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The association between socioeconomic conditions in childhood and risk of self-reported ischemic heart disease in middle-aged Norwegian women

The Norwegian Women and Cancer Study (NOWAC)

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Edvard Munch: Hjertet, 1898-99.

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PREFACE AND ACKNOWLEDGEMENTS

This thesis concludes the degree of Master in Public Health. Throughout the course of the master program I took a special interest in the subject of social inequalities in health, and I am appreciative for being given the opportunity to dive into the immensely intriguing subject.

I would like to express my deepest gratitude and thanks to my brilliant supervisor, associate professor Tonje Braaten for her constructive feedback, steady guidance, and patience throughout the process of writing the thesis.

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ABSTRACT

Background: Ischemic heart disease is one of the leading causes of morbidity and mortality. It is a chronic disease found to be socioeconomically patterned, and declining rates over the past few decades seems to benefit the most advantaged socioeconomic group, creating a greater difference between the most disadvantaged social group and the most advantageous group. Early life exposures have been found to play a key role in development of heart disease.

Aim: To examine if there is an association between childhood socioeconomic conditions and self-reported ischemic heart disease in middle-aged Norwegian women. If an association between childhood socioeconomic circumstances and IHD is observed, we will focus on lifestyle factors in childhood and adolescence as potential explanatory factors.

Materials and methods: Data was gathered from the Norwegian Women and Cancer Study (NOWAC), a nationwide prospective cohort established in 1991. The sample consists of 77,154 women aged 30-70 years at baseline. Information on childhood socioeconomic conditions, IHD, education, and lifestyle factors both in childhood and adulthood were self-reported in questionnaires. Cross tabulations and Cox proportional hazards regression model were applied as statistical methods.

Results: Women having experienced poor (HR=1.50; 95% CI 1.25-1.81) or very poor (HR=1.70; 95% CI 1.08-2.67) childhood socioeconomic conditions had a significantly increased risk of IHD, compared to the women having experienced good socioeconomic conditions in childhood (fully adjusted model).

Conclusion: There is an association between childhood socioeconomic conditions and risk of self-reported ischemic heart disease in middle-aged Norwegian women. Lifestyle factors in childhood and adolescence partly explains the association.

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ABBREVIATIONS

AMI	Acute myocardial infarction
BMI	Body mass index
CBVD	Cerebrovascular disease
CHD	Coronary heart disease
CI	Confidence interval
CSEP	Childhood socioeconomic position
CVD	Cardiovascular disease
HR	Hazard ratio
ICD	International Statistical Classification of Diseases
IHD	Ischemic heart disease
IMT	Intima-media thickness
MI	Myocardial infarction
NOK	Norwegian kroner
NOWAC	Norwegian Women and Cancer study
SEP	Socioeconomic position
SES	Socioeconomic status
WHO	World Health Organization
WWII	World War II

1. INTRODUCTION

1.1. Background

A growing body of evidence shows that early life exposures may play a key role in adult health outcomes (1). Early life determinants, including: poverty, poor early growth, and illness during prenatal life, infancy, childhood, and adolescence can increase vulnerability to development of chronic diseases in adult life, either independently or in combination with adult risk factors (2). Coronary heart disease (CHD) is such a chronic disease; that develops throughout the life course, and usually manifests itself in adulthood (3). Atherosclerosis is an underlying process of CHD, which have been found in children and young adults (2).

Anders Forsdahl was a pioneer researcher within life course epidemiology and found evidence of the potential adverse impact of early life socioeconomic deprivation to adult health. He demonstrated that areas with high infant mortality rates in the past had subsequent high adult mortality rates of atherosclerotic heart disease, suggesting that poor living conditions in childhood and adolescence, followed by affluence in adulthood, increased the risk of arteriosclerotic heart disease (4). Poor living conditions in childhood are, in turn, associated with malnutrition, poor growth, infectious diseases, and stress (2, 5).

Despite of decreasing mortality rates of heart disease over the past few decades, there is an increasing difference in rates between socioeconomic groups (6). It is therefore important to understand the underlying mechanisms and models of the association between early life risk factors and CHD from a public health perspective (2). Focus on preventing poor health in early life may reduce social inequalities in adult health and yield public health benefits.

Health inequalities are socially produced and not natural or inevitable, but influenced by policies. The universal welfare policies associated with the ideal Nordic welfare state have

tended to use the approach of reducing the entire socioeconomic gradient in health (7). However, there are typically two other approaches for welfare policies to impact health inequalities by changing the exposure of different socioeconomic groups to the social determinants of health; focusing on improving the health of the most disadvantaged groups or reducing the health gap between the best and worst off (7).

1.1.1. Socioeconomic position

Socioeconomic position (SEP) is a frequently used concept in health research, as it is a powerful predictor of morbidity and mortality. SEP can generally indicate individual or groups' position or class within a hierarchical social structure and access to material and non-material recourses (8). Galobardes et al. declare: *"SEP is key to understanding inequalities in health and is best considered as an umbrella term for a range of indicators and interconnected concepts"* (9 p99).

Within sociology, terms addressing socioeconomic circumstances, e.g. socioeconomic status, socioeconomic position, social class and social stratification have different contextual meanings. Within epidemiology, however, these terms are frequently used interchangeably. All the terms mentioned above and related terms are treated and interpreted as equivalent to socioeconomic position in the present thesis.

The concept of socioeconomic position used in epidemiological studies is commonly based on the theories of Karl Marx and Max Weber on social class. Marx held that social class was characterised by the two-dimensional division between exploited workers and exploiting capitalists, whereby an individual is defined by their relation to the means of production (10). Weber suggested that society is rather hierarchically stratified along several dimensions, which creates groups whose members share common market position and in turn leading to shared opportunities in life (10).

SEP is traditionally measured by education, income, and/or occupation, either in combination or separately. But also other measures are used, such as: indicators of wealth, proxy indicators, area level measures, or composite indicators (10). Each indicator measures often related, but different aspects of socioeconomic stratification. SEP is a complex and comprehensive phenomenon as there are multiple possible mechanisms and pathways through which SEP influences and determines health outcomes. Galobardes et al. (9, 10) proposed that when SEP is the exposure of interest and when it is considered being a confounding factor, the choice of SEP measure should be informed by considerations of the specific research question and the chosen factors linking SEP to the outcome. But the choice of indicator might not be crucial if the main interest is to demonstrate the existence of a socioeconomic gradient in a particular health outcome (10).

Income is a direct measure of material resources, while education indicates both material and non-material resources. Household income adjusted for number of incomes is the recommended material measure both for adult and childhood SEP, as it yields a more accurate measure of available family resources (10). Occupation indicates social standing and material recourses.

The adult SEP indicator used in this study is educational attainment, as it is closely related to living standards, social status, skills and knowledge (2).

1.1.2. Childhood socioeconomic position

Although a life course approach assesses biological, psychological, and social factors at each stage of life, much focus have been directed to the growing evidence for long-term effects of risk factors during childhood on chronic diseases (10). Childhood socioeconomic position (CSEP) is essentially similar as for adult SEP, except that it indicates the economic and social position of the study participant's parents or household and can be measured by parental

education, parental or household income, parental occupation and/or household conditions (5). Information on both parents' or one of the parent's educational attainment, income or occupational status is possible. When information of only one parent is used, it is usually the one held to be head of the household. Also other indicators of wealth, proxy indicators, composite indicators or area level measures can be used to assess CSEP.

The childhood SEP indicator in the present thesis is broad in that it includes both childhood and adolescence. Participants have reported whether they perceived their economic conditions as very good, good, poor, or very poor when growing up.

1.2. Socioeconomic inequalities in health

Scientists have recognised and described systematic differences in living conditions and health between social classes over the past few centuries.

In the mid-nineteenth century, Eilert Sundt travelled across Norway describing mortality differentials, comparing life expectancy within the country and with other countries (11, 12). He was a theologist by education, but had a broad field of interests, and his inquiries involved combining qualitative and quantitative methodology, which he used to understand and describe social inequality in health.

The industrialisation of Northern Europe and North America in the nineteenth and early twentieth centuries, which created jobs and fuelled economic growth, were followed by substantial social and economic changes. This period gave rise to the early social scientists, in particular Karl Marx and Frederick Engels, who found that the age-old division between the exploited workers and those controlling the means of production (exploiting capitalists) was intensifying with the emerging capitalists systems (2, 8). Engels described the living and working conditions of the working people, as well as their diet and the sanitary state of the

environments in UK's large cities in 1845. He presented a multilevel examination of how individual and area-based indicators of SEP affected mortality (2).

In 1980, the Black Report showed widening differentials in mortality across occupational classes in the UK (13). The results was unexpected, since building of the welfare state provided better sanitation, sewage, and water supply, and the National Health Service established in 1948 enabled universal access of health services. Four different types of possible explanations were proposed from the findings in the Black Report: measurement artefact, a material interpretation, cultural-behaviour explanations, and natural or social selection. The first type of explanations suggests that the relationship between social class and health are inherent in the measures themselves, and as such, not reflecting a causal relationship (14). The material explanations emphasises the role of economic and associated socio-structural factors in distribution of health (15). The cultural-behavioural explanations sees class gradients in health as the result of social class differences in behaviours such as consumption of harmful commodities, which is often taken to imply that such behaviours are largely under individual control (14). The selection explanations hypothesises that social mobility depends on the individual's health. A healthy individual is more likely to be upwardly mobile, and an individual with poor health is more likely to be downwardly mobile than their class peers (14). The authors of the Black Report expressed their preference for the material explanations.

Although the concept of social class is still used, it has been criticised as out-dated, and the criticisms is based on two lines of arguments. First, the service sector has taken over as the dominating engine of economic growth, instead of the industrial sector, and a concept developed to make sense of the social order through the process of industrialisation would have outlived its utility (8). Secondly, the social structure has changed due to new family constellations and patterns of community allegiance, where people not only are breaking free

from class position but also from the multiple structures of inequality grounded in gender, ethnicity and sexuality (8). These arguments are challenged on empirical and theoretical grounds, as evidence point to persistence of socioeconomic inequalities in health and even widening inequalities in some cases, despite general improvements in population health in developed countries (2, 6, 8). On theoretical grounds, social class is seen as strongly influencing people's lives, but the process through which it operates have shifted (8).

Graham (8) emphasised two themes within socioeconomic inequalities, which are themes constituting two sides of a single coin. On the one side unequal external structures regulates individual's socioeconomic position of which individuals have limited ability to influence. Powerful institutions regulated by government policies, including the education system, the labour market and the broader structures of the welfare state, are involved in the process of stratifying people in socioeconomic positions (8). On the other side, individuals actively produce and reproduce the socioeconomic positions in which they are located, not necessarily by conscious choices but rather through learned habits and their capability.

These dual dimensions of socioeconomic inequalities imply that individuals are strongly affected by their social and economic experiences and situation. However, individuals might respond to their experiences differently, either modifying the impact or altering the risk of future exposures (8).

Social mobility is one of the most important ways in which continuity and change in socioeconomic circumstances occur over the life course (5). Parental or childhood SEP affects many aspects of childhood, which in turn influence the chances and direction of social mobility into a different SEP group where future advantage or disadvantage accumulates (16). Studies of social mobility have shown a trend of continuity in socioeconomic positions over the life course (2) and across generations (8). However, there are variations over time and by place, and the strengths of these relationships are context specific (2). Education is the

primary route to social mobility (5). Educational attainment is, in turn, a powerful predictor of adult income and occupation (2). There are gender differences, however, as women are found to have less payoff from education than men in terms of employment, income, and promotion (5). Although implementations of several reforms of the education systems in Norway and other western countries were designed to raise educational levels across the population, inequalities in educational attainment have persisted, and the major expansion of higher education seems to have benefitted young people from advantageous backgrounds the most (2, 8). Educational inequalities play an important role in maintaining socioeconomic inequalities across generations. Hilary Graham suggests that the underlying driving force of the educational inequalities are inequalities in the environments in which children are fostered (8). It is likely that the well-educated parents help their offspring prepare for a similar class position through developing certain social and personal skills in their children (2). Students of advantageous SEP therefore acquire a curriculum for the educational system during childhood and adolescence, which most students from disadvantageous SEP groups do not possess at the beginning of their education process, and would require years to acquire. Pierre Bourdieu's concept of cultural capital can be applied to elucidate this association. He argued that the educational system demands, tests and rewards competences that are class-based and class specific, resulting in unequal achievements (8). Although Bourdieu's method of enquiries was developed on the basis of the French educational system, his concept is susceptible to universal application through recognition of general mechanisms (17). Educational inequality points in the direction that not all can overcome their adverse experiences throughout their formative years to become educationally resilient (5). It is essential to consider the dynamic interaction between the changing individual and changing context, as both the timing and duration of risk experiences play a crucial role in shaping the development of individual recourses (5).

Inequalities in health can be expressed in both absolute and relative differences (2, 8). Absolute differences are arithmetic differences between the rates, percentages, or means, e.g. mortality rate differences of ischemic heart disease (IHD) between poor and rich. While relative differences are based on a ratio of the rates, percentages, or means in the groups being compared, e.g. risk ratios; how likely are poor SEP groups to experience IHD compared to well-off SEP groups (2). Declines in absolute differences can be accompanied by increases in relative differences. Information from both absolute and relative differences is needed in order to understand the magnitude, cause-specific composition, and time-trends of socioeconomic inequalities (2). However, relative measures are considered as more appropriate for tracking changes in health inequalities over time, especially when overall levels of health are improving (8).

The magnitude of socioeconomic inequalities in health, in absolute terms, have declined in Europe due to improvements in living standards and public health (18). In relative terms, however, inequalities in health have persisted and even increased in some Western European countries, including Norway (6, 18). Mortality trends among Norwegian women are less favourable than for men, with stagnating mortality among low educated women (6). All Western European countries are highly developed welfare states that have used extensive resources aiming to reduce socioeconomic inequalities (19). Widening of the gap between groups of higher and lower SEP can thus be regarded as a paradox. The widening relative mortality inequalities is generally the result of the speed in the mortality decline between socioeconomic groups (18). This means that the decline has been proportionally faster in the higher SEP groups than in the lower, mainly due to faster mortality declines in cardiovascular diseases (CVD) for groups of higher SEP (18). Reduction in exposure to some of the risk factors, including smoking, unhealthy diet, and sedentary lifestyle, in combination with more effective health care interventions, can explain the decline in CVD mortality. Researchers

Øyvind Næss and Inger Ariansen at the Norwegian Institute of Public Health describe an excess mortality of CVD comparing groups of high and low education (20). They estimate that more than half of the deaths could have been avoided given that everyone had the same probability of dying from CVD as the well educated. They further question whether prevention constitutes an unfortunate side effect, producing a greater difference between socioeconomic groups (20).

Mackenbach found that higher CVD mortality for men and women of lower SEP groups are especially consistent for ischemic heart disease (IHD) and cerebrovascular disease (CBVD) (18).

Health is sensitive to social and economic factors, and for several chronic diseases including IHD, there exists a social gradient; i.e. for each step down on the socioeconomic staircase, the risk of IHD increases (16). Socioeconomic inequalities in health are inequalities in health associated with people's unequal position in the social structure through which economic resources and rewards are distributed (8). Hilary Graham captures the dual character of SEP: *"Socioeconomic position is both structurally imposed and socially produced, with the resulting inequalities in people's positions woven into the fabric of their daily lives."* (8 p36).

1.3. The life course perspective

The contribution of socioeconomic conditions at different stages of life to adult health is widely acknowledged within the fields of public health and epidemiology, although there exists different hypotheses as to which factors are involved and when exposure matters the most (2, 21). Childhood marks a period of extraordinarily rapid development. Although the development process is genetically regulated, child development is not solely genetically determined, and genetic differences are not socioeconomically patterned (8). Environmental exposures can have biological consequences, and these exposures are, however,

socioeconomically patterned (8). The environment stimulates and shapes physical, cognitive, emotional and behavioural development. Furthermore, the environment might have a greater impact on children than adults, as the body systems are under a developmental phase characterised by considerable plasticity (8). A process through which the body moulds and adapt to the environment, also called embodiment or biological embedding, suggests that inequalities in children's environments becomes 'written into the body' (8). As such, early life social environment can leave enduring biological imprints on the body and become an integrated part of people's emotional register and patterns of behaviour (5, 8).

The life course perspective is essential to the present thesis. Kuh and Ben-Shlomo (2) describes life course epidemiology as the study of a long-term biological, behavioural, and psychosocial process that links adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations. In line with the life course approach (2), the present thesis is based on the assumption of different hypotheses as complementary, rather than as opposing explanations of the complex nature between childhood circumstances and the impact on adult health.

1.3.1. Historical view

The notion that childhood circumstances are pivotal to adult health is not new, as it was the prevailing view within public health science in many western countries in the first half of the twentieth century and the rationale behind welfare reforms aimed at promoting infant and children's health (5). However, public health and epidemiological research have historically gone through various phases of development (22). Early cohort analysis, applied to the age-specific UK death rates from the period 1841-1925, found a lower mortality risk at all ages of each successive generation, the 'generation effect', which was interpreted as evidence for the importance of early environmental factors for adult health (2). Although some believed that

adult health relied solely on genetic factors, others directed attention to developmental critical periods (the life course approach). Constitutional susceptibility to adult disease was seen as the outcome of an interaction between genetic make-up and environmental forces acting primarily during development, but also to some extent throughout the life (2).

As predictions made on the basis of the 'generation effect' failed to be confirmed and lack of improvements in middle-age life expectancy became clear, attention was drawn to the effects of adult life style on chronic disease, especially working conditions as well as tobacco and alcohol consumption. Since mortality rates from CHD rose rapidly after World War II (WWII), clinical research on CHD became important (2). As early post war cohort studies on middle-aged men identified proximal biological risk factors and adult life style factors, interest in early life influences on adult health lessened (22).

After findings of atherosclerosis in young soldiers killed in the Korean war, there was a refocus on the childhood circumstances where attention was directed at lifestyles in childhood. The modern revival of the life course perspective in human biology and anthropology links early development to aging and signifies how early environmental factors (and later factors) affects human physiology at all ages (2). Forsdahl emphasised poor childhood living conditions as leading to an accumulation of disease risk, while Barker found that malnutrition during critical periods of development (in utero and infancy) was the most important environmental risk factor (2). Barker's hypothesis of 'biological programming' was presented as an alternative paradigm to the adult life style model of adult chronic disease that focused on how adult behaviours affect the onset and progression of diseases in adulthood (23).

Since developmental scientists in recent years have called for an interdisciplinary collaboration to construct a unified framework for the study of developmental processes from 'cradle to grave', emphasis has shifted from ideas of homogeneity, continuity, and

universality of developmental processes which dominated in the 1930s to heterogeneity, discontinuity and context-specific development (2).

The life course approach is broad and covers genetic factors and risk factors acting at every stage of life.

1.3.2. Life course conceptual models

With an array of exposures over the life course that may affect disease risk in multiple ways, timing and duration of exposures are potentially important. In that respect, Ben-Shlomo et al. (22) have identified and proposed the use of seven conceptual models (Figure 1). Although these models are gross simplifications of the complex processes that characterises life course approach, they can shed some light on the possible various ways in which exposures may affect disease risk. As the models are not mutually exclusive and may operate simultaneously, it is challenging to empirically distinguish these models (2).

1. 'Critical period model' is expressed as a process through which an exposure acting during a limited time window has lasting effects on the structure or function of organs, tissues, and body systems that are not considerably modified by later experience (2).

2. 'Sensitive period model' is when an exposure within specific time windows has greater or lesser risk of disease, i.e. an exposure within a time period that has a stronger effect on development and subsequent disease risk than it would at other periods, and any excess risk outside this period would be weaker (22).

3. 'Critical/sensitive period model with later effect modification' is an extension of the first models. A disease outcome is not destined to occur, even though the timing of an exposure is important to have any effect or a stronger effect on the outcome. Unrelated exposures later in life may modify disease risk through independent or interactive effects (22).

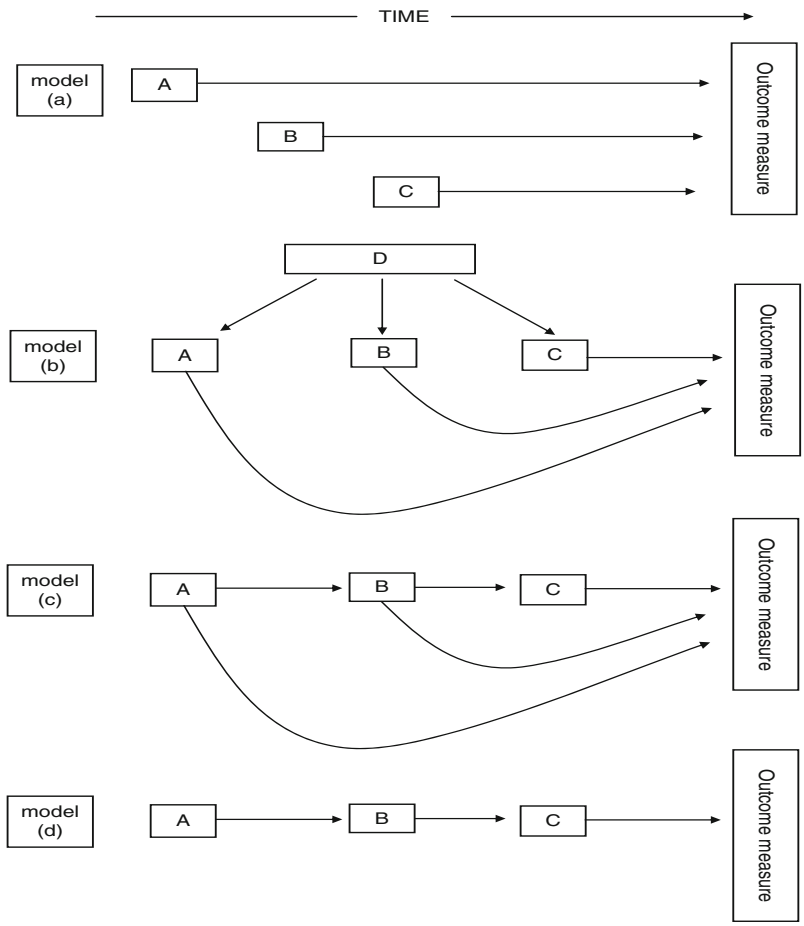
4. 'Accumulation of risk with uncorrelated exposures' (Figure 1a) assumes that exposures acting independently have an additive effect on disease risk. Each exposure increases risk of disease although to varying degree, and being exposed to several factors will give greater risk than being exposed to fewer factors (22).

5. 'Accumulation of risk with correlated exposures' (Figure 1b) holds that exposures are more commonly correlated because of risk clustering, where one exposure (a common factor, D) is a determinant of the other mediating factors (A, B, and C) (22).

6. 'Chain of risk additive model' (Figure 1c) refers to a sequence of linked exposures, where each exposure increase the risk of a subsequent exposure in addition to having an independent effect on later disease (2). One exposure may have a modest effect on the disease, but the overall effect of several exposures, including the indirect pathways, will be much larger (22).

7. 'Chain of risk trigger model' (Figure 1d) relates to disease risk only through the final exposure in the chain (22).

Figure 1 Life course conceptual models



Source: Ben-Shlomo et al. (22 p1529).

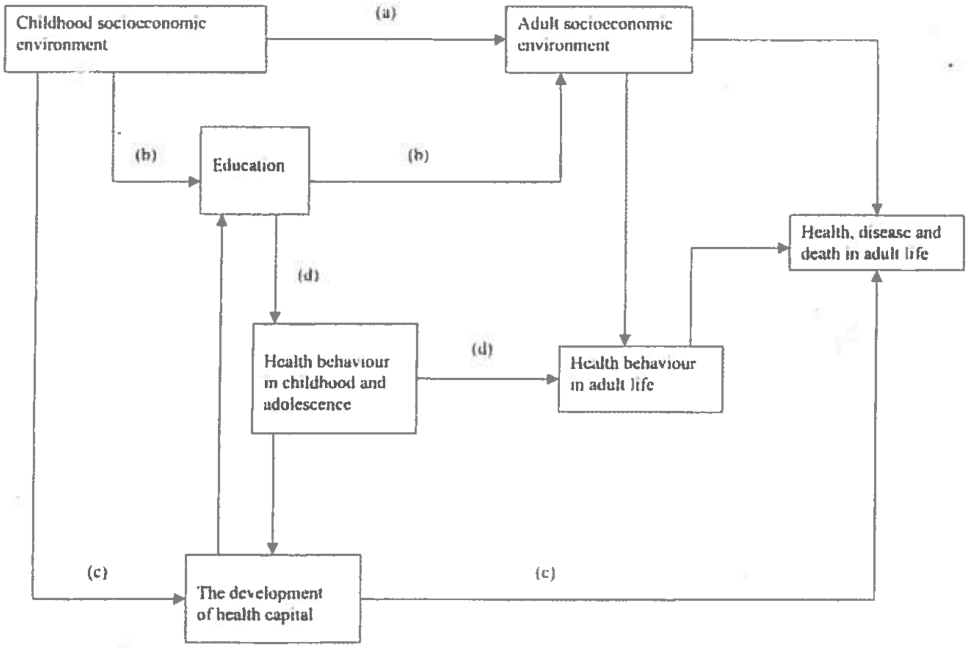
1.3.3. Indirect effects of childhood socioeconomic circumstances

Kuh et al. proposed a broad framework (Figure 2), although simplified it shows the hypothesised major pathways through which aspects of the childhood socioeconomic conditions affect adult health (2).

Childhood or parental SEP constrains adult SEP through access of social and economic resources (route a), especially opportunities for educational experiences (route b), and adult SEP in turn affect disease risk by determining exposure to causal factors in later life (2). Route c outlines that childhood socioeconomic environment influences the development of

health capital, which means the inherited and acquired biological resources through which exposures to causal factors during gestation, infancy, childhood, and adolescence determines current health and future health potential (2). Health capital also affects educational opportunities and attainment. The socioeconomic environment in childhood shapes the development of behaviour that has a tendency to persist into adult life and thus have long-term effects on disease risk, operating either independently, cumulatively, or interactively with later risk exposures (route d) (2).

Figure 2 A broad framework of pathways between childhood and adult health



Source: Kuh et al. (2 p374).

1.3.4. Direct effects of childhood socioeconomic circumstances

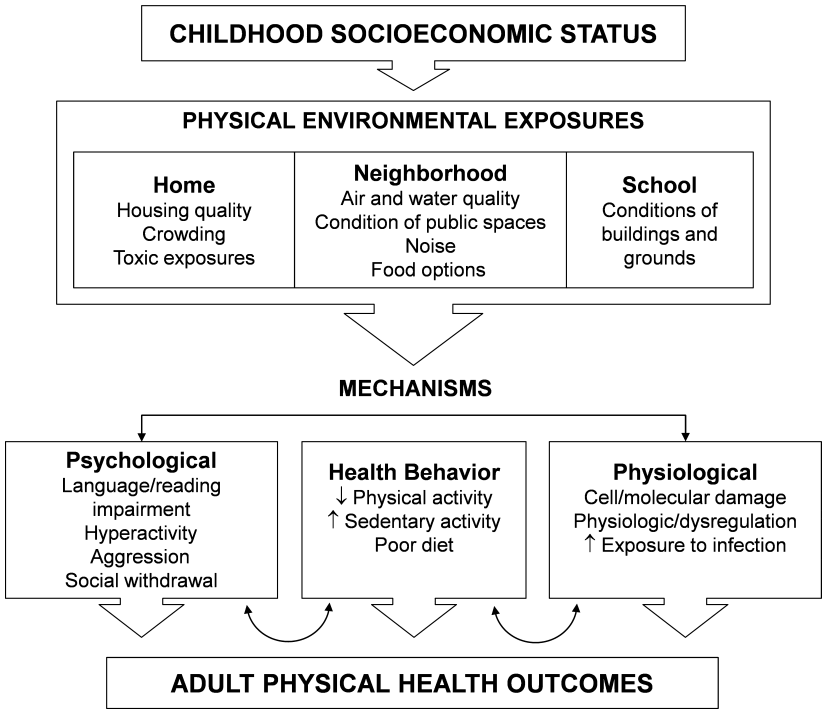
Socioeconomic position in childhood and adolescence influences adult health through a range of environmental exposures, and both the physical and psychosocial environment is important in order to understand the pathways of this association (5). These environments plausibly

affect psychological maturation processes and physiological development and the acquisition of health behaviours. Development of social and cognitive skills and abilities involving coping strategies, habits, attitudes and values are more rapidly accumulated during childhood and adolescence, which strongly influences life course social and behavioural trajectories with implications for adult health (24).

Cohen et al. (21) proposed two schematic representations to depict possible pathways that might link physical (Figure 3) and psychosocial (Figure 4) exposures related to SES in childhood and adolescence to adult health. These figures are simplified representations and not a complete model of all the possible mechanisms and pathways that link childhood socioeconomic circumstances to adult health.

Figure 3 shows that homes, neighbourhoods, and schools can be sources of physical environmental exposures (21). Adverse physical exposures can have immediate effects on psychological development, some of which are: increased stress, depression, anxiety, and lower self-esteem. Impaired cognitive, social, and emotional development are long-term effects that influences future educational and career opportunities (21). Physical exposures can influence health behaviours through diet and physical activity, and lower SES is associated with poorer diet and sedentary lifestyle. Physical environmental exposures, such as: air pollution, tobacco smoke, toxins, and some infectious agents (e.g. *Helicobacter pylori*, cytomegalovirus, herpes simplex virus-1, hepatitis A and hepatitis B) might damage physiological development on cellular and molecular level, that can lead to a vulnerability to future disease (21).

Figure 3 Examples of pathways that may link physical exposures associated with childhood and adolescent SES to adult health

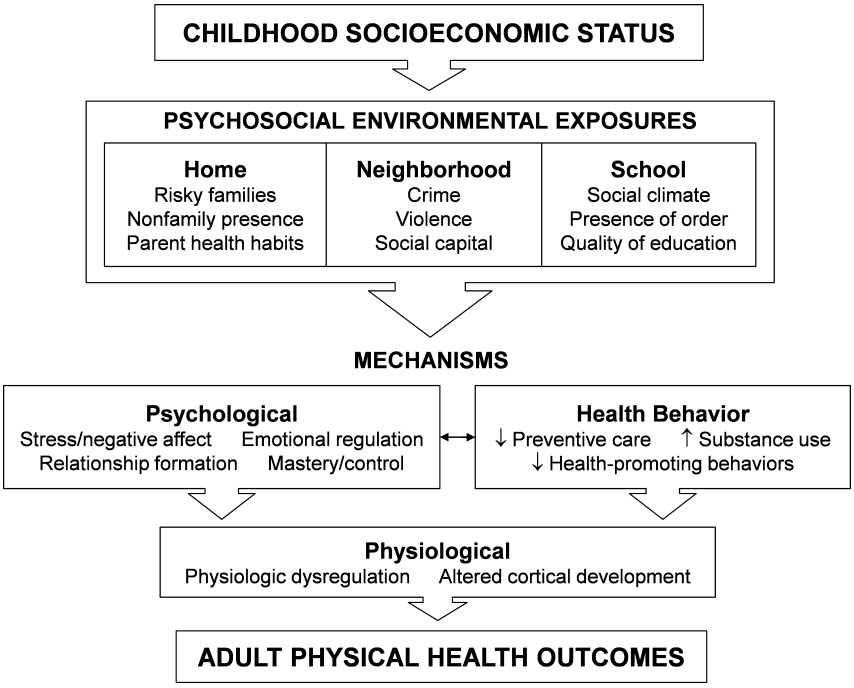


Source: Cohen et al. (21 p41).

Figure 4 outlines that adverse psychosocial exposures can lead to poor emotion regulation, maladaptive social information processing, and poor social adjustment, which in turn predisposes to higher anxiety, depression, and hostility in adulthood. Psychosocial exposures may also influence health behaviours through parents behaviour, who serve as models for the appropriateness of harmful or beneficial health behaviours (21). Environmental exposures may also have an impact on biological systems. Permanent alterations in the nervous, endocrine, and immune systems during early development due to plasticity, can cause dysfunction of the affected systems (21). Adverse psychosocial and physical exposure is also hypothesised to affect epigenetic programming, which refers to the stable changes in the activity of a gene that occurs without alterations to its DNA sequence (21).

Material deprivation and adverse environmental exposures may produce levels of stress as a feature of daily life (16). The extent to which individuals experience repeated stress responses depends on the combination of the environmental and individual conditions (25). Prolonged exposure to psychosocial stress in the early years can cause allostatic load (stress-induced damage) affecting the immune and cardiovascular systems via neuroendocrine pathways, which in turn increases risk of disease onset or more rapid progression of diseases once established (16, 25).

Figure 4 Examples of pathways that may link psychosocial exposures associated with childhood and adolescent SES to adult health



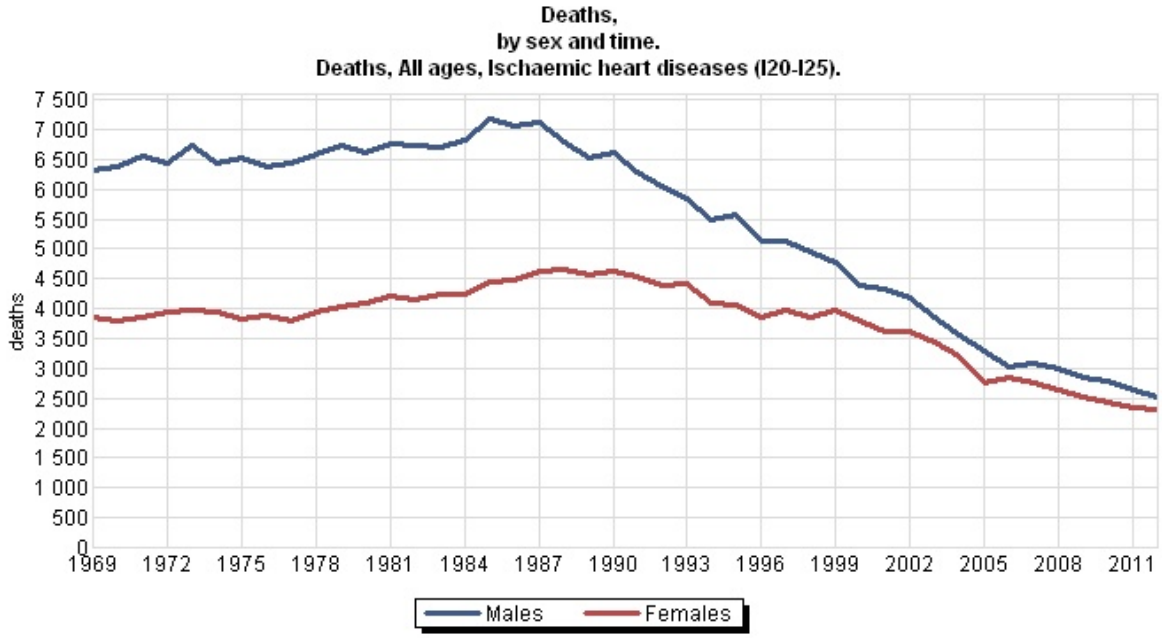
Source: Cohen et al. (21 p 43).

1.4. Ischemic heart disease

The Norwegian Institute of Public Health estimates that approximately 15,000 people experience an acute myocardial infarction (AMI) each year in Norway, and half of these are under the age of 74 (26). An unknown number have angina pectoris, heart failure or other forms of heart disease. Evidence have shown that the northernmost counties in Norway had significantly higher mortality from myocardial infarction (MI) in the beginning of the 1990s, however this difference has later diminished (26). A north-south gradient has also previously been found in other countries, such as UK and France (2, 16).

In 2012, ischemic heart disease accounted for 11.6% of all deaths in Norway, which makes IHD one of the leading causes of mortality (27). According to Statistics Norway, a total of 4,852 people died of ischemic heart disease in 2012, of which 47.9% were women. Although rates have been declining over the past few decades (Figure 5), it remains a major public health issue. Declining mortality rates of IHD may be due to improved public health and/or improved treatment (28). The decline is steeper for men than for women, which may be because prevalence of female smoking has lagged male smoking, and thus, lagged onset of smoking related diseases.

Figure 5 Deaths from IHD in Norway



Source: Statistics Norway

According to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), ischemic heart diseases (I20-I25) includes angina pectoris, acute and subsequent myocardial infarction, certain current complications following acute myocardial infarction, other acute ischemic heart diseases, and chronic ischemic heart disease including atherosclerotic cardiovascular disease (29).

Ischemic heart disease is characterised by reduced blood flow to the heart muscle, and the underlying disease process for this is usually atherosclerosis. In the early stages of atherosclerosis, fatty deposits form plaque in arteries (30). Plaque builds up over years, causing hardening and narrowing of the affected arteries. A tear in plaque can occur and form a blood cloth that can partially or completely block a coronary artery, and without an adequate blood supply, the heart becomes starved of oxygen and the vital nutrients it needs to work properly. This can cause angina, which is characterised by a brief period of poor blood supply to the heart muscle and symptoms last just a few minutes and are usually relieved by rest and/or medications (31). Symptoms include chest pain or discomfort, pain or discomfort in

other areas of the upper body, shortness of breath, palpitations, dizziness, nausea, extreme weakness and sweating (31). When blood supply to a portion of the heart muscle is completely cut off for an extended period of time, or if the energy demand of the heart becomes much greater than its blood supply, a myocardial infarction may occur (31). Symptoms usually last more than a few minutes and includes chest pain or discomfort that last more than a few minutes or goes away and comes back, pain or discomfort in other areas of the upper body, difficulty breathing or shortness of breath, sweating or 'cold' sweat, fullness, indigestion or choking feeling, nausea or vomiting, light-headedness, extreme weakness, anxiety, rapid or irregular heartbeats (31). As a consequence of cessation of oxygen supply, the affected area can become permanently damaged, which in turn can lead to heart failure (30).

Risk factors

Development of coronary heart disease is a multifactorial process, and some of the known risk factors includes: Age, family history of early heart disease, diabetes, hypertension, elevated blood cholesterol, overweight and obesity, smoking, physical inactivity, unhealthy diet, psychological factors (e.g. depression and stress), socioeconomic position, neighbourhood factors, and inflammation (32).

Gender differences

Conventional adult risk factors, such as smoking, hypertension, cholesterol, obesity, and physical inactivity have similar relative risks for CHD in women and men, though absolute risk is lower for women (5). Gender differences in CHD with regards to symptoms, clinical presentation, value of the diagnostic tests and response to treatment, have received increasing attention over the years (26). Some of the observed differences between men and women are

that women experience CHD on average about 10 years later than men, but women with multiple risk factors does not generally benefit from this gender advantage. Women are less likely to experience chest pain than men and have more diffuse atherosclerosis. There also seems to be a lower accuracy of the traditional non-invasive diagnostic tests in women compared to men (32).

Registry data

The Norwegian Myocardial Infarction Registry is a medical quality registry connected to the Norwegian Cardiovascular Registry established in 2012, and the first report reveals that there were 13,043 myocardial infarctions in 12,336 patients recorded in 2013 (33). The average age of the time of infarction was 68 years for men and 76 years for women. The 30-day mortality was 10%, and no difference in mortality between the health regions was found.

1.5. Socioeconomic position and coronary heart disease

There are consistent evidence of an association between socioeconomic position and heart disease, but it seems as though the social gradient has not always been negative. A social class crossover in heart disease mortality supposedly occurred in the earlier part of the twentieth century. Analyses of social class differences in mortality from the 1911 census revealed a higher mortality attributed to IHD among non-manual working men (2). The habit of cigarette smoking was linked to class advantage, more than a century ago (8). It is believed that the habit was a trend confined to affluent well-educated men. Later, manufacturers made cigarettes more accessible to the masses, and smoking became a widespread phenomenon by the mid-twentieth century. Since then it has become a habit associated with socioeconomic disadvantage.

Geoffrey Rose and Michael Marmot (34) investigated the historical trends of social class and CHD mortality, and they discovered that the crossover was evident for men but not for women. Although they expressed using caution when interpreting historical trends, as the diagnostic usage have changed over time and the definitions and composition of social classes have also changed.

Michael Marmot et al. (35) found in the Whitehall I-study with 17,530 male British civil servants aged 40-64 at baseline, that less than half of the differences in mortality of CHD between occupational groups are explained by known factors in adult life, such as smoking, hypertension, cholesterol, and physical inactivity. The findings emphasised the unequal distribution of these characteristics in society, and they suggested that the inverse relationship between height and mortality stems from factors operating at early life (35).

The Oslo study (36, 37) examined men in Oslo for CHD and other atherosclerotic diseases and used combinations of education and income as a measure of SES. They found that the combined risk scores for CHD of cigarette smoking, high serum-cholesterol, and high systolic blood pressure are inversely related to socioeconomic status. They highlighted the role of cigarette smoking, as they observed large socioeconomic differences in the proportions of those regularly smoking cigarettes, where 44% high status men had stopped smoking cigarettes compared to 18% of low status men (37).

The decline in CHD rates have been uneven within countries (28). The decline has been steeper for the advantaged SEP groups, and as a result the socioeconomic differences in CHD have increased.

1.6. Childhood socioeconomic conditions and coronary heart disease

Considerable investigation have been concentrated on risk factors acting in adult life, but the need to focus on risk factors acting in early life is essential, as the pathophysiological process of atherosclerosis can start in childhood (2, 30, 38).

The early ecological studies noted strong correlations between adult mortality from heart disease and past infant mortality rates (2, 4, 39). Forsdahl emphasised that poor living conditions in childhood and adolescence followed by prosperity represents an important risk factor for arteriosclerotic heart disease (4), proposing that the risk accumulates over the life course. Forsdahl's research was influential for the early studies of Barker, who found a strong relation between infant mortality rates and subsequent IHD mortality rates in England and Wales (39), corroborating Forsdal's findings. Barker and colleagues later hypothesised that impaired growth and development in prenatal and early postnatal life may be an important risk factor for IHD, of which they investigated mortality rates of men and later women whose weights at birth and one year were recorded (40, 41). They found that men and women with the lowest birth weight and the lowest weight at one year for men had the highest death rates from CVD (40, 41). These findings and other parallel research directed Barker to the fetal origins hypothesis. The fetal origins hypothesis proposes that coronary heart disease, type 2 diabetes, stroke and hypertension originate in developmental plasticity, in response to undernutrition during fetal life and infancy (42). Undernutrition during critical periods of growth and development causes 'programming' of the structure or function of organs, tissues, or body systems, which has lasting or life long effects (43).

Galobardes et al. (1) performed a systematic review of the influence of CSEP on risk for CVD, which includes 24 prospective, 11 case-control, and 5 cross-sectional studies. The majority (80%) of the prospective studies, as well as all the cross-sectional studies, found an association between poor childhood circumstances and higher risk of CHD in adulthood.

Formal meta-analysis was not performed, because the necessary conditions of comparability of exposures and outcomes, together with homogeneity of direction and strength of association, were not met (1). The systematic review is limited to individual-level observational studies, which highlights that adverse CSEP contribute to a greater CVD risk independently of adult SEP (1). Galobardes et al. (44) later updated the systematic review with additional 11 prospective studies. A greater proportion of these new studies included women and showed that the general pattern of higher mortality risk among those experiencing poor CSEP, is valid for both genders (44). Adjustment of adult SEP and adult risk factors diminished the association similarly in all studies. Lawlor et.al (45) emphasise the importance of studying individuals in more recent decades because the effects of childhood SEP on health outcomes vary over time. Those born after WWII are likely to have experienced better standards of living than those born in earlier years, which would justify anticipation of varying socioeconomic conditions of contemporary children not having an important effect on their future CVD risks (45). The new studies in the updated systematic review shows that this is not the case (44). These studies underlines that the health effects of poor socioeconomic conditions in childhood persist among younger birth cohorts, despite them not having been exposed to the same level of socioeconomic hardship in childhood as previous birth cohorts (44).

Pollitt et al. (46) conducted a systematic review including 49 observational studies evaluating evidence for models of life course socioeconomic factors and cardiovascular outcomes. These studies were categorised according to their life course designs and analytic approach. There was not performed quantitative summarisation of the study findings for similar reasons as for the previous systematic review. Nevertheless, the results modestly support the existence of effects from life course SES on CVD risk, where the cumulative life course model was the most consistently supported of the conceptual models (47).

These systematic reviews include studies from large cohorts mainly from United Kingdom, Finland, Sweden, Norway, Denmark and the United States.

Studies of the Aberdeen Children of the 1950s Cohort Study show that low SEP at birth is associated with adverse behavioural CVD risk factors (smoking, binge drinking and being overweight) independent of adult social class and income (48). Men and women from lower social class backgrounds (measured by occupational social class of participants' father) at birth were observed to be at increased risk of fatal and nonfatal CHD and stroke, mediated in part through educational attainment (45).

Tiikkaja et al. (49) studied intergenerational class mobility among Swedish women and found that moving from a manual (in childhood) to a non-manual class position was associated with only a slight excess risk of CVD mortality compared to maintaining a stable non-manual class position. Moving into adult manual class resulted in an elevated CVD mortality irrespective of childhood position. They found support for the notion that childhood and adult social class contribute independently to overall CVD mortality, with relative risk by childhood manual class being 25% elevated adjusted for adult class, and adult manual class imposing a 76% elevated risk adjusted for childhood class (49). Level of education showed a stronger influence on the mortality estimates than did household income.

The Framingham offspring study revealed evidence of inverse association of cumulative life-course SEP with CHD incidence (50). CSEP was assessed at baseline (father's educational attainment, obtained directly from the Framingham Heart Study Original Cohort) and measures of CHD used clinically validated outcomes.

Another longitudinal study from the US used marginal structural models to estimate the direct effect of adverse childhood social conditions on onset of heart disease, diabetes, and stroke (51). They observed that when applying the marginal structural model approach using inverse-probability weights to adjust for adult risk factors, participants in the third or fourth

most disadvantaged quartiles of early life SES were estimated to have 23% and 30% increased risk of CHD compared with participants in the least disadvantaged quartile of early life SES (51). They further observed that when using conventional regression approach, the association between early life SES and CHD did not reach the conventional statistical significance level.

Most prior research have not focused on lifestyle in childhood and adolescence, however, a recent study from The Cardiovascular Risk in Young Finns Study used information on childhood health behaviours and health factors to generate an index of ideal child cardiovascular health on risk assessment of cardiometabolic outcomes in adulthood (52). Measures of carotid artery intima-media thickness (IMT) was used as a surrogate marker of cardiovascular health, as an alternative to the use of cardiovascular events as disease endpoints. Components of the ideal child health behaviours metrics include BMI, physical activity, consumption of fruits, vegetables, fish or fish products, and soft drinks. Components of the ideal child health factors metrics include cholesterol status, blood pressure, and glucose concentrations. Laitinen et al. (52) found that the participants who exhibited a high number of ideal cardiovascular health metrics in childhood had thinner carotid IMT and were at lower risk to develop hypertension, metabolic syndrome, and dyslipidemia in adulthood.

The ideal cardiovascular health concept for cardiovascular risk assessment was also applied in a study comprising of three international cohort studies. Data collected from Finland (Cardiovascular Risk in Young Finns Study (YFS)), Australia (Childhood Determinants of Adult Health Study (CDAH)), and the United States (Princeton Follow-up Study (PFS)) were used to determine independent childhood predictors of ideal cardiovascular health index (53). They found that among several lifestyle and clinical indicators studied, higher family SES in all cohorts and non-smoking (parental in YFS, own in CDAH) in childhood were independently associated with ideal cardiovascular health 19-31 years later in adulthood.

The childhood lifestyle indicators consisted of family socioeconomic status (family income (YFS) or parental education (CDAH and PFS)), parental and own smoking, physical activity, consumption of fruits, vegetables, fish, milk, whole grains, sodium, and sugared drinks as well as clinical indicators such as blood pressure, BMI, cholesterol and triglycerides.
Research investigating either childhood social origins or developmental origins of adult heart disease share a common interest in the underlying biological processes involved (2).

1.7. The aim of the thesis

The primary aim of the present thesis is to examine if there is an association between childhood SEP and risk of self-reported IHD in middle-aged Norwegian women.
If an association between childhood SEP and risk of IHD is observed, we will focus on lifestyle factors in childhood and adolescence as potential explanation factors.
The life course conceptual models will be discussed according to the findings.

2. MATERIALS AND METHODS

2.1. The Norwegian Women and Cancer study (NOWAC)

Data used in this thesis is gathered from the NOWAC study, a nationwide prospective cohort established in 1991, which consists of data from approximately 172,000 women aged 30-70 years at baseline. The women were randomly selected from the Norwegian Central Person Register. Data collection was carried out through series of questionnaires, with repeated collections of exposure information in irregular intervals.

The initial purpose was to study the relationship between internal and external hormones and breast cancer and other cancers in women (54). Later, the study has expanded to include more information, enabling researchers to address other hypotheses.

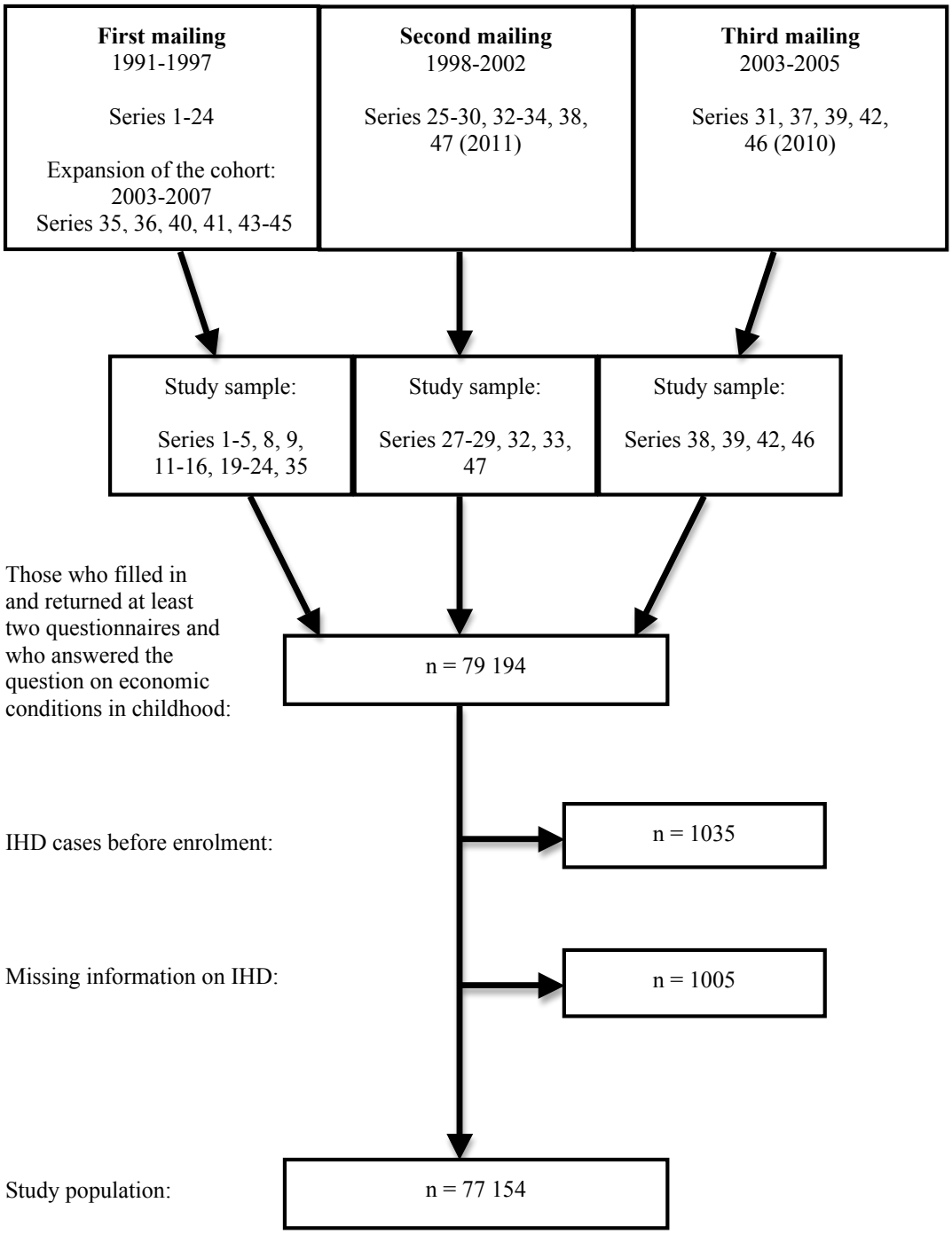
The series of questionnaires are grouped into three mailings. During the years 1991-1997 letters of invitation to participate was sent to 179,387 women, of who 102,540 (57.2%) responded. The cohort expanded during 2003-2007 when additional 178,088 women were invited, and 70,081 (39.4%) of these replied. Second mailing was performed during 1998-2002, and all women enrolled 1991-1997 received an invitation to fill in an exposure update questionnaire, of which 80,810 (81% corrected for death and emigration) women filled in and returned an eight-page questionnaire. In 2011, additional 8,938 women enrolled in 2003 responded to a second mailing. During 2003-2005 (and 2010, response rate not shown) the third mailing was conducted for women enrolled in 1991-1995.

Biological samples have also been collected and stored in a biobank. Collection of questionnaires and biological samples are continuing. Detailed information on NOWAC and articles published based on data from the study, is available on the website (55). The external validity of NOWAC has been verified (56).

2.2. Study sample

Information from first, second and third mailing is used for the purpose of this thesis. Women who filled in and returned at least two questionnaires and those who answered the question of economic conditions in childhood are included. Participants who experienced ischemic heart disease before enrolment in the NOWAC study are excluded. Women with missing information on age at onset of ischemic heart disease are also excluded. The study population consists of 77,154 women. A schematic overview of included series in the present thesis, and exclusion of participants for the aforementioned reasons, is shown in the flow diagram (Figure 6).

Figure 6 Flow diagram



2.3. Variables

All measures described below are self-reported except for age and region of living at enrolment.

Dependent variable:

Time to IHD

IHD was constructed from questions of disease, where the participants were asked to answer whether they have ever had a heart failure/angina pectoris and/or a myocardial infarction (and a list of other options), and if they answered 'yes' to one of these questions, they were asked to enter their age at onset of disease. Women who reported to have or have had heart failure/angina or MI or both and reported their age at onset, constitute the dichotomous variable IHD (no, yes). Age at onset of angina and age at onset of myocardial infarction were recoded into 'Age at onset of IHD'. For those who reported both conditions, age at onset of the first one was applied. Follow-up ended at time of onset of IHD or last questionnaire response. Time of follow-up was computed using the difference between the age at the end of follow-up and the age of enrolment.

Independent variables:

Age

The women's age at enrolment was calculated from year of birth gathered from the Central Population Register. Age at enrolment was included as a continuous variable, after checking for linearity in risk of IHD.

Socioeconomic position

Experience of economic conditions during childhood and adolescence is used as a measure of childhood SEP. This information is mainly obtained from the first questionnaire, although some are gathered from the second questionnaire. The women were asked to recall whether economic conditions when growing up were: very good, good, poor or very poor.

Education was used as a measure of adult SEP. In the questionnaire the participants were asked to enter the total years of schooling. Education was originally a continuous variable in the dataset. Years of education were recoded into the following three categories; ≤ 9 years, 10-12 years, and ≥ 13 years.

Income was considered as a measure of adult SEP, but for reasons discussed further on in the thesis, and identification of education as a much stronger confounder than income, education was chosen for this purpose. In the first set of series where gross household income per year was included, it was pre-categorised into five groups in the questionnaires: <150 000, 151 000-300 000, 301 000-450 000, 451 000-600 000, and >600 000 (NOK). In later series, gross household income per year had six categories: <150 000, 151 000-300 000, 301 000-450 000, 451 000-600 000, 600 001- 750 000, and >750 000 (NOK). For the initial univariate analyses gross household income per year was recoded into four categories, which are: <300 000, 301 000-450 000, 451 000-600 000, and >600 000 (NOK).

Body mass index and body shape

The women were asked to enter their height, weight, and weight at age 18 in the first questionnaire. BMI at age 18 was calculated by the formula weight divided by the squared height in meters, and then grouped in accordance to the WHO Body Mass Index classification (57): <18.50 low, 18.5-24.9 medium, 25-29.9 high, and ≥ 30 very high.

BMI at enrolment were calculated similarly from height and weight, and recoded into the following categorical values: <20 low, 20-24.9 medium, 25-29.9 high, ≥30 very high.
Body shape in childhood was obtained from the first questionnaire where the participants were asked to tick off whether they had very thin, thin, normal, fat, or very fat body shape in first grade of primary school.

Physical activity

Level of physical activity at age 14 and level of activity at enrolment was originally a scale from 1 to 10 in the questionnaires, and recoded into three categories, where levels 1-3 were considered low, levels 4-7 medium, and 8-10 high.

Smoking

The women were asked whether any adults in the household smoked at home in their childhood. Passive smoking is a dichotomous variable (no, yes).
They were also asked about their own smoking habits. Smoking status contains three categories: never-, former-, and current smoker.

Residency

Region of living in adolescence were gathered from the questionnaires, while region of living at enrolment were obtained by linking registered municipality of residence from the National registry to the NOWAC data.
Region of living in adolescence and region of living at enrolment were divided in the following regions: Oslo, east, south, west, middle, and north. It was recoded as dichotomous, where Oslo, east, south, west, and middle were collapsed into one value, and north constitutes

the other value. The dichotomous variable increased the confounding effect on the association between CSEP and IHD.

Living in urban areas during adolescence was dichotomous (no, yes).

Dietary components in childhood

Consumption of milk in childhood had the following pre-categories from questionnaires: Never, 1-3 glasses per day, 4-7 glasses per day, and ≥7 glasses of milk per day.

Consumption of vegetables and consumption of fish in childhood had pre-categories: Never, once a week or less, 2-3 times per week, and ≥4 times per week.

Alcohol

Daily consumption of alcohol in grams was continuous. It was grouped into the following categories: 0 gram, 0.1-4 grams, 4.1-10 grams, and ≥ 10.1 grams. The amount of pure alcohol has been calculated from specified consumed units of alcohol (beer, wine and drinks) in the questionnaires. These units contain about the same amount of pure alcohol as they usually are served in different portion sizes.

Self-reported health

Self-reported health at enrolment originally included four categories: very good, good, poor, and very poor, but were made dichotomous by merging very good with good and poor with very poor into: good, poor.

2.4. Statistical methods

Cross tabulations were run to find the baseline distribution of the study variables by childhood SEP and IHD, respectively. The frequency distributions between groups were tested by use of Pearson chi-square. Age is the only continuous variable included. Spearman's rank correlation coefficient was used to evaluate correlations between ordinal variables.

Cox proportional hazards regression models were run to analyse the association between childhood SEP and IHD. The age at onset of IHD is known and therefore it was possible to compute a time variable. Univariate analyses were performed for each of the independent variables according to risk of IHD. The variables that changed the estimated hazard ratios of the CSEP variable with more than 5%, were considered confounders and included in the multivariable models. Childhood lifestyle factors that acted as confounders after adjusting for the corresponding adult factor, were further fitted in multivariable analyses.

The following variables were included as confounding factors: Education, alcohol consumption, smoking status, physical activity at age 14, age, living in urban areas during adolescence, BMI at enrolment, region of living at enrolment, self-reported health at enrolment, body shape in childhood, and physical activity at enrolment.

All models are adjusted for age at enrolment. Participants with missing data on any of the variables included in the multivariable models were excluded from the analyses. All explanatory variables in the models are mutually adjusted.

Diabetes and hypertension are biological risk factors of IHD. Both are likely to mediate the association between childhood SEP and IHD, and are for that reason inappropriate to adjust for (16, 58). Sensitivity test for diabetes, hypertension and cancer were performed with Wald statistics, which showed that the association of childhood SEP and IHD were not systematically different between participants affected by any of these conditions before or

during follow-up, and those not affected (data not shown). Thus, there is no reason to exclude those with diabetes, hypertension or cancer.

The follow-up started at enrolment and proceeded until onset of IHD or time of last follow-up questionnaire (at the latest 2011).

The proportional hazards assumption was evaluated for all variables by log-minus-log plots and the strongest predictors were tested by time-dependent covariates. The assumption was found to be satisfied. Calculated 95% confidence intervals (CI) were used. Two-sided p-values <0.05 were considered statistically significant.

All analyses were performed using IBM SPSS version 21, except sensitivity test with Wald statistics, which was conducted in SAS version 9.4.

CSEP was tested for linear and quadratic trend in risk of IHD by the introduction of a first and second order continuous variable assigning consecutive integers to the categories of CSEP.

2.5. Ethical aspects

NOWAC is approved by the Regional Committee for Medical and Health Research Ethics (REK). All women have given their written informed consent.

3. RESULTS

3.1. Baseline characteristics and distribution of the study variables by CSEP

There were 25,6% (n=19756) women exposed to economic hardship during childhood, and they were on average older than the women in the good and very good SEP category (Table 1). The percentage of women with IHD in relation to socioeconomic position in childhood increased in line with increasing disadvantageous position (very good: 0.8%, good: 0.9%, poor: 1.5%, very poor: 2.1%). A larger proportion of women in the very poor SEP group reported having a very thin (13.6%), fat (12.8%) and very fat (0.9%) body shape in childhood compared to women in the other SEP groups. The distribution of low level of physical activity at age 14 was increasing for each SEP category from very good childhood SEP (very good: 6.1%, good: 6.9%, poor: 7.5%, very poor: 9.7%). There was a tendency of increasing proportion of high BMI at age 18 with less advantageous socioeconomic conditions (very good: 2.9%, good: 3.7%, poor: 5.2%, very poor: 6.8%). Passive smoking frequency increased with decreasing childhood SEP (very good: 69.9%, good: 71.4%, poor: 72.1%, very poor: 72.3%). There was an increase in proportion of women living in the northern region in adolescence with adverse childhood SEP (very good: 16.8%, good: 22.4%, poor: 33.8%, very poor: 42.8%). A higher percentage of women experiencing very poor socioeconomic conditions in childhood did not consume milk in childhood compared to women in the other SEP categories (very good: 5.9%, good: 6.1%, poor: 7.3%, very poor: 12.4%), and the tendency was decreasing with more favourable childhood SEP. Similar tendency is seen for not consuming vegetables in childhood (very good: 1.5%, good: 2.0%, poor: 4.2%, very poor: 12.7%). A markedly higher proportion of women in the very poor childhood SEP group consumed fish four times per week or more in childhood than did the other groups, and there was a decreasing tendency toward the very good childhood SEP category (very good: 13.5%,

good: 18.1%, poor: 32.0%, very poor: 43.4%). The distribution of variables regarding adulthood (Table 2) shows that there are also tendencies of increasing proportion with decreasing socioeconomic position, which is the case for the following categories: low education, high BMI, poor self-reported health, living in the north, being an abstainer, having a low income, self-reported hypertension, diabetes, and cancer.

3.2. Baseline characteristics and distribution of the study variables by IHD

A total of 908 women reported having experienced IHD during follow-up (Table 3). These women were on average older than the women not affected by IHD. There was a higher proportion of IHD affected women who experienced adverse socioeconomic conditions in childhood (38.2%) compared to women not affected by IHD (25.6%). More of the women with IHD had a fat or very fat body shape in childhood (13.6%) relative to the women without IHD (9.6%). The percentage of women with IHD who were highly physically active at age 14 (41.2%) was higher than women without IHD (32.8%), but the opposite is the case for moderately active (51.1% with IHD and 60.2% without IHD). The proportion of women who reported having high BMI at age 18 was higher for those with IHD (6.1%) compared to those with no IHD (4.1%). Relatively more women with IHD were exposed to passive smoking in childhood (74.2%), lived in the north during adolescence (38%), and lived in rural areas (56.5%), while the corresponding percentages for women without IHD were 71.5%, 25.2%, and 51.3%. A higher proportion of IHD women did not drink milk in childhood (10.2%) vs IHD free women (6.5%). There were 9.1% more women with IHD who had a diet consisting of none or very low intake of vegetables in childhood, relative to those not affected by IHD. A higher proportion of women affected by IHD consumed fish more than 4 times a week in childhood (34.2%) than did women not IHD affected (21.8%). Baseline characteristics of the adult IHD women (Table 4) show that they were lower educated, less physically active, had a

higher BMI, perceived their health as poor, consumed less alcohol, smoked more, had a lower income, more likely to have hypertension and diabetes than those with no IHD.

3.3. Lifestyle factors in childhood and adolescence

Table 5 shows the models of the main analyses, displaying hazard ratios of IHD associated with lifestyle factors in childhood, where 'good' childhood SEP is the reference group.

Model 1

The first model shows that there is a significant association between adverse socioeconomic conditions in childhood and risk of IHD for women, adjusted for age. The hazard ratio for women who reported having experienced poor socioeconomic conditions in childhood is 1.80 (95% CI 1.51-2.16), compared to those who experienced good CSEP. For women who experienced very poor SEP in childhood, the hazard ratio is 2.72 (95% CI 1.74-4.24). Women in the very good SEP group also have a higher risk of IHD than those in the reference group, although not statistically significant (HR=1.25; 95% CI 0.83-1.88).

Model 2

When education is included in the model, the strength of the association between socioeconomic conditions in childhood and IHD attenuates, but remains statistically significant for the two adverse categories. The poor childhood SEP estimate was reduced by 15% after including education, and very poor childhood SEP hazard ratio was reduced by 20%, respectively. The hazard ratio of very good CSEP increased by 44%, but remained insignificant.

Model 3

Including lifestyle factors in childhood in the model further attenuated slightly the association of childhood SEP and IHD, however still significant for the unfavourable SEP groups. Poor CSEP HR was reduced by 3% and very poor SEP estimate declined by 16%. The estimate of very good CSEP was reduced by 19%, however still not significant. Having a very fat body shape in childhood significantly increased the risk of IHD (HR=2.90; 95% CI 1.08-7.80), compared to women with normal body shape. Being highly physically active at age 14 was associated with 50% (95% CI 1.26-1.80) higher risk, compared to moderately active. Living in urban areas in adolescence had no significant effect on IHD in the multivariate model.

Model 4

In the fully adjusted model, the poor childhood SEP group estimate was further reduced by 24% and very poor by 40%, and remaining statistically significant. Having experienced very good CSEP did not significantly increase risk of IHD, and the estimate was not changed when the adult confounding factors was included. There was no longer a significant effect of body shape in childhood. A high level of physical activity at age 14 was significantly associated with increased risk of IHD (HR=1.35; 95% CI 1.13-1.62) compared to moderate activity.

3.4. Dietary components

In Table 6, dietary components in childhood are included, and the hazard ratios of incident IHD associated with diet and other lifestyle factors in childhood are displayed.

Model 1

The effect estimates of all the childhood SEP categories are statistically significant, however there is a loss of statistical power compared to the models in the main analyses due to reduced

sample size. The hazard ratio for women who reported having experienced very good socioeconomic conditions in childhood is 1.63 (95% CI 1.06-2.50). HR for poor childhood SEP is 1.79 (95% CI 1.46-2.19) and for very poor childhood SEP: HR=1.84 (95% CI 1.04-3.23).

Model 2

Fitting childhood consumption of milk, vegetables and fish in a model somewhat changed the effect estimates. The hazard ratio of very good childhood SEP increased by 3%, while the poor childhood SEP estimate was reduced by 9%. HR of very poor childhood SEP category decreased by 19% and was no longer significant. Not consuming any milk in childhood statistically increased the risk of IHD with a hazard ratio of 1.60 (95% CI 1.15-2.25), compared to drinking 1-3 glasses of milk per week. And consuming fish 4 times per week or more increased risk by HR=1.32 (95% CI 1.03-1.70), compared to eating fish once a week or less.

Model 3

When adding the other childhood lifestyle factors in the model, very good and poor childhood SEP still had a significant effect on IHD, however reduced by 15% and 3%, respectively. The hazard ratio of very poor CSEP decreased by 26%, and remained statistically insignificant. Not drinking milk (HR=1.56; 95% CI 1.11-2.19) and eating fish 4 times per week or more (HR=1.31; 95% CI 1.02-1.69) remained significant. High physical activity at age 14 also remained statistically significant with HR=1.60 (95% CI 1.31-1.95).

Model 4

In the fully adjusted model, only poor childhood SEP had a significant effect on IHD, though reduced further by 14%. The estimates for very good and very poor CSEP was reduced by 5% and 46 %, respectively. Women not consuming milk had a HR=1.49 (95% CI 1.06-2.09), compared to women with a daily consumption of 1-3 glasses of milk. Highly physically active participants at age 14 were significantly associated with higher risk of IHD (HR=1.43; 95% CI 1.17-1.76), than participants moderately active at that age.

4. DISCUSSION

Summary of results

The findings from the main analyses indicates that adverse childhood SEP is associated with increased risk of IHD in middle-aged women, which remained significant after multivariable adjustment for both childhood and adult lifestyle factors. Further, the most disadvantaged women (with very poor CSEP) had a higher risk than those in the poor childhood SEP group, indicating a negative socioeconomic gradient. Although the most advantaged women seemed to have a slightly increased risk of IHD, it did not reach statistical significance. After multivariable adjustment, the estimate for very poor CSEP decreased by a higher percentage than the estimate for poor CSEP in each model, which suggests that a higher proportion of the risk for women experiencing very poor childhood SEP can be explained by the underlying variables. High level of physical activity remained statistically significant in the fully adjusted model. Having a very fat body shape in childhood significantly elevated the risk of IHD before adjusting for the adult lifestyle factors, but after adjustment this was no longer significant.

In the analyses including dietary components in childhood, not consuming milk in childhood, and high physical activity in adolescence increased the risk of IHD. Consuming fish more than four times a week significantly increased risk of IHD before adjusting for lifestyle in adulthood, but was not significant in the fully adjusted model. Poor CSEP remained significantly associated with risk of IHD. These models have a smaller sample size compared to the main analyses, and therefore reduced statistical power.

There seems to be a stronger quadratic trend, although the linear trend is significant when the quadratic trend is not included in the analyses. There is seemingly a J-trend, and the group very poor CSEP stands out.

The results may indicate an excess burden of IHD risk among women who have experienced economic hardship in their childhood. Including lifestyle factors and dietary components in childhood in multivariable models, do not fully explain the association between socioeconomic conditions in childhood and ischemic heart disease in middle-aged Norwegian women. Other factors might be involved in this process and it could be the result of residual confounding.

Although the social patterning of the included factors in childhood may explain some of the association between CSEP and IHD, childhood lifestyle factors are likely to have been influenced by parental lifestyle and SEP. Furthermore, the health capital acquired in childhood is known to persist into adulthood (59). The association between childhood SEP and CHD may therefore be explained in part by adverse behavioural risk factors that persist from childhood into adulthood among those who come from the poorest backgrounds (59). Significant correlations were found between the childhood variables with corresponding adult variables in the present thesis, such as SEP (ρ=-0.17), physical activity (ρ=0.11), and BMI (ρ=0.27).

Thus the childhood lifestyle factors and adult lifestyle factors are closely connected and cannot be considered separately.

The traditionally most favoured life course model is accumulation of risk with correlated exposures (earlier versions: 'risk clustering') (2). Many exposures in childhood correlates with exposures in adulthood, as they cluster under the broader exposure of adverse cumulative socioeconomic conditions from childhood to adult life (2).

Pollitt et al. (46) observed in a systematic review that the cumulative life course model has been the most consistently supported model, which is analogous to the accumulation of risk model presented by Ben-Shlomo et al. (22) (Figure 1, a and b). Accumulation model proposes that risk of CHD increases with increasing duration and intensity of poor CSEP exposure

(21). However, it would be naive to conclude that a simple accumulation model is the best fit of the data given a steady increase in IHD risk among SEP groups (22). Both timing and duration of exposure to socioeconomic disadvantage are found to have profound effects on development of IHD (2). It is likely that the association between CSEP and IHD is the result of a synthesis of effects and that more than one model is operating at the same time, as proposed by Ben-Slomo (22). Critical/sensitive period models can also be applied during the broad timeframe of CSEP exposure used in the present thesis, although we are not able to pinpoint the exact timing or period. Such a broad timeframe of the CSEP indicator can be equivalent to the broad timeframe of education (as adult SEP indicator), and might not artefactually favour one model over another (22). Although the focus in the present thesis have been on factors connected to childhood and adolescence, exposures that occur in utero are found to be associated with vulnerability to future disease. Poor fetal growth can have long-term effects that is associated with increased risk of CHD (42).

Ben-Shlomo et al. suggests that it may be more helpful to consider an accumulation model as the default model with sensitive and critical period models considered as special types accumulation models (22).

Evidence suggests that upward mobility from poor childhood SEP to advantaged adult SEP decreases the risk of CHD relative to the socioeconomic group of origin, although the upwardly mobile seem not to attain the same levels of health as those who were advantaged over the whole life course (2). Women moving from a manual to a non-manual class position are observed to have only a slight excess cardiovascular mortality compared to women maintaining a stable non-manual position, while women moving into an adult manual class were found to have an elevated CVD mortality irrespective of childhood position (49).

Though the mechanisms related to the social selection model seems to make only a small contribution to socioeconomic differentials in adult health (2), Ben-Shlomo et al. argues that

social mobility is better limited to a descriptive term rather than as an etiological model which tries to understand how the process of mobility is embodied into pathophysiology (22). The phenomenon of social mobility is consistent with a critical/sensitive period or accumulation model depending on which empirically based patterns emerge from the data analysis (22). The specific mechanisms of the array of exposures in childhood and adolescence that can cause IHD is not fully clear, and therefore limit our ability to conclude which life course model or models are operating.

4.1. Strengths and limitations

There are several methodological issues that need to be addressed. Errors in epidemiological studies are inevitable because of the complexity and heterogeneity of life (60). Two types of errors that are important to distinguish are: random errors and systematic errors (bias). Random errors are non-differential and affect comparison groups equally, however it can be minimized by large sample size. Systematic errors are differential and affects groups unequally. Assessment of the possibility of bias is important, in addition to that of confounding, as it is often a major limitation in the interpretation of results from observational epidemiological studies and pose as a threat to validity (58). The following discussion is presented according to different systematic errors and the possible impact limitations of the estimates of CSEP and IHD could have on internal validity. Other confounding variables are also briefly discussed further on.

4.1.1. Internal validity

Bias can be defined as the result of a systematic error in the design or conduct of a study, and so relates to the process of selection of study participants (selection bias) or gathering of relevant exposure and/or disease information (information bias) (58).

Selection bias

Selection bias is present when individuals have different probabilities of being included in the study sample according to the exposure and the outcome of interest (58). In cohort studies, such as NOWAC, the study participants are selected before any disease is known; differential selection according to disease status is therefore improbable. NOWAC consists of women who were randomly selected, with initial response rate of 57%. Those not responding are likely to differ from the responders, which is a possible hazard for non-response bias (60). Responders in self-administered questionnaire studies are more likely to be well-educated people and have different attitudes, behaviours and health status than non-responders. However, NOWAC has been validated and there was performed a non-responder inquiry, and although a larger proportion of the responders had higher education, no significant difference in educational attainment was found between the non-responders and the responders (56). Although selection might be present, the estimates are not likely to be biased.

Among the women who were asked to state their economic conditions during childhood, the proportion of item non-response is too low to produce any bias. For those not being asked about CSEP, the probability of bias is unlikely.

Women not responding to the follow-up questionnaires are possibly different from the women who remained in the cohort, which relates to differential losses of follow-up. Losses might be due to IHD, as the occurrence of the disease is retrospectively reported. Individuals who are lost to follow-up may have higher incidence of IHD than the responders of the follow-up questionnaire (58). However, we assume that the IHD risk profile for responders and non-responders are similar, and thus not yielding biased estimates.

Information bias

Information bias results from either imperfect definitions of study variables or flawed data collection procedures (58). These measurement errors may lead to misclassification of exposure and/or outcome status for a significant proportion of the study participants. Imperfect definition of the CSEP variable may be relevant, as there could have been a middle value between poor and good, where the participants would have the opportunity to state they experienced for example an 'average' socioeconomic condition in childhood. However, it is unlikely to have affected the estimates of association.

Inaccurate recall of past exposure is a well-known type of exposure identification bias (58). The information used in the present thesis is predominantly self-reported. Self-reported information generally involves participant's perception of their current and/or past situation, although it can be subject to individual and environmental variation (61). If recall bias arise due to the participants (of NOWAC) imprecise recollections of childhood economic conditions, we could assume that it would be non-differential, which would generally weaken the association. The study initially includes women who reported CSEP before onset of IHD. Prevalent cases of IHD at baseline were excluded in order to avoid recall bias, and thus outcome status was not likely to have influenced recollection of CSEP.

In a systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood, conducted by Galobardes et al. (44), they found a stronger association between poor childhood circumstances and CHD in studies where SEP was measured during childhood than those studies relying on retrospective measures of CSEP. There is no validity study conducted to assess the accuracy of adult recall of childhood socioeconomic conditions from NOWAC. But a study of the accuracy of adults' recall of childhood social class from the Aberdeen children of the1950s study (62), found a moderate agreement between middle aged adults' recall of early life social class and social class data

collected prospectively up to five decades earlier. Disagreement were attributed to adults reporting a higher occupational social class to that recorded in early life, although it is possible that some of the disagreement ascribes to coding differences of occupations (62). Similar to self-reported health, which is regarded as a useful measure (63), retrospective measure of CSEP in NOWAC is a broad indicator (also encompasses adolescence) that might prove to be equally useful. In that perspective, self-perceived childhood SEP would be an advantage rather than using e.g. household income as a measure, as it would reflect the actual situation in which the women found themselves to be. However, the women might have compared their childhood circumstances to their situation as adults, which may have magnified or altered their recollections of the past experiences since economic and social conditions generally have improved in Norway, resulting in an overrepresentation of the oldest women in the very poor socioeconomic category. Nevertheless, it is reasonable to assume that a higher proportion of the oldest women actually experienced very poor socioeconomic conditions in childhood. Comparing different birth cohorts in NOWAC, dividing women born before, during, and after WWII, revealed that the estimates were not significantly different. Women born in different time periods will likely have varying references as to what they perceive as poor socioeconomic conditions, but the comparison indicates that the health effects of poor CSEP also applies to younger women.

The timing and duration of exposure cannot be specified in the present thesis, and thus the measure of CSEP used in the study assumes that any particular instance and/or length of disadvantage has the same impact regardless of when it has occurred or for how long it was endured in the life course (64).

McKenzie and Carter (65) argues that despite the shortcomings of retrospective measures of CSEP, they provide useful opportunities to empirically examine theoretical life course models in the absence of complete data across the life course. The use of retrospective CSEP

measures combined with adult SEP measures provide indicators that reflect the accumulation of life course social disadvantage (65).

Outcome identification bias may be present if misclassification of disease status occur (58). One example is outcome ascertainment bias, which is obtained by participant response. In NOWAC the participants were asked to answer whether they had experienced heart failure/angina pectoris and/or a myocardial infarction, which in line with ICD-10 constitutes IHD. Positive IHD symptoms can be mistaken for other conditions. However, this would probably be relevant for very few cases. There is only a small validation study for ischemic heart disease in NOWAC, which is not published. The validation study reports that out of 50 respondents with CHD at baseline, 35 were definite myocardial infarction, 5 cases were definite or possible myocardial infarction (not specifiable), 6 cases were angina pectoris, and 5 cases were no myocardial infarction. This information was obtained through medical records from hospitals and general practitioners, with the respondents' written consent. On the basis of this validation study, misclassification of IHD is not likely to influence the estimates of the association.

Linkage between heart registry and NOWAC would have yielded more accurate IHD information. However, the Norwegian Cardiovascular Disease Registry was established in 2012 and does not include people with IHD before 2010, and therefore not available for the present thesis. A validity study from Finland (66) shows substantial agreement between self-reported and medical records of CHD.

Women who reported having experienced IHD during follow-up but with missing information on age at onset of IHD was excluded, which hampered calculation of incidence rates.

Misclassification also affects the efficiency of adjustment for confounding effects (58). Non-differential misclassification of a confounding variable results in an imperfect adjustment when that variable is matched or controlled for in the analyses, leading to residual confounding.

Residual confounding

Residual confounding (58) can occur because of:

- Insufficient information on confounding factors

Education was found to be a stronger confounding factor than income in the present thesis. Adding income in the fully adjusted model did not further explain the variation in risk of IHD by CSEP. This may reflect insufficient information on income, as income is the most favourable indicator of material living standards (10). An important issue here is that we do not know the number of incomes in the household. Furthermore, income is prone to reverse causation, that is; poor health can contribute to low income (social selection). The causal relationship is difficult to establish (61). Income might also be a 'sensitive' measure, which means that participants are reluctant to report their income, for different reasons. And the income variable should ideally have been collected for all participants at baseline, which it is not.

- Misclassification of confounding variables

Participants may have changed their lifestyle over the course of a long follow-up period, resulting in imperfect adjustment. Duration of follow-up is found to dilute the effects of the explanatory variables (67). Adjusting for imperfectly classified confounders could account for

some of the unexplained association between CSEP and IHD in the present thesis, because only part of the confounding effects of the lifestyle variables would have been removed (67).

- Other important confounders are not included in the model

Psychosocial factors and stress is not adjusted for, but assumed to be an indirect part of CSEP. Not adjusting for stress and psychiatric diagnoses, such as depression and/or anxiety, could potentially account for residual confounding. Emotional stress of recognising relatively inferior SES can lead to neuroendocrine responses hypothesised to increase risk of CHD (59).

4.1.2. External validity

NOWAC is a national population-based cohort study with an initial response rate around 60%. A validation study found only minor differences between responders and the source population (56). A higher proportion of the responders had more than 12 years of education compared to the sample of all eligible women, but no difference in lifestyle factors were found (56). Thus, we believe that women in the NOWAC study are representative for the female Norwegian population in the corresponding age-groups.

Although the association between CSEP and IHD is complicated and difficult to generalise in practice and therefore not expected to show stable patterns across time and place, the evidence of an inverse association is generally consistent (68).

Previous research

Consistent with previous studies, we found evidence of an inverse association between CSEP and CHD in middle-aged women (59, 64, 69). Further we found that childhood lifestyle factors and dietary components partly explain the association.

Findings from the British women's Heart and Health Study reveal that infant and childhood nutrition, insulin resistance, and adult behavioural risk factors play a part in the association between childhood SES and risk of CHD, and that adjusting for adult risk factors attenuates this association (59). In the Stockholm Female Coronary Risk Study traditional adult behavioural and biological risk factors exacerbated rather than attenuated CHD associations with early life socioeconomic disadvantage (64). A study from the US noted an excess risk of total CHD and non-fatal MI in the range of 50-70% between the most disadvantaged socioeconomic group of women and the most advantaged group (69).

In a study from the Netherlands, the results show an independent effect of childhood socioeconomic group on adult health, and childhood socioeconomic circumstances seemed to have an independent effect on health-related behaviour (70). Behavioural factors contributed to a small part to the explanation of differences in adult health between childhood socioeconomic groups and physical activity was found to be the most important behavioural factor in this process (70).

A publication from The Collabortative study demonstrated that there exists substantial differences in CVD mortality risk between groups defined by a small set of socioeconomic and behavioural risk factors (71). They combined socioeconomic and behavioural risk factors to generate an index of life-course exposure, and they postulated that if the entire study population had the CVD mortality risk of the subsample with the most favourable risk factor profile, approximately two thirds of the cardiovascular deaths would not have occurred (71). The socioeconomic and behavioural risk factors that they examined were generally strongly

interrelated and early-life disadvantaged people (indexed by father's social class) were more likely to quit school early, have manual jobs in later adulthood, live in deprived areas as adults, be cigarette smokers, and have high levels of alcohol consumption.

Data from three independent cohort studies from three continents were used to study a comprehensive set of childhood predictors of adult ideal cardiovascular health, which include SEP indicators, childhood lifestyle indicators, and clinical indicators (53). They observed that high family SES in all cohorts and non-smoking (either passive or own smoking) in childhood in two cohorts were independently associated with ideal cardiovascular health two to three decades later in adulthood (53). Passive smoking have been found to increase risk of CHD (72). Passive smoking did not reach statistical significance of confounding in our analyses.

The underlying process of CHD, atherosclerosis is regarded as a nutritional disease of childhood (73). Diet influences obesity, lipoprotein concentrations, and blood pressure, therefore nutrition is implicated as a major environmental factor that underlines the high incidence of atherosclerosis in industrialised countries (73). Adding dietary components in childhood to the analyses in the present study produced loss of statistical power because of item non-response and it is possible that the participants found it difficult to recall dietary habits in childhood.

The association between clustering of risk factors and atherosclerosis, indicates that multiple risk factors tend to cause acceleration of atherosclerotic lesions, especially the progressive type of disease in coronary vessels (73). Kaplan and Salonen (74) hypothesised that IHD develops earlier in people experiencing adverse socioeconomic circumstances in childhood. Publication of The cardiovascular Risk in Young Finns Study showed that the number of ideal cardiovascular health metrics present in childhood predicted subsequent cardiometabolic health in adulthood independent of change in the index during follow-up (52). Because the

ideal child cardiovascular health index was directly associated with the index in adulthood, the authors highlight the importance of promoting a healthy lifestyle early in life (52).

Concluding remarks

We observed an association between socioeconomic conditions in childhood and risk of self-reported ischemic heart disease in middle-aged Norwegian women. Lifestyle factors in childhood and adolescence explains part of the association. A higher percentage of the underlying variables are explained for the most disadvantaged women in childhood (having a very poor CSEP). The life course model most consistently supported for the association between CSEP and IHD is the accumulation of risk model, although there are likely to be a synthesis of several models operating simultaneously.

The effects of modifying adult lifestyle have proven to be disappointingly small (28), therefore it is pivotal to focus on early life exposures to prevent CHD and other chronic diseases, and to equalise health differences. Closing the health-gap between SEP groups is contingent on effective political interventions and policies, which should be based on an understanding of the causes of socioeconomic inequalities in health.

Mackenbach concluded (6 p830): *"Reducing socioeconomic inequalities in mortality in Western Europe critically depends upon speeding up mortality declines from cardiovascular diseases in lower socioeconomic groups, and countering mortality increases from several other causes of death in lower socioeconomic groups."*

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TABLES

Table 1 Distribution of the study variables according to CSEP

Variable	N	Percent	Childhood SEP				
			Very good n=4020 (%)	Good n=53378 (%)	Poor n=18468 (%)	Very poor n=1288 (%)	p-value
Mean age at enrolment (±SD)	77154	100	46,28 (±8.37)	46,45 (±8.37)	48,3 (±8.59)	50,92 (±9.03)	
IHD	77154						<0.001
Yes	809	1	33 (0.8)	467 (0.9)	282 (1.5)	27 (2.1)	
No	76345	99	3987 (99.2)	52911 (99.1)	18186 (98.5)	1261 (97.9)	
Body shape in childhood	75092						<0.001
Very thin	4427	5,9	250 (6.4)	2711 (5.2)	1298 (7.2)	168 (13.6)	
Thin	16240	21,6	809 (20.7)	11196 (21.5)	3984 (22.2)	251 (20.3)	
Normal	47233	62,9	2476 (63.4)	33496 (64.4)	10615 (59.2)	646 (52.4)	
Fat	6978	9,3	360 (9.2)	4488 (8.6)	1972 (11.0)	158 (12.8)	
Very fat	214	0,3	11 (0.3)	118 (0.2)	74 (0.4)	11 (0.9)	
Level of physical activity at age 14	69137						<0.001
Low	4853	7	221 (6.1)	3299 (6.9)	1227 (7.5)	106 (9.7)	
Moderate	41629	60,2	1899 (52.8)	29406 (61.2)	9805 (59.8)	519 (47.6)	
High	22655	32,8	1476 (41.0)	15360 (32.0)	5353 (32.7)	466 (42.7)	
BMI at age 18	72098						<0.001
Low (<18.49 kg/m2)	9990	13,9	653 (17.6)	6954 (13.9)	2208 (12.8)	175 (14.8)	
Medium (18.5-24.9 kg/m2)	58462	81,1	2923 (78.6)	40676 (81.5)	13948 (80.7)	915 (77.4)	
High (25-29.9 kg/m2)	2920	4,1	107 (2.9)	1830 (3.7)	903 (5.2)	80 (6.8)	
Very high (≥30 kg/m2)	726	1	34 (0.9)	464 (0.9)	216 (1.3)	12 (1.0)	
Passive smoking in childhood	63283						0,062
Yes	45231	71,5	2283 (69.9)	31465 (71.4)	10758 (72.1)	725 (72.3)	
No	18052	28,5	981 (30.1)	12632 (28.6)	4161 (27.9)	278 (27.7)	
Region of living in adolescence	64840						<0.001
Oslo, East, South, West and Middle	48510	74,8	2686 (83.2)	34873 (77.6)	10366 (66.2)	585 (57.2)	
North	16330	25,2	541 (16.8)	10055 (22.4)	5297 (33.8)	437 (42.8)	
Living in urban areas during adolescence	77154						<0.001
Yes	37595	48,7	2534 (63.0)	26874 (50.3)	7628 (41.3)	559 (43.4)	
No	39559	51,3	1486 (37.0)	26504 (49.7)	10840 (58.7)	729 (56.6)	
Consumption of milk in childhood	61872						<0.001
None	4006	6,5	183 (5.9)	2617 (6.1)	1081 (7.3)	125 (12.4)	
1-3 glasses per day	39053	63,1	1996 (64.9)	27158 (63.2)	9275 (62.5)	624 (61.7)	
4-6 glasses per day	17620	28,5	821 (26.7)	12394 (28.9)	4168 (28.1)	237 (23.4)	
≥7 glasses per day	1193	1,9	76 (2.5)	782 (1.8)	310 (2.1)	25 (2.5)	
Consumption of vegetables in childhood	62053						<0.001
None	1680	2,7	47 (1.5)	876 (2.0)	628 (4.2)	129 (12.7)	
Once a week or less	14170	22,8	314 (10.1)	7948 (18.5)	5434 (36.5)	474 (46.6)	
2-3 times per week	24252	39,1	963 (31.1)	17600 (40.9)	5430 (36.5)	259 (25.4)	
≥ 4 times per week	21951	35,4	1770 (57.2)	16638 (38.6)	3387 (22.8)	156 (15.3)	
Consumption of fish in childhood	49669						<0.001
None	961	1,9	49 (2.0)	609 (1.8)	259 (2.1)	44 (5.1)	
Once a week or less	15729	31,7	818 (34.0)	11353 (33.3)	3343 (27.2)	215 (25.0)	
2-3 times per week	22162	44,6	1213 (50.4)	15979 (46.8)	4742 (38.6)	228 (26.5)	
≥ 4 times per week	10817	21,8	325 (13.5)	6189 (18.1)	3930 (32.0)	373 (43.4)	

Table 2 Distribution of adulthood variables according to CSEP

Variable	N	Percent	Childhood SEP				
			Very good n=4020 (%)	Good n=53378 (%)	Poor n=18468 (%)	Very poor n=1288 (%)	p-value
Education	73745						<0.001
≤9 years	18908	25,6	547 (14.3)	11425 (22.4)	6318 (35.9)	618 (51.7)	
10-12 years	25619	34,7	1121 (29.3)	18289 (35.8)	5881 (33.4)	328 (27.4)	
≥13 years	29218	39,6	2159 (56.4)	21398 (41.9)	5411 (30.7)	250 (20.9)	
Level of physical activity at enrolment	70898						<0.001
Low	9180	12,9	460 (12.6)	6010 (12.2)	2493 (14.8)	217 (19.0)	
Moderate	49824	70,3	2426 (66.6)	35086 (71.3)	11625 (68.8)	687 (60.1)	
High	11894	16,8	758 (20.8)	8127 (16.5)	2770 (16.4)	239 (20.9)	
BMI at enrolment	67019						<0.001
Low (<19.9 kg/m2)	6469	9,7	428 (12.7)	4659 (10.1)	1291 (7.9)	91 (7.9)	
Medium (20-24.9 kg/m2)	39892	59,5	2074 (61.5)	28145 (60.9)	9100 (55.8)	573 (49.9)	
High (25-29.9 kg/m2)	16603	24,8	686 (20.3)	10934 (23.7)	4626 (28.4)	357 (31.1)	
Very high (≥30 kg/m2)	4055	6,1	187 (5.5)	2441 (5.3)	1300 (8.0)	127 (11.1)	
Self-reported health at enrolment	74863						<0.001
Good	69830	93,3	3697 (94.9)	49187 (94.7)	15981 (89.6)	965 (79.1)	
Poor	5033	6,7	197 (5.1)	2727 (5.3)	1854 (10.4)	255 (20.9)	
Region of living	68792						<0.001
Oslo, East, South, West and Middle	52598	76,5	2939 (85.0)	37498 (79.1)	11462 (68.4)	699 (59.7)	
North	16194	23,5	517 (15.0)	9914 (20.9)	5291 (31.6)	472 (40.3)	
Daily consumption of alcohol	64798						<0.001
0 gram	18290	28,2	714 (22.1)	12167 (27.1)	4995 (32.0)	414 (37.7)	
0.1-4 grams	30139	46,5	1384 (42.9)	21047 (46.9)	7234 (46.3)	474 (43.2)	
4.1-10 grams	11959	18,5	783 (24.3)	8570 (19.1)	2464 (15.8)	142 (12.9)	
>10 grams	4410	6,8	346 (10.7)	3069 (6.8)	928 (5.9)	67 (6.1)	
Smoking status	76001						<0.001
Never smoker	28008	36,9	1385 (35.2)	19691 (37.4)	6532 (35.9)	400 (31.5)	
Former smoker	23991	31,6	1244 (31.6)	16553 (31.5)	5812 (31.9)	382 (30.1)	
Current smoker	24002	31,6	1308 (33.2)	16343 (31.1)	5865 (32.2)	486 (38.3)	
Gross household income at second questionnaire	71664						<0.001
<300 000 NOK	26202	36,6	1075 (29.1)	17008 (34.3)	7441 (43.4)	678 (57.8)	
301 000-450 000 NOK	19917	27,8	853 (23.1)	13947 (28.1)	4848 (28.3)	269 (22.9)	
451 000-600 000 NOK	14588	20,4	864 (23.4)	10610 (21.4)	2969 (17.3)	145 (12.4)	
>600 000 NOK	10957	15,3	904 (24.5)	8076 (16.3)	1895 (11.0)	82 (7.0)	
Hypertension	65679						<0.001
Yes	6696	10,2	287 (8.3)	4317 (9.5)	1946 (12.6)	146 (13.6)	
No	58983	89,8	3190 (91.7)	41348 (90.5)	13521 (87.4)	924 (86.4)	
Diabetes	76634						<0.001
Yes	2058	2,7	113 (2.8)	1305 (2.5)	587 (3.2)	53 (4.2)	
No	74576	97,3	3884 (97.2)	51769 (97.5)	17710 (96.8)	1213 (95.8)	
Cancer	77154						0,002
Yes	6845	8,9	345 (8.6)	4656 (8.7)	1697 (9.2)	147 (11.4)	
No	70309	91,1	3675 (91.4)	48722 (91.3)	16771 (90.8)	1141 (88.6)	

Table 3 Distribution of the study variables according to IHD

Variable	N	Percent	IHD		p-value
			Yes n=809 (%)	No n=76345 (%)	
Mean age at enrolment (±SD)	77154	100	50,6 (±8.84)	46,92 (±8.47)	
Childhood SEP	77154				<0.001
Very good	4020	5,2	33 (4.1)	3987 (5.2)	
Good	53378	69,2	467 (57.7)	52911 (69.3)	
Poor	18468	23,9	282 (34.9)	18186 (23.8)	
Very poor	1288	1,7	27 (3.3)	1261 (1.7)	
Body shape in childhood	75092				<0.001
Very thin	4427	5,9	59 (7.5)	4368 (5.9)	
Thin	16240	21,6	150 (19.1)	16090 (21.7)	
Normal	47233	62,9	469 (59.8)	46764 (62.9)	
Fat	6978	9,3	100 (12.8)	6878 (5.9)	
Very fat	214	0,3	6 (0.8)	208 (0.3)	
Level of physical activity at age 14	69137				<0.001
Low	4853	7	54 (7.6)	4799 (7.0)	
Moderate	41629	60,2	362 (51.1)	41267 (60.3)	
High	22655	32,8	292 (41.2)	22363 (32.7)	
BMI at age 18	72098				0,001
Low (<18.49 kg/m2)	9990	13,9	95 (12.7)	9895 (13.9)	
Medium (18.5-24.9 kg/m2)	58462	81,1	594 (79.2)	57868 (81.1)	
High (25-29.9 kg/m2)	2920	4,1	46 (6.1)	2874 (4.0)	
Very high (≥30 kg/m2)	726	2	15 (2.0)	711 (1.0)	
Passive smoking in childhood	63283				0,128
Yes	45231	71,5	482 (74.2)	44749 (71.4)	
No	18052	28,5	168 (25.8)	17884 (28.6)	
Region of living in adolescence	64840				<0.001
Oslo, East, South, West and Middle	48510	74,8	441 (62.0)	48069 (75.0)	
North	16330	25,2	270 (38.0)	16060 (25.0)	
Living in urban areas during adolescence	77154				0,003
Yes	37595	48,7	352 (43.5)	37243 (48.8)	
No	39559	51,3	457 (56.5)	39102 (51.2)	
Consumption of milk in childhood	61872				<0.001
None	4006	6,5	68 (10.2)	3938 (6.4)	
1-3 glasses per day	39053	63,1	384 (57.7)	38669 (63.2)	
4-6 glasses per day	17620	28,5	198 (29.8)	17422 (28.5)	
≥7 glasses per day	1193	1,9	15 (2.3)	1178 (1.9)	
Consumption of vegetables in childhood	62053				<0.001
None	1680	2,7	28 (4.1)	1652 (2.7)	
Once a week or less	14170	22,8	206 (30.5)	13964 (22.8)	
2-3 times per week	24252	39,1	239 (35.4)	24013 (39.1)	
≥ 4 times per week	21951	35,4	202 (29.9)	21749 (35.4)	
Consumption of fish in childhood	49669				<0.001
None	961	1,9	15 (2.6)	946 (1.9)	
Once a week or less	15729	31,7	163 (28.2)	15566 (31.7)	
2-3 times per week	22162	44,6	203 (35.1)	21959 (44.7)	
≥ 4 times per week	10817	21,8	198 (34.2)	10619 (21.6)	

Table 4 Distribution of adulthood variables according to IHD

Variable	N	Percent	IHD		
			Yes n=809 (%)	No n=76345 (%)	p-value
Education	73745				<0.001
≤9 years	18908	25,6	317 (41.9)	18591 (25.5)	
10-12 years	25619	34,7	249 (32.9)	25370 (34.8)	
≥13 years	29218	39,6	190 (25.1)	29028 (39.8)	
Level of physical activity at enrolment	70898				<0.001
Low	9180	12,9	157 (21.3)	9023 (12.9)	
Moderate	49824	70,3	468 (63.6)	49356 (70.3)	
High	11894	16,8	111 (15.1)	11783 (16.8)	
BMI at enrolment	67019				<0.001
Low (<19.9 kg/m2)	6469	9,7	40 (5.4)	6429 (9.7)	
Medium (20-24.9 kg/m2)	39892	59,5	349 (47.1)	38543 (59.7)	
High (25-29.9 kg/m2)	16603	24,8	258 (34.8)	16345 (24.7)	
Very high (≥30 kg/m2)	4055	6,1	94 (12.7)	3961 (6.0)	
Self-reported health at enrolment	74863				<0.001
Good	69830	93,3	638 (82.6)	69192 (93.4)	
Poor	5033	6,7	134 (17.4)	4899 (6.6)	
Region of living	68792				<0.001
Oslo, East, South, West and Middle	52598	76,5	477 (62.8)	52121 (76.6)	
North	16194	23,5	283 (37.2)	15911 (23.4)	
Daily consumption of alcohol	64798				<0.001
0 gram	18290	28,2	234 (32.6)	18056 (28.2)	
0.1-4 grams	30139	46,5	352 (49.1)	29787 (46.5)	
4.1-10 grams	11959	18,5	90 (12.6)	11869 (18.5)	
>10 grams	4410	6,8	41 (5.7)	4369 (6.8)	
Smoking status	76001				<0.001
Never smoker	28008	36,9	214 (26.7)	27794 (37.0)	
Former smoker	23991	31,6	199 (24.8)	23792 (31.6)	
Current smoker	24002	31,6	389 (48.5)	23613 (31.4)	
Gross household income at second questionnaire	71664				<0.001
<300 000 NOK	26202	36,6	399 (53.3)	25803 (36.4)	
301 000-450 000 NOK	19917	27,8	195 (26.1)	19722 (27.8)	
451 000-600 000 NOK	14588	20,4	98 (13.1)	14490 (20.4)	
>600 000 NOK	10957	15,3	56 (7.5)	10901 (15.4)	
Hypertension	65679				<0.001
Yes	6696	10,2	168 (30.8)	6528 (10.0)	
No	58983	89,8	377 (69.2)	58606 (90.0)	
Diabetes	76634				<0.001
Yes	2058	2,7	80 (10.0)	1978 (2.6)	
No	74576	97,3	722 (90.0)	73854 (97.4)	
Cancer	77154				0,204
Yes	6845	8,9	82 (10.1)	6763 (8.9)	
No	70309	91,1	727 (89.9)	69582 (91.1)	

Table 5 Lifestyle factors in childhood as risk factors for IHD, N=51 297

		Model 1		Model 2		Model 3		Model 4	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Childhood SEP									
	Very good	1.25	(0.83-1.88)	1.36	(0.90-2.04)	1.29	(0.85-1.94)	1.29	(0.85-1.94)
	Good	1.00		1.00		1.00		1.00	
	Poor	1.80	(1.51-2.16)	1.68	(1.40-2.02)	1.66	(1.38-1.99)	1.50	(1.25-1.81)
	Very poor	2.72	(1.74-4.24)	2.38	(1.52-3.72)	2.16	(1.37-3.39)	1.70	(1.08-2.67)
P for linear trend		0.84		0.60		0.84		0.89	
P for quadratic trend		0.04		0.03		0.09		0.22	
Education									
	≤ 9 years			1.83	(1.46-2.28)	1.81	(1.45-2.27)	1.28	(1.02-1.62)
	10-12 years			1.29	(1.04-1.61)	1.30	(1.04-1.62)	1.07	(0.86-1.34)
	≥ 13 years			1.00		1.00		1.00	
Body shape in childhood									
	Very thin					1.29	(0.95-1.76)	1.34	(0.99-1.83)
	Thin					0.96	(0.78-1.19)	1.09	(0.87-1.35)
	Normal					1.00		1.00	
	Fat					1.15	(0.86-1.55)	0.81	(0.59-1.10)
	Very fat					2.90	(1.08-7.80)	1.42	(0.52-3.87)
Level of physical activity at age 14	Low					1.31	(0.96-1.80)	1.30	(0.94-1.79)
	Moderate					1.00		1.00	
	High					1.50	(1.26-1.80)	1.35	(1.13-1.62)
Living in urban areas during adolescence									
	Yes					1.07	(0.90-1.28)	1.10	(0.92-1.31)
	No					1.00		1.00	

Models 1, 2 and 3: Age adjusted

Model 4: Adjusted for age, self-reported health, smoking, consumption of alcohol, body-mass index, region of living, and physical activity at enrolment

Table 6 Dietary components in childhood as risk factors for IHD, N=39 256

		Model 1		Model 2		Model 3		Model 4	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Childhood SEP									
	Very good	1.63	(1.06-2.50)	1.65	(1.07-2.54)	1.55	(1.01-2.39)	1.52	(0.98-2.34)
	Good	1.00		1.00		1.00		1.00	
	Poor	1.79	(1.46-2.19)	1.72	(1.40-2.13)	1.70	(1.38-2.10)	1.60	(1.30-1.98)
	Very poor	1.84	(1.04-3.23)	1.68	(0.95-2.97)	1.50	(0.84-2.66)	1.27	(0.71-2.25)
P for linear trend		0.65		0.62		0.89		0.99	
P for quadratic trend		0.08		0.10		0.23		0.41	
Education									
	≤ 9 years	1.76	(1.38-2.26)	1.71	(1.32-2.20)	1.70	(1.32-2.20)	1.24	(0.95-1.61)
	10-12 years	1.23	(0.96-1.57)	1.22	(0.95-1.56)	1.23	(0.96-1.57)	1.03	(0.80-1.31)
	≥ 13 years	1.00		1.00		1.00		1.00	
Consumption of milk in childhood	None			1.60	(1.15-2.25)	1.56	(1.11-2.19)	1.49	(1.06-2.09)
	1-3 glasses per day			1.00		1.00		1.00	
	4-6 glasses per day			1.21	(0.98-1.50)	1.19	(0.96-1.47)	1.18	(0.95-1.46)
	≥7 glasses per day			1.15	(0.59-2.25)	1.07	(0.55-2.09)	1.00	(0.51-1.95)
Consumption of vegetables in childhood	None			0.94	(0.55-1.60)	0.91	(0.53-1.56)	0.88	(0.51-1.51)
	Once a week or less			1.00		1.00		1.00	
	2-3 times per week			0.98	(0.77-1.26)	0.97	(0.76-1.24)	1.05	(0.82-1.34)
	≥ 4 times per week			1.07	(0.82-1.39)	1.01	(0.78-1.33)	1.13	(0.86-1.49)
Consumption of fish in childhood	None			0.91	(0.44-1.86)	0.87	(0.42-1.79)	0.86	(0.42-1.77)
	Once a week or less			1.00		1.00		1.00	
	2-3 times per week			0.86	(0.68-1.10)	0.86	(0.68-1.10)	0.79	(0.62-1.01)
	≥ 4 times per week			1.32	(1.03-1.70)	1.31	(1.02-1.69)	1.04	(0.79-1.38)
Body shape in childhood									
	Very thin					1.31	(0.93-1.85)	1.36	(0.96-1.92)
	Thin					1.00	(0.79-1.27)	1.10	(0.86-1.40)
	Normal					1.00		1.00	
	Fat					1.20	(0.86-1.66)	0.86	(0.61-1.22)
	Very fat					2.66	(0.85-8.32)	1.38	(0.43-4.40)
Level of physical activity at age 14	Low					1.26	(0.87-1.82)	1.26	(0.87-1.82)
	Moderate					1.00		1.00	
	High					1.60	(1.31-1.95)	1.43	(1.17-1.76)
Living in urban areas during adolescence	Yes					1.18	(0.96-1.43)	1.19	(0.97-1.45)
	No					1.00		1.00	

Models 1, 2 and 3: Age adjusted
Model 4: Adjusted for age, self-reported health, smoking, consumption of alcohol, body-mass index, region of living, and physical activity at enrolment