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Department of Community Medicine

Gender differences in the influence of physical activity and non-smoking on risk of heart failure in a general population

A meta-analysis and systematic review

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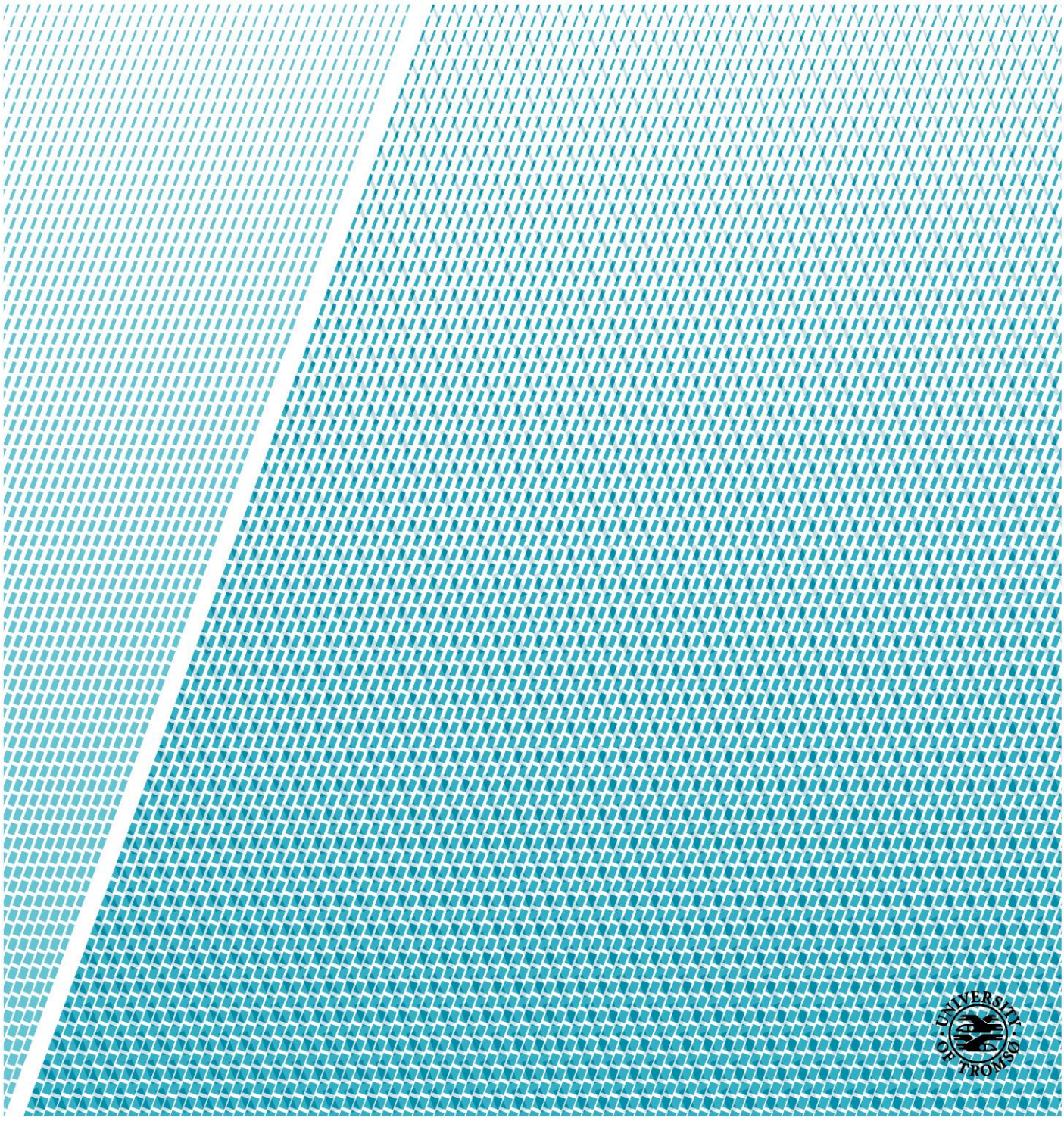
Master's thesis in Public Health, May 2019



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Foreword

Summary:

Background and Introduction: Heart failure (HF) is a serious disease, which shows poor prognoses and high morbidity in both genders. This results in enormous challenges for caregivers, researchers, and policy makers in addition to suffering of affected person and his or her family. There is some controversy regarding the association between life style factors and the incidence of HF in men and women. The relationship between physical activity and smoking and risk of HF has mostly been reported irrespective of gender; however, similar doses of physical activity and smoking cessation may contribute differently to protection against HF in men and women. In the present thesis, a systematic review and a meta-analysis were carried out to investigate the influence of gender on association between smoking and physical activity with the incidence of HF.

Methods: The meta-analysis and systematic review are based on literature identified by search in the MEDLINE, EMBASE and CINHAL databases up to February the 1st, 2019. Risk ratios (RR) and hazard ratios (HR) estimate from observational studies were pooled in a random-effect meta-analysis.

Findings: 2413 articles' abstracts were reviewed and identified 9 population cohort studies (more than 3 million participants, 52.6% women), that adjusted for common cardiovascular risk factors.

For analyses of the effect of smoking on HF, a total of 8 population cohort studies involving 2,986,217 participants (48.55% women) with a mean range of follow-up time of 5.5 to 19 years, with 68,983 cases of HF (2.31% of all participants developed HF, and 48.0% of HF cases were women) were included. The risk of HF among smokers was higher than in non-smokers, with higher risks in women than in men. In women, pooled HR was 1.83; 95% CI, (1.62, 2.05),

I^2=0.0% (p= 0.72), and for men pooled HR was 1.58; 95% CI (1.41, 1.75), I^2= 38.6% (p= 0.180).

For analyses of the effect of physical activity, a total of 6 cohort studies involving 1,105,467 participants (47.0% women) with the range of mean follow-up time of 5.8 to 19 years, with 60,158 cases of HF (5.44% of all participants developed HF) were included. According to estimated effect sizes in the included studies, engaging in high levels of physical activity was associated with a significant reduction of HF incidence in both men and women. The effect of high levels of physical activity on the risk reduction of incident HF was stronger in women than in men. In women, pooled HR was 0.69; 95% CI, (0.61, 0.76), I^2=0.0% (p= 0.676), and for men pooled HR was 0.73; 95% CI (0.66, 0.81), I^2= 70.9% (p= 0.0.32).

Interpretation: Smoking and physical inactivity increased the risk of HF. Risk increase was for both stronger in women than in men. It is not clear whether the different risk of HF among men and women is biological or related to the patterns of behaviors. However, policies addressing smoking and physical inactivity should consider gender specific adaptations particularly in those countries where women are less physically active than men, while at the same time smoking prevalence is increasing among young women.

Key messages

- ✓ This study presents a review of population-based cohort studies, which include contemporary health records from more than 3 million adults with more than 60,000 HF cases.
- ✓ A heterogeneous association between current smoking or being physically active and incidence of HF in men and women was observed.
- ✓ The effect of two important health-related behaviors on HF stratified by gender, which have seldom been studied in large scale cohort or reviews, was investigated.
- ✓ The findings suggest differences in underlying HF mechanisms between men and women which are important for risk prediction, clinical practice and etiological research.

List of abbreviations:

WHO:	World health organization	CVDs:	Cardiovascular diseases
CVD:	Cardiovascular disease	CAD:	Coronary artery disease
ACS:	Acute coronary syndrome	IHD:	Ischemic heart disease
GBD:	Global burden of disease	DALY:	Disability-adjusted life years
BP:	Blood pressure	HF:	Heart failure
HTN:	Hypertension	QOL:	Quality of life
MI:	Myocardial infarction	EF:	Ejection fraction
LVEF:	Left ventricular ejection fraction	HFrEF:	Heart failure with reduced ejection fraction
HFpEF:	Heart failure with preserved ejection fraction	HFmrEF:	Heart failure with mid-range ejection fraction
LV:	Left ventricular	IDCM:	Idiopathic dilated cardiomyopathy
VHD:	Valvular heart disease	DM:	Diabetes mellitus
AF:	Atrial fibrillation	MeSH:	Medical subject headings
MH:	Myocardial hypertrophy	CHD:	Coronary heart disease
HR:	Hazard ratios	RR:	Relative risk, Risk ratios
CI:	Confidence Interval	NYHA:	The New York heart association
hx:	history	LVH:	Left ventricular hypertrophy
HRT:	Hormone replacement therapy	OCP:	Oral contraceptive pill

Hb:	Hemoglobin	WBC:	White blood cells
COPD:	Chronic obstructive pulmonary disease	USA:	United states of America
NHANES:	The national health and nutrition examination survey	UK:	United Kingdom
CHF:	Congestive heart failure	ICD:	International classification of diseases
COSM:	Cohort of Swedish men	SMC:	Swedish mammography cohort
HMO:	Health maintenance organization study	uCI:	Upper confidence interval
lCI:	Lower confidence interval		

1 Introduction

1.1 Background

According to World Health Organization (WHO), cardiovascular disease (CVD) is one of the four most prominent chronic diseases (1). Modifiable biological risk factors for CVD include smoking cigarettes, sedentary life style, being overweight or obese, having elevated blood pressure, and elevated cholesterol (2, 3). Among the non-modifiable risk factors, sex may impact the risk of CVD biologically but also behaviorally; for instance, physical inactivity and smoking cigarettes are not equally distributed between men and women (4).

1.1.1 The global burden of cardiovascular disease

CVD refers to a group of diseases of heart and/or blood vessels (5). CVD includes coronary artery disease (CAD) resulting in acute coronary syndrome (ACS) and ischemic heart disease (IHD), peripheral artery disease, cerebrovascular disease (stroke), hypertension, myopathies, valvular disease and several other conditions (6). Despite all progress in research and significant advances in therapies and preventions, CVD is the leading cause of death among men and women worldwide (7, 8). The global burden of disease (GBD) study estimated that CVD caused 29.6% of all deaths (more than 15.6 million deaths) in 2010, which is more than double the number of deaths caused by cancers. CVD deaths are estimated to grow to more than 17.3 million deaths per year and are expected to grow to more than 23.6 million deaths by 2030 (9-11), (Figure 1). Over the last decade, the age-standardized prevalence rate of CVD and disability-adjusted life years (DALYs) due to CVD have been falling in most countries, particularly in Northern, Southern and Western European countries. However, CVD is still responsible for the loss of more than 64 million DALYs in Europe (23% of all DALYs lost) (12).

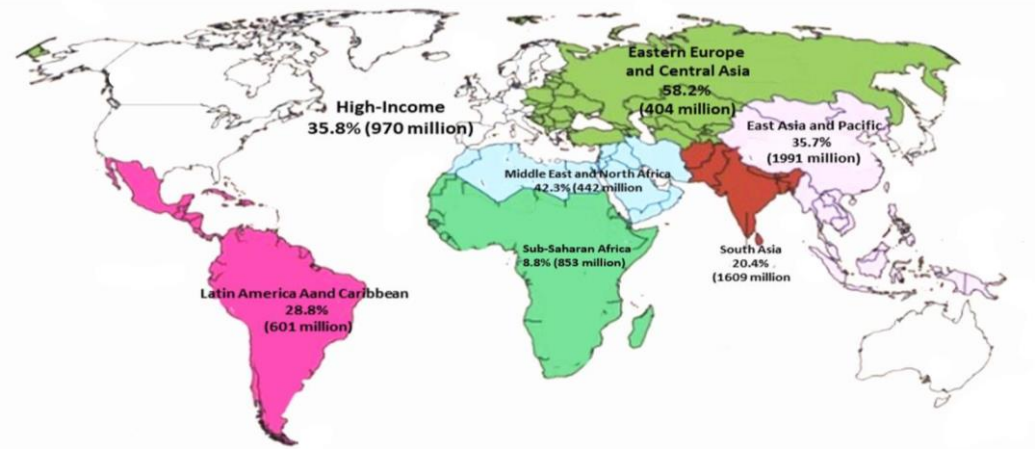


Figure 1 Percentage of CVD deaths in each region, From GBD study, 2010 (13)

1.1.2 Burden of CVD in Norway

According to statistics reported by Norwegian Cause of Death Registry and Norwegian Cardiovascular Disease Registry, mortality due to CVD in Norway peaked in 1970 and has fallen since. From 2000 until today, there has been a strong decline in mortality from CVD in all parts of Norway. During 2000-2013, the mortality rate was almost halved (14). CVD risk factors have improved, demonstrating a decrease in blood pressure (BP), cholesterol levels, and smoking (14), however, CVD still causes most deaths in Norway. The superior longevity in women tends to increase the overall prevalence rates and number of deaths on a sex specific basis (Figure 2).

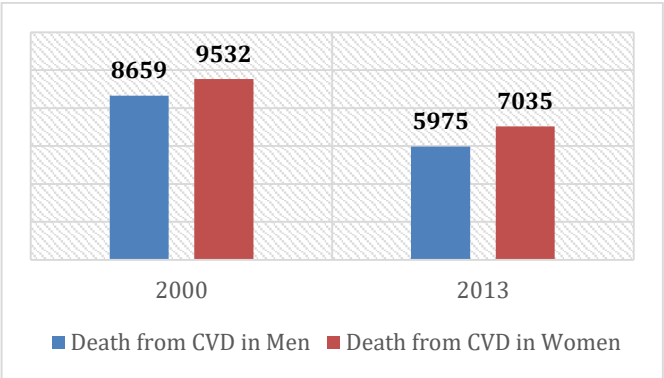


Figure 2 Number of deaths from CVD in Norway, 2000 to 2013 (14), The greater longevity in women tends to increase the overall prevalence rates and number of deaths on a sex specific basis

1.1.3 The impact of heart failure

Cardiovascular diseases culminate in heart failure (HF) (15-17). HF is a serious complication of a wide variety of heart diseases. Coronary artery disease (CAD), either alone or in combination with hypertension (HTN), seems to be the most common cause of HF particularly in industrialized countries (18) (Figure 3). HF contributes to poor prognoses and high morbidity in men and women of the western world as well as worldwide (8, 19, 20). In the USA and Europe, HF is responsible for a large proportion of mortality, and diverse morbidity which leads to diminished quality of life (QOL) in affected patients and their relatives (21). The gradual adoption of a western lifestyle in developing countries may lead to a pandemic of HF in the future. It is estimated that HF afflicts 26 million people worldwide, and the prevalence is increasing as the population ages (22). In western Europe and the United States alone, more than 6 million people are diagnosed with HF annually. In these regions, over 1 million hospitalizations have occurred due to HF (23). Consequently, HF poses high health-care-related costs resulting in a great burden on both patient and society (24). HF affects 5.7 million people in US, and among Medicare recipients, represents the most common reason for hospitalization, with annual costs of more than 30$ billion in treatment expenditure and lost productivity (25, 26).

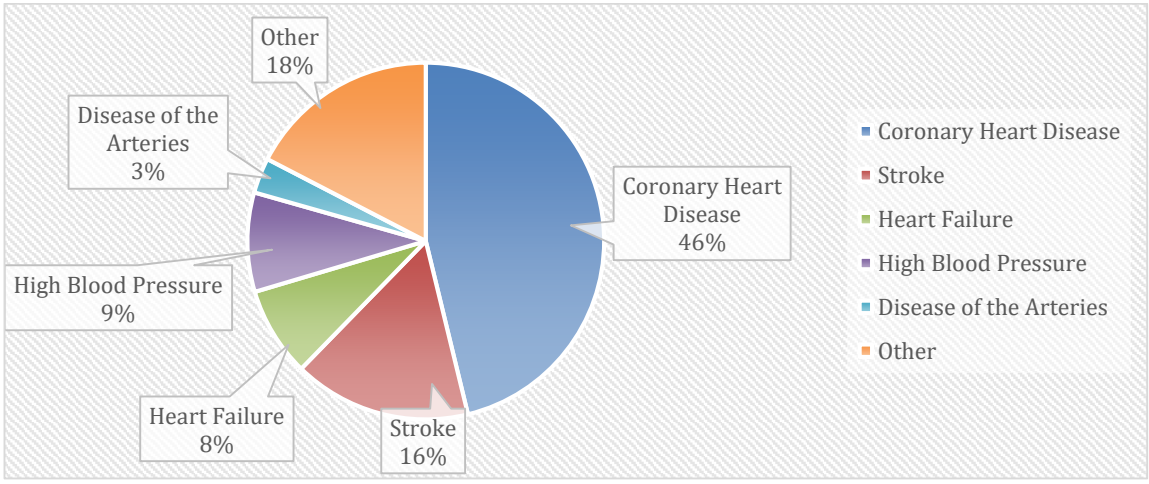


Figure 3 Percentage breakdown of deaths attributable to CVD, USA, 2013 (26)
According to controversy in HF diagnosis, HF is not a true underlying cause of death and HF may accounts for 36% or more of CVD deaths (26)

1.1.4 Heart failure in Norway

According to the Norwegian Cardiovascular Disease Registry, in 2012, HF as underlying cause was responsible for 11.35% of all CVD cases (14) (Figure 4). The prevalence of the HF is expected to increase as the population ages. Sex-specific differences exist in development of HF and addressing these differences can have an impact on HF prevention (27).

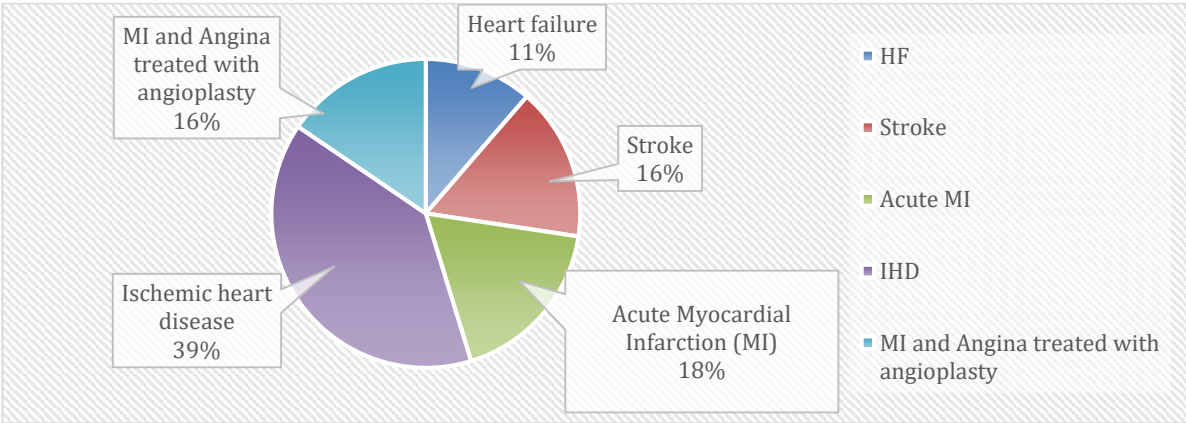


Figure 4 Cause of CVD death in Norway, 2012 (14)

1.2 Terminology, assessment and paradigms

1.2.1 Heart failure definition

HF is defined as reduced ability of the heart to pump and/or fill with blood to supply blood to the tissues commensurate to the metabolic needs or these needs are only met after compensatory adaptation (22, 28-30). Clinically, HF might be labelled a syndrome without uniform diagnostic criteria (28, 29). Repeated attempts to develop an agreement for exact description of the clinical syndrome of HF have been done, however, no single conceptual statement for HF diagnosis has withstood the test of time (31). In spite of this, at the individual level, the New York Heart Association criteria for HF classification based on symptoms and clinical examination is well acknowledged and used worldwide.

1.2.2 Heart failure pathophysiology

HF is a progressive disorder often linked to an index event which either damages the heart muscle or, alternatively, disrupts the ability of the myocardium to generate force, thereby preventing the normal contracting of heart. The index events are varied; they may be myocardial infarction (MI), or hereditary as in the case of genetic cardiomyopathies, or a result of volume overload and increase in hemodynamic pressure. Regardless of the nature of the index events, the feature of HF is common: the pumping capacity of the heart declines (13).

1.2.3 Classification of heart failure

HF is now often characterized based on echocardiographic examination and measurement of ejection fraction (EF): HF with reduced ejection fraction (HFrEF; EF ≤40%), HF with preserved ejection fraction (HFpEF; EF ≥50%), and HF with mid-range ejection fraction or borderline (HFmrEF; 41%-49%) (22, 32, 33).

HFrEF is associated with poor contractility and systolic cardiac dysfunction, whereas HFpEF is associated with impaired myocardial relaxation and diastolic dysfunction (34). About half of the HF patients have a HFpEF (20). Also, about 50% of hospitalizations due to HF is related to HFpEF, which is more common at advance age and in women (35). The HFpEF and HFmrEF remain without effective proven therapies and represent an important challenge in the future, particularly in developing countries (22, 36).

1.2.4 Presentations of heart failure

In most cases, after the initial decline in pumping capacity of the heart, patients will remain asymptomatic or minimally symptomatic or symptoms develop only after the dysfunction has been present for some time. The explanation for this is that a number of compensatory mechanisms become activated to modulate left ventricle (LV) function within a

physiologic/homeostatic range, so the patient's functional capacity is preserved or is depressed only minimally (13). End-organ changes with LV remodeling happen as the result of sustained activation of neurohormonal and cytokine systems, which cause symptomatic HF. However, LV remodeling is sufficient for progression of HF independent of the neurohormonal status of the patient. Experimental and clinical evidence suggest overexpression of biologically active molecules causing HF progression by exerting deleterious effect on heart and circulation (13, 31).

1.2.5 Etiology of heart failure

According to clinical trials and registers, the etiology of HF can be ischemic or non-ischemic heart disease, hypertensive heart disease, idiopathic dilated cardiomyopathy (IDCM), and valvular heart disease (VHD) with or without comorbidities of diabetes (DM), hypertension (HTN), atrial fibrillation (AF), angina, and respiratory disease. According to the Framingham heart study in 1965, hypertension was the most common cause of HF, as a primary cause in 30% of men and 20% of women and as a cofactor in another 33% of men and 25% of women. However, as CAD became more prevalent, CAD was increasingly identified as the cause of new cases of HF, increasing from 22% in the 1950s to around 70% in the 1970s (18).

1.2.6 Heart failure risk factors

Due to the first NHANES epidemiologic follow up study, risk factors for HF include male sex, physical inactivity, cigarette smoking, overweight and obesity status, hypertension, diabetes mellitus, coronary heart disease (CHD) and valvular heart disease (37-39). The distribution of the aforementioned risk factors, and the prevalence and manifestations of HF, however, differ among men and women.

1.3 Smoking and physical inactivity as modifiable risk factors for heart failure

1.3.1 Cigarette smoking, CVD and heart failure

According to WHO, 5.4 million deaths annually are attributable to smoking cigarettes worldwide (40, 41). If the current trend in smoking continues, by 2025 ten million deaths per year are anticipated due to smoking (42-44). Amongst all deaths caused by tobacco smoking, 35-40% of them are related to CVD (45, 46). Tobacco increases the risk of CVDs not only for active smokers but also, for passive smokers the risk of CVD increases to 25 to 30% (47). Smoking is a mixture of several toxic chemicals (48, 49). In the pathogenesis of HF, carbon monoxide, nicotine and oxidant chemicals are commonly implicated (50). Tobacco has numerous effects on the human body, which may contribute to foster development of HF. These effects include endothelial dysfunction, insulin resistance, alteration in lipid profile and hyper coagulated state. The synergy of all these pathobiological mechanisms may cause atherothrombosis and HF (51).

1.3.2 Physical Activity, CVD and heart failure

According to animal and human studies, physical activities and exercise cause structural and functional cardiovascular responses which reduce the risk for chronic disease (34). Physical activity is defined as any bodily movement produced by contraction of skeletal muscles which results in energy consumption above the basal level (52). Physical activity may be categorized into occupational (associated with the performance of a job), commuting (daily journeys) and leisure-time physical activity (with sports, recreational, and exercise/training, performed during free time based on personal interests and needs) (53). Physical fitness is defined as the ability to carry out vigorous tasks without fatigue with ample energy to enjoy leisure-time pursuits and

to meet unforeseen emergencies (52). In healthy general populations, cardiorespiratory fitness and aerobic physical activity significantly reduces the risk of CVD morbidity and mortality (54-58). Physical activity modulates biological pathways relevant to atherosclerosis, myocardial ischemia and myocardial infarction (MI), blood pressure regulation, lipid and lipoprotein metabolism, insulin sensitivity, glycemic control, adiposity distribution, skeletal muscle mass and function, oxidative stress, immunologic reactivity, demand/supply of cardiac oxygen, and myocardial electrical stability. All these factors lead to beneficial structural adaptions for HF prevention and improve the health status of HF patients (34).

1.4 The role of gender and sex in heart disease and heart failure risk factors

The term "sex" refers to physical and physiological features. This reflects the biology at the cellular level as well as the integrated physiology of the individual including chromosomes, the hormone levels and functions, and reproductive systems (59), whereas the term "gender" additionally refers to the socially constructed roles of people in the term of typical habits, behaviors and attitudes typically associated with males and females (60). In the present thesis, we refer to sex and gender differences between men and women as "gender" differences to incorporate sex-related (biological) and gender-related (sociocultural) dimensions. The factors associated with development of HF differ to some extent by both sex and gender aspects (61, 62). According to the sex definition, differences in HF between men and women are mainly related to pathophysiological mechanisms, whereas the gender definition suggest that differences in HF between men and women are mainly explained by differences life style factors.

1.4.1 Sex differences in cardiovascular pathophysiology

Generally, females differ from men in several aspects, including having smaller ventricles and stiffer hearts, with hypertrophy, apoptosis, fibroblast and proliferation being typically less pronounced in aged female hearts (63). Moreover, compared to male hearts, female human hearts adapt differently to pressure overload (8). Physiological myocardial hypertrophy (MH) may be a result of exercise and pregnancy (64), and transition from physiological MH to pathological MH is less common in females than in males (65). Interstitial fibrosis appears more often in male hearts than in females' (66). In terms of myocardial structure, a study has shown that change in myocyte numbers and myocyte sizes differ considerably between men and women (63). There are wide variations in male and female sex hormones. There are sex hormone receptors in extra-gonadal tissue including the heart related to the hormonal effects on the myocardium and cardiac vessels and their coordinated regulation of functions (8, 15, 67, 68). HF in the female heart is often diastolic because of diabetes and hypertension, whereas HF in male heart is often systolic associated with CAD (8).

1.4.2 Gender differences in heart failure

HF decreases quality of life (QOL) for patients and their relatives. QOL in HF patients decreases because changes in skeletal muscles, lungs and circulation contribute to fatigue, dyspnea and limited exercise capacity (69). There is a study that has shown physical health status and social functions among women with HF are worse than in men with HF (69). Women more frequently have HTN, DM, obesity, and other attributable risk factors for HF, and impaired myocardial metabolism is more severe in women than in men (8).

1.4.3 Epidemiology of heart failure in men and women

HF is becoming a large and growing public health burden, especially among women at advanced ages (70). Epidemiological studies show a higher incidence of HF in women than in men in adults older than 55 years (27). HF seems to develop at more advanced ages in women than in men (15) (Figure 5). Approximately 10% of 70-year-olds are affected by HF, and the prevalence of HF is continuously increasing with advancing age. Women with HF are older than their male counterparts due to their longer lifespan (8, 15). In women, HF accounts for 35% of all cardiovascular mortality and the higher incidence is related to post-menopausal ages (71). Among women, the underlying cause of HF differs in premenopausal and post-menopausal women. In men, HF mainly presents with CAD and MI, while in premenopausal women LV dysfunction is the frequent underlying cause of HF, and in post-menopausal women, HTN is the predominant underlying cause of HF (17, 71).

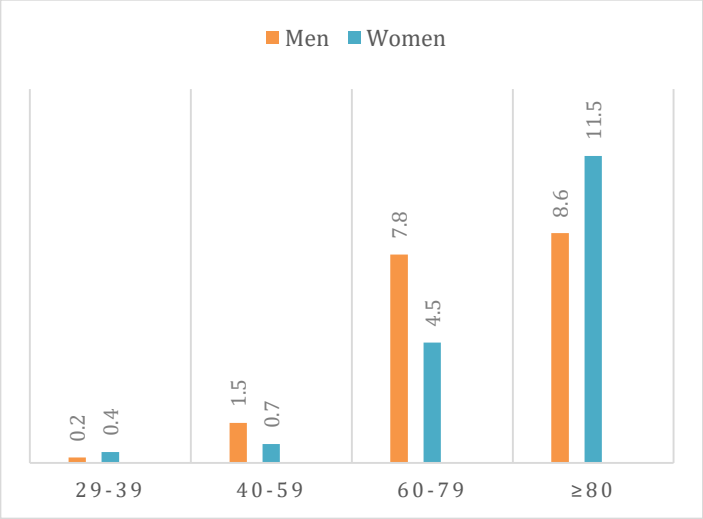


Figure 5 Prevalence of HF by gender (72)

1.5 Role of gender in smoking and physical activity

1.5.1 Gender-specific patterns of smoking

The pattern of smoking behavior among men and women varies by time and society. For decades, in some societies, women were less likely to smoke cigarettes than men, due to widespread social disapproval of women's smoking. However, during the mid-twentieth century, in some western countries including USA, smoking adoption by women increased due to a general liberalization of norms for women's behaviors, increasing equality between the genders, and growing social acceptance of women's smoking (73). Socially and financially, women have become more equal to men, which contributes to changes in women's behaviors with a shift toward men's behaviors, and the behavioral pattern of smoking is no exception. In contemporary times in some societies, the general characteristics of traditional male roles and men's greater social power generally contribute to widespread social pressures against women's behavior and greater restrictions on women's smoking. Another issue is related to traditional female role expectations that cause gender differences in personal experiences and influence smoking adoption by women. Some aspects of female roles have contributed to gender differences in costs and benefits of smoking such as physical attractiveness that is more emphasized for females. The beauty ideal of being slender is an incentive of smoking for women (73). Currently, one fifth of world smokers are women which contributes to annually 1.5 million deaths of smoker women out of 5 million occurred directly due to tobacco (41, 74). Some countries have reported an increase in smoking among young women compared with young men. Smoking might affect men and women unequally, which is shown to be true by some studies (27, 75-78), and there is debate about whether potentially sex difference influences the effect of risk factor for different CVD phenotypes e.g. HF.

1.5.2 Gender-specific patterns of physical activity

The health benefits of physical activity is well documented (79, 80), and a sedentary lifestyle has been observed in populations of both developing and developed countries (81, 82). There is inconsistency in studies as to whether men are more active in leisure-time than women (82-86), but recent data suggest there is no gender differences in terms of the sum of all-domain of physical activity (87). However, the involved variables that are associated with physical activity and the pattern of physical activity in women and men fluctuate considerably in high, low or middle-income countries among traditional and modern style of living. Also, there is a strong association between socioeconomic level and leisure-time physical activity (88, 89). The bias of gender and sex is exemplified by the fact that men more likely tend to practice sports while women mostly perform daily walking (90). Lower levels of education are associated with low levels of physical activity, which may have negative health effects (91, 92), potentially impacting women more than men. Some studies suggest that gender differences in physical activity are age-dependent, with middle-aged men and older women being more sedentary (93).

Considering such epidemiological information might contribute to improving the long-term of cardiovascular health for men and women.

1.6 Rationale for the study

Although improved primary prevention and recent advances in treatment have led to increased survival of CAD, HF is still a major consequence of CAD, MI and hypertension (35, 94-102). By considering gender differences in the pathophysiology of HF and health-related behaviors, this review will contribute to increased understanding of HF as a major public health burden worldwide. CVD and risk factors are expressed differently according to gender, a perspective that is often neglected by traditional medicine. While the pathophysiology of development of

HF in men and women is different, many of the protective approaches for HF prevention are still similar for men and women. Recent studies suggest there is a lower risk of developing HF in adults who are physically active and non-smokers (103-105). Strong evidence reported the protective effect of regular physical activity against CHD (HF risk factor) (37, 106-108). Benefits of physical activity for risk of HF has been reported irrespective to genders, while the same dose of physical activity may have different protective effects against HF in men and women. The link between smoking and CVD is proven and well-documented. Regarding HF, smoking cigarettes is a leading cause of preventable HF (39). Generally, the focus of previous smoking research has been on other CVDs' phenotypes such as MI, CAD, or fatal HF among patients rather than general population. Research addressing non-fatal HF stratified by genders have been less commonly studied (109).

1.7 Aim of the study

The main objective and purpose of this thesis was to examine evidence for potential gender differences in the association of physical activity and non-smoking with risk of HF in a general population by conducting a meta-analysis and a systematic review.

Four main goals were addressed: (a) To examine the association of smoking and physical inactivity with risk of HF. (b) To examine whether the included study results are homogeneous and consistent. (c) To obtain a global effect size of the relationship between smoking, physical activity, and HF. (d) To examine whether the association between smoking, physical inactivity and HF differ between men and women.

It was hypothesized that gender plays an important role for the effect of smoking and physical activity on the risk of HF, and that similar doses of physical activity and a similar history of smoking have different effects on the incidence of HF in men and women.

2 Method of the study

2.1 Design

Using a meta-analysis and a systematic review, available scientific evidence of the association of smoking and physical activity with HF in men and women was reviewed and discussed.

2.2 Criteria for considering studies for this review

2.2.1 Types of studies

Observational cohort population studies that directly compared men and women are considered eligible to be included in the review.

2.2.2 Types of participants

Furthermore, studies had to include general populations in community settings (free of CVDs), that were followed over time, irrespective of age and ethnicity.

2.2.3 Types of exposures

Exposure must include cigarette smoking and physical activity. We sorted exposures to smoking vs non-smoking, and high physical activity vs low physical activity.

2.2.4 Types of outcome measures

The outcome of interest is incidence of HF. The result is considered as binary outcome:

Difference in incidence of HF was measured between smoker vs non-smoker men and women.

Difference in incidence of HF was measured between high physical active vs low physical active men and women.

2.3 Search method for identification of studies

The MEDLINE, EMBASE and CINHAL databases were searched for eligible studies. For assessing the effect of physical activity, studies published from January 1st, 1995 (in 1995, the physical activity categorization changed due to statements by U.S. Centers for disease control) (110) to February the 1st, 2019, are considered. For assessing the effect of smoking, studies from inception 1995 to February the 1st, 2019, were considered. The search was conducted by using the following combination of medical subject headings (MeSH) terms and free words of "smoking", "smoking tobacco", "smoking cigarettes", "physical activity", "lifestyle factors", "exercise", "sedentary lifestyle", "physical inactivity", pairing with "heart failure", "gender differences", "sex differences". The controlled vocabulary of MeSH from PubMed/MEDLINE, and (Emtree) from EMBASE, including subheadings, publication types and supplementary concepts, were used. The objective was kept in focus by avoiding too many different search concepts by using a wide variety of search terms in combination (text words, mesh term, Emtree), and by using "or" between them. This made our search strategies sensitive in the different search engines. In the main database search, the combination of four sets of entry terms were applied (Figure 6). The search was performed three times. The search details are provided in the supplementary search list in Appendix 1. The reference lists of the identified studies and articles were also manually screened to identify any additional relevant studies. The language was limited to English.

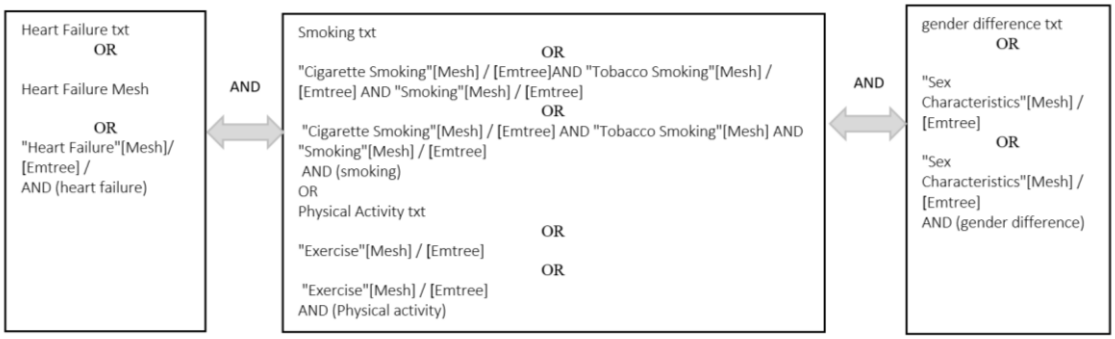


Figure 6 search term boxes

2.4 Assessment of risk of bias in included studies

The assessment of the methodological quality of included studies was done according to the Cochrane Collaboration tool for assessing risk of bias (111). Six domains of bias were assessed: (i) Selection bias. (ii) Performance bias. (iii) Detection bias. (iv) Attrition bias: incomplete outcome data. (v) Reporting bias: Selective outcome reporting. (vi). Other sources of bias and potential threats to validity.

All selected studies were assessed and categorized into high, low or unclear risk of bias for all aforementioned domains. The details are summarized in Appendix 2 and Appendix 3.

2.5 Data collection

2.5.1 Data extraction and management

Results from studies that met the inclusion criteria were extracted. The risk ratios (RR) estimates and the hazard ratios (HR) estimates from cox proportional analysis with 95% confidence intervals (CIs) with available p-value for related risk factors of HF among men and women were extracted from included studies and analyzed. The following information was extracted and recorded for each study using a standardized form: name of the first author, year of publication, country of the study, study design, study name, mean follow-up duration, population characteristics at the baseline, inclusion and exclusion criteria for each study, sample size (participants, HF cases), outcome measures, diagnostic criteria for HF if mentioned, diagnosis measurements such as Framingham criteria and NYHA Classification to diagnose and categorized HF patients, number of men and women in each category, information regarding methodological quality and exposures definition, HF events, the relative risk and risk ratios (RR), hazard ratio (HR) for each group with 95% confident interval (95% CI) with their

p-value, and the co-variables in multivariable adjusted HR. These forms with summary of included studies are presented in Appendix 2 and Appendix 3.

2.6 Data synthesis

A meta-analysis was conducted when possible due to consistency of available data of included studies. For pooling the effect size from the studies in which clinical heterogeneity was observed, a random-effect model was applied. The RR for each group of studies with 95% confident interval (95%CI) and p-value were extracted. Heterogeneity among the included studies was investigated using Cochran's Q test and I^2 with a P value of <0.1 considered statistically significant (111). Publication bias was considered. Data syntheses were conducted using STATA software (Stata 15-Windows). The software was used to calculate the pooled RR and HR values and 95% CIs for risk of HF in relation to the exposures and show them in forest plots. The extent of heterogeneity was tested with I^2 0%, 25%, and 75% representing low, medium, and high heterogeneity, respectively.

2.7 Identifying and measuring heterogeneity

The heterogeneity of studies and variability among studies was assessed with $\mathbf{I^2}$, and the overlap of the CIs in the forest plot graphs and whiskers. The statistical heterogeneity was assessed by checking the p value of $\mathbf{I^2}$. Studies are regarded as homogeneous if CIs of all studies overlap and if $\mathbf{I^2}$ was 40% or lower. (Figure 7) (112). When we observed high heterogeneity between studies (I^2) > 80.0%, subgroup meta-analyses were reperformed across studies to explore the observed heterogeneity.

I^2: (Ranges between 0 to 100%)	Heterogeneity (= Diversity between studies)
The importance of inconsistency of the results of studies due to I^2	
0% to 40%	might not be important
30% to 60%	may represent moderate heterogeneity
50% to 90%	may represent substantial heterogeneity
75% to 100%	considerable heterogeneity

Figure 7 The magnitude and direction of the effects and the strength of evidence for heterogeneity such as p value from the chi-squared test, or a confidence interval for I^2, explain the importance of the observed value of I^2 (111, 113)

2.8 Measure of exposure effects and dealing with missing data

2.8.1 Interpreting the HR

The HR may also have been referred to as relative risk (RR). The measured outcome is dichotomous (HF event). Therefore: If the calculated RR or HR was > 1 this shows higher risk of HF in exposure group. If the calculated RR or HR was < 1 this shows reduced risk of HF in exposure group.

2.8.2 Missing data

For missing statistical data, an available case analysis was executed and important numbers for analyzing data were calculated: the percentage of women and men in each category, the prevalence of HF where it was applicable, the crude numbers from given percentage.

The hazard ratios for each lifestyle factor are presented for one unit of the variable analyzed.

The HF incidence rate for each study was calculated following this formula:

$$\text{Incidence rate} = \frac{Number\ of\ new\ HF\ case}{Population\ at\ risk \times years} \times 10^5$$

3 Results

The study selection process based on the literature search is shown in figure 8. The descriptions of included studies are available in table of "Characteristics of included studies" in appendix 2 and appendix 3. The listed of excluded studies is available in appendix 4.

3.1 Description of studies

For the first step, a basic search was done with the total of 2007 obtained references by electronic search through CINHAL (n= 355), MEDLINE (n= 409), and EMBASE (n=1243). An advance search was then carried out obtaining a total 359 articles by electronic search through CINHAL (n=39), MEDLINE (n=195), and EMBASE (n= 125). All the obtained articles from the basic search and advanced searched were screened to identify relevant studies. Also a manual check of reference list of included papers has done which resulted in 47 articles. All the references (2413 articles) were screened by titles and abstracts. Of the retrieved articles, 154 references were kept for possible inclusion. Assessment according to the inclusion criteria resulted in 46 eligible studies, of which 9 studies were finally included in the systematic review and meta-analysis. The flow diagram depicts the summary of the different stages of the systematic literature review (Figure 8). The list of excluded and included articles are available in appendix 2-4.

Nine studies were finally included (seven articles on the effect of smoking, and six articles on the effect of physical activity) in the systematic review and meta-analysis. Four articles included data for both the effect of smoking and physical activity (2, 37, 103, 114). Three articles included data, only for effect of smoking (109, 115, 116). Two articles include data only for effect of physical activity (53, 117). One cohort from Finland contributes to three publications for the effect of physical activity (2, 53, 117). One cohort of UK contribute to 2

publications for the effect of smoking (103, 109). One publication consists of results from two cohort studies in Sweden (114).

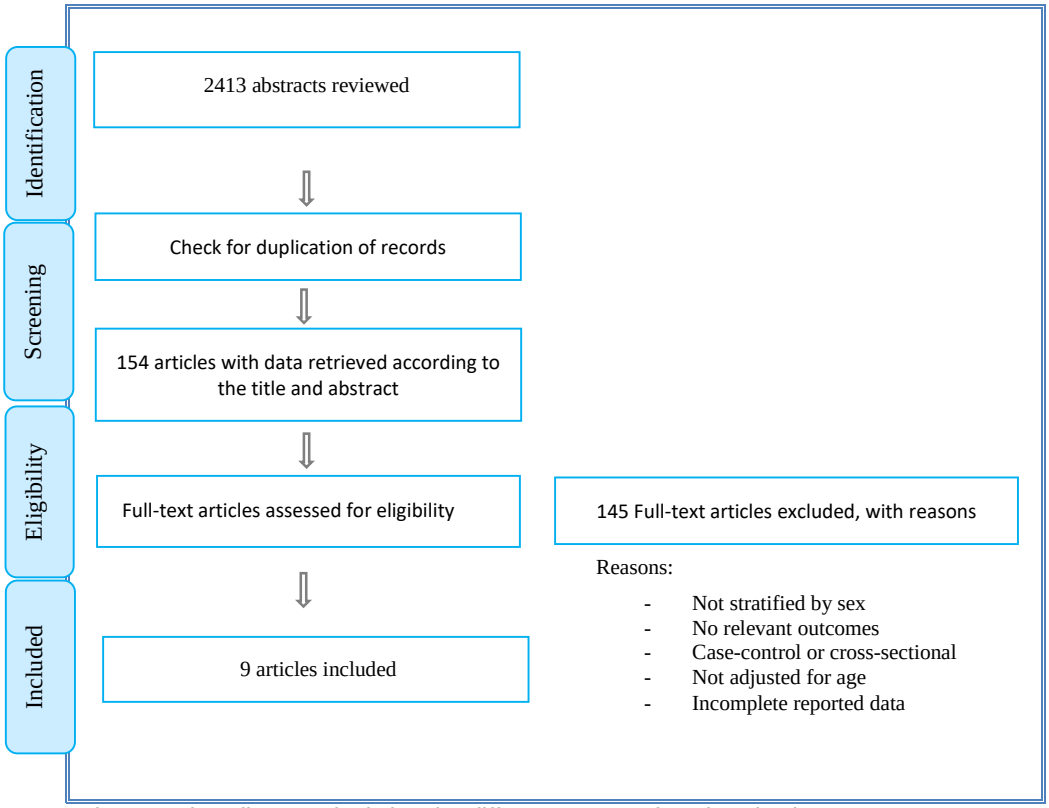


Figure 8 Flow diagram depicting the different stages of study selection

3.2 Results of the search

3.3 Description of the participants

3.3.1 Baseline characteristics of participants in studies assessing the effect of smoking

For analyses of the influences of gender on the association of smoking and HF, seven studies were included (2, 37, 103, 109, 114-116) in the meta-analysis and systematic review according to eligibility criteria. Baseline in the cohort studies occurred in the 1960s and end of follow-up was at latest 2010. The four developed countries UK, USA, Finland and Sweden were the settings of the studies. Two population studies from UK (103, 109) used the same data sources

(CALIBER). Since their study aims, follow-up time and their inclusion/exclusion criteria were different, the number of participants and HF events differed in their studies. To avoid overestimation, studies from the same data sources are considered separately in each meta-analysis. The baseline age of the participants was not restricted to a specific age group. The range of mean follow-up time was 5.5 to 19 years. At baseline, mean BMI of the included populations ranged from 23.2 to 29.1 kg/m2 for men and from 22.4 to 29.9 kg/m2 for women. A detailed summary of the baseline characteristics of participants in the included studies is shown in table 1 and table 2.

3.3.1.1 Incidence rates of HF in studies to addressing the effect of smoking

HF incidence rates differed between sexes and varied between studies. Overall, incidence rates were higher in men than in women except in the study of Alexander et al. (115), and in the study of Rodríguez et al. (109), in which, the HF events were higher in women. The highest incidence rate was observed for in the study of Uijl et al. (103) with HF incidence of 9.93 per 1000 populations per year for men, and 9.1 per 1000 populations per year for women (Table 1).

3.3.2 Baseline Characteristics of participants in studies assessing the effect of physical activity

For analyses of the influence of gender on the association between physical activity and HF, seven cohort studies from six publications were included (2, 37, 53, 103, 114, 117) in accordance with the eligibility criteria and the availability of data. The cohort studies started in 1972 and ended at latest in 2010. The four developed countries of UK, USA, Finland and Sweden were the setting of the studies. Three population studies (2, 53, 117) used the same data sources (FINRISK study). Since their study aims, follow-up time, and their inclusion/exclusion criteria were different, the number of participants and HF events differed in those studies. To

avoid overestimation, studies from the same data sources are considered separately in each meta-analysis. The baseline age of the participants was not restricted. The range of mean follow-up time was 5.8 to 19 years. Mean baseline BMI ranged from 23.2 to 29.1 kg/m2 for men and from 22.4 to 29.9 kg/m2 for women. Participants engaging in ≥150 minutes of physical activity per week were considered physically active, which is consistent in all included studies, and at least 5.3% of participants were physically active at baseline. A summary table of baseline characteristics of participants in included studies on physical activity and HF is available in table 3 and table 4.

3.3.2.1 Incidence rates of HF in studies addressing the effect of physical activity

HF incidence rates differed between genders and varied between studies. Overall, incidence rates were higher in men than in women. The highest incidence rate was observed in the study by Uijl et al. (103) from UK with HF incidence of 9.93 per 1000 populations per year for men and 9.1 per 1000 populations per year for women (Table 3).

Additional data from the studies were sourced for in the articles and are summarized in tables 1-4.

3.4 Effect of the exposures and outcome

We present the results of the studies as shown in tables 5-8 and plots in graph 1 and 6. All studies estimated the effect of physical activity and smoking on HF by HR or RR from cox proportional hazards regression analyses.

Table 1. Baseline characteristic of studies for investigating the effect of smoking on risk of HF. Part 1

	Authors	Year	Country	Study name	Participants		Mean years of follow-up	HF cases		Incidence rate Per 1000 population		Age range of participants
					Men	Women		Men	Women	Men	Women	
1.	Alicia Uijl (103)	2019	UK	CALIBER	871 687		5.8	47 987		9.49		≥ 55 y/o
					404 645	467 042		23 314	24 673	9.93	9.1	
2.	Jiang He (37)	2001	USA	NHANES 1	13 643		19	1 382		5.33		1 – 74 y/o
					5 545	8 098		741	641	7.33	4.16	
3.	Yujie Wang (2)	2011	Finland	FinRisk	38 072		14.1	1 083		2.02		25 –74 y/o
					18 346	19 726		638	445	2.46	1.6	
4.	Mark Alexander (115)	1995	USA	HMO	57 842		9.5	1 330		2.42		≥40 y/o
					27 708	30 134		618	712	2.34	2.48	
5.	Mar Pujades-Rodriguez (109)	2014	UK	-	1 937 360		5.5	14 359		1.34		≥ 30 y/o
					958 329	979 031		6 206	8 153	1.17	1.51	
6.	Andreas Kalogeropoulos (116)	2009	USA	-	2 934		7.1	258		12.38		70 – 79 y/o
					1 405	1 529		140	118	14.03	10.86	
7.	Susanna C. Larsson (118)	2016	Sweden	COSM & SMC	64 679		13	2 584		3.07		45 – 83
					33 966	30 713		1 488	1 096	3.36	2.74	
Total					2 986 217			68 983				
					1 449 944	1 536 273		33 145	35 838			

Table 2Baseline characteristic of studies for investigating the effect of smoking on risk of HF. Part 2

	Authors	Women (%)	Categories		Physically active (%)		Mean Age (y/o)		Mean BMI (kg/m2)		Smokers (%)	
					men	women	men	women	men	women	men	women
1.	Alicia Uijl (103)	53.58	Age: 55-64 y		56.5	47.2	-	-	28.5	29.8	32.4	26.2
			Age: 65-74 y		51.9	39.7	-	-	27.3	28.1	19.7	16.5
			Age: ≥75 y		37.7	24.5	-	-	25.7	25.5	12.5	7.3
2.	Jiang He (37)	59.36	-		63	51	52.2	48.1	25.7	26.6	40.7	31.1
3.	Yujie Wang (2, 114)	51.82	No. healthy factor: 0		0.0	0.0	47.5	44.9	29.1	29.9	100	100
			No. healthy factor: 1		16.7	5.3	48.2	48.8	27.8	28.9	53.8	41.5
			No. healthy factor: 2		41.8	19.9	47.2	47.8	26.9	27.1	28.3	21.5
			No. healthy factor: 3		70.2	52.7	44.3	44.0	25.3	24.5	11.5	8.9
			No. healthy factor: 4		100	100.0	41.4	41.0	23.2	22.4	0.0	0
4.	Mar Pujades-Rodriguez (109)	58.82	All with smoking data		-	-	46.0	47.9	26.7	26.1	23.64	17.50
			Missing smoking data		-	-	45.4	50.9	27.3	26.7	-	-
5.	Andreas Kalogeropoulos (116)	52.1	-		-		73.6		27.3		10.5	
6.	Susanna C. Larsson (118)	47.48%	-		77	73	59.3	60.9	26	25	24	23
7.	Mark Alexander (115)	52.10	African-American	Without CHF	-		51.7		-		59.8	
				With CHF	-		59.8		-		63.5	
			White	Without CHF	-		55.4		-		56.7	
				With CHF	-		67.4		-		59.1	

Table 3 Baseline characteristic of studies for investigating the effect of physical activity on risk of HF. Part 1

No	Authors	Year	Country	Study name	Participants		Mean years of follow-up	HF cases		Incidence rate Per 1000 population		Age range of participants
					Men	Women		Men	Women	men	women	
1.	Alicia Uijl (103)	2019	UK	CALIBER	871 687		5.8 y	47 987		9.49		≥ 55 y/o
					404 645	467 042		23 314	24 673	9.93	9.1	
2.	Jiang He (37)	2001	USA	NHANES 1	13 643		19 y	1 382		5.33		1 – 74y/o
					5 545	8 098		741	641	7.33	4.16	
3.	Yujie Wang (2)	2011	Finland	FinRisk	38 072		14.1 y	1 083		2.02		25 –74 y/o
					18 346	19 726		638	445	2.46	1.6	
4.	Gang Hu (117)	2010	Finland	FinRisk	59 178		18.4 y	3 614		3.32		24 – 74y/o
					28 842	30 336		1 921	1 693	3.62	3.03	
5.	Yujie Wang (53)	2010	Finland	FinRisk	58 208		18.4 y	3 508		3.27		25 – 74y/o
					28 334	29 874		1 868	1 640	3.58	2.98	
6.	Susanna C. Larsson (118)	2016	Sweden	COSM & SMC	64 679		13 y	2 584		3.73		
					33 966	30 713		1 488	1 096	3.36	2.74	45 – 83y/o
Total					1 105 467			60 158				
					519 678	585 789		29 970	30 188			

Table 4 Baseline characteristic of studies for investigating the effect of physical activity on risk of HF. Part 2

No	Authors	Women(%)	categories		Physically active (%)		Mean Age (y/o)		Mean BMI (kg/m2)		Smokers (%)	
					men	Women	men	women	men	women	men	women
1.	Alicia Uijl (103)	50.75	Age: 55-64 y		56.5	47.2	-	-	28.5	29.8	32.4	26.2
			Age: 65-74 y		51.9	39.7	-	-	27.3	28.1	19.7	16.5
			Age: ≥75 y		37.7	24.5	-	-	25.7	25.5	12.5	7.3
2.	Jiang He (37)	59.36	-		63	51	52.2	48.1	25.7	26.6	40.7	31.1
3.	Yujie Wang (2)	51.82	No. healthy factor: 0		0.0	0.0	47.5	44.9	29.1	29.9	100	100
			No. healthy factor: 1		16.7	5.3	48.2	48.8	27.8	28.9	53.8	41.5
			No. healthy factor: 2		41.8	19.9	47.2	47.8	26.9	27.1	28.3	21.5
			No. healthy factor: 3		70.2	52.7	44.3	44.0	25.3	24.5	11.5	8.9
			No. healthy factor: 4		100	100.0	41.4	41.0	23.2	22.4	0.0	0.
4.	Gang Hu (103, 117)	51.26	-		61.8	60.0	45.0	45.0	26.4	26.4	41.1	18.0
5.	Yujie Wang (53)	51.32	Occupational physical activity	Low	-	-	48.5	46.8	26.5	26.0	41.8	19.3
				Med	-	-	42.2	42.4	26.4	25.7	36.6	18.7
				High	-	-	43.0	44.2	26.3	26.6	43.2	16.3
			Commuting Physical Activity	Low	-	-	46.2	47.1	26.5	26.5	45.3	18.3
				Med	-	-	42.2	42.1	26.3	25.8	38.1	19.0
				High	-	-	46.0	43.9	26.1	25.6	39.6	17.7
			Leisure-Time physical Activity	Low	-	-	45.5	45.7	26.7	26.9	50.0	21.6
				Med	-	-	46.3	45.2	26.5	25.8	41.8	17.8
				High	-	-	41.0	41.3	25.7	25.0	27.8	12.4
6.	Susanna C. Larsson (118)	47.48%	-		77	73	59.3	60.9	26	25	24	23

Table 5 Smoking and risk of HF in women

Author		Year	Country	Study name	Study design	Statistical test	Exposure, Endpoint	Effect measure	RR, HR	95%l CI	95%uCI	Reference group
Alicia Uijl (103)	55 – 64 y/o	2019	UK	UK-based CALIBER	Cohort	Cox proportional hazards regression	Current smoking, HF	Multivariate HR	1.33	1.18	1.49	Never smoker
	65 – 74 y/o								1.21	1.11	1.32	
	≥75 y/o								1.08	0.99	1.19	
Jiang He (37)		2001	USA	NHANES I	Cohort	Cox proportional hazards regression	Current smoking, CHF	Multivariate RR	1.88	1.53	2.30	Never and ex-smoker, p < 0.001
Yujie Wang (2)		2011	Finland	FINRISK	Prospective cohort	Cox proportional hazards regression	Current smoking, HF	Multivariable HR	2.09	1.59	2.74	Never smoker, p for trend < 0.001
Mark Alexander (115)		1995	USA	HMO	Retrospective Cohort	Cox proportional hazards regression	Smoked > 1year, First Hospitalization for CHF	Multivariate RR	1.64	1.12	2.39	Non-smoker, (Smoked ≤ 1 year)
Mar Pujades-Rodriguez (109)		2014	UK	CALIBER	Cohort	Cox proportional hazard regression	Current smoking, fatal or non-fatal CVD across	Age adjusted HR	1.77	1.47	2.13	Never smokers, p for interaction ≤ 0.05
Andreas Kalogeropoulos (116)	Black	2009	USA	Health ABC study	cohort	Cox proportional hazards regression	Current smoking, HF	unadjusted RR	1.75	0.85	3.32	Never and ex-smoker, p = 0.87
	White								2.72	1.17	5.64	p = 0.22
Susanna C. Larsson (114)		2016	Sweden	COSM and SMC	Prospective cohort	Cox proportional hazards regression	noncurrent smoking, HF	Multivariable RR	0.63	0.54	0.73	-

uCI: upper confidence interval, lCI: lower confidence interval, HR: hazard ratio, RR: relative risk, risk ratio

Table 6 Smoking and risk of HF in men

Author		Year	Country	Study name	Study design	Statistical test	Exposure, Endpoint	Effect measure	RR, HR	95%l CI	95%uCI	Reference group
Alicia Uijl (103)	55 – 64 y/o	2019	UK	UK-based CALIBER	Cohort	Cox proportional hazards regression	Current smoking, HF	Multivariate HR	1.27	1.14	1.40	Never smoker
	65 – 74 y/o								1.15	1.07	1.24	
	≥75 y/o								1.05	0.95	1.16	
Jiang He (37)		2001	USA	NHANES I	Cohort	Cox proportional hazards regression	Current smoking, CHF	Multivariate RR	1.45	1.24	1.70	Never and ex-smoker p <0.001
Yujie Wang (2)		2011	Finland	FINRISK	Prospective cohort	Cox proportional hazards regression	Current smoking, HF	Multivariable HR	1.86	1.51	2.30	Never smoker, p for trend < 0.001
Mark Alexander (115)		1995	USA	HMO	Retrospective Cohort	Cox proportional hazards regression	Smoked > 1year, First Hospitalization with CHF	Multivariate RR	2.18	1.46	3.25	Non-smoker, (Smoked ≤ 1 year)
Mar Pujades-Rodriguez (109)		2014	UK	CALIBER	Cohort	Cox proportional hazards regression	Current Smoking, fatal or non-fatal CVD	Age adjusted HR	1.57	1.47	2.13	Never smokers, p for interaction ≤ 0.05
Andreas Kalogeropoulos (116)	Black	2009	USA	Health ABC study	cohort	Cox proportional hazards regression	Current smoking, HF	unadjusted RR	1.88	1.01	3.35	Never and ex-smoker, p = 0.87
	white								1.32	0.42	3.21	Never and ex-smoker, p = 0.35
Susanna C. Larsson (114)		2016	Sweden	COSM and SMC	Prospective cohort	Cox proportional hazards regression	noncurrent smoking, HF	Multivariable RR	0.75	0.71	0.79	-

uCI: upper confidence interval, lCI: lower confidence interval, HR: hazard ratio, RR: relative risk, risk ratio

Table 7 Physical activity and risk of HF in women

Author		Year	Country	Study name	Study design	Statistical test	Exposure, endpoint		HR	95% lCI	95% uCI	Reference group
Alicia Uijl (103)	55 – 64 y/o	2019	UK	UK-based CALIBER	Cohort	Cox proportional hazard regression	Sedentary life style, HF	Multivariate HR	1.09	1.00	1.19	Physical active
	65 – 74 y/o								1.09	1.01	1.17	
	≥75 y/o								1.08	1.02	1.15	
Jiang He (37)		2001	USA	NHANES I	Cohort	Cox proportional hazard regression	Low physical activity, CHF	Multivariable RR adjusted for some variables	1.34	1.15	1.58	Physical active p < 0.001
								Multivariate RR	1.31	1.11	1.54	p = 0.002
Yujie Wang (2)		2011	Finland	FINRISK	Prospective cohort	Cox proportional hazard regression	High Occupational and leisure time physical activity, HF	Multivariable HR	0.64	0.48	0.86	Light physical active, P for trend= 0.009
Gang Hu (117)		2010	Finland	-	Prospective Cohort	Cox proportional hazard regression	High Physical activity, HF	Multivariate adjusted for age and study year	0.54	0.47	0.61	Low physical activity, p_{trend} < 0.001
								Multivariate adjusted HR	0.68	0.59	0.78	p_{trend} < 0.001
Yujie Wang (53)		2010	Finland	-	Prospective Cohort	Cox proportional hazard regression	High leisure time physical activity, HF	Adjusted for some covaraibles	0.74	0.59	0.92	Low physical activity p_{trend} < 0.001
								Adjusted for more covaraibles	0.75	0.60	0.94	p_{trend} = 0.001
Susanna C. Larsson (114)		2016	Sweden	COSM and SMC	prospective cohort	Cox proportional hazard regression	Physical activity, HF	Multivariable RR	0.71	0.63	0.81	-

uCI: upper confidence interval, lCI: lower confidence interval, HR: hazard ratio, RR: relative risk, risk ratio

Table 8 Physical activity and risk of HF in men

Author		Year	Country /Reports	Study name	Study design	Statistical test	Exposure, endpoint		RR, HR	95%lCI	95%uCI	Reference group
Alicia Uijl (103)	55 – 64 y/o	2019	UK	UK-based CALIBER	Cohort	Cox proportional hazard regression	Sedentary life style, HF	Multivariate HR	1.06	0.99	1.13	Physical active
	65 – 74 y/o								1.11	1.04	1.17	
	≥75 y/o								1.09	1.02	1.16	
Jiang He (37)		2001	USA	NHANES I	Cohort	Cox proportional hazard regression	Low physical activity, CHF	Multivariable RR adjusted for some variables	1.30	1.08	1.57	Physical active, p = 0.007
								Multivariate RR, adjusted for all listed Co-variables	1.14	0.94	1.38	p = 0.19
Yujie Wang (2)		2011	Finland	FINRISK	Prospective cohort	Cox proportional hazard regression	High Occupational and leisure time physical activity, HF	Multivariable HR	0.67	0.53	0.86	Light physical activity, p for trend= 0.006
Gang Hu (117)		2010	Finland	-	Prospective Cohort	Cox proportional hazard regression	High Physical activity, HF	Multivariate adjusted for age and study year	0.75	0.66	0.86	Low physical activity p_{trend} < 0.001
								Multivariate adjusted HR	0.86	0.75	0.99	p_{trend} < 0.001
Yujie Wang (53)		2010	Finland	-	Prospective Cohort	Cox proportional hazard regression	High leisure time physical activity, HF	Adjusted for some covaraibles	0.66	0.55	0.79	Low physical activity p_{trend} < 0.001
								Adjusted for more covaraibles	0.65	0.54	0.77	p_{trend} < 0.001
Susanna C. Larsson (114)		2016	Sweden	COSM and SMC	prospective cohort	Cox proportional hazard regression	Physical activity, HF	Multivariable RR	0.83	0.74	0.94	-

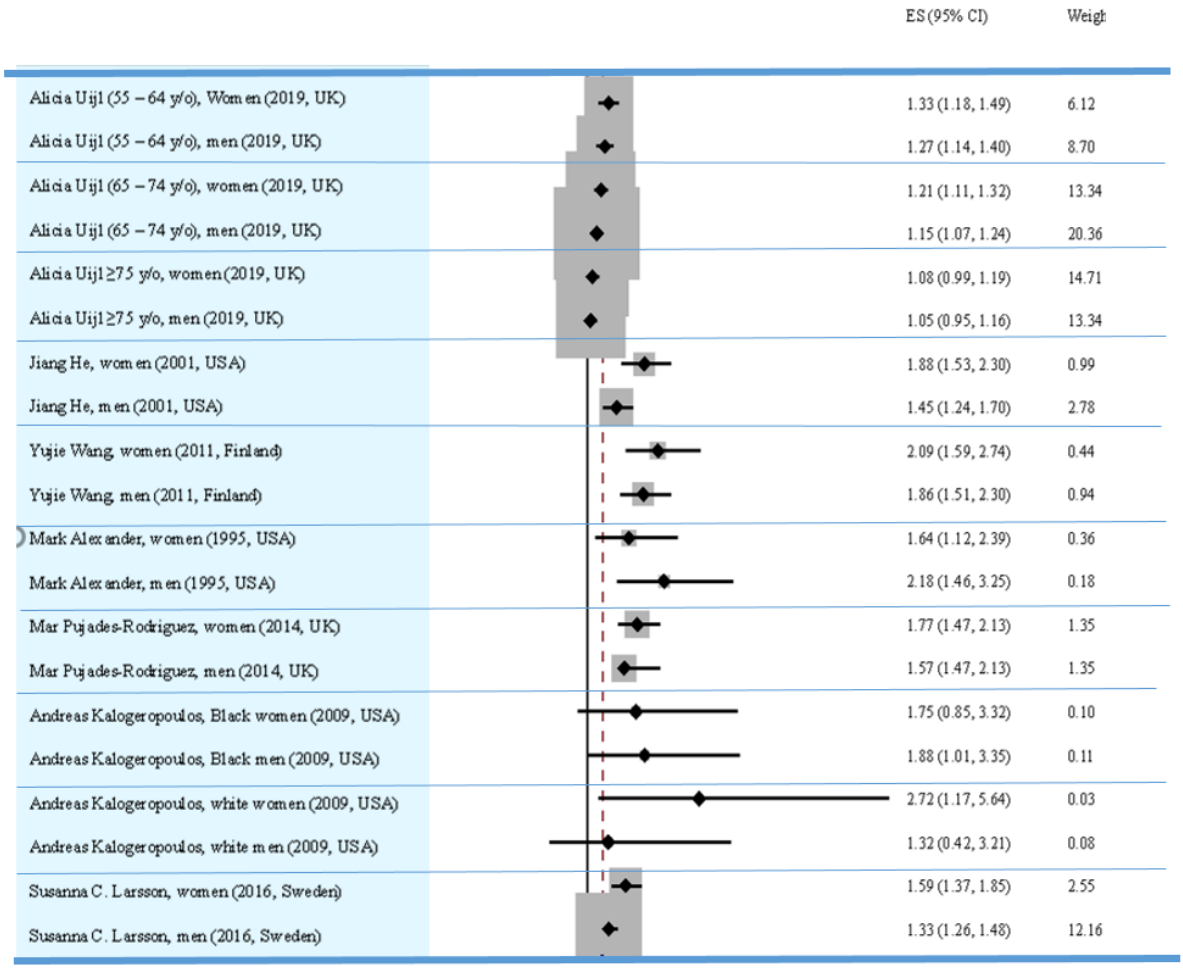
uCI: upper confidence interval, lCI: lower confidence interval, HR: hazard ratio, RR: relative risk, risk ratio

3.4.1 Effect of smoking

According to the results of the included studies, the risk of HF among smoker is higher than non-smokers with higher risk increase in smoker-women than in smoker-men.

In seven of ten studies, smoking has stronger effect on HF risk in women than in men; only in two reports from US studies (115, 116) smoking has stronger effect on HF in men (116) and this occurred in African-American population and the effect size was unadjusted (Graph 1).

Graph 1 Forest plot showing HR [95% CI] for HR in relation to of risk factors stratified by gender from included studies in the review. The gray squares indicate the weights allocated to each reports based on precision of the 95%CI.the Black vertical line shows 1.



Adjustment variables included in the regression models in each study are summarized in table 9. Adjustment in the studies differed, however, the variables that were most frequently included were age, race/ethnicity, BMI, SBP, hx of MI, hx of DM, and hx of VHD.

Table 9 Adjustment variables in articles assessing the effect of smoking on HF.

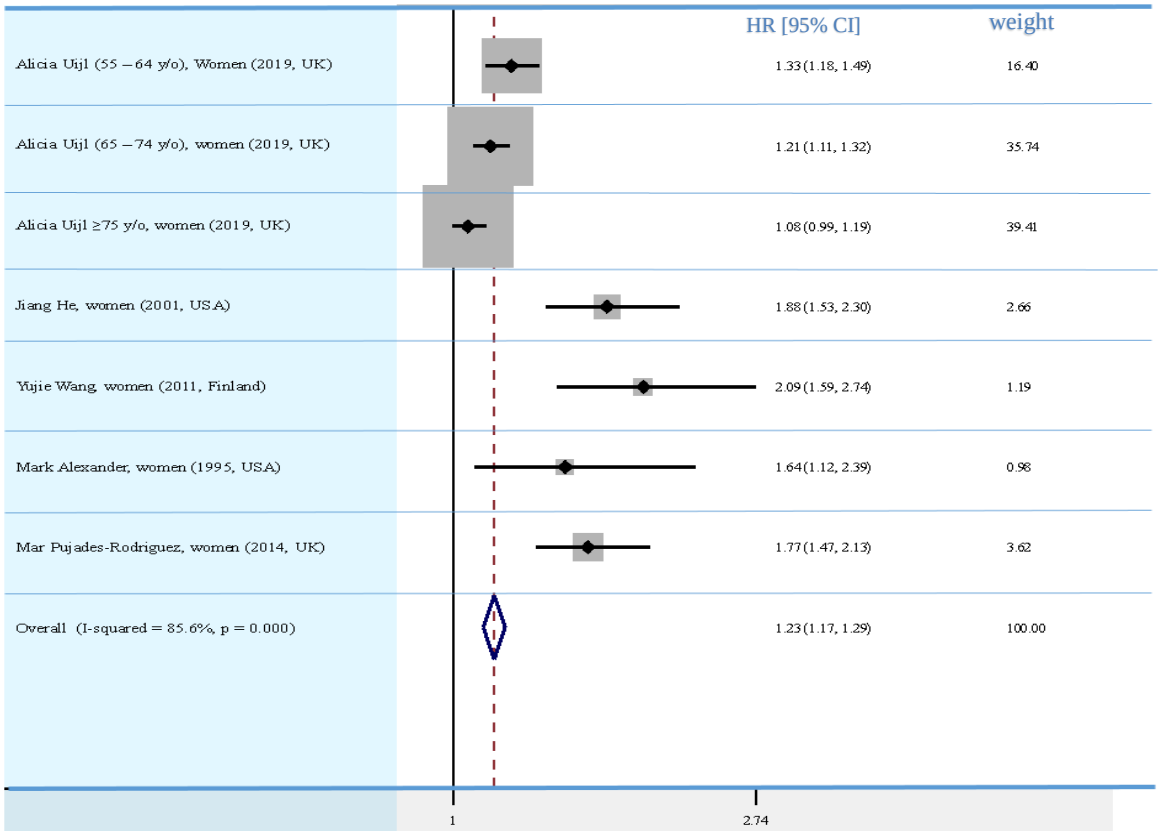
	Age	Race/ ethnicity	BMI	Overweight	SBP	Serum cholesterol	Medication For HTN/ BP	Education	Alcohol drinking	VHD	MI	CHD	DM	Sedentary life style	Low Physical Activity	Others
Uijl (103)		×	×		×		×						×	×		AF, Social deprivation, lipid regulating medication, COPD, Hb, WBC, Creatinine, DBP, stratified by age
He (37)	×	×	×	×	×	×		×	×	×		×	×	×	×	Cholesterolemia
Wang (2)	×		×		×	×	×	×	×	×	×		×			Vegetable and fruit consumption, Anti HTN
Larsson (114)	×				×	×		×					×			AF, all other healthy lifestyle factors, HTN
Alexander (115)	×		×			×		×	×	×	×					Serum Uric Acid, serum creatinine, proteinuria
Rodriguez (109)	×		×		×		×		×				×			Index of multiple Deprivation, HRT, OCP, DBP, WBC, Hb, Creatinine, Alanine transferase, baseline medication on for liver disease, COPD, cancer, renal disease, depression
Kalogeropoulos (116)																Unadjusted RR reported

According to the adjustment performed, we selected seven reports from five articles for meta-analysis (2, 37, 103, 109, 115). One reports were excluded from the meta-analysis due to unadjusted models (116), and 1 report was excluded due to estimation of HR for noncurrent smoker and not for smoker (114). The risk of HF was significantly higher among smokers than non-smokers, both overall and among women and men separately (Table 10, Graph 2 and 3).

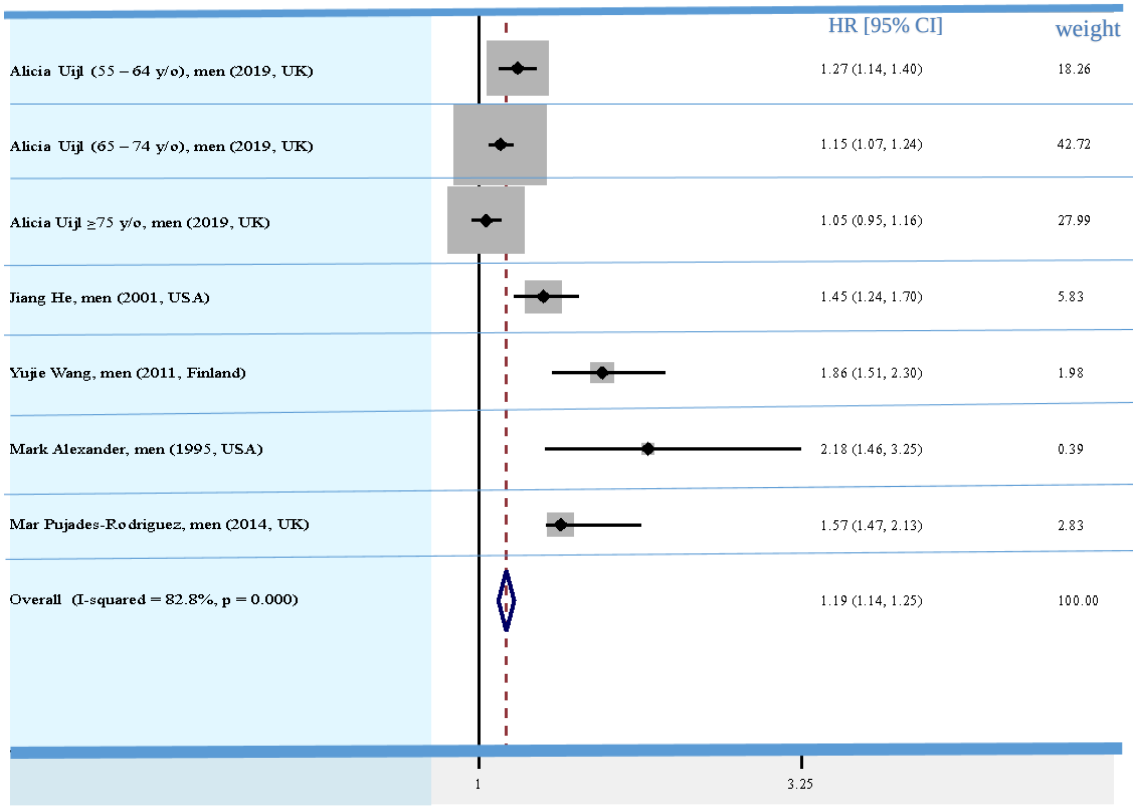
Table 10 The estimated effect size of smoking on risk of HF

	Pooled Effect size, 95%CI	I^2	ρ
Women	1.23 (1.17-1.29)	85.6%	<0.0001
Men	1.19 (1.14-1.25)	82.8%	<0.0001

Graph 2 Forest plot showing HR [95% CI] for HF in relation to smoking status in women. The gray squares indicate the weights allocated to each reports based on precision of the 95%CI.the Black vertical line shows 1.



Graph 3 Forest plot showing HR [95% CI] for HF in relation to smoking status in men. The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.

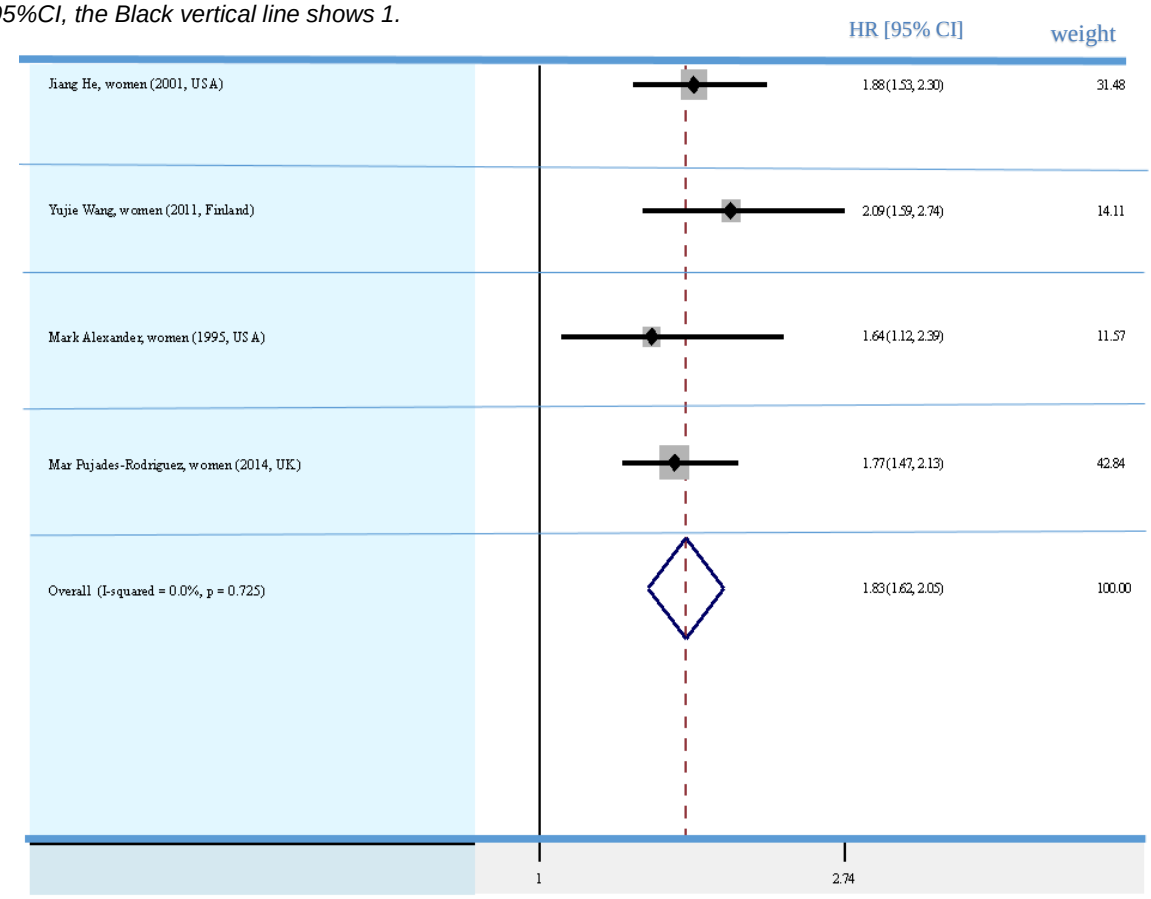


We observed heterogeneity between the studies (I^2 > 80.0%). Sub-group analyses were conducted between the studies to explore the observed heterogeneity. Meta-analysis between the studies of Wang (2), He (37), Alexander (115), and Rodriguez (109) shows no evidence of heterogeneity in the final model (Table 11, Graph 4 and 5)

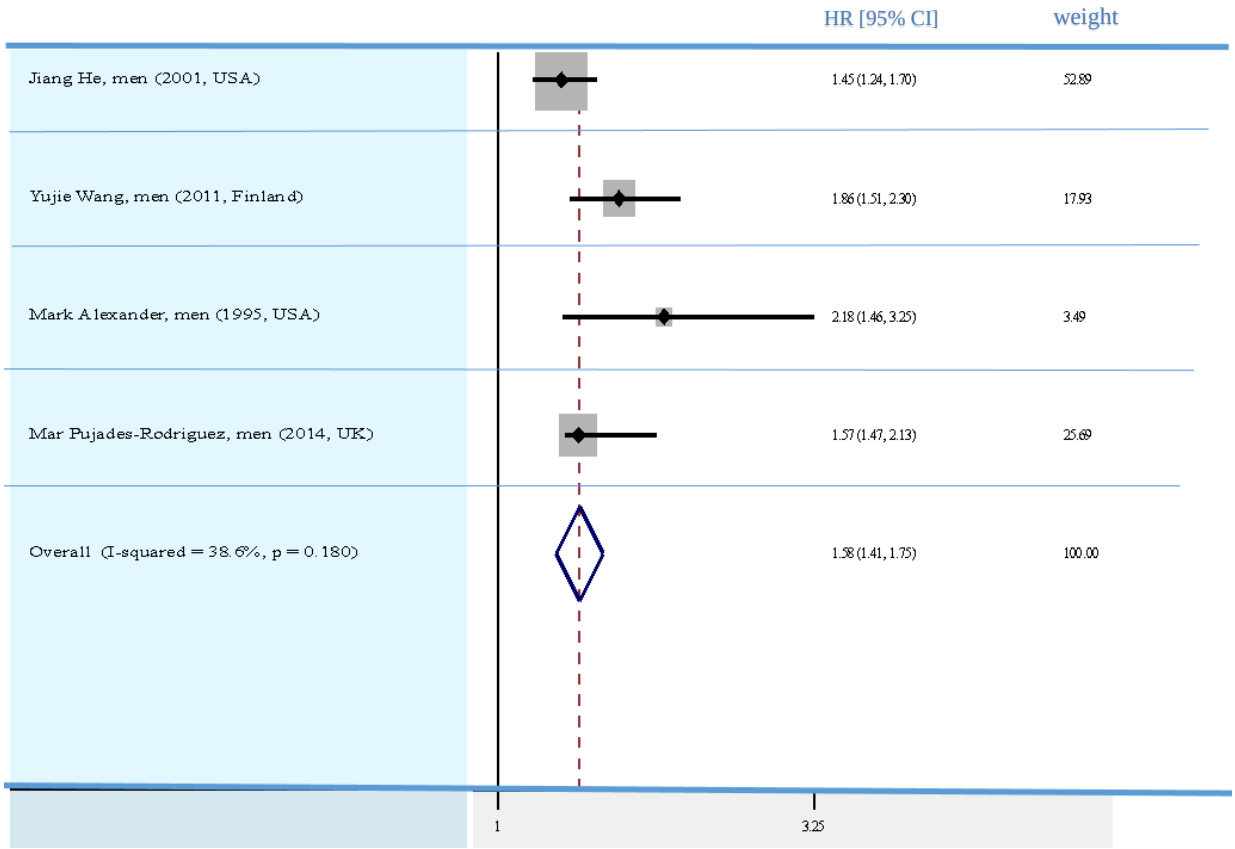
Table 11 The effect of smoking on risk of HF according four studies (2, 37, 109, 115)

	Pooled Effect size, 95%CI	I^2	ρ
Women	1.83 (1.62, 2.05)	0.0%	0.725
Men	1.58 (1.41, 1.75)	38.6 %	0.180

Graph 4 Forest plot showing HR [95% CI] for HF in relation to smoking status in women, according four studies (2, 37, 109, 115). The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.



Graph 5 Forest plot showing HR [95% CI] for HF in relation to smoking status in men according four studies (2, 37, 109, 115). The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.



3.4.2 Effect of physical activity

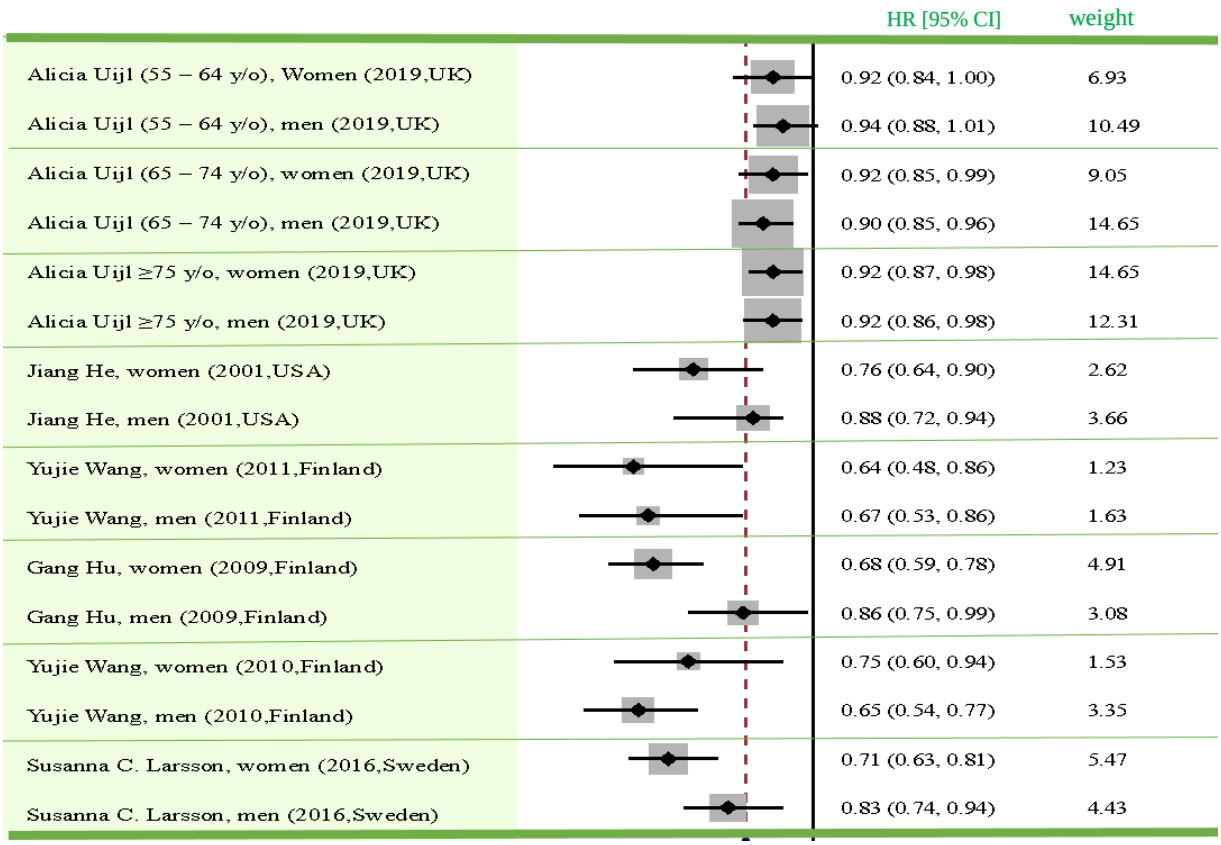
For assessing the effect of physical activity, data from six articles (2, 37, 53, 103, 114, 119) with 1,105,467 individuals were available for the analysis, in whom there were at least 60,158 fatal and non-fatal HF events. Three articles based on the FINRISK study (2, 53, 117) reported HF events from the same data source and therefore the actual number of events could not be precisely determined. The prevalence of physical activity was varied in different subcategories of included populations. In all studies, the prevalence of physical activity was higher in men than in women. All studies reported results as multivariate HR. Adjustment variables that each study used in their model to adjust the final ratios are summarized in table 12. Adjustment differed between studies, however, the variables that were most frequently included were age, race/ethnicity, smoking, BMI, SBP, hx of MI, hx of DM, and hx of VHD. In one study, the

outcome was CHF. Detection of HF cases is described in appendix 3. All extracted information on adjusted HRs or RRs with related statistical tests, exposure and outcome, and references group is summarized in table 7 and 8. The plot in figure 6 shows a summary of estimated effects of physical activity on HF.

Table 12 Adjustment variables in articles assessing the effect of smoking on HF.

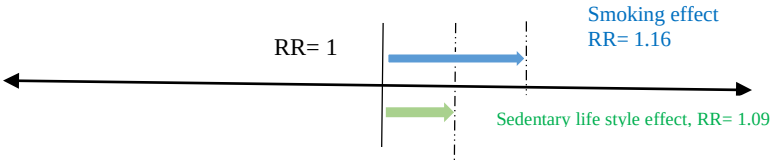
	Age	Race	BMI	Over weight	SBP	HTN	Serum cholesterol	BP controlling drugs	Lipid regulating drugs	Education	Alcohol drinking	VHD	MI	CHD	DM	Smoking	Others
Uijl (103)		×	×		×			×	×						×	×	AF, Social deprivation, COPD, Hb, WBC, Creatinine, DBP, stratified by age
He (37)	×	×	×	×	×	×	×			×	×	×		×	×	×	
Wang 2011 (2)	×		×		×		×	×		×	×	×	×		×	×	Fruit & vegetable consumption
Larsson (114)	×						×			×					×		Family hx of HTN, AF, all healthy life style factors
Hu (117)	×		×		×		×			×	×	×	×		×	×	
Wang 2010 (53)	×		×		×		×	×			×	×	×		×	×	Lung disease, other types of physical activities

Graph 6 Forest plot showing HR [95% CI] for HF in relation to physical activity startified by sex. The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.



Uijl et al. (103) analyzed data from the UK-CaLIBER study to assess the effect of physical activity on HF. They used the physically active group as reference group (HR=1). They staratified by age into three subcategories of 55-64, 65-74 and ≥75 years old. However, they adjusted the HR for age, race, history of used BP lowering medication and lipid regulating drugs. The HR with 95% CI was 1.09 (1.05, 1.13), I^2= 0.0%, p= 0.589 for men and 1.09 (1.04, 1.13), I^2= 0.0%, p= 0.976 for women (Figure 9, graph 7 and 8). The result was homogenous but insingnificant for trend. The authors found a stronger effect on HF for smoking than physical inactivity (Figure 9). Furthermore, their results showed that it was a stronger effect of smoking and sedentary life style on HF in women than in men.

Figure 9 Comparing the effect of physical inactivity and smoking according to the study of Uijl et al. (103)



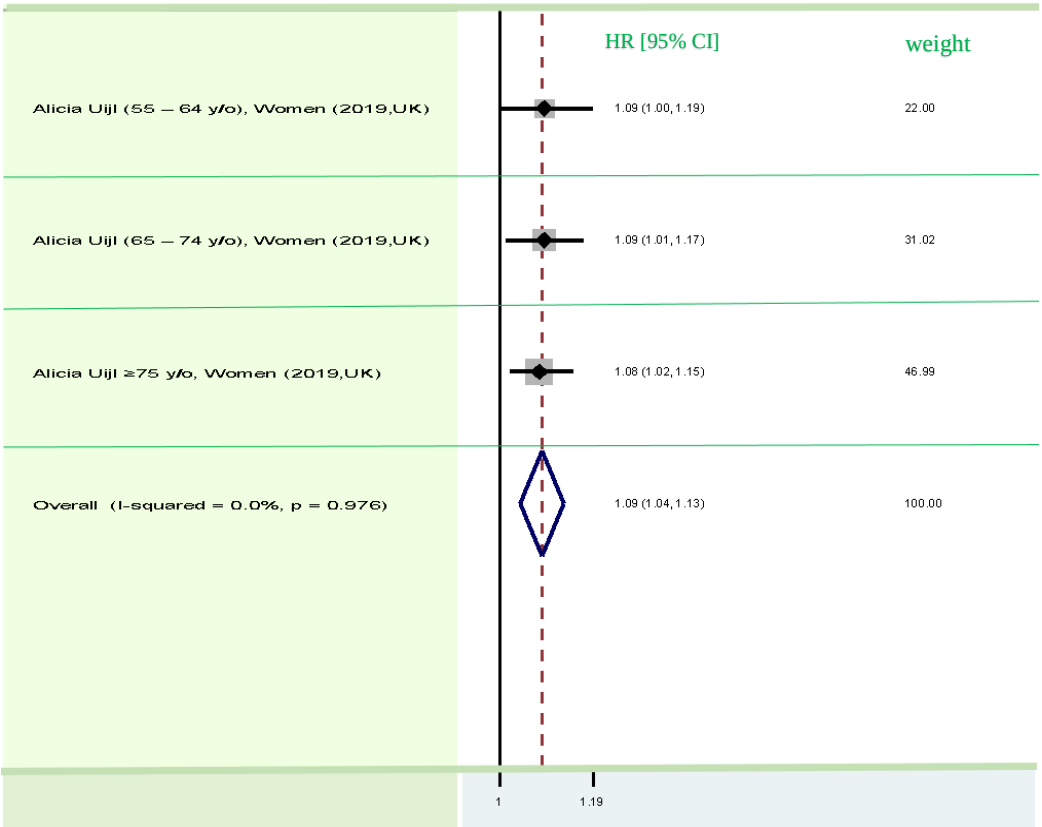
The effect of smoking on development of HF, according to the study of Uijl et al.

	Pooled Effect size, 95%CI	I^2	ρ value
Total	1.16 (1.11-1.20)	66.6%	0.011

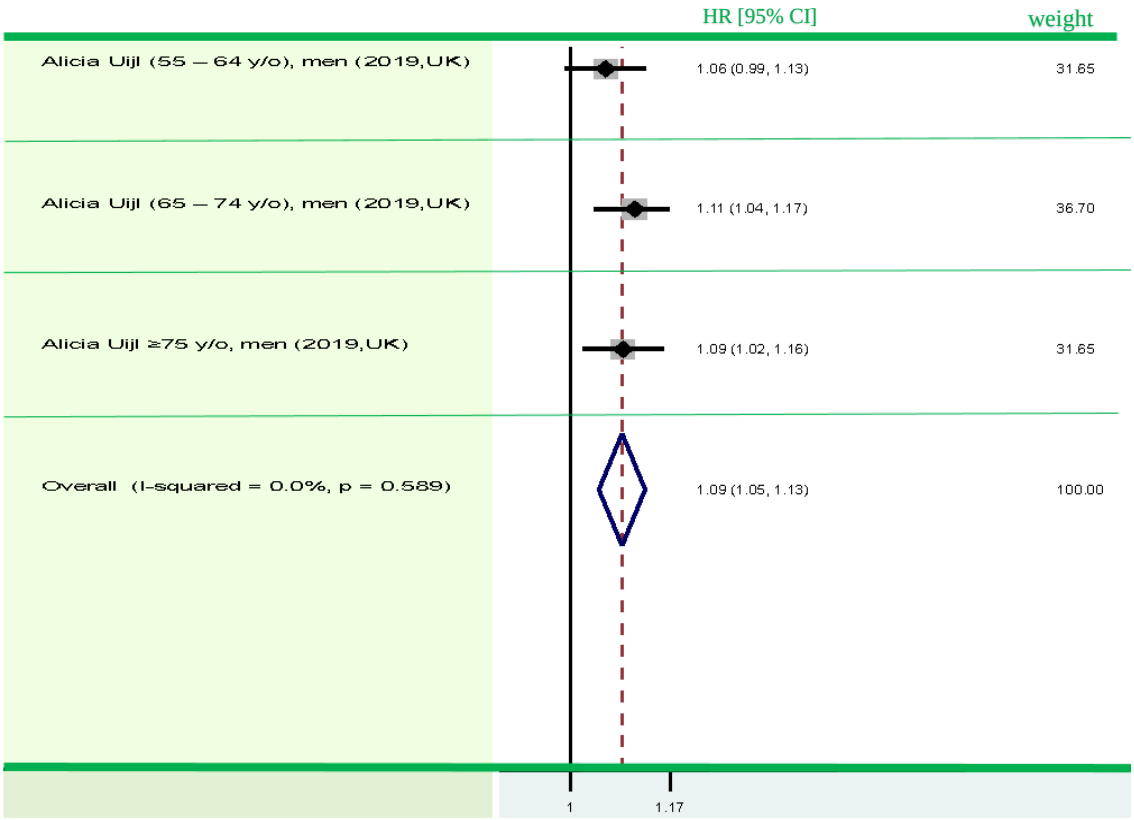
The effect of sedentary life style on development of HF according to the study of Uijl et al.

	Pooled Effect size, 95%CI	I^2	ρ value
Total	1.09 (1.06-1.12)	0.0%	0.953

Graph 7 The pooled estimated effect of smoking in women according the study of Uijl et al. (103). The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.

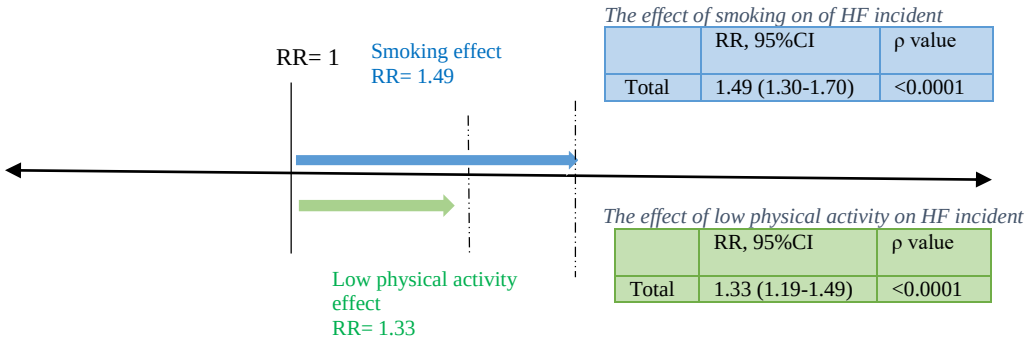


Graph 8 The pooled estimated effect of smoking in men according the study of Uijl et al. (103). The gray squares indicate the weights allocated to each reports based on precision of the 95%CI, the Black vertical line shows 1.



The NHANES I study (37) investigated the effect of low physical activity on CHF. They defined the physically active group as reference group (RR=1). The RR (95% CI) for men was 1.14 (0.94, 1.38), p= 0.19 and for women was 1.31 (1.11, 1.54), p= 0.002. Risk of HF in relation to physical inactivity was stronger for women than men. They found a stronger effect on HF risk for smoking than for low physical activity (Figure 9).

Figure 10 Compare the effect of smoking and low physical activity on HF event due to NHNES I study result



The effect of smoking on of HF incident

	RR, 95%CI	ρ value
Total	1.49 (1.30-1.70)	<0.0001

The effect of low physical activity on HF incident

	RR, 95%CI	ρ value
Total	1.33 (1.19-1.49)	<0.0001

Three articles of Finland (2, 53, 117), from the same data source of FINRISK, were published in 2010 and 2011. One article investigated the relationship between physical activity and HF

(117). Two other articles subcategorized physical activity according to leisure-time physical activity, commuting physical activity, and occupational physical activity (2, 53). All three articles considered low physical activity as reference group (HR=1). Two reports showed a stronger protective effect of physical activity on HF risk in women, while one article reported a stronger protective effect of physical activity in men (RR= 0.75 in women vs RR= 0.65 in men). The pooled HR effect size of physical activity from three FINRISK articles show stronger protective effect of physical activity for women in than in men (Table 13).

Table 13 The effect of high physical activity on development of HF. The three studies (2, 53, 117) of Finland with the same data sources.

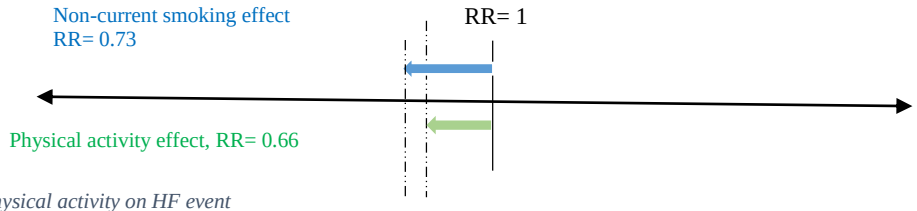
	Pooled Effect size, 95%CI	I^2	ρ value
Total	0.71 (0.66-0.76)	40.4%	0.136
Women	0.69 (0.61-0.76)	0.0%	0.676
Men	0.73 (0.66- 0.81)	70.9%	0.032

Those three article from FINRISK (2, 53, 117) compared the effect of current smoking and high physical activity on the risk of HF. The increased risk of HF for current smokers was greater than the risk reduction from physical activity (Figure 11). They found a stronger effect of smoking and physical activity on HF risk in women than in men.

Figure 11 Compare the effect of current smoking and high physical activity on HF event due to FINRISK study result (2, 53, 117)

The effect of current smoking on HF event

	Pooled Effect size, 95%CI	I^2	ρ
Total	1.93 (1.61, 2.26)	0.0%	0.518



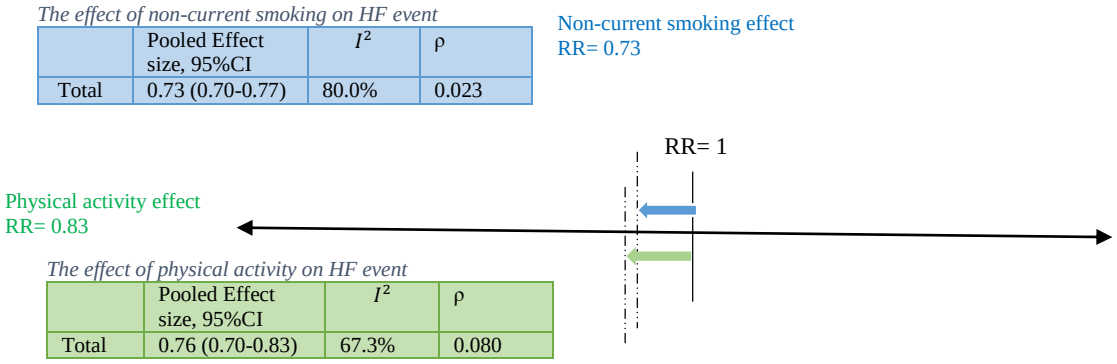
The effect of high physical activity on HF event

	Effect size, 95%CI	I^2	ρ
Total	0.66 (0.53-0.78)	0.0%	0.815

An article based on Swedish COSM and SMC study (114) reported the effect of physical activity on HF events, adjusted for education, family hx of hypertension, hypercholesterolemia,

diabetes mellitus, AF, and all healthy lifestyle factors simultaneously in the same model. They found a stronger protective effect of non-current smoking than physical activity on HF risk (Figure 12). Moreover, they found a greater protective effect of non-current smoking and physical activity on HF risk in women than in men. (RR: 0.71 (0.63, 0.81) for women vs RR: 0.83 (0.74, 0.94) for men).

Figure 12 Compare the effect of ono-current smoking and physical activity on HF event due to Swedish cohort study result (114)



3.5 Risk of Bias in included studies

The risk of bias summary is available in table 14 for studies assessing the effect of smoking and in table 15 for studies assessing the effect of physical activity. All domains of bias were evaluated for each included study. The supplementary information about assessing each domain of bias for studies are presented in appendix 2 and 3.

3.5.1 Selection bias (selection of exposed non-exposed cohorts)

All studies were large population cohort studies. The study of NHANES I (37), oversampled a certain population of low income, women of childbearing age, and elderly. The study of Kalogeropoulos et al. (116) sampled from the insured population. Except these two aforementioned studies, in other studies there were no systematic differences, overrepresented or underrepresented between baseline characteristics of the groups that are compared which may lead to either an overestimation or underestimation of the association between exposure

and risk of HF. The exposed and unexposed groups were drawn from the same population and from the same administrative data bases in a same time frame. So, they were considered of being at low risk of selection bias. The proportions of women varied from to 47.8% to 58.82% in studies assessing the effect of smoking, and from 47.48% to 59.36% in studies assessing the effect of physical activity. Age range of participants were from 24 years with a similar mean age range for men and women except in the study of Larsson et al. (114) where mean age of men and women at baseline differed. Other factors at baseline such as BMI, smoking and physical activity, were also considered for assessing the selection bias among studies.

3.5.2 Performance bias (assessment of exposure)

All the studies provided information how their data were obtained. Studies used secured record achieved by interview or questionnaire asking about the exposure. Studies used self-reported data and individual were asked for the exposure and may be subject to the risk of recall bias. except NHANES I study (37) in which the validity of information for smoking exposure have been presented and shows 85% to 95% validity (120, 121). The study of Wang et al. (53) checked the information of physical activity. They have has shown a high correlation with physical fitness, as measured by maximal oxygen uptake. In the included studies it was not clear if the people who participated in acquiring data in the retrospective studies and the participants were blind to the research aim while they answered the questioners or not.

3.5.3 Detection bias

The outcome of interest (HF incident) was obtained from medical records which is sufficient for certainty and validity but might vary somewhat from hospital to hospital and between countries. The follow-up time considered long enough to have observed effect size. Data were collected from data base with documentation of accuracy of prognostic data. The criteria and

validity of diagnosis for FINRISK study and CALIBER study were mentioned in their studies (2, 103), and for NHANES I elsewhere (122). The validity of HF detection were checked with BNP level, echocardiographical findings, and prescribed medications. For each article comprehensive matching and statistical analysis adjustment for prognostic variables had been done except for the study of Kalogeropoulos (116). In the study of Kalogeropoulos (116), there were no deaths from incident HF because HF was not allowed as a cause of death.

3.5.4 Attrition bias (incomplete outcome data)

In one study (109) they started with 5,372,790 participants and ended up with 1,937,360 due to their inclusion and exclusion criteria. One study (115) the number of patients with incomplete data in the groups was not reported, so these two studies were judged to contain a high risk of attrition bias. In other studies, as the reasons of the exclusions are stated and the number of excluded people was balanced between the groups, and missing data have been included using an appropriate method, the study was judged to be at low risk of attrition bias.

3.5.5 Reporting bias (selective reporting)

It was not possible to assess if the outcomes specified in the protocol were reported since protocols were not available for the studies.

3.5.6 Other potential sources of bias

Studies have declared the source of funding. The differences in the participants' characteristics, including co-morbidities, between subgroups were not significant in the reviewed studies. There is difference in the considered range of BMI for overweigh and obese. In the study of He et al. (37) overweight was BMI ≥ 27.8 for men, and ≥ 27.3 for women, while in study of Larsson et al. (114) 18.5≤ BMI ≤ 25 kg/m2 was considered normal healthy weight. The study of Wang et al. (2) defined BMI as 20-25 kg/m2 for normal weight, 25 to 29.9 kg/m2 for overweight, and

≥30 kg/m2 for obese. The studies collected their data from different sources and each had their own measurement error, which increase the risk for measurement error and/or misclassification. Follow-up participants were passive rather than active. It was not clear how electrocardiography and echocardiography were undertaken and the results judged, and how left ventricular dysfunction were studied. They collected data once at the baseline, and it might possible that a person changes life style during the follow-up time. There are some unmeasured factors such as OCP or HRT. Pregnancy and lactation interfere in physical activity or smoking behavior which none of the selected studies mentioned to this. Using insured population could cause bias in the outcomes due to selection of a population with secure economy.

Table 14 Summary of the risk of bias for each included study for investigating the effect of smoking and heart failure, Green: Low-risk, Red: High-risk, Yellow: Unclear Risk

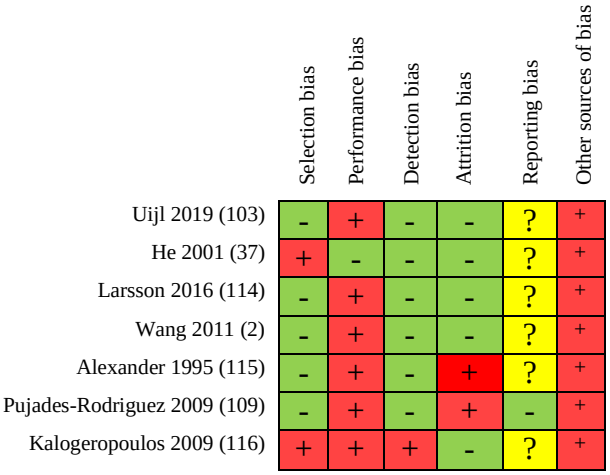
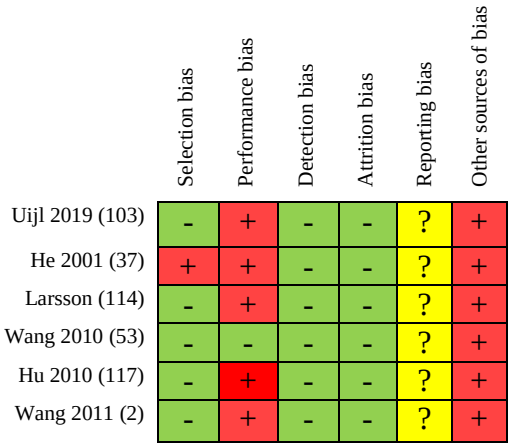


Table 15 Summary of the risk of bias for each included study for investigating the effect of physical activity and heart failure, Green: Low-risk, Red: High-risk, Yellow: Unclear Risk



3.6 Publication Bias

Seven articles were reviewed to assess the effect of smoking and six articles were reviewed to assess the effect of physical activity. For fewer than ten articles in the meta-analysis, tests for funnel plot asymmetry should not be used due to low test power to distinguish chance from real asymmetry. In particular, when there is a high level of heterogeneity, more than ten articles is needed to obtained meaningful results from testing funnel plot symmetry (123). Therefore, the funnel plot for assessing publication bias was not constructed due to insufficient number of studies and high level of heterogeneity that we observed between studies. Egger's test was not applied firstly, there are less than ten articles, secondly, Egger's test is a test for continuous outcomes (123).

4 Discussion

4.1 Summary of findings

The current thesis reviewed nine studies to examine to what extent the association between smoking and physical inactivity and risk of HF differ among men and women.

As expected, we observed that no-smoking and physical activity were each associated with a significant lower risk of incident HF in both men and women.

Four studies (2, 37, 103, 114) revealed that both smoking and physical inactivity increased the risk of HF, and the effect of smoking was stronger than physical inactivity for risk of HF (2, 37, 103).

According to our review, smoking increased the risk of HF more in women than in men (2, 37, 103, 109, 114, 116). Similarly, engaging in high physical activity reduced the risk of HF more in women than in men (2, 37, 114, 117).

Two articles (53, 103) found an interaction between gender and the influence of physical activity on HF within different age groups, and for different subgroups of physical activity types (occupational, commuting, and leisure-time physical acuity).

The study (53) that subcategorized physical activity into three types consisting of commuting, leisure time and occupational, found that engaging in high level of leisure-time physical activity was significantly more effective in men than in women, while their results showed engaging in high level of commuting physical activity had greater risk reduction in women than in men even after adjusting for two other types of physical activity.

4.2 Overall completeness and applicability of evidence

These findings should be interpreted with caution due to potential residual confounding of other HF risk factors. Adjustment of results for additional risk factors (e.g. CAD, MI, AF, VHD, high

fat diet, age, HTN) varied in included studies considerably. As shown in figure 13 and figure 14, there are many modifiers involved in the casual pathway between smoking and physical activity and development of HF. The risk reduction of HF associated with physical activity and non-smoking may be mediated through prevention of HTN and CHD which are known as major risk factors of HF (37). Other conditions such as VHD, MI, and AF may represent other situations with acute and chronic damage to the heart muscles that can affect the cardiac output and result in HF development (13).

Smoking affects HF risk through different mechanisms as is shown in figure 14. One important factor, which can cause gender differences in effect of smoking, is influence on estrogen level (124). Among studies assessing the effect of smoking, only one study (109) considered using OCP and HRT as a cofactor and reported adjusted result for OCP and HRT. Other studies did not mention information regarding HRT and OCP. The relationship between smoking and HF development remained even after adjustment for other HF risk factors suggesting additional underlying mechanisms contributing to HF development.

Physical activity is a common and accessible mean for improve health among adults (125). In this thesis, physical activity is observed to reduce the risk of HF. In addition, the magnitude of this association was stronger in women. These findings suggest the potential contribution of gender in the preventive mechanism of physical activity, a finding which can be important for public health implications. Physical activity can mediate its risk reduction by reducing the HTN or regulate the body composition and BMI. Although, even after adjusting for factors e.g. BMI, overweight, and BP, physical activity remains as a preventive factor for HF.

From the point of view for public health policy makers and healthcare providers, highlighting the modifiable risk factors for HF, is important when preventive strategies are planned. People who abstinence from smoking and engaging in high level of physical activity are substantially less likely to develop HF with a stronger effect for women. From the point of view for the

researcher, the association between smoking and physical activity with HF, even after adjusting for known risk factors (e.g. age, race, sex/gender, MI and HTN) suggests the possibility of other, not yet acknowledged underlying mechanisms for HF development. Thus, the results might inspire further mechanistic research into the physiology and pathophysiology. A better understanding of the relationship between gender differences in the association between lifestyle factors and HF will ultimately improve the QOL for both men and women.

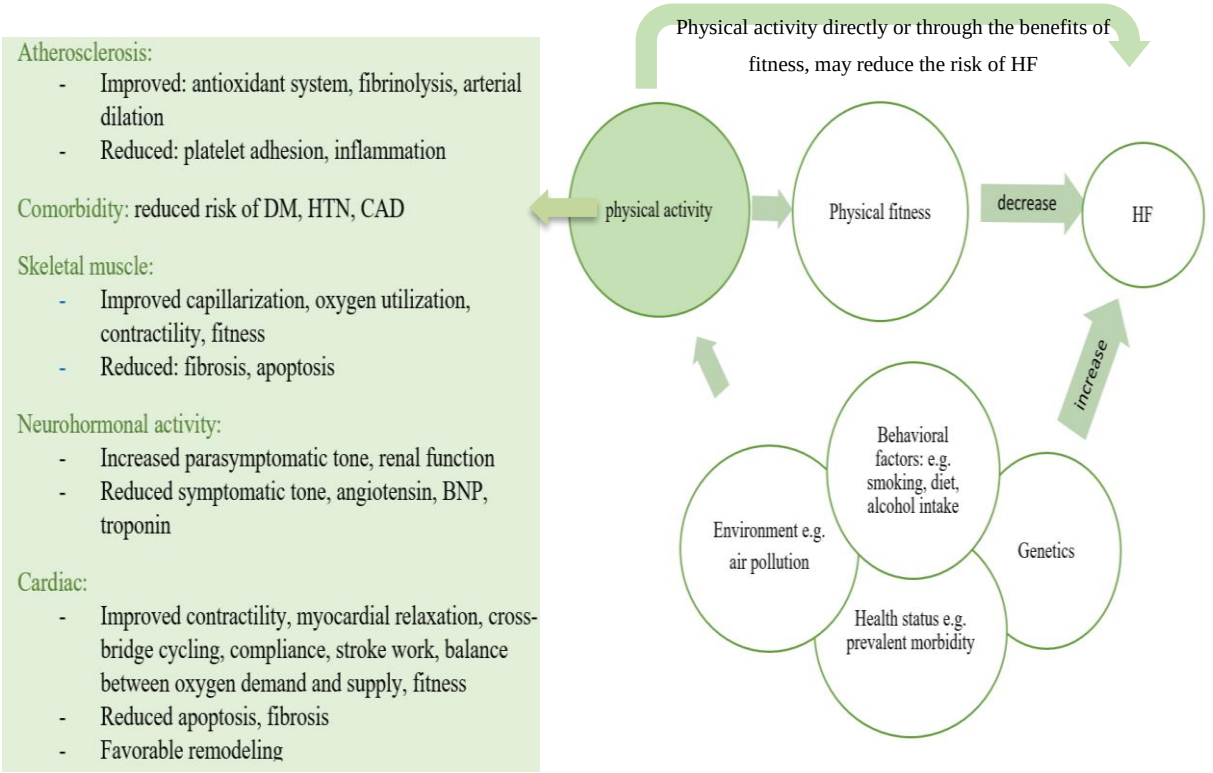


Figure 13 A schematic description of possible relationship between physical activity and heart failure (right side of the picture) with potential mechanisms through which physical activity contribute to heart failure risk reduction (left side of the picture) (126)

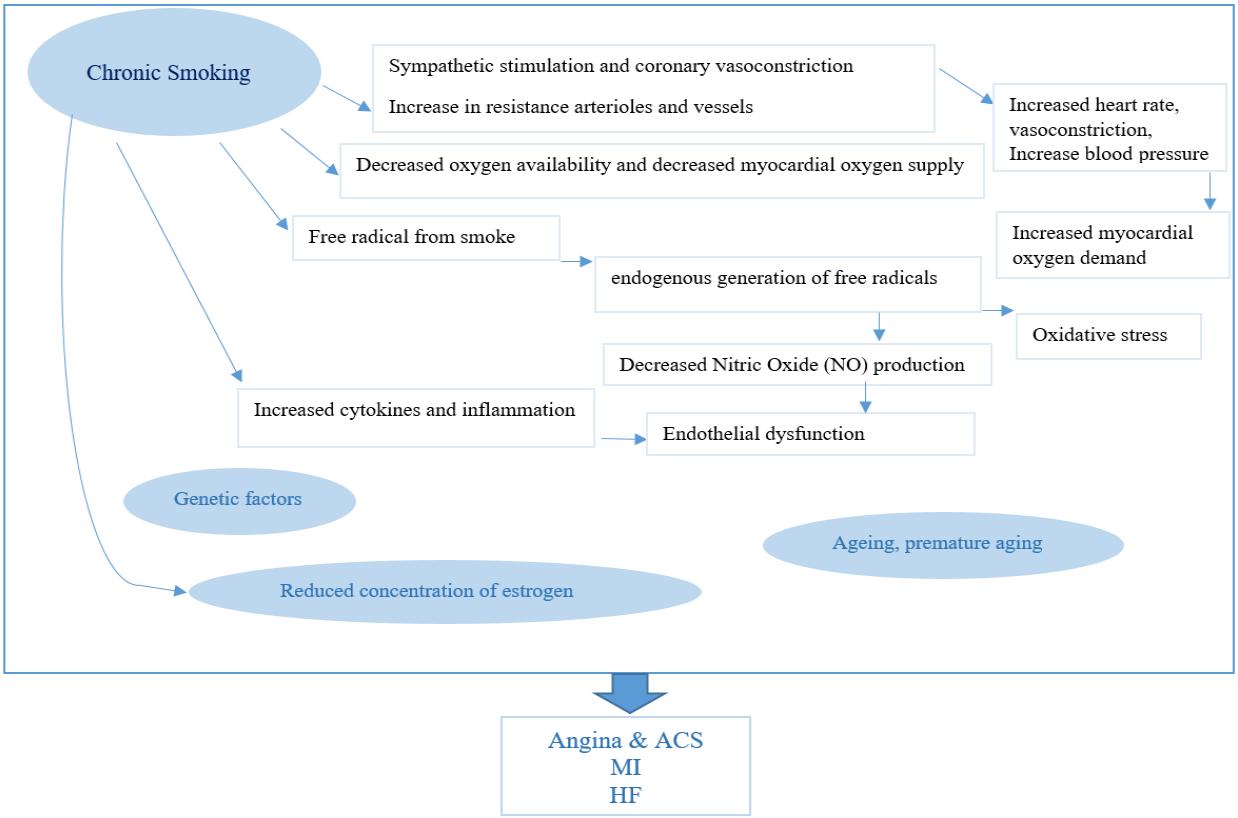


Figure 14 Various pathophysiological mechanisms stimulated by smoking tobacco potentially promoting heart failure development (51, 127)

4.3 Quality of the evidence

According to the assessment of risk of bias, the included studies present high quality studies, however, they were not free of bias. Self-reported data were collected for exposures and other cofactors such as alcohol consumption and diet.

The study of Uijl et al. (103) chose a population older than 55 years from four different ethnicity subcategories which were Caucasians, black, Asian, and other. Their first endpoint was incident HF. To define HF, they used two different data sources with their own measurement error. So, the risk of measurement error and/or misclassification exists in their study. They did not mention dose of smoking (e.g. pack/year). They categorized their participants as never, current, and ex-smoker (quit < 2y, 2-5 y, 5-10 y, >10y). For investigating physical activity, two subcategories of sedentary life style or active life style were defined without complementary

information for quality or type of physical activity. The participants were stratified by age which reduced the confounding effect of age. The validity of HF detection was checked in the record with LV dysfunction confirmed by cardiac imaging, an elevated BNP concentration, referral to HF care, referral to a cardiologist, the use of loop diuretics, and symptoms and signs suggestive of HF (128).

The other study (109) from CALIBER study, started with 5,372,790 participants and after exclusion ended up in 1,937,360 participants. They classified smokers in groups of: never smoker, ex-smoker, and current smoker. Ex-smokers were grouped into categories of time since quitting to < 2 years, 2-5 years, 5-10 years, >10 years and missing.

The study of He et al. (37) used a large cohort sample but oversampled certain population subgroups (those with a low income, women at childbearing age, and elderly). They used self-reported information with a passive follow-up rather than active follow-up. They did not provide information for dose of smoking and physical activity and only categorized participants to subgroups of non-smoker vs current-smoker and low physical activity vs high physical activity. The validity and reliability of surrogate information on smoking data were checked and estimated to 85% to 95% (121). Detecting HF patients was done based on obtaining hospital records, pathology reports, electrocardiograms, and death certificates (122).

The study of Larsson et al. (114) consists of two cohort studies with a large sample with a mean follow-up time of 13 years. The data collected was based on self-reported questionnaire which increase the risk of recall bias. Their information for smoking and physical activity did not detail doses. However, the incident of HF were obtained by National Patient Register and the Swedish Cause of Death Register with the validation of 95% of primary HF diagnosis.

The articles of FINRISK study (2, 53, 119) used a large sample of cohort population of five independent cross-sectional surveys, which might increase the risk of measurement error and/or misclassification. The data on exposures were collected with self-reported questionnaire with

the risk of recall bias. The questionnaires were mailed to participants and the follow-up was passive rather than active. While the information of smoking was categorized as never, ex and current smoker without more details of dose and duration, a comprehensive information of physical activity was collected. The questionnaire used for the assessment of physical activity has shown a high correlation with physical fitness, as measured by maximal oxygen uptake (53). However, the exposure data was collected only once during the follow-up without information of data on possible changes on lifestyle factors during follow-up. The validity of HF detection in FINRISK study was more than 80% based on the European Society of Cardiology definition (53).

The study of Alexander et al. (115) used a cohort of insured population. They collected medical and social history with self-reported questionnaire, and a series of clinical laboratory tests, chest x-rays, electrocardiogram, and an examination record provided by a physician. They did not mention the number of participants that were excluded or the dose of smoking. Smoking was defined as smoked more than 1 year and other as non-smoker.

The health ABC study of USA (116) collected data based on self-reported history with no deaths from incident HF because HF was not allowed as a cause of death in the death registry.

4.4 Potential biases in the review process

Observed different results in the included studies might be due to varying follow-up time, diversity in study population or quality of data, and regional/cultural differences. However, each study we reviewed, have reported adjusted results for some co-variables such as education, alcohol consumption, diet, and age (Table 9 and Table 12). The bio-psycho-social variation in a sample of different studies, across different places and times may determine whether gender differences in the effect of physical activity and smoking meet criteria for disparity. One unacknowledged factor that may promote the difference in men and women is considering other

tobacco products consumption. All studies mentioned smoking as the one and only source of consuming tobacco, while other alternative of tobacco products may affect and altered smoking behavior. Other potentially important factors may include pregnancy and lactation, which often affects life style regarding smoking and physical activity for women. The quality of physical activity (e.g. change in heart beats) was not mentioned in the included studies. Six studies for assessing the effect of physical activity and seven studies for assessing the effect of smoking may be insufficient to draw a conclusion. The endpoint in included studies were HF presentation. Any attempt to describe the epidemiology must take into account the difficulty in the diagnosis of HF. Another problem for prevalence estimation is how the researchers take into account the asymptomatic HF patients. Subclinical HF might be present and undiagnosed due to compensatory mechanisms or sedentary life style, which does not provoke need for increase in cardiac output. The discovery of first ANF and then BNP (NT-proBNP) in the 1980s, and the development of their use as biomarkers of HF was a great advancement. With no elevation of BNP, HF is unlikely, but elevated BNP does not alone confirm the diagnosis. Additional, more specific biomarkers might be available in the future making population studies of HF easier.

The process of selection of studies, data extraction, and assessing risk of bias are recommended to be conducted by at least two authors (111), but in this thesis it has done by the candidate alone. The search strategy was comprehensive, but still there is a risk of unidentified studies and risk of bias as the review was done by one person.

4.5 Agreements and disagreements with other studies or reviews

In different study reports, the overall prevalence of HF varies from 3/1000 in RCGP (1958) UK national data, Framingham (1971) Framingham, USA, and Landahl et al (1984) Sweden (males

only), to 21/1000 in Garrison et al (1966) Georgia, USA. Considering aged population, the range of HF prevalence varies from 28/1000 for older than 65 years in Parameshwar et al (1992) London, UK, to 130/1000 for older than 67 years in Eriksson et al (1989) Gothenburg, Sweden (18). Several risk factors have been previously identified for incident of HF. However, a systemic review of large population studies may provide the opportunity to examine the consistency of the results of various studies to draw a conclusion. We found higher HF incident rates for men than women that is consistent with previous sex-stratified studies (103). An article published in a public health journal in 1996 discussed the higher risk of HF among men compared to women (129), and further evidence clearly shows higher overall HF risk among men (27, 130, 131).

Current preventive guidelines assume CVDs as a single family of related diseases, while studies have shown important differences within different types of CVDs (109). Initial occurrence of one CVD strongly influence the development of another (e.g. MI predisposes to HF).

Current evidence supports that smoking consistently increases risk of HF (132-134). Hence, abstinence from smoking plays an important role in reducing the public health burden of HF worldwide. Our review confirms and extend results of previous studies that firstly, abstinence from smoking has a stronger effect on HF risk reduction than physical activity, and secondly, by abstinence from smoking, women may benefit more than men in reducing the risk of HF. Few previous cohort studies have examined the sex-stratified association between smoking cigarettes with HF. According to a Swedish cohort studies of men in Gothenburg, smoking at age of 50 years increased risk of CHF by 60%, RR= 1.6, 95% CI (1.2, 3.2), after adjusting for other important risk factors such as HTN (135). The etiology of HF has been changing through the time due to progress in HTN management and interventions and medications development for CAD therapies (136). CHD is a major cause of HF, therefore, these findings imply that smoking cigarettes might directly increase the risk of HF, in addition to its effects on increasing

risk HTN and CHD. Thus, smoking cessation should be an important component of HF preventive strategies in general population, particularly for women. Smoking, AF, and DM showed stronger associations with HF development in women compared to men (103). The study of Dunlay et al. (4) showed smoking increased risk of HF in women more than in men which is consistent with observation in this review.

Many observations and studies suggest that physical activity reduce risk of HF (34, 126, 137, 138). But recommendations on types and amount has been discussed. All adults regardless of their age are encouraged to engage in high physical activity (34). Physical activity can reduce the risk of HF through different paradigm e.g. by regulating weight, BMI and body composition (Figure 13). It has been suggest that a lean but sedentary life style has higher risk of HF than an overweight but active life style (117). This study did not discuss the body composition regarding balance between fat and muscles. A masculine body with a body composition of muscles and higher BMI may not have the same risk factor as the body with the composition of more fat but lower BMI. This may suggest that physical activity benefit HF via an independent physiological pathway (Figure 13). This perspective about HF pathophysiology may extends our understanding of risk factors for HF in other ways.

4.6 Study strength and limitation

Strengths of this review are the linkage of multiple large population studies with a large number of incident HF cases diagnosed. This allowed for review of studies with large samples. Moreover, information for outcome was objective with a high accuracy as data on diagnoses of HF were acquired by health registries rather than self-reports. Another strength is that we were aware of the variables in each study adjusted for potential confounders. HF is a long-term outcome, and follow-up duration was considered long enough in all of the included studies. However, several limitations of this review should be considered. We used data from different

data sources, which have had their own measurement errors. Due to the nature of the included studies in the review, the accuracy and the amount of detailed information recorded are limited. Residual confounding may impact the observed associations. There are missing data and inconsistency in the reported results which can exemplified by limitation of each study by lack of information on clinical important biomarkers and measurements for HF (e.g. echocardiography, cholesterol level, blood pressure, serum creatinine). These aforementioned factors could help the researchers to evaluate the potential intermediates of the associations of exposures with HF risk. Not all studies provide a clear description of the definition of smoking and physical activity, which likely caused a greater degree of heterogeneity. This types of heterogeneity include variability in the participants, which may lead to heterogeneity in the exposure effect. Differences between included studies in terms of exposure measurement methods may lead to differences in the observed outcome, and heterogeneity in outcomes measures does not necessarily suggest that the true exposure effect varies. Information on smoking and physical activity was obtained only at the baseline from a self-administered questionnaire. It might be possible that some participants have changed their smoking habits or physical activity habits during follow-up. Considering that information of exposures collected before the outcomes presentation, misclassification of exposures might happen and caused an underestimation of the magnitude of the association. We mostly reviewed adult populations, hence, we cannot generalize our data to younger population. Finally, the included studies are limited by lack of information about the dosage of smoking, so, we were unable to examine the results in a dose-response fashion.

5 Conclusions

5.1 Implication for practice and research

Cellular molecular mechanisms differ between women and men in terms of structures of the organ and hormonal systems and receptors of chemical signals. Behaviors and habits lead to gender differences in risk factors for HF such as diet and physical activity, and medication, treatment and follow-up procedures will be different in different social situations. Therefore, knowledge of gender differences may affect the preventive, diagnostic and therapeutic guidelines of HF and CVD.

The heterogeneous associations between smoking and physical activity and the risk of HF suggest variations in the underlying mechanisms in men and women, which highlights the implications for research, clinical screening and risk prediction. Animal models and clinical studies offer convincing evidence for dimorphism of sex in heart structure, mechanism and diseases. We need general academic agreement about terminology of HF in clinical studies. Interaction of physical activity, smoking behavior and gender affect the risk of HF and requires further investigations. Much of the evidence related to HF is based on observational studies. Randomized controlled trials with a focus on prevention, instead of treatment and management, are needed with consideration of the ethical aspects in designing clinical trials when it is well-documented that smoking and physical inactivity increase risk of HF development.

5.2 Implication for public health

There is evidence for the importance of focus on prevention of HF. For example, early and intensive treatment for systematic hypertension can reduce up to 64% of the incidence of HF (25, 139). Similarly, interventions that can address major risk factors directly or indirectly

should be taken into account. In order to reduce the burden of HF, sex-related (biologic) and gender-related (sociocultural) research are suggested (22, 59, 140). In this study, we aim to provide a comprehensive summary of evidence to assess the generalizability of our findings across all types of participants. Our data would be useful as a support in policy making in order to plan interventions to increase the population level of cardiovascular health. Gender and age targeted interventions should be considered for smoking cessation and improving physical activity to decrease the rate of HF.

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Appendices

Appendix 1

Search strategies

MEDLINE:

Search through PubMed platform

(Filters: Humans; MEDLINE):

#1 "Heart Failure"[Mesh] OR heart failure/tw OR "Cardiovascular Diseases"[Mesh] or "Cardiovascular Diseases"tw

#2 "Cigarette Smoking"[Mesh] OR "Tobacco Smoking"[Mesh] OR "Smoking"[Mesh] OR smoking OR "Smoking Tobacco"[Mesh] OR "Exercise"[Mesh] OR (Physical activity) OR Physical inactivity OR sedentary lifestyle

#3 "Sex Characteristics"[Mesh] OR (gender difference)

#4 (#1 AND #2 AND #3)

EMBASE:

Search through Ovid platform

(limit 5 to “human” and exclude “MEDLINE journals” and “EMBASE status”)

#1 heart failure*/tw OR heart failure/exp OR heart failure.mp OR Cardiovascular disease/tw OR Cardiovascular/exp

2 smoking*/tw OR smoking/exp OR cigarette smoking/tw OR smoking cessation/tw OR smoking habit/tw OR tobacco smoke/tw OR tobacco/tw OR tobacco/exp OR physical activity*/tw OR physical activity/exp OR Physical fitness.mp. OR fitness/tw OR

Physical fitness/exp OR sedentary lifestyle.mp. OR sedentary lifestyle/tw OR physical activity/tw OR exercise/tw OR sedentary lifestyle/exp

3 gender differences*/tw OR gender difference.mp. OR sex difference/tw OR gender differences.mp. OR sex difference/tw OR gender difference/exp sex difference.mp. OR sex difference/tw OR sex differences.mp. OR sex difference/tw OR sex difference/exp

#4 (#1 AND #2 AND #3)

3. CINHAL:

Chosen databases: CINAHL Plus with Full Text

#1 heart failure

#2 smoking OR smoking cigarette OR smoking tobacco OR smoking cessation OR lifestyle factor OR Physical activity OR physical fitness OR sedentary lifestyle OR lifestyle risk factor OR Physical inactivity

#3 Gender differences OR sex differences OR gender OR sex

#4 (#1 AND #2 AND #3)

Appendix 2

Studies assessing the effect of smoking and heart failure

1. Alicia Uijl, UK, 2019, UK-based CALIBER,

Risk Factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records

2. Jiang He, US, 2001, NHANES 1 Epidemiologic Follow-up Study

Risk Factors for Congestive Heart Failure in US Men and Women

3. Susanna C. Larsson, 2016

Healthy Lifestyle and Risk of Heart Failure

Results from 2 Prospective Cohort Studies

4. Yujie Wang, 2011, Finland, FINRISK

Lifestyle Factors in Relation to Heart Failure Among Finnish Men and Women

5. Mark Alexander, 1995, USA, A large Health Maintenance Organization Study (HMO)

Hospitalization for Congestive Heart Failure

6. Mar Pujades-Rodriguez, 2015, Oxford, UK, the CALIBER program,

Heterogeneous association between smoking and a wide range of initial presentations of cardiovascular disease in 1 937 360 peoples in England: Lifetime risks and implications for risk prediction

7. Andreas Kalogeropoulos, 2009, USA,

Epidemiology of Incident Heart Failure in a contemporary Elderly Cohort

(103)

Title, Author, Study Name, Year	Risk Factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records, Alicia Uijl, UK, 2019, UK-based CALIBER	
Methods	Cohort Study	
Participants	871 687 free of HF at baseline (large electronic health records)	Men= 381 314, Women= 442 369
Ages of Participants	≥ 55 y/o (55-64, 65-74, >75)	
HF cases	47 987	Men= 23 314, Women= 24 673
Mean year of follow-up duration	5.8 y/o (2.7-9.9 years), median time to event: 3.7 years	From 2000 to 2010
Exposure	Smoking (Never, current, Ex: (quit: <2y, 2-5 y, 5-10y, >10y)	
Outcomes	The Primary Endpoint: First records of HF from primary or secondary care	
Results Multivariate Hazard Ratio All statistically significant (p<0.001)	Men: Current: (55-64y/o): 1.27 (1.15-1.43) Ex-Smoker: 1.08 (0.96-1.21) (65-74 y/o): 1.15 (1.07-1.24) 1.03 (0.97-1.10) (75 ≤): 1.06 (0.96-1.17) 1.00 (0.94-1.06) Women: Current: (55-64y/o): 1.35 (1.20-1.52) Ex-smoker: 1.15 (1.44-1.70) (65-74 y/o): 1.21 (1.11-1.33) 1.30 (1.23-1.38) (75 ≤): 1.09 (0.99-1.20) 1.16 (1.11-1.20)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"… A cohort of 871687 individuals was constructed from the CALIBER resource…which links four sources of HER in England... Individuals were included if they were 55years or older between 1 January 2000 and 25 March 2010, if they had been registered with a general practitioner for at least 1year, in a practice that had at least 1year of up-to-standard data recording in CPRD… The last date of the previously mentioned occasions was considered cohort entry date (index date)…" (103)*
Performance bias	High risk	*"…smoking status as never, ex- or current smokers… Baseline risk factors were identified as the closest measurement to index date up to 3years before and 1year after. index date…" (103)* Risk of recall bias for self-reported data about smoking
Detection bias	Low risk	*"…The primary endpoint was incident HF and was based on the first record of HF from CPRD or HES…were defined by a diagnosis of HF or diagnosis of chronic left ventricular dysfunction on echocardiogram with READ codes, and in HES by a diagnosis of HF with ICD-10. Secondary endpoint was the first record of HF, excluding patients with a previous myocardial infarction (MI) event at baseline…" (103)* According to CALIBER data base document, HF diagnosed with: *"…clinical details in the PC record relevant to diagnosis and management, including LV dysfunction confirmed by cardiac imaging, an elevated BNP concentration, referral to HF care, referral to a cardiologist, the use of loop diuretics, and symptoms and signs suggestive of HF…"(128)*
Attrition bias	Low risk	*"…Missing data in all baseline risk factors were imputed, except comorbidities and prescriptions, using multiple imputation, from the mice algorithm in the statistical software package R…" (103)*
Reporting bias	Unclear risk	
Other bias	High risk	All measurements are prone to measurement error and/or misclassification. To define HF, they used data from two different EHR sources, each having their own measurement error.

(37)

Title, Author, year, study name	Risk Factors for Congestive Heart Failure in US Men and Women, Jiang He, US, 2001, NHANES 1 Epidemiologic Follow-up Study	
Methods	Prospective Cohort Study	
Participants	13 643	Men= 5 545, Women= 8 098
Ages of Participants	24 – 74 y/o (1 to 74 y/o)	
Heart Failure cases	1 382	Men= 741, Women= 641
Mean year of follow-up duration	19 years (1971, 1975, 1992)	
Exposure	Smoking	
Outcomes	Congestive Heart Failure	
Results	Men: Low Physical Activity: 1.14 (0.94-1.38), Women: Low Physical Activity: 1.31 (1.11-1.54)	

Bias	Authors' judgement	Support for judgement
Selection bias	High risk	*"…a multistage, stratified, probably sampling design was used to select a representative sample of the US civilian …certain population subgroups, including those with a low income, women at childbearing age…and elderly …were oversampled…" (37)*
Performance bias	Low risk	*"…smoking status was obtained in a random subsample of 6913 participants who underwent a more detailed evaluation of the time of their examination…smoking status at baseline was derived from responses to questions regarding lifetime smoking history administered at follow-up interviews …" (37)* The reliability of surrogate information on smoking were checked and it was 85% to 90% (121)
Detection bias	Low risk	*"…obtaining hospital … records …pathology reports, electrocardiograms… death certificates…" (37)* Validity of the outcome checked elsewhere (122)
Attrition bias	Low risk	They started by 14407 and after exclusion they ended up by 13634 participants. They exclude CVD patients, people who lost to follow up.
Reporting bias	Unclear risk	
Other bias	High risk	Detected diabetes CHF with self reported information, follow up of participants was passive rather than active fashion. Electrocardiography and echocardiography were not available and left ventricular dysfunction was not studied.

(114)

Title, author, year, study name	Healthy Lifestyle and Risk of Heart Failure, Susanna C. Larsson, 2016, (Result from 2 Prospective Cohort Studies), Sweden	
Methods	In Two population-based prospective cohort study Residing in Orebro or Vastmanland County	
Participants	64 679	Men= 33 966 (Cohort of Swedish Men): COSM, Women= 30 713 (Swedish Mammography Cohort): SMC
Ages of participants	45 – 83 years free of HF and IHD at Baseline	
Heart failure cases	2 584	Men= 1 488, Women= 1 096
Mean year of follow-up duration	13 years	From 1 Jan 1998 to: 31 Dec 2010
Exposure	Smoking: (never or ever) vs (current smoker), a current nonsmoker versus current smoker	
Outcomes	Heart failure diagnosis	
Results Cox proportional regression	Men: Physically inactive = 1.00, Physically active = 0.83 (0.74-0.94) Women: Physically inactive = 1.00, Physically active = 0.71 (0.63-0.81)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"…The COSM was initiated in the late autumn of 1997 when 48 850 men who were 45 to 79 years of age … The SMC began in 1987 to 1990 when all women who were born between 1914 and 1948 … received a questionnaire about diet and reproductive factors. SMC participants received an expanded questionnaire (similar to the questionnaire used in the COSM) in the autumn of 1997; 39 227 women (49–83 years of age in 1997) completed the questionnaire..." (114)*
Performance bias	High risk	*"…information on smoking, physical activity, and other major risk factors for cardiovascular disease was obtained first in 1997, the 1997 questionnaire…" (114)* Risk of recall bias
Detection bias	Low risk	Incident of HF were ascertained by linkage with the Swedish National Patient Register and the Swedish Cause of Death Register. ICD10 & ICD11: I50, the validation of Swedish Patient Register found 95% of primary HF diagnosis were definite HF.
Attrition bias	Low risk	*"…Men and women were excluded if they had an incorrect or a missing personal identification number (n=297 men and n=243 women), had a previous diagnosis of HF or ischemic heart disease (n=4823 men and n=1891 women) or cancer other than nonmelanoma skin cancer (n=2592 men and n=1811 women), or died between the administration of 1997 questionnaire and start of follow-up (January 1, 1998; n=55 men and n=26 women). Those with extreme energy intakes (ie, 3 SDs from the loge-transformed mean energy intake in men and women separately; n=468 men and n=432 women) or with missing data on any of the lifestyle factors (including missing information on any component of the Mediterranean diet; n=6649 men and n=4111 women) were also excluded..." (114)* 48 850 men and 39 227 women, ended up in 33 966 men and 30 713 women for analysis.
Reporting bias	Unclear risk	
Other bias	High risk	Self reported BMI, Alcohol consumption, Diet, Physical activity.

(2)

Title, author, year, study name	Lifestyle Factors in Relation to Heart Failure Among Finnish Men and Women, Yujie Wang, 2011, Finland, FINRISK	
Methods	Prospective cohort	
Participants	38 072	Men= 18 346, Women= 19 726
Ages of participants	25 – 64 y/o, 65 – 74 y/o	
Heart failure cases	1 083	Men= 638, Women= 445
Mean year of follow-up duration	14.1 years (5.9-20.9), 1982, 1987, 1992, 1997, 2007	
Exposure	Participants classified as never, ex-smoker and current smoker. *"…Participants were classified as never, ex-smokers and current smokers, based on their responses to the questionnaire."(2)*	
Outcomes	Heart failure	
Results	Men: Light = 1.00, Moderate= 0.79 (0.64-0.97), High = 0.67 (0.53-0.86) Women: Light = 1.00, Moderate= 0.87 (0.70-1.08), High = 0.64 (0.48-0.86)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	"…Five independent cross-sectional, population-based health examination surveys (FINRISK) … in 6 geographic areas of Finland in 1982, 1987, 1992, 1997, and 2002…. stratified by area, sex, and 10-year age group according to (WHO) …protocol…" (2)
Performance bias	High risk	*A self-administered questionnaire was mailed to the participants …, smoking,… Data on the history of myocardial infarction or diabetes mellitus at baseline were obtained from the questionnaire and collected by hospital discharge diagnosis or drug register… valvular heart disease at baseline were collected by hospital discharge register"(2)* Risk of recall bias
Detection bias	Low risk	"…ascertain HF cases … has been used in Scandinavian countries,… positive predictive value of HF diagnosis to be 82% (false-positive rate, 18%)… found the specificity of the HF diagnoses to be acceptable for the epidemiological study…"(2)
Attrition bias	Low risk	"…The total sample size…was 38 737. The final sample comprised 18 346 men and 19 729 women after excluding the participants with a history of HF (n=457) at baseline and the participants with incomplete data on any variables required for this analysis (n=205)…" (2)
Reporting bias	Unclear risk	
Other bias	High risk	"Information were collected on self-reported for physical activity and smoking, once at baseline. No data on possible changes on lifestyle factors during follow-up… Cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors"(2)

(115)

Title, author, year, study Name	Hospitalization for Congestive Heart Failure, Mark Alexander, 1995, USA, A large Health Maintenance Organization Study (HMO)	
Methods	Retrospective Cohort Study	
Participants	64 877 (27% African American, 73% White)	Men= 27 708, Women= 30 134
Ages of participants	≥40 years free of CHF at baseline	
Heart failure cases	1 330	Men= 618, Women= 712
Mean year of follow-up duration	9.5 years (ranged from 1 month to 14.9 years)	1960s- 1991, they received MHC between 1978 and 1984
Exposure	Smoked > 1 year, healthcare reports were used	
Outcomes	Heart Failure (First Hospitalization with a principle diagnosis of CHF)	
Results	Men; age< 60, Smoke > 1 year, 2.18 (1.46-3.25), Women; age< 60, Smoke > 1 year, 1.64 (1.12-2.39)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	Participants of Northern California Kaiser Permanent Medical Care Program Who took at the Kaiser Permanent Medical Care Program. Who took at least one multiphasic checkup (MHC) at the age of 40 and were free of HF at the time. They collected medical and social history questionnaire, a series of clinical laboratory tests, a chest x-rays, electrocardiogram, and an examination by a physician.
Performance bias	High risk	Self-reported data base by asking from patients. Risk of recall bias
Detection bias	Low risk	Used hospital databases
Attrition bias	High risk	They did not mention to the number of participants that excluded during the follow up time
Reporting bias	Unclear risk	
Other bias	High risk	According to their nature of their data bases they just use the insured population.

(109)

Title, author, year, study name	Heterogeneous association between smoking and a wide range of initial presentations of cardiovascular disease in 1 937 360 peoples in England: Lifetime risks and implications for risk prediction, Mar Pujades-Rodriguez, 2015, Oxford, UK, The CALIBER programme	
Methods	Population-based Cohort Study of electronic health records	
Participants	1 937 360, Smoking status data: 1 413 749	Men= 1 605 729, Women= 1 745 380
Ages of participants	≥ 30 y/o	
Heart failure cases	14 359	Men= 6 206, Women= 8 153
Mean year of follow-up duration	5.5 year (6 years), 11.6 million person-year	From 1st Jan 1997 to 25th March 2010
Exposure	Examined association of smoking and smoking cessation based on sex classified in: #Never smoker #ex-smoker #current smoker Ex-smokers were grouped into categories of time since quitting (<2, 2-5, 5-10, >10 years and missing)	
Outcomes	12 CVD presentations including Heart failure	
Results	Men: Never = 1.00, Current = 1.57 (1.40-1.77) Women: Never = 1.00, Current = 1.77 (1.47- 2.13)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	"…cohort of 1937360 patients drawn from individuals registered in the general practices in England contributing with data to the CALIBER programme, between January 1997 and March 2010, was analysed. Patient data were linked across four data source…"
Performance bias	High risk	Patients self-reported smoking status was prospectively collected. The most recent smoking record before the study entry was used. Risk of recall bias
Detection bias	Low risk	Check through the available data bases of CALIBER study
Attrition bias	High risk	Start with 5372 790 participants and ended up in 1 937 360
Reporting bias	Low risk	Through the access to their supplementary file
Other bias	High risk	*"…unavailable and residual confounding cannot be completely excluded…Smoking status might also have changed over time, and this could have resulted in underestimation of associations… to define CVDs we used data from four different EHR sources, each of which has its own error…unable to resolve disease subtypes including systolic or diastolic heart failure, which might mask an even greater degree of heterogeneity… cannot exclude that some associations might have resulted from multiple testing" (109)*

(116)

Title, Author, Study Name, Year	Epidemiology of Incident Heart Failure in a contemporary Elderly Cohort, Andreas Kalogeropoulos, 2009, USA, Health ABC study	
Methods	Population-based study of 3075 community-dwelling Cohort	
Participants	2 934	Men= 1 405, Women= 1 529
Ages of participants	70 – 79 y/o (mean age = 73.6 ± 2.9)	
Heart failure cases	258 (8.8%), 13.6 per 1000 p.y (12.1-15.4)	Men= 140, Women= 118
Mean year of follow-up duration	7.1 years Follow-up (25^{th}-75^{th}: 6.6- 7.5 years)	From April 1997 to June 1998
Exposure	Smoking (Current, past (if ≥100 lifetime cigarettes) or never.	
Outcomes	Heart Failure	
Results	White: Men: Current = 1.32 (0.42-3.21) Women: Current = 1.88 (1.01-3.35)	Black: Men: Current = 2.72 (1.17-5.64) Women: Current = 1.75 (0.85-3.32)

Bias	Authors' judgement	Support for judgement
Selection bias	High risk	*"…The Health ABC Study is a population-based study of 3075 community-dwelling men and women aged 70 to of 3075 community-dwelling Cohort…Cardiovascular disease status at baseline, including prevalent HF, was based on self-reported history,"(116)* Risk of recall bias
Performance bias	High risk	Questionnaire, self reported
Detection bias	High risk	*"…Local adjudicators classified events as HF based on symptoms, signs, chest radiograph results, and echocardiographic findings based on criteria similar to those used in the Cardiovascular Health Study. The HF criteria required at least a HF diagnosis from a physician and treatment for HF (i.e., a current prescription for a diuretic agent and either digitalis or a vasodilator); these criteria have been used in previous investigations. Because HF was not allowed as a cause of death, there were no deaths from incident HF…"(116)*
Attrition bias	Low risk	*"…Of 3075 subjects enrolled in the Health ABC Study, 95 had definite or possible HF at baseline, and 46 were excluded because of missing data on HF status. The final cohort analyzed for this study included 2934 participants…"(116)*
Reporting bias	Unclear risk	
Other bias	High risk	*"…was based on HF hospitalization; therefore, we likely underestimated the true incidence. Echocardiography was not performed…The Health ABC Study did not collect detailed data on valvular heart disease; however, it is unlikely that a large proportion of participants had significant subclinical valvular heart disease that would affect the results overall…because ventricular function during hospitalization for HF was not prospectively assessed, we could not reliably assess the differential effect of risk factors on development of HF with preserved vs reduced LVEF….The available data on LVEF are based on medical record reviews and do not refer to a single modality. Therefore, we cannot be confident that the distribution of LVEF is representative of older persons hospitalized with new-onset HF…These differences may represent sex, race, severity of illness, or therapy related differences…"(116)*

Appendix 3

Studies for the effect of physical activity effect and heart failure

1. Alicia Uijl, 2019, UK, UK-based CALIBER

Risk Factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records

2. Jiang He, 2001, USA, NHANES 1 Epidemiologic Follow-up Study

Risk Factors for Congestive Heart Failure in US Men and Women

3. Susanna C. Larsson, 2016, Sweden

Healthy Lifestyle and Risk of Heart Failure

Results from 2 Prospective Cohort Studies

4. Yujie Wang, 2011, Finland, FINRISK

Lifestyle Factors in Relation to Heart Failure Among Finnish Men and Women

5. Gang Hu, 2009, Finland,

Joint effect of Physical Activity, Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio on the Risk of Heart Failure

6. Yujie Wang, 2010, Finland,

Occupational, Commuting, and Leisure-Time Physical Activity in Relation to Heart Failure Among Finnish Men and Women

Gang Hu et al, 2009 and Yujie Wang et al, 2010 and Yujie Wang et al, 2011 used the same data source during the same time period.

(103)

Title, author, study name, year		Risk Factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records, Alicia Uijl, UK, 2019, UK-based CALIBER	
Methods		Cohort study	
Participants		871 687 free of HF at baseline (a large electronic health records)	Men= 381 314, Women= 442 369
Ages of participants		≥ 55 y/o (55-64, 65-74, >75)	
HF cases		47 987	Men= 23 314, Women= 24 673
Mean year of follow-up duration		5.8 y/o (2.7-9.9 years), median time to event: 3.7 years	From 2000 to 2010
Exposure		Sedentary lifestyle	
Outcomes		The Primary Endpoint: First records of HF from primary or secondary care	
Results (Hazard Ratios) *all HR are statistically significant: p<0.001*		Men: (55-64y/o): 1.06 (0.99-1.13), (65-74 y/o): 1.11 (1.04-1.17), (75 ≤): 1.09 (1.02-1.16) Women: (55-64y/o): 1.09 (1.00-1.19), (65-74 y/o): 1.09 (1.01-1.17), (75 ≤): 1.08 (1.02-1.15)	Multiple regression analysis: Men: (55-64y/o): 9.07 (4.97-12.84), (65-74 y/o): 5.03 (2.35-7.97), (75 ≤): 5.31 (1.83-9.06) Women: (55-64y/o): 5.96 (1.56-10.41), (65-74 y/o): 5.69 (1.19-9.79), (75 ≤): 6.36 (1.49-10.78)
Bias	Authors' judgement	Support for judgement	
Selection bias *(selection of exposed and non-exposed cohort)*	Low risk	*"… A cohort of 871687 individuals was constructed from the CALIBER resource…which links four sources of HER in England... Individuals were included if they were 55years or older between 1 January 2000 and 25 March 2010, if they had been registered with a general practitioner for at least 1year, in a practice that had at least 1year of up-to-standard data recording in CPRD… The last date of the previously mentioned occasions was considered cohort entry date (index date)…" (103)*	
Performance bias *(assessment of exposure)*	High risk	*"…patient's level of physical activity as recorded in primary care was classified as sedentary life style or active life style. Definitions of all risk factors can be found at … Baseline risk factors were identified as the closest measurement to index date up to 3years before and 1year after. index date…" (103)* Risk of recall bias for self-reported data about sedentary lifestyle	
Detection bias	Low risk	*"…The primary endpoint was incident HF and was based on the first record of HF from CPRD or HES…were defined by a diagnosis of HF or diagnosis of chronic left ventricular dysfunction on echocardiogram with READ codes, and in HES by a diagnosis of HF with ICD-10. Secondary endpoint was the first record of HF, excluding patients with a previous myocardial infarction (MI) event at baseline…" (103)* According to CALIBER data base document, HF diagnosed with: *"…clinical details in the PC record relevant to diagnosis and management, including LV dysfunction confirmed by cardiac imaging, an elevated BNP concentration, referral to HF care, referral to a cardiologist, the use of loop diuretics, and symptoms and signs suggestive of HF…"(128)*	
Attrition bias	Low risk	*"…Missing data in all baseline risk factors were imputed, except comorbidities and prescriptions, using multiple imputation, from the mice algorithm in the statistical software package R…" (103)*	
Reporting bias	Unclear risk		
Other bias	High risk	All measurements are prone to measurement error and/or misclassification. To define HF, they used data from two different EHR sources, each having their own measurement error.	

(37)

Title, author, year, study name	Risk factors for congestive heart failure in US men and women, Jiang He, US, 2001, NHANES 1 Epidemiologic Follow-up Study	
Methods	Prospective cohort study	
Participants	13 643	Men= 5 545, Women= 8 098
Ages of participants	1 – 74 y/o	
Heart failure cases	1 382	Men= 741, Women= 641
Mean year of follow-up duration	19 years (1971, 1975, 1992)	
Exposure	Recreational physical activity, Having regular physical activity	
Outcomes	Congestive heart failure	
Results	Men: Low Physical Activity: 1.14 (0.94-1.38), Women: Low Physical Activity: 1.31 (1.11-1.54)	

Bias	Authors' judgement	Support for judgement
Selection bias	High risk	*"…a multistage, stratified, probably sampling design was used to select a representative sample of the US civilian …certain population subgroups, including those with a low income, women at childbearing age…and elderly …were oversampled…" (37)*
Performance bias	High risk	*"…physical activity…obtained based on responses to interview-administered questionnaire." (37)* Risk of recall bias
Detection bias	Low risk	*"…obtaining hospital … records …pathology reports, electrocardiograms… death certificates…" (37)* *Validity of the outcome checked elsewhere (122)*
Attrition bias	Low risk	They started by 14407 and after exclusion they ended up by 13634 participants. They exclude CVD patients, people who lost to follow up.
Reporting bias	Unclear risk	
Other bias	High risk	Detected diabetes CHF with self reported information, follow up of participants was passive rather than active fashion. Electrocardiography and echocardiography were not available and left ventricular dysfunction was not studied.

(114)

Title, author, study name, year	Healthy lifestyle and risk of heart failure (Result from 2 prospective cohort studies), Susanna C. Larsson, 2016, Sweden	
Methods	In two population-based prospective cohort study Residing in Orebro or Vastmanland County	
Participants	64 679	Men= 33 966 (Cohort of Swedish men): COSM Women= 30 713 (Swedish mammography cohort): SMC
Ages of Participants	45 – 83 years free of HF and IHD at Baseline	
Heart Failure cases	2 584	Men= 1 488, Women= 1 096
Mean year of follow-up duration	13 years	From 1 Jan 1998 to: 31 Dec 2010
Exposure	physically active (≥150 min/wk of physical activity) versus inactive (<150 min/wk) *"Physical activity was assessed with a prior validated questionnaire on time spent on various activities during the previous year. In this study, we added up time per week spent engaged in walking/bicycling and exercise." (114)*	
Outcomes	Heart failure	
Results Cox proportional hazard regression	Men: Physically inactive = 1.00, Physically active = 0.83 (0.74-0.94) Women: Physically inactive = 1.00, Physically active = 0.71 (0.63-0.81)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"…The COSM was initiated in the late autumn of 1997 when 48 850 men who were 45 to 79 years of age … The SMC began in 1987 to 1990 when all women who were born between 1914 and 1948 … received a questionnaire about diet and reproductive factors. SMC participants received an expanded questionnaire (similar to the questionnaire used in the COSM) in the autumn of 1997; 39 227 women (49–83 years of age in 1997) completed the questionnaire..." (114)*
Performance bias	High risk	*"…information on smoking, physical activity, and other major risk factors for cardiovascular disease was obtained first in 1997, the 1997 questionnaire…" (114)* Risk of recall bias
Detection bias	Low risk	Incident of HF were ascertained by linkage with the Swedish National Patient Register and the Swedish Cause of Death Register. ICD10 & ICD11: I50, the validation of Swedish Patient Register found 95% of primary HF diagnosis were definite HF.
Attrition bias	Low risk	*"…Men and women were excluded if they had an incorrect or a missing personal identification number (n=297 men and n=243 women), had a previous diagnosis of HF or ischemic heart disease (n=4823 men and n=1891 women) or cancer other than nonmelanoma skin cancer (n=2592 men and n=1811 women), or died between the administration of 1997 questionnaire and start of follow-up (January 1, 1998; n=55 men and n=26 women). Those with extreme energy intakes (ie, 3 SDs from the loge-transformed mean energy intake in men and women separately; n=468 men and n=432 women) or with missing data on any of the lifestyle factors (including missing information on any component of the Mediterranean diet; n=6649 men and n=4111 women) were also excluded..." (114)* 48 850 men and 39 227 women, ended up in 33 966 men and 30 713 women for analysis.
Reporting bias	Unclear risk	
Other bias	High risk	Self reported BMI, Alcohol consumption, Diet, Physical activity

(2)

Title, author, year, study name	Lifestyle factors in relation to heart failure among Finnish men and women, Yujie Wang, 2011, Finland, FINRISK	
Method	Prospective cohort	
Participants	38 072	Men= 18 346, Women= 19 726
Ages of participants	25 – 64 y/o, 65 – 74 y/o	
Heart failure cases	1 083	Men= 638, Women= 445
Mean year of follow-up duration	14.1 years, (5.9-20.9), 1982, 1987, 1992, 1997, 2007	
Exposure	Dichotomized to low vs moderate or high physical activity Physical Activity (Occupational, Commuting, and Leisure-Time Physical Activity) -occupational PA was divided into 3 categories: (1). Low: sitting at office (2). Walking, (3). High: walking and lifting, heavy manual labor -daily commuting PA was divided into 3 categories: (1). Motorized transportation or no physical work (2). Walking or bicycling 1 to 29 min/day (3). Walking or bicycling more than 30 min/day -leisure time PA was divided into 3 categories: (1). Low: almost sitting, (2). Moderate: some PA more than 4 h/w, (3). High: vigorous PA more than 3 h/w. *"…because we found that moderate and high occupational or leisure time physical activity independently and significantly reduces risk of HF the groups were merged into 3categories: "low" when subjects reported light levels of both occupational and leisure time physical activity; "moderate" when subjects reported moderate or high level of either occupational or leisure time physical activity; and "high" when subjects reported moderate or high level of both occupational and leisure time physical activity."(2)*	
Outcomes	Heart failure	
Results (Multivariable cox regression)	Men: Light = 1.00, Moderate= 0.79 (0.64-0.97), High = 0.67 (0.53-0.86) Women: Light = 1.00, Moderate= 0.87 (0.70-1.08), High = 0.64 (0.48-0.86)	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"…Five independent cross-sectional, population-based health examination surveys (FINRISK) … in 6 geographic areas of Finland in 1982, 1987, 1992, 1997, and 2002…. stratified by area, sex, and 10-year age group according to (WHO) …protocol…" (2)*
Performance bias	High risk	*A self-administered questionnaire was mailed to the participants …, physical activity,… Data on the history of myocardial infarction or diabetes mellitus at baseline were obtained from the questionnaire and collected by hospital discharge diagnosis or drug register… valvular heart disease at baseline were collected by hospital discharge register"(2)* Risk of recall bias
Detection bias	Low risk	*"…ascertain HF cases … has been used in Scandinavian countries,… positive predictive value of HF diagnosis to be 82% (false-positive rate, 18%)… found the specificity of the HF diagnoses to be acceptable for the epidemiological study…"(2)*
Attrition bias	Low risk	*"…The total sample size…was 38 737. The final sample comprised 18 346 men and 19 729 women after excluding the participants with a history of HF (n=457) at baseline and the participants with incomplete data on any variables required for this analysis (n=205)…" (2)*
Reporting bias	Unclear risk	
Other bias	High risk	*"Information were collected on self-reported for physical activity and smoking, once at baseline. No data on possible changes on lifestyle factors during follow-up… Cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors"(2)*

(117)

Title, author, year, study name	Joint effect of Physical Activity, Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio on the Risk of Heart Failure, Gang Hu, 2009, Finland	
Methods	Population-based Cohort	
Participants	59 178	Men= 28 842, Women= 30 336
Ages of participants	24 – 74 y/o	
Heart failure cases	3 614	Men= 1 921, Women= 1 693
Mean year of follow-up duration	18.4 years	
Exposure	Physical activity	
Outcomes	Heart failure	
Results *low, medium and high physical activity.*	Men: Low = 1.00, Moderate = 0.79 (0.68-0.92), High= 0.69 (0.60-0.80), p trend<0.001 Women: Low = 1.00, Moderate = 0.86 (0.75-0.99), High= 0.68 (0.59-0.78), p trend<0.001	

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"…Seven independent cross-sectional population surveys … in 6 geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997, and 2002…according to the (WHO) … (MONICA) protocol."(117)*
Performance bias	High risk	*"…A self-administered questionnaire was mailed to the participants to be completed at home and returned to the survey site. …physical activity, … On the basis of the responses, the participants were classified as…"(117)* Risk of recall bias
Detection bias	Low risk	A study from Sweden found the positive predictive value of HF diagnosis to be 82%. Another study from Finland confirm the specificity of the HF diagnosis to be acceptable for the epidemiological study.
Attrition bias	Low risk	*"…total sample size … was 62 013. The final sample comprised 28 842 men and 30 336 women after the exclusion of participants with a history of HF (n=998) at baseline, participants who were underweight (BMI <18.5 kg/m2) (n =488), and the participants with incomplete data on any variables required for this analysis (n=1349). …The excluded participants with incomplete data did not differ significantly from remaining participants in mean age and the sex distribution." (117)*
Reporting bias	Unclear risk	
Other bias	High risk	Information were collected on self-reported for physical activity and smoking, once at baseline. No data on possible changes on lifestyle factors during follow-up. Cannot completely either exclude the effects of residual confounding due to measurement error in the assessment of confounding factors, or some unmeasured dietary factors.

"…Occupational, commuting, and leisure-time physical activity levels were assessed with a self-administered questionnaire. …

occupational physical activity according to the following 3 categories: low (work that is physically very easy such as sitting office work [e.g., secretary]), moderate (work including standing and walking [e.g., store assistant and light industrial worker]), and high (work including walking and lifting or heavy manual labor [e.g., industrial or farm work]).

Daily commuting return journey was divided into 3 categories: motorized transportation or no work (no walking or cycling), walking or bicycling 1 to 29 minutes per day, or walking or bicycling >30 minutes per day.

Self-reported leisure-time physical activity was classified into 3 categories: low, defined as almost completely inactive such as reading, watching television, or doing some minor physical activity but not at a moderate or high level; moderate, defined as doing some physical activity >4 h/wk such as walking, cycling, or light gardening, excluding travel to work; and high, defined as performing vigorous physical activity >3 h/wk such as running, jogging, swimming, or heavy gardening or competitive sports several times a week.

Because we found that moderate and high occupational, commuting, or leisure-time physical activity independently and significantly reduces risk of HF, the groups were merged into 3 categories: low, which included those subjects who reported light levels of occupational, commuting (<1 minute), and leisure-time physical activity; moderate, which included those subjects who reported only 1 of the all 3 types of moderate to high physical activity; and high, which included those subjects who reported 2 or 3 types of moderate to high physical activity. This method had been used to assess other outcomes such as incidence of diabetes mellitus and mortality in the same study samples…" (117)

(53)

Title, author, year, study name	Occupational, commuting, and leisure-time physical activity in relation to heart failure among Finnish men and women, Yujie Wang, 2010, FINRISK, Finland		
Methods	Study cohort		
Participants	58 208 free of HF at baseline	Men= 28 334, Women= 29 874	
Ages of participants	25 – 74 y/o		
Heart failure cases	3 508	Men= 1 868, Women= 1 640	
Mean year of follow-up duration	18.4 years	From 1972 to 2002	
Exposure	Physical activity (Occupational, Commuting, and Leisure-Time Physical Activity) -occupational PA was divided into 3 categories: (1). Low: sitting at office (2). Walking, (3). High: walking and lifting, heavy manual labor -daily commuting PA was divided into 3 categories: (1). Motorized transportation or no physical work (2). Walking or bicycling 1 to 29 min/day (3). Walking or bicycling more than 30 min/day -leisure time PA was divided into 3 categories: (1). Low: almost sitting, (2). Moderate: some PA more than 4 h/w, (3). High: vigorous PA more than 3 h/w.		
Outcomes	Heart failure		
Results	Occupational: Men: low: 1.00 Moderate: 0.90 (0.78-1.03), p<0.005 High: 0.83 (0.73-0.93), p<0.005 Women: low: 1.00 Moderate: 0.80 (0.70-0.92), p<0.007 High: 0.92 (0.82-1.05), p<0.007	Leisure Time: Men: low: 1.00 Moderate: 0.83 (0.76-0.92), p<0.001 High: 0.65 (0.54-0.77), p<0.001 Women: low: 1.00 Moderate: 0.84 (0.75-0.94), p=0.001 High: 0.75 (0.60-0.94), p=0.001	Commuting: Men: low: 1.00 Moderate:1.01 (0.90_1.13), p<0.954 High: 0.99 (0.87-1.12), p<0.954 Women: low: 1.00 Moderate:0.87 (0.76-0.99), p<0.159 High: 0.94 (0.82-1.07), p<0.159

Bias	Authors' judgement	Support for judgement
Selection bias	Low risk	*"…Seven independent population surveys … in 6 geographic areas of Finland in 1972, 1977, 1982, 1987, 1992, 1997, and 2002 …the sample was stratified by area, gender, and 10-year age group according to the World Health Organization Monitoring Trends and Determinants of Cardiovascular Disease protocol…" (53)*
Performance bias	Low risk	*"Occupational, commuting, and leisure-time physical activity levels were assessed using a self-administered questionnaire only at baseline" (53)* *"…The questionnaire used for the assessment of physical activity has been used successfully elsewhere, and it has shown a high correlation with physical fitness, as measured by maximal oxygen uptake…"(53)*
Detection bias	Low risk	*"…An HF diagnosis was made by the treating physicians, based on a clinical assessment, X-ray examination, and to various extents, echocardiography. Follow-up of each cohort member continued until the date of the diagnosis of HF obtained from the Hospital Discharge Register, the National Social Insurance Institution's register or mortality, death resulting from causes other than HF, ... The accuracy of the HF cases … more than 80% based on the European Society of Cardiology definition" (53)*
Attrition bias	Low risk	"…The total sample size of the 7 surveys was 62,013. After excluding 998 subjects with a history of HF at baseline and 2,807 subjects with incomplete data on any required variables, the present analyses include 28,334 men and 29,874 women…" (53)
Reporting bias	Unclear risk	
Other bias	High risk	Assessment of PA (with self-administered questioners only at baseline). Information were collected on self-reported for physical activity and smoking, once at baseline. No data on possible changes on lifestyle factors during follow-up.

"… the participants were classified as never smokers, former smokers, and current smokers. Current smokers were categorized into those who smoked fewer than 20 or 20 or more cigarettes/day…"(53)

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Appendix 4

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