verlag.

Wilson, E. B. (1927) 'Probable inference, the law of succession, and statistical inference', *Journal of the American Statistical Association*, 22(158), pp. 209–212. doi: 10.2307/2276774

Wood, A. M. *et al*. (2018) 'Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies', *The Lancet*, 391(10129), pp. 1513–1523. doi: 10.1016/S0140-6736(18)30134-X

Xu, W. *et al*. (2023) 'The influence of psychological factors on coronary heart disease: a review of the evidence and implications for psychological interventions', *Medicine (Baltimore)*, 102(27):e34248. doi: 10.1097/MD.0000000000034248

Yiannakouris, N. *et al*. (2014) 'Additive influence of genetic predisposition and conventional risk factors in the incidence of coronary heart disease: a population-based study in Greece', *BMJ Open*, 4:e004387. doi: 10.1136/bmjopen-2013-004387

Yin, G. and Cai, J. (2004) 'Additive hazards model with multivariate failure time data', *Biometrika*, 91(4), pp. 801–818. doi: 10.1093/biomet/91.4.801

Young, J. G. *et al*. (2020) 'A causal framework for classical statistical estimands in failure-time settings with competing events', *Statistics in Medicine*, 39(8), pp. 1199–1236. doi: 10.1002/sim.8471

Zeng, Z. *et al*. (2022) 'Violations of proportional hazards assumption in Cox regression model of transcriptomic data in TCGA pan-cancer cohorts', *Computational and Structural Biotechnology Journal*, 20, pp. 496–507. doi: 10.1016/j.csbj.2022.01.004

Zhang, J. *et al*. (2021) 'The reporting quality of observational studies relevant to the STROBE-nut statement in journals of nutrition', *Asia Pacific Journal of Clinical Nutrition*, 30(1), pp. 174–183. doi: 10.6133/apjcn.202103_30(1).0020

Zhang, Z. *et al*. (2021) 'Long-term exposure to iron and copper in fine particulate air pollution and their combined impact on reactive oxygen species concentration in lung fluid: a population-based cohort study of cardiovascular disease incidence and mortality in Toronto, Canada', *International Journal of Epidemiology*, 50(2), pp. 589–601. doi: 10.1093/ije/dyaa230

Zhu, X. *et al*. (2017) 'Reporting and methodological quality of survival analysis in articles published in Chinese oncology journals', *Medicine (Baltimore)*, 96(50):e9204. doi: 10.1097/MD.0000000000009204

Ziemann, S. *et al*. (2022) 'Poor reporting quality of observational clinical studies comparing treatments of COVID-19 – a retrospective cross-sectional study', *BMC Medical Research Methodology*, 22(1):23. doi: 10.1186/s12874-021-01501-9

Zou, G. Y. (2008) 'On the estimation of additive interaction by use of the four-by-two table and beyond', *American Journal of Epidemiology*, 168(2), pp. 212–224. doi: 10.1093/aje/kwn104

APPENDICES

APPENDIX 1. Prospective cohort studies on the association of coronary heart disease with its behavioral risk factors in men.

Study	FU	DM	OW	TC	TS	PI
Adventist Health Study	6–12	1.57	1.20	N/A	N/A	N/A
APCSC (40 cohorts)	3–25	N/A	N/A	N/A	1.52	N/A
APCSC–ANZ (9 cohorts)	7–10	1.58	1.44	1.20	N/A	N/A
APCSC–Asia (27 cohorts)	7	1.47	2.41	1.28	N/A	N/A
ARIC	4–19	1.81	1.56	1.28	N/A	1.20
Baltimore Longitudinal	N/A	N/A	N/A	1.29	N/A	N/A
BRHS	17–22	N/A	N/A	N/A	2.15	2.04
British male doctors	50	N/A	N/A	N/A	1.67	N/A
Caerphilly	11	N/A	N/A	N/A	N/A	1.82
CCHS + CMS + Glostrup	12	N/A	N/A	N/A	1.78	N/A
CCRM	12	N/A	N/A	N/A	2.10	N/A
CHA	9–22	3.79	N/A	1.20	N/A	N/A
Collins *et al*. – Indians	11	3.15	N/A	N/A	N/A	N/A

Study	FU	DM	OW	TC	TS	PI
Collins et al. – Melanesians	11	1.60	N/A	N/A	N/A	N/A
Consultation	12	N/A	3.01	N/A	N/A	N/A
CPS1	6	N/A	N/A	N/A	1.73	N/A
CPS2NC + HPFS + NIH-AARP	10	N/A	N/A	N/A	2.70	N/A
Danish Diet	8	N/A	1.88	N/A	N/A	N/A
DECODE (7 cohorts)	5–21	2.09	N/A	N/A	N/A	N/A
Dubbo	5	1.53	N/A	N/A	N/A	N/A
EPESE	6	1.55	N/A	N/A	N/A	N/A
EPIC-Norfolk	9	N/A	1.74	N/A	N/A	N/A
EPOCH-JAPAN	10	N/A	N/A	1.25	N/A	N/A
Evans County	5–20	1.00	N/A	1.47	N/A	N/A
FINE	10	N/A	N/A	1.17	N/A	N/A
Finnish and Swedish	13	N/A	N/A	1.31	N/A	N/A
Finnmark	14	N/A	N/A	1.36	N/A	N/A
Framingham	16–44	1.50	1.65	1.31	N/A	N/A
Framingham + FO	12–20	2.10	N/A	1.12	N/A	N/A
GMPPT	20	N/A	N/A	N/A	N/A	1.19

Study	FU	DM	OW	TC	TS	PI
Göteborg 70-year-old cohorts	15	N/A	1.45	N/A	N/A	N/A
Haapanen-Niemi *et al*.	16	N/A	N/A	N/A	N/A	1.69
HAHS	15	N/A	N/A	N/A	N/A	1.25
Hawaii-LA-Hiroshima	10–18	1.54	N/A	N/A	N/A	N/A
Health in Men Study	10	N/A	N/A	N/A	1.73	N/A
Health Watch	3–21	N/A	N/A	N/A	3.12	N/A
HIP	3	N/A	N/A	N/A	2.24	N/A
Hirayama	17	N/A	N/A	N/A	1.82	N/A
Hisayama	14	1.26	N/A	N/A	N/A	N/A
Hong Kong Chinese	4	N/A	N/A	N/A	1.42	N/A
Honolulu Heart Program	15–23	N/A	N/A	1.33	N/A	1.05
HPFS	12	N/A	N/A	N/A	N/A	1.20
HUNT	10–17	1.80	0.84	N/A	N/A	1.20
HUNT 2	14	N/A	N/A	1.08	N/A	N/A
IIHD	21–28	N/A	N/A	1.29	1.76	1.28
JACC	19	N/A	2.14	N/A	N/A	N/A
JACC + JPHC + TPCS	10	N/A	N/A	N/A	2.09	N/A

Study	FU	DM	OW	TC	TS	PI
Japan CVD	18	N/A	1.90	N/A	N/A	N/A
Japanese male physicians	13	N/A	N/A	N/A	2.62	N/A
JPHC	10	N/A	2.30	N/A	N/A	N/A
KIHD	5	N/A	N/A	N/A	N/A	2.63
Korean male servants	9	N/A	N/A	N/A	2.63	N/A
Kuopio and North Karelia	17	2.11	N/A	N/A	N/A	N/A
Leiden 85-plus Study	10	N/A	N/A	0.75	N/A	N/A
MONICA Finland	19–35	N/A	N/A	1.34	N/A	1.19
MONICA/KORA Augsburg	13–19	N/A	N/A	N/A	2.81	N/A
MRFIT	10	N/A	N/A	N/A	2.14	N/A
NHANES I	9	2.37	N/A	N/A	N/A	N/A
NHANES III	13	1.29	1.06	1.00	N/A	N/A
Oslo + Counties in Norway	25–31	N/A	N/A	N/A	3.63	N/A
Peoples Gas (Chicago)	30	N/A	N/A	1.05	N/A	N/A
Post Office	40	N/A	1.32	N/A	N/A	N/A
Rancho Bernardo	10–14	1.89	N/A	1.19	N/A	N/A
Renfrew and Paisley	15–25	1.17	N/A	N/A	1.67	N/A

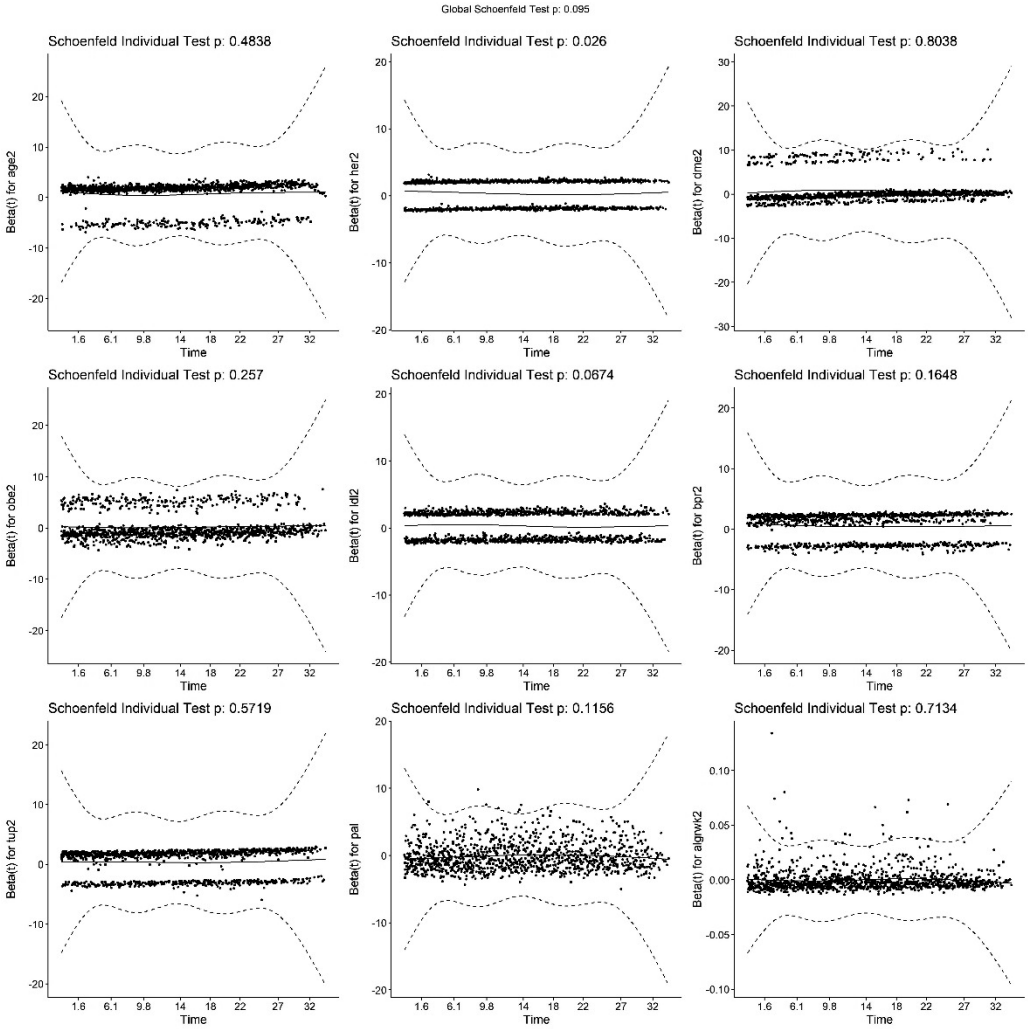
Study	FU	DM	OW	TC	TS	PI
Reykjavik	17–28	1.34	N/A	1.30	2.08	N/A
Rotterdam	7	N/A	N/A	1.20	N/A	N/A
SCS: Europe, USA, Japan	25	N/A	N/A	N/A	1.41	N/A
SCS: Finland	30	N/A	N/A	1.25	N/A	N/A
SCS: Italy	25	N/A	N/A	1.26	N/A	N/A
SHH	8	N/A	N/A	N/A	1.65	N/A
SHHEC	16–20	2.49	1.57	1.25	N/A	N/A
Strong Heart Study	12	1.66	N/A	N/A	N/A	N/A
Swedish 1963 Smoking	33	N/A	N/A	N/A	1.77	N/A
Takayama	7	2.96	N/A	N/A	N/A	N/A
TCHS	12–20	3.00	N/A	1.38	N/A	N/A
Tehran Lipid and Glucose	9–10	N/A	N/A	1.22	3.84	N/A
Tromsø	11–16	N/A	1.77	N/A	1.82	N/A
VHM&PP	14	N/A	N/A	1.21	N/A	N/A
Western Electric (Chicago)	24	N/A	N/A	1.24	N/A	N/A
Whitehall	25	N/A	N/A	N/A	N/A	1.14
Zutphen Elderly Study	5	N/A	N/A	1.29	N/A	N/A

Notes. FU, DM, OW, TC, TS, PI denote follow-up time in years, diabetes, obesity, total cholesterol, tobacco smoking, and physical inactivity, respectively. Risks are risk ratios comparing diabetes to no diabetes, obesity to normal weight, a 1-mmol/L increase in TC to no increase, smoking to never smoking, and low to high physical activity. Hazard ratios were interpreted as RRs. N/A signifies not assessed.

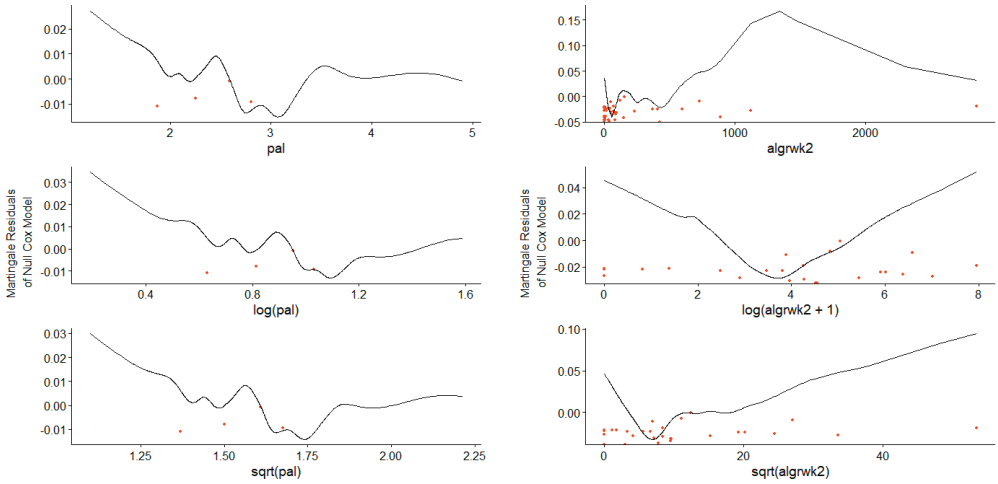
Abbreviations of studies. ANZ: Australia and New Zealand; APCSC: Asia Pacific Cohort Studies Collaboration; ARIC: Atherosclerosis Risk in Communities; BRHS: British Regional Heart Study; CCHS: Copenhagen City Heart Study; CCRM: Chinese Cohort of Retired Men; CHA: Chicago Heart Association Detection Project in Industry; CMS: Copenhagen Male Study: Consultation: Consultation Bureau Project on Cardiovascular Diseases; CPS: Cancer Prevention Study; DECODE: Diabetes Epidemiology, Collaborative analysis of Diagnostic criteria in Europe; EPESE: Established Populations for Epidemiologic Studies of the Elderly; EPIC: European Prospective Investigation into Cancer; EPOCH-JAPAN: Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; FINE: Finland, Italy and the Netherlands Elderly Study; FO: Framingham Offspring; GMPPT: Göteborg Multifactorial Primary Prevention Trial; HAHS: Harvard Alumni Health Study; HIP: Health Insurance Plan of Greater New York; HPFS: Health Professionals Follow-up Study; HUNT: Nord-Trøndelag Health Study; IIHD: Israeli Ischemic Heart Disease Study; JACC: Japan Collaborative Cohort; Japan CVD: Japanese Cardiovascular Risk Surveys; JPHC: Japan Public Health Center; KIHD: Kuopio Ischaemic Heart Disease Risk Factor Study; KORA: Cooperative Health Research in the Region of Augsburg; LA: Los Angeles; MONICA: World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases; MRFIT: Multiple Risk Factor Intervention Trial; NC: Nutrition Cohort; NHANES: National Health and Nutrition Examination Survey; NIH-AARP: National Institutes of Health and American Association of Retired Persons, Diet and Health Cohort; SCS: Seven Countries Study; SHH: Scottish Heart Health; SHHEC: Scottish Heart Health Extended Cohort; TCHS: Tecumseh Community Health Study; TPCS: Three-Prefecture Cohort Study; VHM&PP: Vorarlberg Health Monitoring and Prevention Programme.

Numbers are from Lee *et al*. (2000); Anum and Adera (2004); Sofi *et al*. (2008); Peters, Huxley and Woodward (2014); Mongraw-Chaffin et al. (2015); Peters *et al*. (2016); and Hackshaw *et al*. (2018).

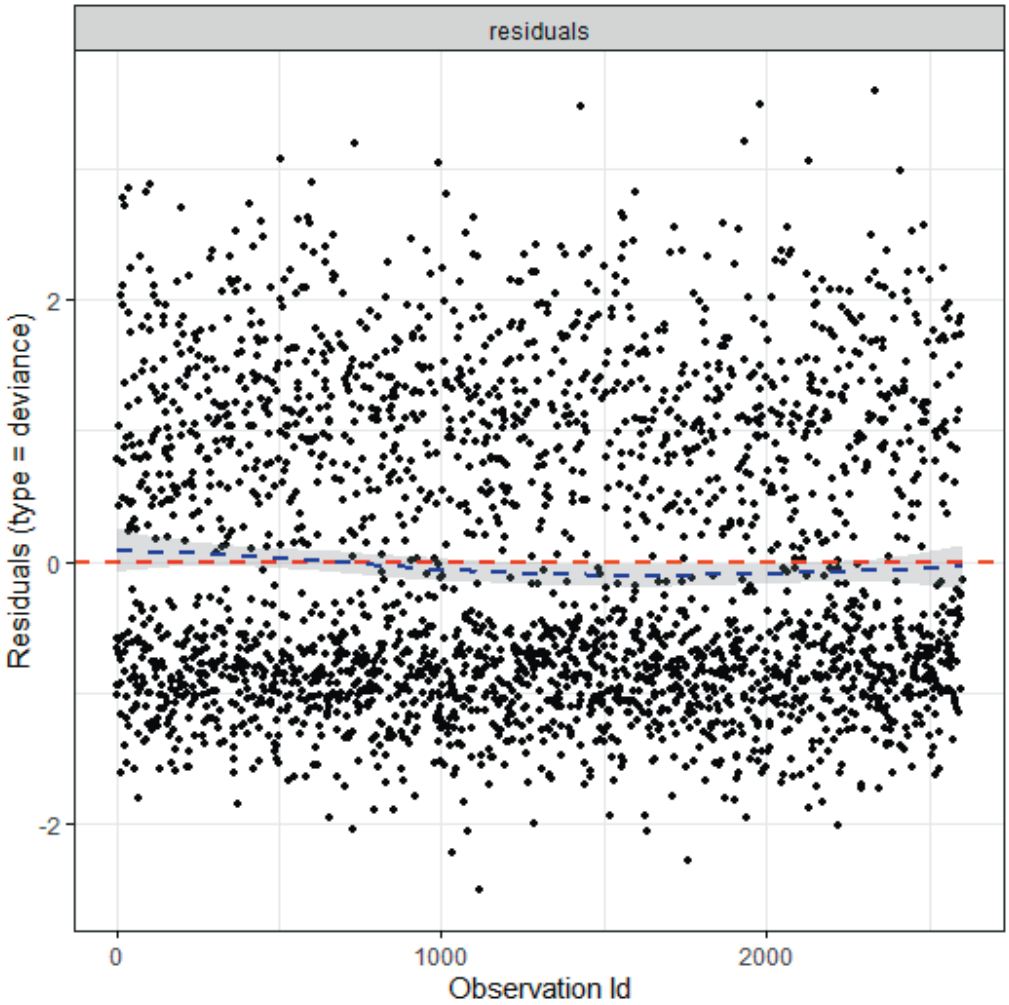
APPENDIX 2. Covariate-specific relationships between Schoenfeld residuals and follow-up time with *p*-values to test the proportional hazards assumption.



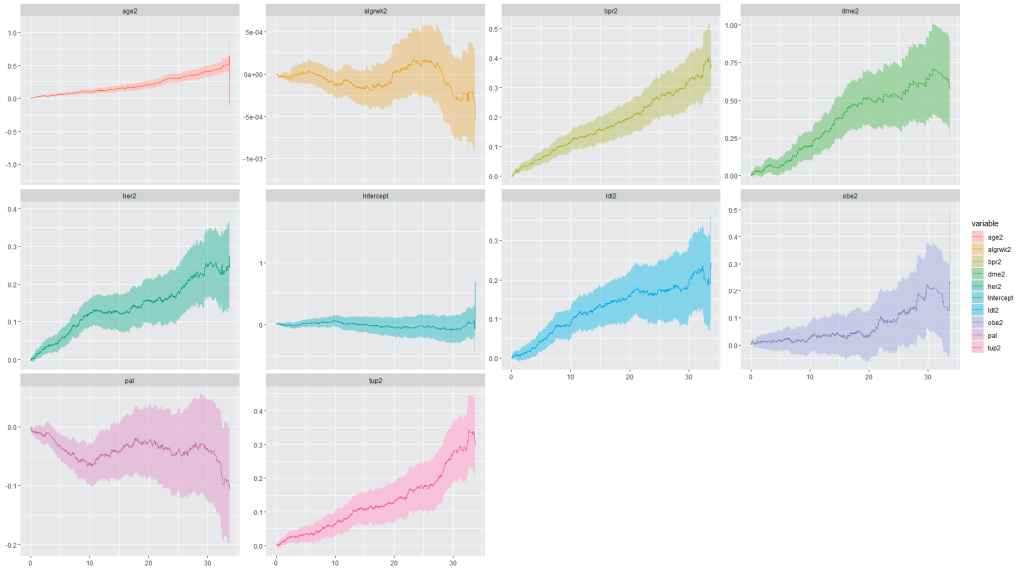
APPENDIX 3. Martingale residuals against two covariates: physical activity (the leftmost column) and alcohol consumption (the rightmost column). The uppermost row presents crude covariate values, the centermost row $\log_{10}(\text{values})$, and the undermost row $\sqrt{\text{values}}$. Note different scales of the y-axes.



APPENDIX 4. Subject-specific deviance residuals from a Cox regression to model incident coronary heart disease in the KIHD study cohort of 2682 men.



APPENDIX 5. Covariate-specific relationships between coefficients from an Aalen's additive regression model and follow-up time.



APPENDIX 6. Epidemiology journals with the existing Web of Science status in 2021.

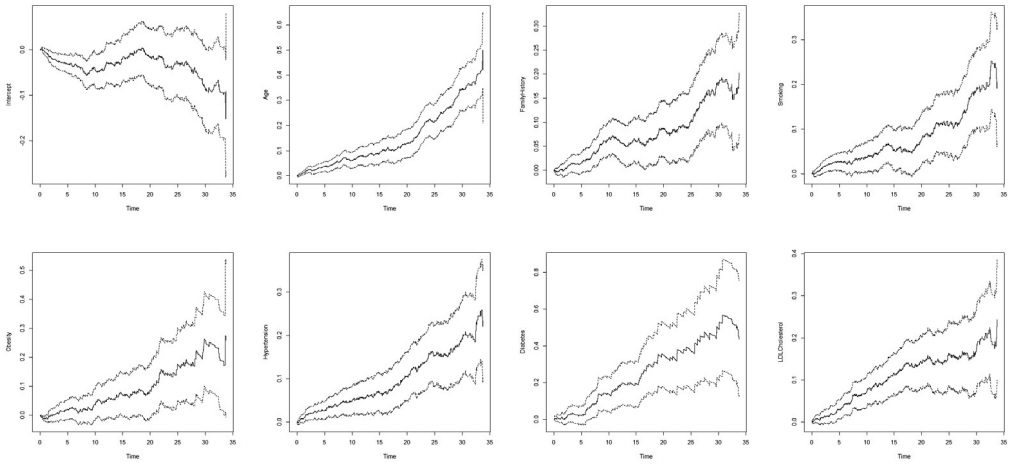
Journal	Region	Rank	Issues	Articles	CHDs
European Journal of Epidemiology	Netherlands	11.	12	121	4
International Journal of Epidemiology	England	13.	6	249	4[1]
Journal of Clinical Epidemiology	USA	25.	12	316	0
American Journal of Epidemiology	USA	38.	12	335	4
Annals of Epidemiology	USA	39.	12	154	1
Journal of Epidemiology and Community Health	England	45.	12	200	4
Journal of Exposure Science and Environmental Epidemiology	USA	52.	6	97	0
Epidemiology	USA	54.	6	126	1
Clinical Epidemiology	New Zealand	56.	1	106	0[1]
Epidemiology and Health	South Korea	61.	1	103	0
Paediatric and Perinatal Epidemiology	England	76.	6	89	0
Journal of Epidemiology	Japan	83.	12	93	0

Journal	Region	Rank	Issues	Articles	CHD
Neuroepidemiology	Switzerland	86.	6	56	0
Cancer Epidemiology Biomarkers & Prevention	USA	100.	12	285	0[1]
Journal of Epidemiology and Global Health	France	119.	4	66	0
Infection Control and Hospital Epidemiology	USA	125.	12	397	0
Spatial and Spatio-Temporal Epidemiology	England	129.	4	41	0
Community Dentistry and Oral Epidemiology	Denmark	147.	6	76	0
Epidemiology and Infection	England	150.	1	258	0
Cancer Epidemiology	England	179.	6	139	0
Emerging Themes in Epidemiology	England	179.	1	19	0
Pharmacoepidemiology and Drug Safety	England	188.	12	183	0
Parasite Epidemiology and Control	USA	240.	4	29	0
Epidemiologia e Servicos de Saude	Brazil	245.	4	102	0
Clinical Epidemiology and Global Health	India	254.	4	293	0
Injury Epidemiology	USA	300.	1	71	0

Journal	Region	Rank	Issues	Articles	CHD
Global Health Epidemiology and Genomics	England	303.	1	3	0
Nepal Journal of Epidemiology	Nepal	303.	4	22	0
Epidemiologia & Prevenzione	Italy	331.	6	95	0
Revue d'Epidemiologie et de Sante Publique	France	363.	6	59	0
30 journals	**N/A**	**N/A**	**192**	**4183**	**18**

Notes. Rank refers to the rank of the journal based on the Journal Citation Indicator among 392 journals categorized into the public, environmental & occupational health topic in Journal Citation Reports. CHD denotes the number of articles dealing with the epidemiological relationship of CHD with its known or potential risk factors. [1]Plus one CHD article with no actual follow-up. N/A signifies not applicable.

APPENDIX 7. Covariate-specific cumulative additive contributions on the risk of CHD by time. To simplify the interpretation the covariates were dichotomized (absent versus present). The intercept term can be interpreted as the hazard of CHD when all risk factors are absent.



ORIGINAL PUBLICATIONS (I – III)

I

Effects of data preprocessing on results of the epidemiological analysis of coronary heart disease and behaviour-related risk factors

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ORIGINAL ARTICLE

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Effects of data preprocessing on results of the epidemiological analysis of coronary heart disease and behaviour-related risk factors

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ABSTRACT

Background: We carried out this study to demonstrate the effects of outcome sensitivity, participant exclusions, and covariate manipulations on results of the epidemiological analysis of coronary heart disease (CHD) and its behaviour-related risk factors.

Material and methods: Our study population consisted of 1592 54-year-old men, who participated in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study. We used the Cox proportional-hazards model to predict the hazard of CHD and applied different sets of outcomes concerning outcome sensitivity and data preprocessing procedures regarding participant exclusions and covariate manipulations.

Results: The mean follow-up time was 23 years, and 730 men received the CHD diagnosis. Cox regressions based on data with no participant exclusions most often discovered statistically significant associations. Loose inclusion criteria for study participants with any CVD during the follow-up and strict exclusion criteria for participants with no CVD were best in discovering the associations between risk factors and CHD. Outcome sensitivity affected the associations, whereas the covariate type, continuous or categorical, did not.

Conclusions: This study suggests that excluding study participants who are not disease-free at baseline is probably unnecessary for epidemiological analyses. Epidemiological research reports should present results based on no data exclusions together with results based on reasoned exclusions.

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Categorical covariate; continuous covariate; coronary heart disease; exclusion criterion; outcome sensitivity

Introduction

Typically, epidemiologic research produces at least partly contradictory results. Some reasons explaining this incoherence i.e. unexpectedly large variations in results across closely related studies, are only indirectly related to research, such as clinical factors and healthcare systems. Many reasons, however, originate from study designs, methodological choices, concept definitions, and observed data [1,2]. Reasons related to datasets include at least differences in sample size and representativeness of covariates. In prospective cohort studies, also the length of follow-up with respect to age at baseline amongst study participants, as in the risk of coronary heart disease (CHD) associated with high levels of C-reactive protein [3], and possible competing events affect the interpretation of study results [4].

Research regarding the epidemiologic relationship between CHD and risk factors has received a consensus during the past decades. There are six undisputable behaviour-related risk factors for CHD: tobacco smoke [5], overweight [6], physical inactivity [7], hypertension [8], diabetes [9], and hypercholesterolaemia [10].

Other behaviour-related factors, such as alcohol consumption and stress also may increase the risk for CHD, but their associations with CHD vary across studies. The association between alcohol and CHD is nonlinear [11], and stress is a symptom of different conditions, such as psychosocial aspects of work [12], which may or may not be associated with the risk of CHD. Yet other risk factors of CHD that at least indirectly relate to behaviour through diet are homocysteine, fibrinogen, and inflammation [13]. Moreover, there may be a weak association between iron status and CHD [14].

In addition to the behaviour-related factors, nonmodifiable factors including age, male gender,

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genetics, and a family history of CHD increase the risk for CHD [13,15,16]. Differences between men and women regarding the risk of CHD relate mainly to oestrogens and, thus, premenopausal women [13]. The role played by personality in the development of CHD is controversial [17].

The purpose of this study was to demonstrate the effects of data exclusions, outcome variable selection, and covariate manipulations on the interpretation of the epidemiologic relationship between CHD and its traditional risk factors. These are predominantly subjective researcher-related actions unlike more technical questions, such as whether to consider competing events in statistical analyses or whether to use non-conventional statistical methods, such as neural networks [18], to deal with data-related matters. As a result of this study, we expected a combination of outcome variable selection, participant exclusion, and covariate manipulation procedures that best discovers presumable associations between CHD and risk factors.

Material and methods

Material

Men, $n = 1592$, from the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study served as a study material. The KIHD Study is an ongoing prospective cohort study originally established to discover previously unestablished reasons for the extremely high AMI prevalence among eastern Finnish men [19]. To control the effect of age on CHD we selected men representing the same age cohort, 54-year-old at baseline between March 1984 and December 1989. Briefly, 778 of them had one or more CVDs at baseline based on self-reports to the question: Has your doctor told you that you have 'the name of CVD', and 1181 of them were diagnosed, during an inpatient special health care admission, as having CVDs, ICD-10 codes I00-I99 [20], by the end of 2017. Moreover, 381 men used medication for hypertension, 77 had insulin or non-insulin treated diabetes, and nine used medication for hypercholesterolaemia at baseline. The mean (SD) follow-up time was 23.4 (9.3) years. Table 1 presents study participants' baseline characteristics with respect to variables used as exclusion criteria, covariates, and conditions and events diagnosed during the follow-up. All KIHD participants had given written informed consent, and the ethical committee of the Kuopio University had approved the KIHD Study (December 1, 1983). In 1980s, the committee did not necessarily provide study numbers but identified studies by date.

Outcome variables

The KIHD Study includes annually updated data from the Care Register for Health Care of the Finnish Institute for Health and Welfare regarding diagnoses given during special health care admissions (License THL/93/5.05.00/2013) and from the Causes of Death Register of the Statistics Finland (License TK-53-1770-16). To study the effects of outcome sensitivity on model results we constructed four different outcome variables based on these register linkages. The first outcome was 'CVD' referring to ICD 10 codes I00 – I99. The second outcome was 'CHD' referring to codes I20 – I25. The third outcome was 'MI or UA' and it referred to codes I20.0 and I21 – I22. The fourth outcome 'a fatal AMI' referred to as I21.

Covariates

First, we selected the most common risk factors of CHD based on literature and, second, we searched variables that represent these risk factors from the KIHD Study database. The chosen risk factors were smoking, obesity, physical inactivity, hypertension, diabetes, and hypercholesterolaemia. Hajar [21], for example, summaries the association between these six risk factors and CHD. In addition to the indisputable risk factors of CHD, we included alcohol consumption as a covariate in the analyses. Alcohol, in general, increases mortality and morbidity [22], but the association between alcohol consumption and CHD is visualized by a J-shaped curve; light-to-moderate drinking acts as a protective factor, whereas heavy drinking increases the risk of CHD [11]. We expected that our analyses at best would demonstrate this nonlinear relationship between alcohol consumption and CHD.

In the KIHD Study, participants self-reported their smoking behaviour, alcohol consumption, and physical activity at baseline. As a continuous smoking variable, we chose a cigarette-year that indicates the number of cigarettes per day multiplied by the number of years smoked. Moreover, we classified the participants as never-smokers, former smokers, and current smokers. Former smokers informed that they have not smoked within a month.

The KIHD continuous alcohol consumption variable indicates the amount of alcohol as grams per week. For this study, we categorized the participants into those with no health risk due to the alcohol

Table 1. Baseline characteristics (the total column) and numbers of study participants with the following conditions diagnosed during the follow-up: any cardiovascular disease (CVD), coronary heart disease (CHD), a myocardial infarction (MI) or unstable angina (UA), and a fatal acute myocardial infarction (AMI).

		Conditions and events diagnosed during the follow-up			
Characteristic	Total	CVD	CHD	MI or UA	AMI
n	1592	1181	730	502	136
CVD, excluding hypertension, *n* (%)	672 (42)	542 (46)	375 (51)	260 (52)	83 (61)
Use of hypertension medication, *n* (%)	381 (24)	318 (27)	240 (33)	168 (34)	58 (43)
Diabetes, *n* (%)	77 (4.8)	61 (5.2)	47 (6.4)	41 (8.2)	10 (7.4)
Use of cholesterol medication, *n* (%)	9 (0.6)	9 (0.8)	8 (1.1)	5 (1.0)	2 (1.5)
Cigarette-year[a], mean (SD)	336 (392)	339 (402)	356 (403)	387 (428)	431 (478)
Never-smokers, *n* (%)	517 (33)	377 (32)	217 (30)	133 (27)	34 (25)
Former smokers, *n* (%)	572 (36)	443 (38)	274 (38)	196 (39)	42 (31)
Current smokers, *n* (%)	503 (32)	361 (31)	239 (33)	173 (35)	60 (44)
Alcohol, grams/week, mean (SD)	71 (141)	66 (105)	62 (92)	64 (96)	75 (100)
No risk, $\leq$ 1 portion/week, *n* (%)	604 (38)	449 (38)	285 (39)	186 (37)	53 (39)
Moderate risk, $\leq$ 3 portions/day, *n* (%)	906 (57)	676 (57)	415 (57)	295 (59)	75 (55)
High risk, $>$ 3 portions/day, *n* (%)	82 (5.2)	56 (4.7)	30 (4.1)	21 (4.2)	8 (5.9)
Body Mass Index (BMI), mean (SD)	27 (3.7)	27 (3.7)	27 (3.7)	27 (3.7)	28 (4.5)
Normal weight, BMI $<$ 25.0 kg/m^2, *n* (%)	480 (30)	324 (27)	183 (25)	118 (24)	35 (26)
Overweight, BMI 25.0 $-$ 29.9 kg/m^2, *n* (%)	830 (52)	622 (53)	400 (55)	278 (55)	60 (44)
Obese, BMI $\geq$ 30.0, kg/m^2, *n* (%)	282 (18)	235 (20)	147 (20)	106 (21)	41 (30)
Physical activity[b], kcal/day, mean (SD)	2380 (899)	2377 (886)	2349 (888)	2326 (877)	2381 (987)
Moderate, PAL[c] $<$ 2.00, *n* (%)	293 (18)	222 (19)	144 (20)	101 (20)	29 (21)
Vigorous, PAL 2.00 $-$ 2.40, *n* (%)	507 (32)	377 (32)	236 (33)	165 (33)	41 (30)
Extreme, PAL $>$ 2.40, *n* (%)	774 (49)	571 (49)	341 (47)	229 (46)	65 (48)
No data available, *n*	18	11	9	7	1
Systolic blood pressure, mean (SD)	136 (18)	137 (18)	136 (18)	137 (19)	139 (18)
Desirable, $<$ 120 mmHg, *n* (%)	269 (17)	186 (16)	122 (17)	89 (18)	17 (13)
Borderline, 120 $-$ 139 mmHg, *n* (%)	763 (48)	552 (47)	331 (45)	213 (42)	61 (45)
High, $\geq$ 140 mmHg, *n* (%)	560 (35)	443 (38)	277 (38)	200 (40)	58 (43)
Fasting blood glucose, mean (SD)	4.8 (1.2)	4.9 (1.3)	4.9 (1.4)	5.0 (1.5)	5.1 (1.6)
Desirable, $<$ 5.6 mmol/L, *n* (%)	1435 (90)	1056 (89)	636 (87)	432 (86)	112 (82)
Borderline, 5.6 $-$ 6.9 mmol/L, *n* (%)	96 (6.0)	71 (6.0)	53 (7.3)	40 (8.0)	12 (8.8)
High, $>$ 6.9 mmol/L, *n* (%)	61 (3.8)	54 (4.6)	41 (5.6)	30 (6.0)	12 (8.8)
Serum total cholesterol, mean (SD)	6.0 (1.1)	6.0 (1.1)	6.1 (1.2)	6.2 (1.2)	6.3 (1.2)
Desirable, $<$ 5.2 mmol/L, *n* (%)	383 (24)	270 (23)	151 (21)	93 (19)	25 (19)
Borderline, 5.2 $-$ 6.2 mmol/L, *n* (%)	607 (38)	443 (38)	274 (38)	190 (38)	46 (34)
High, $>$ 6.2 mmol/L, *n* (%)	602 (38)	468 (40)	305 (42)	219 (44)	65 (48)

[a]Cigarettes per day times years of smoking.
[b]Total energy expenditure (TEE) minus basal energy expenditure (BEE).
[c]Physical activity level, TEE divided by BEE.

consumption, one portion (12 grams of pure alcohol according to Finnish standards) per week at most, those with a moderate health risk, three portions per day at most, and those with a high health risk. This categorization is mainly data-specific, although it sparsely follows Finnish current care guidelines published only in Finnish. Broadly, alcohol increases mortality and morbidity and, in men, more than three to four portions, 40 grams of pure alcohol, per day increase them significantly [22].

To determine study participants' physical activity we, first, calculated the basal energy expenditure (BEE) based a body weight, body height, and age applying the Mifflin-St Jeor Equation [23]. Second, we subtracted BEE from the total energy expenditure (TEE) and used this TEE $-$ BEE variable in the analyses as a continuous variable. To create activity ranks, we computed the physical activity level (PAL) by dividing TEE by BEE and classified the participants as follows: moderately active, PAL $<$ 2.00, vigorously active, PAL 2.00 $-$ 2.40, and extremely active, PAL $>$ 2.40 [24]. In the KIHD cohort, practically, all participants were at least moderately active at baseline. Eight participants of this study had not reported their physical activity.

Body weights and heights were not self-reported but measured by a research nurse during the baseline examination. Based on these measures we calculated the Body Mass Index (BMI) by dividing the weight in kilograms by the square of height in metres. In the analyses, we obeyed the standard guidelines for BMI: $<$25.0 kg/m^2 refers to normal weight, 25.0$-$29.9 kg/m^2 to overweight, and $\geq$30.0 kg/m^2 to obesity [25] and classified the participants according to them.

On the first baseline examination day, one research nurse measured the participant's blood pressure six times with a random-zero mercury sphygmomanometer. After a supine rest of five minutes, the nurse took three measurements in supine, two in sitting,

and one in a standing position with 5-min intervals. In the present analyses, we used the mean of six systolic blood pressures (SBP) values as a continuous variable. To distribute study participants into groups according to SBP, we followed the thresholds suggested by Mayo Clinic: SBP $<$ 120 mmHg is a desirable level and SBP $>$ 139 mmHg indicates hypertension [26].

Study participants gave blood samples between 8 and 10 a.m. after abstaining from alcohol for three days and from smoking and eating for 12 h. After a supine rest of 30 min, a research nurse draw blood with Terumo Venoject VT-100PZ vacuum tubes (Terumo Corp., Tokyo, Japan) using no tourniquet. The laboratory of our institute used an enzymatic method to measure STC concentrations (CHOD-PAP, Boehringer Mannheim, Mannheim, West Germany) and a glucose dehydrogenase method (Merck, Darmstadt, West Germany) after protein precipitation with TCA using a clinical chemistry analyzer (Kone Specific, KONE Instruments Oy, Espoo, Finland) to measure FBG concentrations. Salonen *et al.* [27] describe the lipid analysis in detail. For the present analyses, we classified the participants according to the serum total cholesterol (SCT) as follows: $<$5.2 mmol/L is a desirable level and $>$6.2 mmol/L indicates hypercholesterolaemia [28]. Correspondingly, we distributed the participants into groups according to the fasting blood glucose (FBG) as follows: $<$ 5.6 mmol/L is a desirable level and $>$ 6.9 indicates diabetes [29].

Statistical analyses

The Cox proportional-hazards model [30] served as an analysis method and IBM® SPSS® Statistics Version 25 served a statistical platform. In all analyses, we applied three different data exclusion criteria (Figure 1). The first criterion, termed as Criterion A later in the text, excluded study participants according to conditions. Precisely, we excluded participants, who reported that they have any CVD or diabetes at baseline or that they use hypercholesterolaemia medication. This exclusion criteria reduced the number of study participants from 1592 to 794. The second criterion, Criterion B, excluded study participants, who reported that they have a CVD, except for hypertension, at baseline. This criterion resulted in 920 participants. The third criterion, Criterion C, meant no exclusions. Correspondingly, in all analyses, we used CVD, CHD, AMI or UA, and a fatal AMI as dependent variables. These four "nested" outcomes demonstrate the outcome variable selection process with respect to outcome sensitivity. Moreover, to study the effect of covariate manipulations on the Cox model results, we executed Cox regressions adjusted for seven covariates, the six traditional risk factors and alcohol consumption that were either in their original continuous form or distributed in predetermined categories.

Altogether, we performed three analysis sets (Figure 1). The first set included covariates as

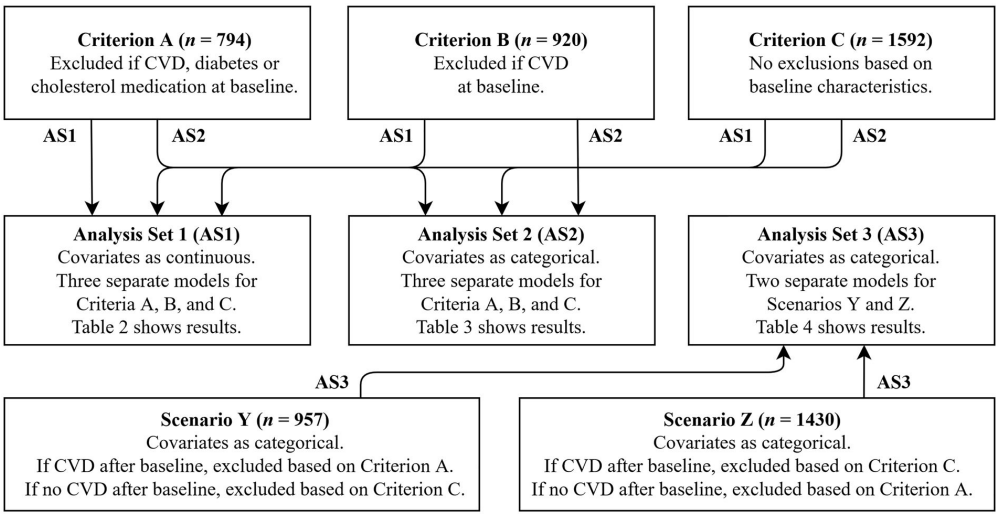

Figure 1. Procedure for statistical analyses. First, analysis sets (AS) 1 and 2 studied effects of participants exclusions on analysis results prospectively; the exclusions were based on baseline characteristics (Criteria A – C). Second, AS 1 and 2 studied effects of covariate manipulations (continuous vs. categorical) on analysis results. Third, AS 3 studied effects of participant exclusions on analysis results retrospectively; the exclusions were based on outcomes (Scenarios Y and Z). Fourth, all AS studied effects of outcome sensitivity on analysis results (see Tables 2–4).

Table 2. Hazard ratios and corresponding *p*-values of any cardiovascular disease (CVD), coronary heart disease (CHD), a myocardial infarction (MI) or unstable angina (UA), and a fatal acute myocardial infarction (AMI) with respect to one unit (1 U) or one standard deviation (1 D) increase in seven factors used as continues covariates in the Cox proportional-hazards model.

	CVD			CHD			MI or UA			AMI		
Covariate	1U	1D	*p*	1U	1D	*p*	1U	1D	*p*	1U	1D	*p*
A. Smoking[a]	**1.00**	**1.20**	**<.01**	**1.00**	**1.26**	**<.01**	**1.00**	**1.36**	**<.01**	1.00	1.27	.16
B. Smoking	**1.00**	**1.17**	**<.01**	**1.00**	**1.23**	**<.01**	**1.00**	**1.32**	**<.01**	1.00	1.18	.28
C. Smoking	**1.00**	**1.18**	**<.01**	**1.00**	**1.22**	**<.01**	**1.00**	**1.33**	**<.01**	**1.00**	**1.42**	**<.01**
A. AC[b]	1.00	1.05	.32	1.00	1.01	.89	1.00	1.01	.87	1.00	1.15	.39
B. AC	1.00	1.05	.30	1.00	1.00	.96	1.00	0.97	.68	1.00	1.11	.48
C. AC	1.00	1.00	.95	1.00	0.94	.24	1.00	0.95	.39	1.00	1.06	.58
A. BMI[c]	**1.03**	**1.12**	**.02**	1.04	1.13	.05	1.03	1.12	.14	1.08	1.29	.06
B. BMI	**1.04**	**1.14**	**<.01**	**1.05**	**1.19**	**<.01**	**1.05**	**1.19**	**.01**	**1.08**	**1.31**	**.04**
C. BMI	**1.05**	**1.20**	**<.01**	**1.05**	**1.20**	**<.01**	**1.05**	**1.21**	**<.01**	**1.08**	**1.32**	**<.01**
A. PAL[d]	1.00	0.99	.78	1.00	0.95	.43	1.00	0.96	.64	1.00	1.14	.42
B. PAL	1.00	0.98	.66	1.00	0.93	.25	1.00	0.94	.43	1.00	1.15	.36
C. PAL	**1.00**	**0.93**	**.04**	**1.00**	**0.90**	**.02**	**1.00**	**0.89**	**.02**	1.00	0.90	.28
A. SBP[e]	**1.01**	**1.18**	**<.01**	1.00	1.05	.44	1.00	1.03	.73	1.01	1.18	.32
B. SBP	**1.01**	**1.17**	**<.01**	1.01	1.09	.15	1.01	1.09	.21	1.01	1.24	.14
C. SBP	**1.01**	**1.18**	**<.01**	**1.01**	**1.10**	**.02**	**1.01**	**1.13**	**.01**	1.01	1.16	.09
A. FBG[f]	**1.19**	**1.13**	**.03**	**1.39**	**1.26**	**<.01**	**1.51**	**1.32**	**<.01**	**1.55**	**1.35**	**.01**
B. FBG	**1.18**	**1.19**	**<.01**	**1.14**	**1.15**	**<.01**	**1.19**	**1.20**	**<.01**	**1.25**	**1.27**	**.01**
C. FBG	**1.13**	**1.16**	**<.01**	**1.10**	**1.12**	**<.01**	**1.09**	**1.11**	**.01**	**1.12**	**1.15**	**.02**
A. STC[g]	1.04	1.04	.34	**1.17**	**1.18**	**.01**	**1.20**	**1.21**	**.01**	1.18	1.19	.30
B. STC	1.03	1.04	.42	**1.15**	**1.17**	**.01**	**1.22**	**1.24**	**<.01**	1.22	1.24	.11
C. STC	**1.08**	**1.09**	**.01**	**1.18**	**1.20**	**<.01**	**1.20**	**1.23**	**<.01**	**1.25**	**1.28**	**<.01**

Note. A refers to a dataset excluding CVD, diabetes, and high total cholesterol at baseline ($n = 794$). B refers to a dataset excluding CVD, except for hypertension, at baseline ($n = 920$). C refers to a dataset with no exclusions ($n = 1592$). Bold font indicates a statistically significant HR.
[a]Cigarettes per day times years of smoking.
[b]Alcohol consumption grams/week.
[c]Body Mass Index, weight in kg divided by the square of height in m.
[d]Physical activity level, total energy expenditure minus basal, in kcal per day.
[e]Systolic blood pressure in mmHg.
[f]Fasting blood glucose in mmol/L.
[g]Serum total cholesterol in mmol/L.

continuous variables and tested their associations with CVD, CHD, AMI or UA, and a fatal AMI separately for each data exclusions criterion, A, B, and C. The second set included covariates as categorical variables. The reference categories were as follows: never-smoker, no health risk due to the alcohol consumption, normal weight, moderately physically active, desirable SBP, desirable FBG, and desirable STC. As the first set, the second set tested associations of covariates with CVD, CHD, AMI or UA, and a fatal AMI separately for each data exclusions criterion, A, B, and C. The third set, also, included covariates as categorical variables but used different data exclusion criteria for study participants, who received a CVD diagnosis during the follow-up, and for those, who did not.

The third analysis set constituted two analysis scenarios (Figure 1). In the first scenario, termed as Scenario Y later in the text, the exclusion of men with CVD during the follow-up was based on Criterion A and that of men with no CVD during the follow-up was based on Criterion C i.e. no exclusions. This resulted in 957 study participants eligible for the analysis. In the second scenario, Scenario Z, the exclusion of men with CVD during the follow-up was based on Criterion C and that of men with no CVD during the follow-up on Criterion A. Scenario Z resulted in 1430 study participants.

Results

Outcome sensitivity

CVD and a fatal AMI associated with covariates differently compared to each other as well as compared to CHD and MI or UA (Tables 2–4). CVD was the outcome that most evidently associated with SBP; a high SBP increased the risk of CVD. A fatal AMI in turn was the only outcome that showed only statistically non-significant associations with SBP and physical activity. CHD and MI or UA highlighted the same risk factors. Specifically, they associated with STC more strongly than CVD and a fatal AMI did.

Participant exclusions

Cox regressions based on data with no exclusions most often discovered statistically significant associations of CHD with its risk factors, irrespective of covariate manipulations (Tables 2 and 3). In all these associations, the direction of the association was correct i.e. the risk factors related to hazard ratios (HR)

Table 3. Hazard ratios (HR), probabilities (P), and corresponding *p*-values of any cardiovascular disease (CVD), coronary heart disease (CHD), a myocardial infarction (MI) or unstable angina (UA), and a fatal acute myocardial infarction (AMI) with respect to seven factors used as categorical covariates in the Cox proportional-hazards model.

	CVD			CHD			MI or UA			AMI		
Covariate	HR	P	*p*	HR	P	*p*	HR	P	*p*	HR	P	*p*
A. Former smoker	1.07	0.52	.53	1.15	0.53	.35	**1.49**	**0.60**	**.03**	0.76	0.43	.51
B. Former smoker	1.11	0.53	.30	1.19	0.54	.20	**1.42**	**0.59**	**.04**	0.72	0.42	.38
C. Former smoker	**1.19**	**0.54**	**.02**	**1.24**	**0.55**	**.02**	**1.40**	**0.58**	**<.01**	1.09	0.52	.71
A. Current smoker	**1.50**	**0.60**	**<.01**	**1.78**	**0.64**	**<.01**	**2.31**	**0.70**	**<.01**	**2.36**	**0.70**	**.03**
B. Current smoker	**1.49**	**0.60**	**<.01**	**1.64**	**0.62**	**<.01**	**2.05**	**0.67**	**<.01**	**2.00**	**0.67**	**.04**
C. Current smoker	**1.50**	**0.60**	**<.01**	**1.69**	**0.63**	**<.01**	**1.94**	**0.66**	**<.01**	**2.74**	**0.73**	**<.01**
A. AC[a] 13 – 252	1.05	0.51	.64	0.95	0.49	.68	0.98	0.49	.92	0.63	0.39	.18
B. AC 13 – 252	1.04	0.51	.68	0.90	0.47	.35	0.97	0.49	.82	0.84	0.46	.58
C. AC 13 – 252	1.03	0.51	.64	0.90	0.47	.17	0.96	0.49	.66	0.80	0.44	.22
A. AC >252	1.29	0.56	.30	1.13	0.53	.73	1.05	0.51	.92	1.48	0.60	.60
B. AC >252	1.20	0.55	.41	0.94	0.48	.85	0.86	0.46	.72	1.19	0.54	.82
C. AC >252	1.16	0.54	.31	0.91	0.48	.64	0.98	0.49	.93	1.23	0.55	.59
A. BMI[b] 25.0 – 29.9	1.14	0.53	.20	1.19	0.54	.21	1.33	0.57	.09	0.90	0.47	.78
B. BMI 25.0 – 29.9	1.18	0.54	.07	1.27	0.56	.06	**1.41**	**0.59**	**.03**	0.93	0.48	.84
C. BMI 25.0 – 29.9	**1.26**	**0.56**	**<.01**	**1.42**	**0.59**	**<.01**	**1.49**	**0.60**	**<.01**	1.04	0.51	.86
A. BMI ≥30.0	**1.41**	**0.59**	**.02**	**1.51**	**0.60**	**.03**	1.47	0.60	.12	**2.85**	**0.74**	**.02**
B. BMI ≥30.0	**1.54**	**0.61**	**<.01**	**1.64**	**0.62**	**.01**	**1.70**	**0.63**	**.02**	**2.51**	**0.72**	**.02**
C. BMI ≥30.0	**1.75**	**0.64**	**<.01**	**1.79**	**0.64**	**<.01**	**1.90**	**0.66**	**<.01**	**2.37**	**0.70**	**<.01**
A. PAL[c] Vigorous	1.05	0.51	.73	0.94	0.48	.73	0.93	0.48	.74	0.79	0.44	.63
B. PAL Vigorous	1.07	0.52	.59	0.98	0.49	.89	0.99	0.50	.96	1.14	0.53	.78
C. PAL Vigorous	0.91	0.48	.24	0.86	0.46	.17	0.84	0.46	.19	0.72	0.42	.18
A. PAL Extreme	1.02	0.50	.85	0.89	0.47	.46	0.89	0.47	.56	1.06	0.51	.90
B. PAL Extreme	1.03	0.51	.79	0.87	0.47	.34	0.89	0.47	.52	1.31	0.57	.54
C. PAL Extreme	**0.84**	**0.46**	**.03**	**0.78**	**0.44**	**.01**	**0.74**	**0.43**	**.02**	0.72	0.42	.16
A. SBP[d] 120 – 139	1.11	0.53	.38	0.99	0.50	.96	0.89	0.47	.57	1.98	0.66	.22
B. SBP 120 – 139	1.16	0.54	.20	1.02	0.50	.90	0.87	0.47	.45	2.26	0.69	.13
C. SBP 120 – 139	1.12	0.53	.20	0.96	0.49	.68	0.84	0.46	.18	1.24	0.55	.44
A. SBP ≥140	**1.50**	**0.60**	**<.01**	1.17	0.54	.39	1.02	0.50	.95	2.15	0.68	.19
B. SBP ≥140	**1.50**	**0.60**	**<.01**	1.20	0.55	.27	1.06	0.51	.79	2.71	0.73	.07
C. SBP ≥140	**1.42**	**0.59**	**<.01**	1.13	0.53	.28	1.09	0.52	.52	1.48	0.60	.18
A. FBG[e] 5.6 – 6.9	1.51	0.60	.07	1.67	0.63	.08	1.91	0.66	.05	0.78	0.44	.81
B. FBG 5.6 – 6.9	1.40	0.58	.08	**1.68**	**0.63**	**.03**	**2.11**	**0.68**	**.01**	1.12	0.53	.88
C. FBG 5.6 – 6.9	**1.30**	**0.57**	**.04**	**1.73**	**0.63**	**<.01**	**1.78**	**0.64**	**<.01**	**2.05**	**0.67**	**.02**
A. FBG >6.9	**3.07**	**0.75**	**<.01**	**7.21**	**0.88**	**<.01**	**5.29**	**0.84**	**<.01**	2.95	0.75	.16
B. FBG >6.9	**3.03**	**0.75**	**<.01**	**3.64**	**0.78**	**<.01**	**3.90**	**0.80**	**<.01**	2.73	0.73	.07
C. FBG >6.9	**2.53**	**0.72**	**<.01**	**2.61**	**0.72**	**<.01**	**2.28**	**0.70**	**<.01**	**2.95**	**0.75**	**<.01**
A. STC[f] 5.2 – 6.2	1.16	0.54	.20	**1.42**	**0.59**	**.04**	1.32	0.57	.19	1.41	0.59	.47
B. STC 5.2 – 6.2	1.07	0.52	.52	1.23	0.55	.16	1.17	0.54	.38	0.91	0.48	.82
C. STC 5.2 – 6.2	1.09	0.52	.29	**1.24**	**0.55**	**.03**	**1.35**	**0.57**	**.02**	1.21	0.55	.45
A. STC >6.2	1.19	0.54	.14	**1.47**	**0.60**	**.02**	**1.57**	**0.61**	**.03**	1.91	0.66	.15
B. STC >6.2	1.07	0.52	.52	1.27	0.56	.10	**1.41**	**0.59**	**.04**	1.48	0.60	.28
C. STC >6.2	**1.20**	**0.55**	**.02**	**1.39**	**0.58**	**<.01**	**1.56**	**0.61**	**<.01**	**1.62**	**0.62**	**.04**

Note. A refers to a dataset excluding CVD, diabetes, and high total cholesterol at baseline ($n = 794$). B refers to a dataset excluding CVD, except for hypertension, at baseline ($n = 920$). C refers to a dataset with no exclusions ($n = 1592$). Bold font indicates a statistically significant HR.
[a]Alcohol consumption in g/week.
[b]Body Mass Index, kg/m^2.
[c]Physical activity level, the total energy expenditure divided by the basal energy expenditure, moderate <2.00, extreme >2.40.
[d]Systolic blood pressure in mmHg.
[e]Fasting blood glucose in mmol/L.
[f]Serum total cholesterol in mmol/L.

larger than one and the protective factors related to HRs below one. Only regressions based on data with no exclusions identified, statistically significantly, the protective effect of physical activity; the highest category versus the lowest one. Appendix presents sample size calculations regarding the main outcome of this study, CHD, and Criterion A that excluded study participants according to conditions at baseline.

The comparison between Scenarios Y and Z showed that strict data exclusions regarding men with no CVD during the follow-up combined with no exclusions regarding men with CVD during the follow-up yielded more often statistically significant and plausible results than no data exclusions concerning men with no CVD and strict exclusions regarding men with CVD (Table 4).

Covariate manipulations

There were only minor differences in Cox model results between analyses including covariates as continuous variables and those including covariates as

Table 4. Hazard ratios (HR), probabilities (P), and corresponding *p*-values of any cardiovascular disease (CVD), coronary heart disease (CHD), a myocardial infarction (MI) or unstable angina (UA), and a fatal acute myocardial infarction (AMI) with respect to seven factors used as categorical covariates in the Cox proportional-hazards model.

	CVD			CHD			MI or UA			AMI		
Covariate	HR	P	*p*	HR	P	*p*	HR	P	*p*	HR	P	*p*
Y. Former smoker	1.06	0.51	.56	1.01	0.50	.52	1.37	0.58	.09	0.75	0.43	.48
Z. Former smoker	**1.18**	**0.54**	**.02**	**1.25**	**0.56**	**.02**	**1.45**	**0.59**	**<.01**	1.17	0.54	.52
Y. Current smoker	**1.36**	**0.58**	**.01**	**1.56**	**0.61**	**<.01**	**1.96**	**0.66**	**<.01**	1.96	0.66	.07
Z. Current smoker	**1.59**	**0.61**	**<.01**	**1.79**	**0.64**	**<.01**	**2.14**	**0.68**	**<.01**	**3.16**	**0.76**	**<.01**
Y. AC[a] 13 – 252	1.08	0.52	.42	0.96	0.49	.75	1.03	0.51	.88	0.69	0.41	.26
Z. AC 13 – 252	1.00	0.50	.98	0.89	0.47	.14	0.90	0.47	.31	0.73	0.42	.10
Y. AC > 252	1.22	0.55	.42	0.86	0.46	.67	0.87	0.47	.74	1.25	0.56	.77
Z. AC > 252	1.19	0.54	.24	1.13	0.53	.52	1.16	0.54	.53	1.42	0.59	.37
Y. BMI[b] 25.0 – 29.9	1.12	0.53	.23	1.13	0.53	.36	1.21	0.55	.26	0.83	0.45	.62
Z. BMI 25.0 – 29.9	**1.25**	**0.56**	**<.01**	**1.42**	**0.59**	**<.01**	**1.55**	**0.61**	**<.01**	1.13	0.53	.59
Y. BMI ≥ 30.0	**1.46**	**0.59**	**.01**	1.23	0.55	.29	1.17	0.54	.52	1.97	0.66	.13
Z. BMI ≥ 30.0	**1.66**	**0.62**	**<.01**	**1.94**	**0.66**	**<.01**	**2.16**	**0.68**	**<.01**	**3.08**	**0.75**	**<.01**
Y. PAL[c] Vigorous	1.01	0.50	.95	0.94	0.48	.70	0.92	0.48	.68	0.82	0.45	.68
Z. PAL Vigorous	0.92	0.48	.32	0.87	0.47	.20	0.85	0.46	.20	0.71	0.42	.16
Y. PAL Extreme	0.97	0.49	.83	0.87	047	.41	0.86	0.46	.44	1.09	0.52	.85
Z. PAL Extreme	0.86	0.46	.07	**0.79**	**0.44**	**.02**	**0.76**	**0.43**	**.02**	0.70	0.41	.12
Y. SBP[d] 120 – 139	1.16	0.54	.21	0.97	0.49	.84	0.86	0.46	.46	1.97	0.66	.22
Z. SBP 120 – 139	1.08	0.52	.36	0.98	0.49	.86	0.88	0.47	.33	1.30	0.57	.35
Y. SBP ≥ 140	**1.57**	**0.61**	**<.01**	1.19	0.54	.33	1.05	0.51	.82	2.02	0.67	.22
Z. SBP ≥ 140	**1.38**	**0.58**	**<.01**	1.14	0.53	.26	1.09	0.52	.54	1.54	0.61	.14
Y. FBG[e] 5.6 – 6.9	1.12	0.53	.61	1.34	0.57	.31	1.46	0.59	.25	0.57	0.36	.59
Z. FBG 5.6 – 6.9	**1.52**	**0.60**	**<.01**	**1.93**	**0.66**	**<.01**	**2.15**	**0.68**	**<.01**	**2.55**	**0.72**	**<.01**
Y. FBG > 6.9	1.86	0.65	.07	**2.86**	**0.74**	**<.01**	**2.21**	**0.69**	**.04**	1.89	0.65	.39
Z. FBG > 6.9	**2.96**	**0.75**	**<.01**	**3.27**	**0.77**	**<.01**	**2.99**	**0.75**	**<.01**	**4.36**	**0.81**	**<.01**
Y. STC[f] 5.2 – 6.2	1.19	0.54	.14	**1.49**	**0.60**	**.02**	1.48	0.60	.06	1.50	0.60	.38
Z. STC 5.2 – 6.2	1.07	0.52	.36	**1.26**	**0.56**	**.02**	1.25	0.56	.08	1.11	0.53	.68
Y. STC > 6.2	1.20	0.55	.12	**1.48**	**0.60**	**.02**	**1.66**	**0.62**	**.01**	1.93	0.66	.14
Z. STC > 6.2	**1.20**	**0.55**	**.02**	**1.43**	**0.59**	**<.01**	**1.50**	**0.60**	**<.01**	1.54	0.61	.07

Note. Y refers to a dataset with no exclusions for study participants with no CVD during the follow-up ($n = 411$) and excluding CVD, diabetes, and high total cholesterol at baseline for study participants with CVD during the follow-up ($n = 546$). Z refers to a dataset excluding CVD, diabetes, and high total cholesterol at baseline for study participants with no CVD during the follow-up ($n = 248$) and no exclusions for study participants with CVD during the follow-up ($n = 1182$). Bold font indicates a statistically significant HR.
[a]Alcohol consumption (g/week).
[b]Body Mass Index (kg/m^2).
[c]Physical activity level, the total energy expenditure divided by the basal energy expenditure, moderate <2.00, extreme >2.40.
[d]Systolic blood pressure (mmHg).
[e]Fasting blood glucose (mmol/L).
[f]Serum total cholesterol (mmol/L).

categorical variables (Tables 2–4). Continuous and categorical covariates led to the same conclusions regarding the association of CHD with its risk factors. Being a former or current smoker, being overweight or obese, and having borderline high or high FBG or STC levels significantly increased the risk of CHD. The effect of high SBP levels on the risk of CHD was uncertain as well as the protective effect of physical activity. Our analyses found no statistically significant association between CHD and alcohol consumption.

Discussion

Traditionally, epidemiological studies use in their analyses only study participants who are free of the disease of interest at baseline. Our study suggests that excluding study participants who have the disease already at baseline is probably unnecessary. Specifically, our analyses led to the best results when we included all study participants who received the diagnosis during the follow-up irrespective of their self-reported baseline statuses but excluded all study participants who did not receive the diagnosis during the follow-up but had self-reported the disease at baseline. Moreover, our study does not, unconditionally, support participant exclusions with respect to covariates either. Excluding participants who are at risk already at baseline may enable discovering the strongest associations, such as the relationship between diabetes and CHD, but, simultaneously, it may fade out weaker, although relevant, associations, such as the relationship between physical activity and CHD. In other words, a combination of "loose cases" and "strict controls" may yield the best results. In the next paragraphs, we evaluate our results from the viewpoint of CHD risk factors.

In our study, smoking, overweight, and high blood glucose levels, evidently, associated with CHD. Outcome variable selection, participant exclusion, and covariate manipulation procedures had no effects on

conclusions drawn from results related to these three cornerstone risk factors. Being a current smoker or being obese (BMI $\geq$ 30.0) resulted in 1.5 times higher hazard compared to never smokers and normal-weight study participants, whereas diabetes (FBG $>$ 6.9 mmol/L) approximately tripled the hazard of CHD. Large prospective cohort studies have reported even stronger effects of smoking and obesity on CHD already in 1960s [31]. The three times higher hazard of CHD among diabetic men seems to be a rule of thumb [9].

Total cholesterol and blood pressure were the covariates that most evidently revealed differences related to outcome sensitivity. Total cholesterol is only one of many measures of the lipid status of which all show somewhat unique associations with CHD and other CVDs [10,13]. Total cholesterol, for example, does not associate as strongly with the risk of stroke [32] as it associates with the risk of CHD [10]. Conversely, high blood pressure increases, specifically, the risk of stroke [33], which may for its part explain, together with reasons related to the sample size, why SBP associated statistically significantly with CVD but not with CHD and MIs in our study.

Irrespective of outcome variable selection, participant exclusions, and covariate manipulations, our study found no statistically significant effects of alcohol consumption on the hazard of CHD. Although alcohol, in general, increases mortality and morbidity [22], light-to-moderate drinking may protect against CHD [11], which for its part may complicate the statistical detection of the association between alcohol consumption and CHD. Moreover, the association relates to the pattern of consumption i.e. binge drinking *via* the progression of atherosclerosis [34], which we did not considered in this study.

Limitations

Our results are based on one dataset and, therefore, them are not straightforwardly generalizable. Moreover, our study does not consider severity of diseases per se or diagnoses other than CVD, CHD, MI or UA, and AMI.

All KIHD study participants, practically, were at least moderately active at baseline and nearly half of them were extremely active based on PAL values. This indicates the active lifestyles of the KIHD study participants; many of them were farmers or lumberjacks and highly interested in cross-country skiing, which to some extent distinguishes the KIHD cohort from otherwise similar cohorts. On the other hand, extreme physical activity levels, PAL $>$ 2.4, are unrealistic in the long run because they lead to a negative energy balance i.e. weight loss [35]. This contradiction, most probably, is due to the KIHD assessment method of physical activity. In general, self-assessment physical activity questionnaires show low validity and reliability [36]. Consequently, the present TEE and PAL values are adequate for creating data-specific activity ranks [37] but not for comparing the KIHD cohort to other cohorts as such.

Conclusions

Our Cox model example of the epidemiological relationship between CHD and its common risk factors evidently demonstrated that outcome variable selection and participant exclusions must be considered when interpreting results of epidemiological analyses. Preprocessing procedures that were loose regarding study participants with any CVD during the follow-up and strict concerning study participants with no CVD during the follow-up were best in discovering the association between risk factors and CHD. Outcome sensitivity affected associations across covariates and outcomes. For example, total cholesterol associated, specifically, with CHD and MI or UA but weakly with CVD or AMI. The covariate type, continuous or categorial, had only minor effects on Cox model results. We strongly suggest that research reports present results based on no data exclusions together with results based on reasoned exclusions.

Disclosure statement

The authors report no potential conflict of interest.

Data availability statement

On request, the University of Eastern Finland's Institute of Public Health and Clinical Nutrition can admit an access to the KIHD database.

References

[1] Souverein PC, Abbing-Karahagopian V, Martin E, et al. Understanding inconsistency in the results from observational pharmacoepidemiological studies: the case of antidepressant use and risk of hip/femur fractures. Pharmacoepidemiol Drug Saf. 2016;25(Suppl 1): 88–102.

[2] Linden AH, Hönekopp J. Heterogeneity of research results: a new perspective from which to assess and promote progress in psychological science. Perspect Psychol Sci. 2021;16(2):358–376.

[3] Pirro M, Bergeron J, Dagenais GR, et al. Age and duration of follow-up as modulators of the risk for ischemic heart disease associated with high plasma C-reactive protein levels in men. Arch Intern Med. 2001; 161(20):2474–2480.

[4] Puddu PE, Amaduzzi PL, Ricci B. Coronary heart disease incidence and competing risks: an important issue. J Geriatr Cardiol. 2017;14(7):425–429.
[5] Hackshaw A, Morris JK, Boniface S, et al. Low cigarette consumption and risk of coronary heart disease and stroke: meta-analysis of 141 cohort studies in 55 study reports. BMJ. 2018;360:j5855.
[6] Bogers RP, Bemelmans WJE, Hoogenveen RT, et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels. A meta-analysis of 21 cohort studies including more than 300 000 persons. Arch Intern Med. 2007;167(16):1720–1728.
[7] DeFina LF, Haskell WL, Willis BL, et al. Physical activity versus cardiorespiratory fitness: two (partly) distinct components of cardiovascular health? Prog Cardiovasc Dis. 2015;57(4):324–329.
[8] Weber T, Lang I, Zweiker R, et al. Hypertension and coronary artery disease: epidemiology, physiology, effects of treatment, and recommendations: a joint scientific statement from the Austrian Society of Cardiology and the Austrian Society of Hypertension. Wien Klin Wochenschr. 2016;128(13 – 14):467 – 479.
[9] Juutilainen A, Kortelainen S, Lehto S, et al. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care. 2004;27(12):2898–2904.
[10] Arsenault BJ, Rana JS, Stroes ESG, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2010;55(1):35–41.
[11] Ronksley PE, Brien SE, Turner BJ, et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671.
[12] Dranago N, Siegrist J, Nyberg ST, et al. Effort-reward imbalance at work and incident coronary heart disease: a multicohort study of 90,164 individuals. Epidemiology. 2017;28(4):619–626.
[13] Roeters van Lennep J, Westerveld HT, Erkelens DW, et al. Risk factors for coronary heart disease: implications of gender. Cardiovasc Res. 2002;53(3):538–549.
[14] Das De S, Krishna S, Jethwa A. Iron status and its association with coronary heart disease: systematic review and meta-analysis of prospective studies. Atherosclerosis. 2015;238(2):296 – 303.
[15] Hawe E, Talmud PJ, Miller GJ, et al. Family history is a coronary heart disease risk factor in the Second Northwick Park Heart Study. Ann Hum Genet. 2003; 67(Pt 2):97–106.
[16] Tada H, Melander O, Louie JZ, et al. Risk prediction by genetic risk scores for coronary heart disease is independent of self-reported family history. Eur Heart J. 2016;37(6):561–567.
[17] Smith TW, Glazer K, Ruiz JM, et al. Hostility, anger, aggressiveness, and coronary heart disease: an interpersonal perspective on personality, emotion, and health. J Pers. 2004;72(6):1217–1270.
[18] Chen R, Stewart WF, Sun J, et al. Recurrent neural networks for early detection of heart failure from longitudinal electronic health record data: implications for temporal modeling with respect to time before diagnosis, data density, data quantity, and data type. Circ Cardiovasc Qual Outcomes. 2019; 12(10):e005114.
[19] Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. Ann Clin Res. 1988;20(1-2): 46–50.
[20] WHO. 2016. International Statistical Classification of Diseases and Related Health Problems. 10th revision (ICD-10); [cited 2019 Dec 17]. Available from: https://icd.who.int/browse10/2016/en#/IX.
[21] Hajar R. Risk factors for coronary artery disease: historical perspectives. Heart Views. 2017;18(3):109–114.
[22] Rehm J, Gmel G, Sempos CT, et al. Alcohol-related morbidity and mortality. Alcohol Res Health. 2003; 27(1):39–51.
[23] Mifflin MD, St Jeor ST, Hill LA, et al. A new predictive equation for resting energy expenditure in healthy individuals. Am J Clin Nutr. 1990;51(2):241–247.
[24] FAO/WHO/UNU. Human energy requirements. FAO Food and Nutrition Technical Report Series. 2001;1:1–96.
[25] CDC. 2019. Defining adult overweight and obesity; [cited 2019 Dec 17]. Available from: https://www.cdc.gov/obesity/adult/defining.html.
[26] Mayo Clinic. 2019a. High blood pressure (hypertension); [cited 2019 Dec 17]. Available from: https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/diagnosis-treatment/drc-20373417.
[27] Salonen JT, Salonen R, Seppänen K, et al. HDL, HDL2, and HDL3 subfractions, and the risk of acute myocardial infarction. A prospective population study in eastern Finnish men. Circulation. 1991;84(1):129–139.
[28] Mayo Clinic. 2019b. Cholesterol test; [cited 2019 Dec 17]. Available from: https://www.mayoclinic.org/tests-procedures/cholesterol-test/about/pac-20384601.
[29] Mayo Clinic. 2019c. Diabetes; [cited 2019 Dec 17]. Available from: https://www.mayoclinic.org/diseases-conditions/diabetes/diagnosis-treatment/drc-20371451.
[30] Cox DR. Regression models and life-tables. J R Stat Soc B. 1972;34(2):187–220.
[31] Hammond EC, Garfinkel L. Coronary heart disease, stroke, and aortic aneurysm. Factors in the etiology. Arch Environ Health. 1969;19(2):167–182.
[32] Zhang Y, Tuomilehto J, Jousilahti P, et al. Total and high-density lipoprotein cholesterol and stroke risk. Stroke. 2012;43(7):1768–1774.
[33] Lawes CMM, Bennett DA, Feigin VL, et al. Blood pressure and stroke. An overview of published reviews. Stroke. 2004;35(4):1024–1033.
[34] Rantakömi SH, Laukkanen JA, Kurl S, et al. Binge drinking and the progression of atherosclerosis in middle-aged men: an 11-year follow-up. Atherosclerosis. 2009;205(1): 266–271.
[35] Westerterp KR. Alterations in energy balance with exercise. Am J Clin Nutr. 1998;68(suppl):970S–974S.
[36] Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med. 2003;37(3):197–206.
[37] Westerterp KR. Assessment of physical activity: a critical appraisal. Eur J Appl Physiol. 2009;105(6):823–828.

Appendix

Table A1. Results of sample size calculations regarding the main outcome of this study, coronary heart disease (CHD), with respect to Criterion A that excluded study participants according to conditions at baseline.

	Observed				
	n	CHD *n* (%)	No CHD *n* (%)	Required *n*	
Smoking: Never-smoker (Reference)	296	100 (34)	196 (66)	4213	1140
Smoking: Former smoker	270	101 (37)	169 (63)	3792	
Smoking: Current smoker	228	92 (40)	136 (60)		912
Alcohol consumption: Light	308	112 (36)	196 (64)		2854
Alcohol consumption: Moderate	454	172 (38)	282 (62)	1843	
Alcohol consumption: Heavy (Reference)	32	9 (28)	23 (72)	184	285
Normal weight (Reference)	278	94 (34)	184 (66)	1886	794
Overweight	415	156 (38)	259 (62)	2829	
Obese	101	43 (43)	58 (57)		318
Physical activity: Moderate	144	55 (38)	89 (62)		6390
Physical activity: Vigorous	251	93 (37)	158 (63)	29089	
Physical activity: Extreme (Reference)	391	141 (36)	250 (64)	48481	15975
Systolic blood pressure: Desirable	141	52 (37)	89 (63)	5860	
Systolic blood pressure: Prehypertension (Reference)	404	140 (35)	264 (65)	19535	1364
Systolic blood pressure: Hypertension	249	101 (41)	148 (59)		818
Fasting blood glucose: Desirable (Reference)	753	269 (36)	484 (64)	5945	239
Fasting blood glucose: Prediabetes	31	14 (45)	17 (55)	238	
Fasting blood glucose: Diabetes	10	10 (100)	0 (0)		2
Serum total cholesterol: Desirable (Reference)	190	55 (29)	135 (71)	432	177
Serum total cholesterol: Pre-hypercholesterolaemia	315	118 (37)	197 (63)	734	
Serum total cholesterol: Hypercholesterolaemia	289	120 (42)	169 (58)		266

Note. Required *n* refers to comparisons across the category in which the proportion of CHD diagnoses during the follow-up was lowest (reference) and other categories applying a predetermined *p*-value of .05 (α) and a predetermined power of 0.80 ($1-\beta$).

An example of sample size calculations: serum total cholesterol

$$n_1 = \frac{\left[z_{1-\frac{\alpha}{2}} \times \sqrt{\overline{p} \times \overline{q} \times \left(1+\frac{1}{k}\right)} + z_{1-\beta} \times \sqrt{p_1 \times q_1 + \left(\frac{p_2 \times q_2}{k}\right)}\right]^2}{\Delta^2}$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2,$$

$$\overline{p} = \frac{p_1 + kp_2}{1+k},$$

$$\overline{q} = 1 - \overline{p}.$$

n_1 = The number of participants in Group 1
n_2 = The number of participants in Group 2.
α = The probability of Type I error
β = The probability of Type II error.
z = The standardized value re the predetermined α and β.
k = The ratio of n_2 to n_1.
p_1 = The proportion of participants with a follow-up CHD diagnose in Group 1.
p_2 = The proportion of participants with a follow-up CHD diagnose in Group 2.

$$n_1 = \frac{\left[1.96 \times \sqrt{0.368 \times 0.632 \times \left(1+\frac{1}{1.5}\right)} + 0.84 \times \sqrt{0.29 \times 0.71 + \left(\frac{0.42 \times 0.58}{1.5}\right)}\right]^2}{0.13^2} = 177$$

$n_2 = k \times n_1 = 266.$

References

Rosner B. *Fundamentals of Biostatistics*. 8th ed. Boston (MA): CENGAGE Learning; 2016.

II

Epidemiological analysis of coronary heart disease and its main risk factors: are their associations multiplicative, additive, or interactive?

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Epidemiological analysis of coronary heart disease and its main risk factors: are their associations multiplicative, additive, or interactive?

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ABSTRACT

Objective: The purpose of this study was to discover how considering multiplicative, additive, and interactive effects modifies results of a prospective cohort study on coronary heart disease (CHD) incidence and its main risk factors.

Material and methods: The Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study provided the study material, 2682 Eastern Finnish middle-aged men, followed since the 1980s. We applied multiplicative and additive survival models together with different statistical metrics and confidence intervals for risk ratios and risk differences to estimate the nature of associations.

Results: The mean (SD) follow-up time among men who were free of CHD at baseline ($n = 1958$) was 21.4 (10.4) years, and 717 (37%) of them had the disease and 301 (15%) died for CHD before the end of follow-up. All tested non-modifiable and modifiable risk factors statistically significantly predicted CHD incidence. We detected three interactions: circulating low-density lipoprotein cholesterol (LDL-C) × age, obesity × age, and obesity × smoking of which LDL-C × age was the most evident one. High LDL-C increased the risk of CHD more among men younger than 50 [risk ratio (RR) 2.10] than those older than 50 (RR 1.22). LDL-C status was the only additive covariate. The additive effect of high LDL-C increased almost linearly up to 18 years and then reached a plateau. The simple multiplicative survival model stressed glycemic status as the strongest modifiable risk factor for developing CHD [hazard ratio (HR) for diabetes vs. normoglycemia was 2.69], whereas the model considering interactions and time dependence emphasised the role of LDL-C status (HR for high LDL-C vs. lower than borderline was 4.43). Age was the strongest non-modifiable predictor.

Conclusions: Including covariate interactions and time dependence in survival models potentially refine results of epidemiological analyses and ease to define the order of importance across CHD risk factors.

KEY MESSAGES

- Including covariate interactions and time dependence in survival models potentially refine results of epidemiological analyses on coronary heart disease.
- Including covariate interactions and time dependence in survival models potentially ease to define the order of importance across coronary heart disease risk factors.

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Additive; coronary heart disease; cohort study; incidence; multiplicative; interactive

Introduction

Coronary heart disease (CHD) is one of the most common chronic illnesses in the world and its main risk factors are well-known [1]. These risk factors are male gender, old age, ethnic background, family history of CHD, diabetes, smoking, obesity, dyslipidemia, hypertension, and physical inactivity of which the first four are non-modifiable and the latter six are modifiable [2,3]. Out of many unorthodox predictors of CHD, for example, proteinuria and inflammatory biomarkers have shown strong associations with CHD incidence, but their causal roles in the development of CHD are typically uncertain [4–7].

Traditionally, most epidemiological studies and treatment algorithms have considered the CHD risk factors as independent predictors [8], which may distort conclusions due to unidentified interactions. This

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is somewhat surprising as studies addressing the interactions across CHD risk factors have emphasised their importance and revealed associations of modifiable risk factors particularly with the family history and genetic risk [9–13], but also across the modifiable risk factors, for example, between dyslipidemia and smoking, dyslipidemia and hypertension, dyslipidemia and obesity, and diabetes and hypertension [11,14,15].

Moreover, epidemiological studies have typically not investigated the type of the relationship between CHD and its risk factors, multiplicative or additive, before choosing statistical methods and simply applied multiplicative models, such as the Cox regression analysis. With respect to CHD, fortunately, multiplicative models are probably the correct choice for many studies, as the effects of coexisting CHD risk factors as such appear to be multiplicative rather than additive, although also additive effects evidently exist [8,14,16,17]. In general, on the other hand, additive models should be more appropriate in determining epidemiological relationships [18].

The aim of this prospective study was to discover the combination of multiplicative, additive, and interactive effects that best recognise the main risk factors for CHD incidence and their order of importance in a cohort of middle-aged men followed since the 1980s.

Material and methods

Material

The ethical committee of the Kuopio University approved the KIHD Study on December 1, 1983. The KIHD study plan was published in 1988 [19] and the actualised study protocol in separate papers in the late 1980s and early 1990s. Salonen et al. [20] provides a comprehensive presentation concerning variables applied in the present study. Briefly, the primary KIHD study sample consisted of 3235 middle-aged men living in Eastern Finland in the city of Kuopio and its surrounding rural areas. Of those men, 2682 were willing to participate to baseline examinations and interviews between March 1984 and December 1989. All study participants gave written informed consent.

To enable the identification of study participants who were not free of CHD at baseline, KIHD examinations included a maximal symptom-limited exercise tolerance test carried out at the Kuopio Research Institute of Exercise Medicine [21]. Bicycle ergometers with a linear (Medical Fitness Equipment 400 L, Mearn, the Netherlands) or a step-by-step (Tunturi EL 400, Turku, Finland) increase in the workload by 20 W per minute served as devices for the assessment of physical work. Measurements of oxygen uptake were based on a breath-by-breath method (MGC 2001, Medical Graphics, St. Paul, MN) or a mixing-chamber method (Mijnhardt Oxycon 4, Odijk, the Netherlands). The test procedure consisted standard 12-lead ECG recordings (Kone, Turku, Finland) before, during, and after the ergometer test. The before recordings corresponded a resting ECG. Moreover, KIHD questionnaires included the following CHD-related questions: (a) has your physician told you that you have had a myocardial infarction, (b) has your physician told you that you suffer from angina pectoris, (c) have you used medicines for angina pectoris during the past 7 days, (d) do you use sublingual nitroglycerine once a week or more frequently, and (e) have you undergone a coronary bypass operation? Based on results of the exercise test and ECG recordings and answers to questionnaire items we defined study participants having CHD at baseline as follows: unable to complete the ergometer test due to angina pectoris-type chest pain, or Q waves on the ECG indicating a myocardial infarction, or horizontal or downsloping ST depression $\geq$1 mm in aVF or V5 leads, or answering "yes" to at least one of the questions a – e. As certain inaccuracies relate to exercise stress testing in general [22], in this study, we carried out statistical analyses and reported their results also concerning the dataset without exclusions.

Before giving blood samples between 8 and 10 a.m. study participants abstained from alcohol for 3 days, smoking for 12 h, and eating for 12 h. After a rest of 30 min, a research nurse drew blood with Terumo Venoject VT-100PZ vacuum (Terumo Corp., Tokyo, Japan) without using a tourniquet.

Endpoints

Study endpoints were i) CHD diagnosed during hospitalisations or specialised medical care visits, ii) death, and iii) the end of follow-up on 31 December 2019. CHD referred to ICD 10 codes I20 – I25. The KIHD Study receives ICD 10 codes *via* annual linkages to the Care Register for Health Care provided by the Finnish Institute for Health and Welfare (License THL/93/5.05.00/2013 valid until 31 December 2022) and verifies deaths by annual linkages to the Causes of Death Register provided by the Statistics Finland (License TK-53-1770-16 valid until 31 December 2026).

Covariates

Family history of CHD based on the following questionnaire items: (a) has your biological mother CHD, (b) has

your biological father CHD, and (c) have your biological siblings CHD? This covariate combines effects of heredity and familial environment on the risk of CHD and, consequently, it does not represent genetic factors as such or effects of adulthood environment.

Age referred to four categories, 42, 48, 54, and 60 years, reflecting the primary KIHD recruitment.

The assessment of the absence and presence of borderline diabetes and diabetes at baseline based on a fasting blood glucose (FBG) level measured by a glucose dehydrogenase method (Merck, Darmstadt, Federal Republic of Germany) together with the following questionnaire items: (a) do you have diet-controlled diabetes, (b) do you use oral diabetes medications, and (c) do you use insulin? For statistical analyses we categorised study participants into three groups as follows: FBG <5.6 mmol/L indicating no diabetes, FBG $5.6-6.9$ mmol/L and/or diet for controlling diabetes, and FBG ≥ 7.0 mmol/L and/or glucose-lowering medication indicating diabetes [23,24]. We classified men with diet-treated diabetes and men taking diabetes medicines into different groups as, based on preliminary analyses, the risk of CHD was evidently higher among the latter.

Smoking status based on a self-administered questionnaire of which items dealt with the frequency and duration of regular smoking as well as the types of tobacco products consumed. We classified the study participant as a smoker if he had ever smoked regularly and a current smoker if he had smoked regularly within the past 30 days.

KIHD baseline examinations included height and weight measurements. We calculated the Body Mass Index (BMI) for each study participants by dividing the weight in kilograms by the square of height in metres and categorised study participants as follows: BMI <25.0 kg/m^2 indicating healthy weight, BMI 25.0–29.9 kg/m^2 indicating overweight, and BMI ≥ 30.0 kg/m^2 indicating obesity [25].

In this study, we used the fasting serum low-density lipoprotein cholesterol (S-LDL-C) concentration instead of the fasting serum total cholesterol (STC) concentration to detect high cholesterol levels. In our previous paper, we had used STC [26], but preliminary analyses of this study revealed that S-LDL-C could provide even stronger associations with CHD. Based on S-LDL-C concentration we categorised study participants as follows: S-LDL-C <3.4 mmol/L indicating below borderline concentrations, S-LDL-C $3.4-4.1$ mmol/L indicating borderline high concentrations, and S-LDL-C >4.1 mmol/L or cholesterol-lowering medication indicating high concentrations. These cut-off points do not strictly follow clinical guidelines or research findings concerning desirable S-LDL-C levels [27] because, in the KIHD cohort, the proportion of men with the desirable S-LDL-C concentration for individuals at low risk (<3.0 mmol/L) is low (14.7%) whereas men having dyslipidemia are overrepresented. Therefore, we combined optimal and near optimal S-LDL-C groups into a below borderline group to achieve as balanced 3-group distribution as possible for statistical analyses. To some extent, the desirable S-LDL-C levels are always only directional as, by and large, the lower the circulating LDL-C concentration, the lower the risk of cardiovascular diseases [28]. Salonen et al. [29] describe the KIHD lipid analyses in detail. Briefly, the main fractions, very low-density lipoprotein, S-LDL-C, and high-density lipoprotein (HDL) referred to the respective serum fractions: the top fraction, a computational difference between the bottom and HDL fractions, and the supernatant after precipitation of the bottom fraction.

KIHD baseline examinations included several blood pressure measurements. In this study, we refer to the mean of three measurements in supine, two in sitting, and one in a standing position with a random-zero mercury sphygmomanometer after a supine rest of five minutes. Based on systolic (SBP) and diastolic blood pressure (DBP) values we categorised study participants as follows: SBP <120 and DBP <80 mmHg indicating no hypertension, SBP $120-139$ or DBP $80-89$ mmHg indicating borderline hypertension, and SBP >139 or DBP >89 mmHg or blood pressure medication indicating hypertension. These cut-off points are compromises across clinical guidelines, research findings, and distributions of SBP and DBP values in the KIHD cohort [30,31]. Mainly, they follow criteria applied in the Framingham Heart Study that resembles, in many ways, the KIHD Study [32].

We did not use ethnic background and gender as covariates because all study participants were White Finnish males. We also excluded measures of physical activity since the proportion of physically inactive men in the KIHD cohort is practically zero and, consequently, it is impossible to estimate the impact of sedentary lifestyle on the risk of CHD. Moreover, based on our previous analyses physical activity levels very poorly predict the risk of CHD in this cohort [26]. Other studies also have found the contradictory nature of physical activity, as in some study populations physical activity, not inactivity, is associated with an increased risk of CHD [9].

Statistical analyses

To detect interactions, we computed risk ratios (RR) and risk differences (RD) with 95% confidence intervals

Table 1. Distribution of study participants by the main CHD risk factors at baseline.

Risk factor	Severity	Description	*n* (*N*)
Age	0	42 years	294 (334)
	1	48 years	274 (358)
	2	54 years	1148 (1592)
	3	60 years	242 (398)
Family history	0	No close relatives with CHD	1061 (1351)
	1	One close relative with CHD	638 (898)
	2	Two or more close relatives with CHD	244 (413)
			missing 15 (20)
Diabetes	0	FBG <5.6 mmol/L	1800 (2425)
	1	FBG 5.6 – 6.9 mmol/L or diagnosis and diet	102 (159)
	2	FBG >6.9 mmol/L or medication	56 (98)
Smoking	0	Never	672 (861)
	1	Previously	675 (955)
	2	Currently	611 (866)
Obesity	0	BMI <25 kg/m^2	622 (843)
	1	BMI 25 – 29.9 kg/m^2	993 (1351)
	2	BMI ≥30 kg/m^2	334 (476)
			missing 9 (12)
Cholesterol	0	S-LDL <3.4 mmol/L	539 (705)
	1	S-LDL 3.4 – 4.1 mmol/L	568 (772)
	2	S-LDL >4.1 mmol/L or medication	816 (1156)
			missing 35 (49)
Hypertension	0	SBP <120 and DBP <80 mmHg	205 (257)
	1	SBP 120 – 139 or DBP 80 – 89 mmHg	645 (799)
	2	SBP >139 or DBP >89 mmHg or medication	1098 (1614)
			missing 10 (12)

Notes. *n* refers to 1958 men free of coronary heart disease (CHD) at baseline, and N refers to the entire cohort of 2682 men. FBG: fasting blood glucose; BMI: body mass index; S-LDL: serum low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure.

(CI) for each pair of covariates. In RD, CIs refer to the Wilson intervals [33]. We also fitted a binomial regression model as a part of generalised linear models to each pairwise interaction. Basically, non-overlapping confidence intervals indicate statistically significant interactions, RRs regarding multiplicative interactions and RDs regarding additive interactions. Moreover, we used the interaction contrast ratio (ICR), with 95% CIs based on the variance recovery method [34], to verify additive interactions. ICR expresses the additional risk due to the interaction and it is also known as RERI, the relative risk for interaction [35–37]. If the additive interaction is present, ICR differs from zero. We also calculated the attributable fraction and the synergy index [35,37] as a part of a preliminary analysis, but them did not affect conclusions based on ICR.

To simplify the interpretation of interactions we dichotomised the covariates as follows: Family history (no close relatives with CHD vs. close relative(s) with CHD), age (<50 vs. >50), glycemic status (FBG <5.6 mmol/L and no glucose-lowering medication or diet vs. FBG ≥5.6 mmol/L or glucose-lowering medication or diet), smoking status (never smoked vs. former or current smoker), weight (BMI <30 kg/m^2 vs. BMI ≥30 kg/m^2), cholesterol status (S-LDL-C ≤ 4.1 mmol/L and no cholesterol-lowering medication vs. S-LDL-C > 4.1 mmol/L or cholesterol-lowering medication), and blood pressure status (SBP ≤139 mmHg, DBP ≤89 mmHg, and no blood pressure medication vs. SBP >139 mmHg, or DBP >89 mmHg, or blood pressure medication).

Regarding multiplicativity and additivity we, first, performed a conventional Cox proportional hazards model that assumes multiplicative associations [38]. Precisely, the proportional hazard assumption denotes that covariate coefficients do not change over time, i.e. $\beta(t) = c$ [39]. In the Cox survival model, the CHD endpoint served as the dependent variable and all covariates served as independent variables. We used the covariates as categorical variables and investigated the Schoenfeld residuals to test the proportional hazards assumption [40]. Based on our previous study the type of covariate, categorical or continuous, has probably no statistically significant effect on Cox model results [26] but including continuous covariates in the model requires the assessment of nonlinearity by means of martingale residuals [41]. Second, we added statistically significant covariate interactions to the Cox model. Third, we performed the Cox-Aalen model with a proportionality test based on martingale residuals [42,43]. The Cox-Aalen model allows covariates to result in either multiplicative or additive effects [43]. Fourth, to estimate effects of additive covariates we executed the Aalen's additive regression model [44,45]. As the KIHD study utilises the IBM® SPSS® software platform, we also applied the SPSS built-in time variables to estimate effects of additive covariates. When covariates are time-dependent, another option

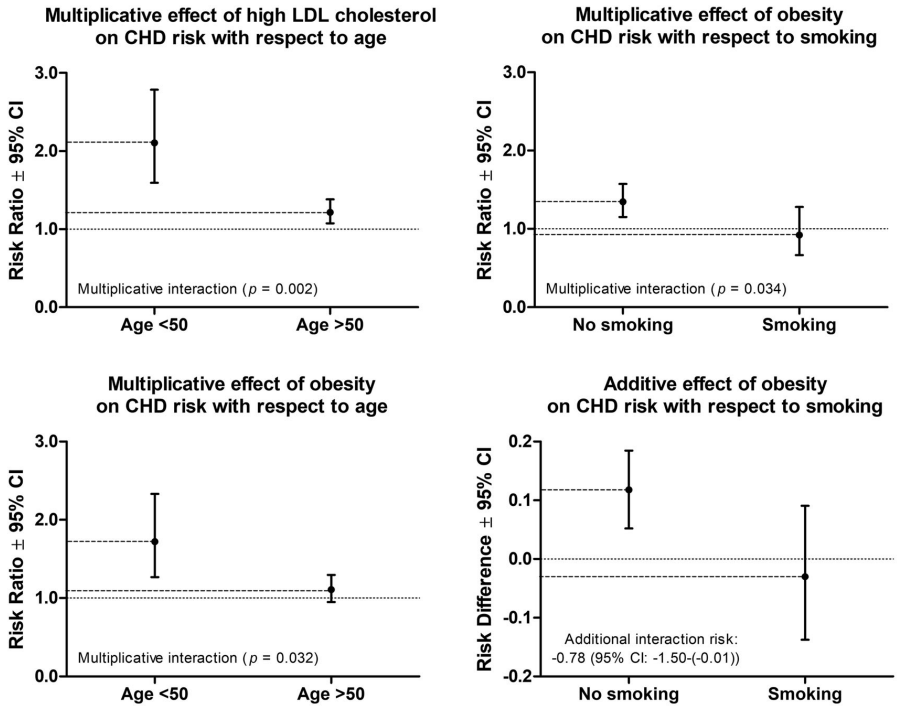

Figure 1. Statistically significant interactions across the main coronary heart disease (CHD) risk factors.

is to divide the follow-up period into shorter covariate-specific time segments. In this study, however, we did not test this method, since it may lead to the use of even several different time segments if the number of time-dependent covariates is high. However, in case of few covariates the method is worth exploring [39].

To better illustrate the possible additive nature of CHD risk factors we created a severity grading from 0 to 15. Grade 0 referred to the following baseline characteristics: No close relatives with CHD, age 42, FBG <5.6 mmol/L and no glucose-lowering medication or diet, never smoked, BMI <25 kg/m^2, S-LDL-C < 3.4 mmol/L and no cholesterol-lowering medication, and SBP <120 mmHg, DBP <80 mmHg, and no blood pressure medication. Correspondingly, Grade 15 referred to the most severe risk profile with respect to CHD risk factors at baseline (Table 1). We do not suggest the grading as an alternative for well-established CHD risk scores, for example, but a way to concretise cohort-specific effects of CHD risk factors. In the grading, we applied the same severity classes as in other analyses to maintain coherence across results.

R 4.0.2 with the R packages "interactionR," "survival," and "timereg" served as a statistical platform [43,46–50].

Results

Baseline characteristics

All study participants were men, and their respective mean (SD) age, FBG concentration, BMI, S-LDL-C concentration, SBP, and DBP were 53.1 (5.1) years, 4.8 (1.2) mmol/L, 26.9 (3.6) kg/m^2, 4.0 (1.0) mmol/L, 134.2 (17.1) mmHg, and 88.7 (10.5) mmHg. Among those, who had ever smoked ($n = 1821$) the mean (SD) pack-year was 16.2 (18.9). Based on baseline examinations and interviews 724 men had CHD. Table 1 presents distributions of study participants by CHD risk factors and risk factor severity gradings.

Endpoints

Of men who were free of CHD at baseline ($n = 1958$), 717 (37%) had the disease and 301 (15%) died for CHD before the end of follow-up. All in all ($n = 2682$), 1777 (66%) men died, 541 (20%) men died for CHD, 905 (34%) men were alive, and 737 (27%) men were alive and free of CHD at the end of follow-up. The mean (SD) follow-up time was 21.4 (10.4) years among men who were free of CHD at baseline, 14.7 (10.6) years among men who had CHD at baseline ($n = 724$),

Table 2. CHD risk factor specific category-to-category hazard ratios (95% CI) together with *p*-values without and with covariate interactions and time dependence.

Risk factor	Model 1	Model 2	Model 3
Age of 42 years	1.48 (1.35 – 1.63)	1.91 (1.52 – 2.40)	1.94 (1.54 – 2.44)
Age of 48 years	$p < .001$	$p < .001$	$p < .001$
Age of 54 years		× Weight = 0.152	× Weight = 0.156
Age of 60 years		× S-LDL-C = 0.036	× S-LDL-C = 0.023
No family history	1.30 (1.17 – 1.44)	1.29 (1.16 – 1.43)	1.29 (1.16 – 1.43)
One with CHD	$p < .001$	$p < .001$	$p < .001$
Two or more with CHD			
No diabetes	1.64 (1.39 – 1.92)	1.63 (1.38 – 1.91)	1.63 (1.38 – 1.91)
Borderline or diet-treated	$p < .001$	$p < .001$	$p < .001$
Diabetes			
Never smoking	1.31 (1.19 – 1.45)	1.44 (1.23 – 1.69)	1.45 (1.23 – 1.70)
Previous smoker	$p < .001$	$p < .001$	$p < .001$
Current smoker		× Weight = 0.142	× Weight = 0.132
Normal weight	1.26 (1.13 – 1.42)	1.68 (1.23 – 2.29)	1.68 (1.23 – 2.30)
Overweight	$p < .001$	$p = .001$	$p = .001$
Obesity		× Age = 0.152	× Age 0.156
		× Smoking = 0.142	× Smoking = 0.132
Below borderline S-LDL-C	1.30 (1.18 – 1.42)	1.64 (1.29 – 2.08)	1.95 (1.43 – 2.67)
Borderline	$p < .001$	$p < .001$	$p < .001$
High S-LDL-C		× Age = 0.036	× Age = 0.023
			× TIME = 0.073
No hypertension	1.31 (1.16 – 1.49)	1.32 (1.16 – 1.49)	1.32 (1.17 – 1.50)
Borderline	$p < .001$	$p < .001$	$p < .001$
Hypertension			

Notes. Study participants were free of coronary heart disease (CHD) at baseline ($n = 1958$). Model 1: Basic multiplicative survival model. Model 2: With covariate interactions. Model 3: With covariate interactions and time dependence. S-LDL-C: Serum low-density lipoprotein cholesterol.

and 19.6 (10.8) years among all men. The respective risks of all-cause (and CHD) mortality were 0.62 (0.15), 0.77 (0.33), and 0.66 (0.20).

Interactions

We detected three multiplicative and one additive interactions across the covariates (Figure 1, Supplementary table 1). High S-LDL-C and obesity increased the risk of CHD more among men younger than 50 (RR for high S-LDL-C: 2.10, RR for obesity: 1.72) than those older than 50 (RR for high S-LDL-C: 1.22, RR for obesity: 1.11), and obesity increased the risk of CHD particularly among non-smokers (RR in non-smokers: 1.35, RR in smokers: 0.92). The interaction between weight and smoking statuses was significant both at multiplicative and additive scales.

Multiplicative and additive effects

Most covariates were multiplicative. In a basic multiplicative survival model, glycemic status related to the highest hazard ratio (HR). After considering covariate interactions and time dependence, the model emphasised age, weight status, and glycemic status as the strongest multiplicative covariates with the respective category-to-category HRs of 1.94, 1.68, and 1.63 (Table 2). The HR (95% CI) of age 60 compared to age 42 was 5.69 (2.22 – 14.58), that of obesity compared to normal weight was 1.72 (0.78 – 3.81), and that of diabetes compared to no diabetes was 2.75 (1.89 – 4.00). Improvements in the model fit from the basic model to the model with interactions and further to the model with interactions and time dependence were statistically only modest. In the first step, the −2 times the log of the likelihood (-2LL) decreased from 16,055 to 16,034 with the *p*-value of .183 and in the second step, -2LL decreased from 16,034 to 16,028 with the *p*-value of .461.

The only additive covariate was S-LDL-C status. Schoenfeld residuals indicated no violations of the proportional hazards assumption whereas the proportionality test pointed out S-LDL-C status. The *p*-value was = .033 when the model included covariate interactions and .043 when it did not. The additive effect of borderline high S-LDL-C compared to below borderline S-LDL-C and that of high S-LDL-C compared to borderline high S-LDL-C suggested two extra CHD cases per 1000 men during 10 years of follow-up, as the mean coefficient was 1.84×10^{-4}. The cumulative coefficient for S-LDL-C status increased almost linearly up to 18 years with the slope of c. 0.006 and then reached a plateau (Figure 2). When comparing high S-LDL-C to the combined group of borderline high and below borderline S-LDL-C, the additive effect suggested 2.5 extra CHD cases per 1000 men during 10 years of follow-up with the mean coefficient of 2.51×10^{-4}.

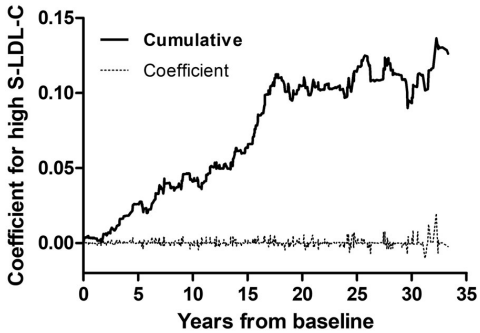

Figure 2. Additive effect of high serum low-density lipoprotein cholesterol (S-LDL-C) concentrations on the risk of coronary heart disease.

Concerning the severity grading of CHD risk factors, a one-point increase in the severity score increased the absolute risk of CHD by 6% regardless of whether men with CHD at baseline were included or excluded (Figure 3). From Grades 2 to 12, the relationship was linear with the *p*-value of $<.0001$, and it explained 97% of the variation in the absolute CHD risk. Between Grades 12 and 2, the respective RD (95% CI) and RR (95% CI) were 0.62 ($-0.45-0.85$) and 13 ($3.22-52.54$). The CIs were wide due to low number of men belonging to these grade categories, 15 and 39, respectively. Computationally, the 6% point-to-point increase in the risk corresponds to the RD of 0.60 and RR of 6.00, when the interval is 10 points. If including the uttermost grades (0, 1, 13, and 14) and men with CHD at baseline, the simple linear regression still explained 89% of the variation. Grade distributions followed a normal distribution, and no men reached the maximum score of 15 (Figure 3).

Discussion

Based on our findings considering covariate interactions and time dependence in survival modelling may refine results and ease to define the order of importance across the main CHD risk factors. Previous simulations and real data demonstrations have proposed that extending conventional Cox survival models improves model fit when predicting CHD by means of its risk factors [16,51]. Additive models also appear to emphasise partly different CHD risk factors than multiplicative models [16,17] and replacing both additive and multiplicative models with other techniques, such as survival trees and Fuzzy Logic-based models, highlights yet more risk factors [52,53]. Traditionally, studies have identified dyslipidemia as a pivotal CHD risk factor [8]. Comparisons across studies with respect to the order of significance among risk factors, however, are difficult because studies have applied different risk factor combinations and within-covariate variations greatly differ across studies. Among the main modifiable CHD risk factors, studies have pointed out at least unfavourable glycemic status [9,10] and smoking [6,51,52] as the strongest one, and survival tree analyses have suggested slightly different combinations of CHD risk factors for different age groups and genders [52].

Our study suggested high S-LDL-C as the strongest modifiable predictor of CHD in middle-aged men, which is in accordance with the traditional opinion [8]. At the same time, our study revealed the interaction between high S-LDL-C and age, the strongest non-modifiable predictor, as well as the time dependence of high S-LDL-C, as the relative significance of high S-LDL-C diminished together with increasing age and follow-up time. This time dependent interaction also is in accordance with earlier findings [54]. However, without considering both interactions and time dependence in the statistical model this study would have stressed other covariates, such as glycemic status, and omitted the importance of high S-LDL-C.

The associations of CHD with its main risk factors in the KIHD cohort appeared to be additive in that sense that each one-point increase in the risk factor severity grading increased the absolute risk of CHD just about equally and irrespective of the risk factor type. For example, becoming 6 years older, becoming overweight, and developing a precondition equally increase the risk of CHD i.e. by 6% over the next three decades. This finding for its part supports the traditional opinion of CHD as a multifactorial disease without any single dominant risk factor [8].

The additive effect of obesity on the CHD risk in the presence of smoking was negative i.e. the absolute risk of CHD was slightly lower among obese smokers (0.35) than among normal or overweight smokers (0.38). This effect for its part reflects the fact that smoking per se increases the risk of all-cause mortality, even more than obesity does [55]. In the KIHD cohort, the absolute risk of all-cause and non-CHD mortalities are highest specifically among non-obese smokers (0.78 and 0.61), evidently higher than among obese smokers (0.73 and 0.50). Correspondingly, multiplicative interactions of age with high S-LDL-C and obesity suggested the significance of high S-LDL-C and obesity among men younger than 50. A reason for this somewhat

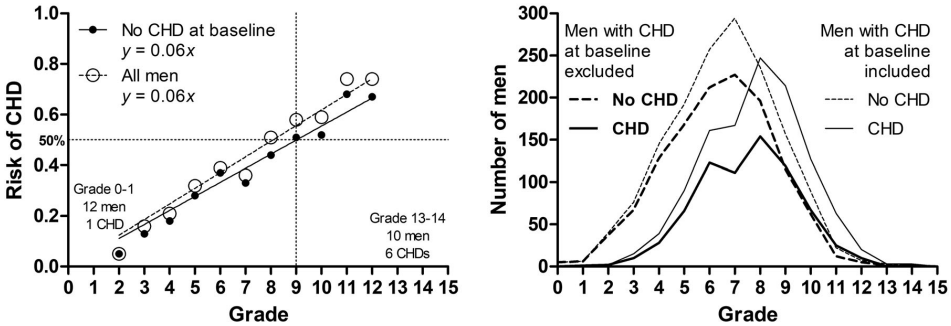

Figure 3. Relationship between the risk of coronary heart disease (CHD) and the severity grading of CHD risk factors.

surprising age-obesity relationship can partly relate to the duration of obesity, as the KIHD study participants who were obese and younger than 50 at KIHD baseline had the highest mean (95% CI) BMI in young adulthood (23.3, 22.9 – 23.8), statistically significantly ($p = .001$) higher than that of obese study participants who were older than 50 at KIHD baseline (22.5, 22.3 – 22.7). In other words, the KIHD study participants who were obese and younger than 50 at KIHD baseline could have exposed to obesity longer than the KIHD study participants who were obese but older than 50 at KIHD baseline. Irrespective of the direction of the interaction, however, the interaction should be considered in statistical models.

All in all, considering how long and intensively studies have underlined the importance of combining multiplicative, additive, and interactive effects in general and in the epidemiology of CHD [8–18], it is astonishing that covariate interactions and their time dependencies do not belong to the routine statistical procedures of epidemiological studies on CHD. One reason for the inequality between multiplicative and additive survival models may relate to the interpretation of their results. Results of multiplicative models can be understood as risk ratios but results of additive models should be at least partly reported as risk differences and additional cases, which, however, does not denote additive models are difficult to interpret per se [56].

Strengths and limitations

The present study is a longitudinal study with an exceptionally long follow-up period, whereas a whole range of previous findings concerning the nature of associations across CHD and its main risk factors originate from cross-sectional and case-control studies. This study also included information from all 10 main non-modifiable and modifiable CHD risk factors, whereas previous studies have typically included only some of them. On the other hand, this study focussed only on White Finnish males without detailed information regarding their genetic risk for CHD, which limits possibilities to generalise its findings [57]. Moreover, this study refers specifically to CHD, ICD 10 codes I20 – I25, as an endpoint, and because the main CHD risk factors are to some extent outcome sensitive [26], i.e. explanatory powers and the order of importance among risk factors slightly differ across endpoints, such as CHD, an acute myocardial infarction (AMI), and a fatal AMI, the present results are not directly generalisable to AMI and sudden cardiac death, although them are typical manifestations of CHD. Our previous paper provides analyses to verify this outcome sensitivity [26]. To control possible bias originated from inaccuracies related to exclusions of study participants based on the ergometer test we executed statistical analyses and reported their results also concerning the dataset without exclusions. The exclusions did not affect the results of this study, which is in accordance with our previous findings [26].

Conclusions

Considering interactions across the main CHD risk factors together with their time dependencies in a survival model on CHD incidence changed the order of importance among the risk factors compared to a simple multiplicative model. Without considering both interactions and time dependence the survival model stressed glycemic status as the strongest modifiable risk factor, whereas the extended model emphasised S-LDL-C status that research, traditionally, has identified as a pivotal CHD risk factor. Age overcame the family history of CHD as the strongest non-modifiable risk factor. This study seriously reminds the benefits of dealing simultaneously with multiplicative, additive, and interactive associations for validity.

From the clinical perspective, this study suggests high S-LDL-C concentrations being a very strong explanator of CHD risk among men younger than 50. Also, obesity is a strong explanator, but both age and smoking confound the relationship between CHD and obesity. Furthermore, this study proposes the order of importance among the main CHD risk factors, also in the clinical context, may slightly differ from the conventional order. Smoking, for example, could be a so strong predictor of non-CHD mortality that its role in the development of CHD, at least, at the population level may show moderate.

Author contributions

AV and TPT designed the study. AV analysed the data and draft the paper. CB, MK, and TPT were involved in the interpretation of the data and results, and they revised the paper critically for intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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Data availability statement

On request, the University of Eastern Finland's Institute of Public Health and Clinical Nutrition can admit an access to the KIHD database.

References

[1] Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke Statistics-2022 Update: a report from the American Heart Association. Circulation. 2022;145(8): e153–e639.
[2] Antman EM, Loscalzo J. Ischemic heart disease. In Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's principles of internal medicine. 20th ed. New York (NY): McGraw-Hill Education; 2018. p. 1–1866.
[3] Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes: the task force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2020;41(3):407–477.
[4] Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and Meta-analysis. PLoS Med. 2008;5(10): e207.
[5] The Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant Meta-analysis. Lancet. 2010;375(9709):132–140.
[6] The Lp-PLA_2 Studies Collaboration. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. Lancet. 2010;375(9725):1536–1544.
[7] C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC). Association between C reactive protein and coronary heart disease: mendelian randomization analysis based on individual participant data. BMJ. 2011;342:d548.
[8] Poulter N. Coronary heart disease is a multifactorial disease. Am J Hypertens. 1999;12(10 Pt 2):92S–95S.
[9] Yiannakouris N, Katsoulis M, Trichopoulou A, et al. Additive influence of genetic predisposition and conventional risk factors in the incidence of coronary heart disease: a population-based study in Greece. BMJ Open. 2014;4(2):e004387.
[10] Ding XQ, Ge PC, Liu Z, et al. Interaction between microRNA expression and classical risk factors in the risk of coronary heart disease. Sci Rep. 2015;5:14925.
[11] Li C, Ma R, Zhang X, et al. Risk of coronary heart disease in the rural population in Xinjiang: a nested case-control study in China. PLoS One. 2020;15(3): e0229598.
[12] Ye Y, Chen X, Han J, et al. Interactions between enhanced polygenic risk scores and lifestyle for cardiovascular disease, diabetes, and lipid levels. Circ Genom Precis Med. 2021;14(1):e003128.
[13] Huang Y, Hui Q, Gwinn M, et al. Interaction between genetics and smoking in determining risk of coronary artery diseases. Genet Epidemiol. 2022;46(3-4): 199–212.
[14] Silberberg JS. Estimating the benefits of cholesterol lowering: are risk factors for coronary heart disease multiplicative? J Clin Epidemiol. 1990;43(9):875–879.
[15] Wang Z, Yang T, Fu H. Prevalence of diabetes and hypertension and their interaction effects on cardiocerebrovascular diseases: a cross-sectional study. BMC Public Health. 2021;21(1):1224.
[16] Yin G, Cai J. Additive hazards model with multivariate failure time data. Biometrika. 2004;91(4):801–818.
[17] Nordahl H, Rod NH, Frederiksen BL, et al. Education and risk of coronary heart disease: assessment of mediation by behavioral risk factors using the additive hazards model. Eur J Epidemiol. 2013;28(2): 149–157.
[18] Lefebvre F, Giorgi R. A strategy for optimal fitting of multiplicative and additive hazards regression models. BMC Med Res Methodol. 2021;21(1):100.

[19] Salonen JT. Is there a continuing need for longitudinal epidemiologic research? The Kuopio Ischaemic Heart Disease Risk Factor Study. Ann Clin Res. 1988; 20(1 – 2):46–50.
[20] Salonen JT, Nyyssönen K, Korpela H, et al. High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish men. Circulation. 1992;86(3):803–811.
[21] Lakka TA, Venäläinen JM, Rauramaa R, et al. Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction. N Engl J Med. 1994;330(22):1549–1554.
[22] Banerjee A, Newman DR, Van den Bruel A, et al. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and Meta-analysis of prospective studies. Int J Clin Pract. 2012; 66(5):477–492.
[23] Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. –
[24] American Diabetes Association 2021. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care. 2021; 44(Supplement_1):S15–S33.
[25] Centers for Disease Control and Prevention. 2022. Defining adult overweight and obesity; [cited 2022 Feb 16]. Available from: https://www.cdc.gov/obesity/adult/defining.html.
[26] Voutilainen A, Brester C, Kolehmainen M, et al. Effects of data preprocessing on results of the epidemiological analysis of coronary heart disease and behaviour-related risk factors. Ann Med. 2021;53(1): 890–899.
[27] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–188. –
[28] Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer – even at low risk. BMC Med. 2020;18(1): 320.
[29] Salonen JT, Salonen R, Seppänen K, et al. HDL, HDL2, and HDL3 subfractions, and the risk of acute myocardial infarction. A prospective population study in Eastern Finnish men. Circulation. 1991;84(1):129–139.
[30] Atasoy S, Johar H, Peters A, et al. Association of hypertension cut-off values with 10-year cardiovascular mortality and clinical consequences: a real-world perspective from the prospective MONICA/Kora study. Eur Heart J. 2019;40(9):732–738. –
[31] Antza C, Doundoulakis I, Stabouli S, et al. American, European and international hypertension guidelines: time to shake hands? Int J Cardiol Hypertens. 2021;8: 100075.
[32] Franco OH, Peeters A, Bonneux L, et al. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis. Hypertension. 2005;46(2):280–286.
[33] Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Stat Sci. 2001;16(2): 101–133.
[34] Zou GY. On the estimation of additive interaction by use of the four-by-two table and beyond. Am J Epidemiol. 2008;168(2):212–224.
[35] Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia (PA): Lippincott Williams & Wilkins; 2008.
[36] Knol MJ, VanderWeele TJ, Groenwold RHH, et al. Estimating measures of interaction on an additive scale for preventive exposures. Eur J Epidemiol. 2011; 26(6):433–438. –
[37] Rothman KJ. Epidemiology: an introduction. New York (NY): Oxford University Press; 2012.
[38] Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol. 1972;34(2): 187–202.
[39] Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the Cox model. Survival Vignettes. 2017;2(3): 1–25.
[40] Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81(3):515–526.
[41] Therneau TM, Grambsch PM, Fleming TR. Martingale-based residuals for survival models. Biometrika. 1990; 77(1):147–160.
[42] Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993;80(3):557–572.
[43] Martinussen T, Scheike TH. Dynamic regression models for survival data. New York (NY): Springer; 2006.
[44] Aalen OO. A linear regression model for the analysis of life times. Stat Med. 1989;8(8):907–925.
[45] Aalen OO. Further results on the non-parametric linear regression model in survival analysis. Stat Med. 1993;12(17):1569–1588.
[46] Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York (NY): Springer; 2000.
[47] Scheike TH, Zhang MJ. Analyzing competing risk data using the R timereg package. J Stat Softw. 2011;38(2): i02.
[48] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
[49] Therneau T. A package for survival analysis in R. R Package Version 3.1-12. 2020. Available from: https://CRAN.R-project.org/package=survival.
[50] Babatunde YA. InteractionR: an R package for full reporting of effect modification and interaction. Software Impacts. 2021;10:100147.
[51] Yuan A, Guo Y, Shara NM, et al. An additive Cox model for coronary heart disease study. J Appl Stat. 2018;45(7):1325–1346.
[52] Ramezankhani A, Bagherzadeh-Khiabani F, Khalili D, et al. A new look at risk patterns related to coronary heart disease incidence using survival tree analysis: 12 years longitudinal study. Sci Rep. 2017;7(1): 3237.
[53] Brester C, Stanovov V, Voutilainen A, et al. Evolutionary fuzzy logic-based model design in predicting coronary heart disease and its progression. In:

Guervós JJM, Garibaldi J, Linares-Barranco A, Madani K, Warwick K, editors. Proceedings of the 11th International Joint Conference on Computational Intelligence, IJCCI 2019, Vienna, Austria, 2019 Sept 17–19. ScitePress; 2019. p. 360–366.

[54] Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ. 1994;308(6925):367–372.

[55] Freedman DM, Sigurdson AJ, Rajaraman P, et al. The mortality risk of smoking and obesity combined. Am J Prev Med. 2006;31(5):355–362.

[56] VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiol Methods. 2014;3(1):33–72.

[57] Yang C, Wang X, Ding H. Is coronary artery disease a multifactorial inherited disorder with a sex-influenced trait? Med Hypotheses. 2008;71(3): 449–452.

Supplementary table 1. 95% CIs for odds ratios (OR) to detect multiplicative interaction and the interaction contrast ratio (ICR) together with the risk difference (RD) to detect additive interaction.

Interaction	Multiplicative[1]	Multiplicative[2]	Additive[1]	Additive[2]
Age × No family history (0) Family history (1)	$p = 0.640$ OR0: 1.90–3.63 OR1: 1.28–2.33	$p = 0.228$ OR0: 1.88–2.84 OR1: 1.04–2.70	ICR: -1.27–0.85 RD0: 0.13–0.24 RD1: 0.06–0.20	ICR: -1.23–1.91 RD0: 0.16–0.27 RD1: 0.09–0.21
Diabetes × No family history (0) Family history (1)	$p = 0.969$ OR0: 1.22–3.04 OR1: 1.21–3.15	$p = 0.671$ OR0: 1.48–2.66 OR1: 0.92–3.20	ICR: -1.02–2.43 RD0: 0.05–0.26 RD1: 0.05–0.28	ICR: -1.29–3.43 RD0: 0.09–0.27 RD1: 0.07–0.24
Smoking × No family history (0) Family history (1)	$p = 0.127$ OR0: 0.81–1.41 OR1: 0.58–1.04	$p = 0.131$ OR0: 0.88–1.26 OR1: 0.97–2.37	ICR: -1.28–0.05 RD0: -0.07–0.05 RD1: -0.01–0.13	ICR: -0.12–2.34 RD0: -0.07–0.04 RD1: 0.00–0.11
Obesity × No family history (0) Family history (1)	$p = 0.594$ OR0: 0.96–1.88 OR1: 1.08–2.18	$p = 0.825$ OR0: 1.04–1.61 OR1: 0.73–2.01	ICR: -0.39–1.41 RD0: -0.01–0.14 RD1: 0.02–0.19	ICR: -0.95–1.68 RD0: -0.02–0.11 RD1: 0.00–0.14
Dyslipidemia × No family history (0) Family history (1)	OR0: 1.31–2.22 OR1: 1.41–2.44 $p = 0.665$	OR0: 1.43–2.03 OR1: 1.21–2.69 $p = 0.809$	ICR: -0.16–1.31 RD0: 0.06–0.17 RD1: 0.08–0.22	ICR: -0.24–2.32 RD0: 0.07–0.17 RD1: 0.09–0.19
Hypertension × No family history (0) Family history (1)	$p = 0.291$ OR0: 1.36–2.31 OR1: 1.10–1.90	$p = 0.351$ OR0: 1.69–2.41 OR1: 1.08–2.46	ICR: -0.78–0.62 RD0: 0.07–0.18 RD1: 0.02–0.15	ICR: -0.84–1.69 RD0: 0.12–0.22 RD1: 0.08–0.19
Diabetes × Age <50 (0) Age >50 (1)	$p = 0.563$ OR0: 1.12–4.46 OR1: 1.22–2.57	$p = 0.813$ OR0: 0.97–3.19 OR1: 1.42–2.56	ICR: -2.08–2.33 RD0: 0.02–0.34 RD1: 0.05–0.23	ICR: -0.50–2.83 RD0: 0.00–0.27 RD1: 0.09–0.23
Smoking × Age <50 (0) Age >50 (1)	$p = 0.767$ OR0: 0.69–1.54 OR1: 0.88–1.40	$p = 0.898$ OR0: 0.76–1.52 OR1: 0.92–1.34	ICR: -0.55–0.81 RD0: -0.07–0.08 RD1: -0.03–0.08	ICR: -0.49–0.71 RD0: -0.05–0.09 RD1: -0.02–0.07
Obesity × Age <50 (0) Age >50 (1)	$p = 0.032$ OR0: 1.36–3.50 OR1: 0.91–1.58	$p = 0.174$ OR0: 1.05–2.48 OR1: 0.92–1.45	ICR: -2.22–0.42 RD0: 0.06–0.27 RD1: -0.02–0.11	ICR: -1.30–0.59 RD0: 0.01–0.21 RD1: -0.02–0.09
Dyslipidemia × Age <50 (0) Age >50 (1)	$p = 0.002$ OR0: 1.89–4.17 OR1: 1.13–1.74	$p = 0.005$ OR0: 1.76–3.48 OR1: 1.19–1.71	ICR: -2.24–0.29 RD0: 0.12–0.28 RD1: 0.03–0.13	ICR: -1.45–0.52 RD0: 0.12–0.27 RD1: 0.04–0.13
Hypertension × Age <50 (0) Age >50 (1)	$p = 0.932$ OR0: 1.05–2.26 OR1: 1.26–1.96	$p = 0.194$ OR0: 1.11–2.15 OR1: 1.65–2.40	ICR: -0.27–1.27 RD0: 0.01–0.15 RD1: 0.06–0.16	ICR: 0.60–1.92 RD0: 0.02–0.16 RD1: 0.12–0.21
Smoking × No diabetes (0) Diabetes (1)	$p = 0.956$ OR0: 0.87–1.32 OR1: 0.53–2.09	$p = 0.194$ OR0: 0.94–1.33 OR1: 0.48–1.38	ICR: -1.26–1.75 RD0: -0.03–0.06 RD1: -0.15–0.18	ICR: -1.55–0.61 RD0: -0.01–0.07 RD1: -0.18–0.08
Obesity × No diabetes (0) Diabetes (1)	$p = 0.923$ OR0: 1.00–1.70 OR1: 0.66–2.41	$p = 0.980$ OR0: 0.92–1.44 OR1: 0.69–1.90	ICR: -1.22–1.92 RD0: 0.00–0.13 RD1: -0.10–0.21	ICR: -0.95–1.35 RD0: -0.02–0.09 RD1: -0.09–0.15

[1]Study participants free of coronary heart disease at baseline ($n = 1958$). [2]All study participants ($n = 2682$). Borderlines highlight statistically significant interactions.

Supplementary table 1. Continues.

Interaction	Multiplicative[1]	Multiplicative[2]	Additive[1]	Additive[2]
Dyslipidemia × No diabetes (0) Diabetes (1)	p = 0.478 OR0: 1.48–2.19 OR1: 0.74–2.69	p = 0.542 OR0: 1.48–2.06 OR1: 0.89–2.46	ICR: -1.59–2.25 RD0: 0.09–0.18 RD1: -0.07–0.24	ICR: -1.08–1.95 RD0: 0.10–0.17 RD1: -0.03–0.21
Hypertension × No diabetes (0) Diabetes (1)	p = 0.755 OR0: 1.31–1.94 OR1: 0.70–2.88	p = 0.812 OR0: 1.59–2.23 OR1: 1.10–3.77	ICR: -1.68–1.77 RD0: -0.09–0.25 RD1: 0.06–0.15	ICR: -0.66–2.14 RD0: 0.11–0.19 RD1: 0.02–0.32
Obesity × No smoking (0) Smoking (1)	p = 0.034 OR0: 1.25–2.16 OR1: 0.53–1.46	p = 0.007 OR0: 1.19–1.90 OR1: 0.54–1.19	ICR: -1.50–(-0.01) RD0: 0.05–0.18 RD1: -0.04–0.09	ICR: -1.29–(-0.19) RD0: 0.04–0.16 RD1: -0.15–0.04
Dyslipidemia × No smoking (0) Smoking (1)	p = 0.830 OR0: 1.37–2.16 OR1: 1.28–2.51	p = 0.953 OR0: 1.41–2.06 OR1: 1.28–2.22	ICR: -0.52–0.68 RD0: 0.07–0.18 RD1: 0.06–0.21	ICR: -0.49–0.50 RD0: 0.08–0.18 RD1: 0.06–0.19
Hypertension × No smoking (0) Smoking (1)	p = 0.649 OR0: 1.27–2.01 OR1: 1.26–2.44	p = 0.887 OR0: 1.65–2.46 OR1: 1.49–2.59	ICR: -0.39–0.78 RD0: 0.05–0.16 RD1: 0.05–0.21	ICR: -0.47–0.68 RD0: 0.12–0.21 RD1: 0.10–0.23
Dyslipidemia × No obesity (0) Obesity (1)	p = 0.870 OR0: 1.43–2.16 OR1: 1.17–2.87	p = 0.895 OR0: 1.45–2.05 OR1: 1.16–2.44	ICR: -0.53–1.67 RD0: 0.08–0.18 RD1: 0.04–0.26	ICR: -0.54–1.05 RD0: 0.09–0.17 RD1: 0.04–0.22
Hypertension × No obesity (0) Obesity (1)	p = 0.953 OR0: 1.28–1.94 OR1: 0.88–2.74	p = 0.676 OR0: 1.30–3.59 OR1: 1.62–2.30	ICR: -0.91–0.87 RD0: 0.06–0.15 RD1: -0.03–0.23	ICR: -1.55–0.25 RD0: 0.12–0.20 RD1: 0.07–0.29
Hypertension × No dyslipidemia (0) Dyslipidemia (1)	p = 0.100 OR0: 1.48–2.51 OR1: 1.05–1.84	p = 0.074 OR0: 1.84–2.89 OR1: 1.34–2.17	ICR: -1.00–0.69 RD0: 0.08–0.19 RD1: 0.01–0.15	ICR: -0.65–0.88 RD0: 0.14–0.24 RD1: 0.07–0.19

[1]Study participants free of coronary heart disease at baseline (n = 1958). [2]All study participants (n = 2682). Borderlines highlight statistically significant interactions.

III

What is the most appropriate follow-up time for detecting the epidemiological relationship between coronary artery disease and its main risk factors: novel findings from a 35-year follow-up study

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ARI VOUTILAINEN

A prospective cohort study (PCS) is one of the main study types in epidemiology. This thesis evaluated the current statistical validity in PCSs of coronary heart disease (CHD) and demonstrated how the statistical choices that researchers make affect the study results. The statistical validity of PCSs of CHD was found to be poor. The demonstrations did not find a statistical reason to exclude study participants having CHD at baseline; they detected mostly multiplicative associations; and they found the most appropriate follow-up time as being dependent on the risk factor and CHD manifestation.

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