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LIFE COURSE DETERMINANTS OF CORONARY HEART DISEASE AND STROKE IN MIDDLE-AGED SWEDISH MEN

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ABSTRACT

The general aim of the thesis was to study how socioeconomic and behaviour-related factors measured in childhood, late adolescence or adulthood are related to coronary heart diseae (CHD) and stroke in middle age among Swedish men. The life course approach was central to the aim, and the potential impact of socioeconomic differences in adulthood among the men was considered throughout.

The thesis was based on the 1969 conscription cohort, i.e. a cohort of almost 50 000 Swedish men who in 1969/70 went through a conscription examination for compulsory military service. They were between 18 and 20 years of age at that time. Information from physiological assessments, cognitive tests, and questionnaires were used in combination with (1) register-based indicators of social circumstances in childhood and adulthood, and information on educational level, and (2) register-based information on fatal and non-fatal events of CHD and stroke between 1971 and 2007. Multivariable regression methods were used to analyse data.

In study I and II, higher levels of BMI and blood pressure in late adolescence were shown to be significantly associated with increased risks of CHD and stroke before 55 years of age. Men with higher BMI were more likely to be in lower socioeconomic positions later in adulthood, but differences among the men in adult socioeconomic positions did not seem to affect, i.e. mediate or modify, associations between BMI/blood pressure in late adolescence and CHD/stroke in middle age.

BMI, smoking, and body height in late adolescence were shown, in study III, to contribute to explain associations between childhood socioeconomic position and CHD/stroke in middle age. Possibly, study III also showed that childhood social disadvantage may have an independent long-term effect on CHD and stroke in middle age. In study IV, it was shown that large parts of the associations between educational attainment and CHD/stroke in middle age may be explained by confounding from social and behaviour-related risk factors measured in childhood and late adolescence.

Thus, it was shown that factors in childhood and adolescence may be critical in relation to CHD and stroke in middle age among men. Increased risks of CHD and stroke could be an effect of disadvantages in childhood, acting through biological and/or behavioural development early in life. The findings may also be compatible with the view that social disadvantages and adverse behavioural responses from childhood and onwards increase risks of disease, such as CHD and stroke, in a cumulative manner over the life course. Moreover, the findings showed that such accumulation of cardiovascular risk may be most prevalent among men born to parents of lower socioeconomic positions and among men who attain lower educational levels; these are the same categories of men that tend to end up in lower socioeconomic positions in adulthood. In this way, social differences in cardiovascular disease among adult men could possibly be explained by confounding from factors earlier in life.

LIST OF PUBLICATIONS

I. Falkstedt, D, Hemmingsson, T, Rasmussen, F, & Lundberg, I (2007). Body mass index in late adolescence and its association with coronary heart disease and stroke in middle age among Swedish men. *International Journal of Obesity (Lond),* 31(5), 777-783.

II. Falkstedt, D, Koupil, I, & Hemmingsson, T (2008). Blood pressure in late adolescence and early incidence of coronary heart disease and stroke in the Swedish 1969 conscription cohort. *Journal of Hypertension,* 26(7), 1313-1320.

III. Falkstedt, D, Lundberg, I & Hemmingsson, T. Childhood socioeconomic position and risk of coronary heart disease and stroke in middle age: a life course study of 49321 male conscripts. Submitted.

IV. Falkstedt, D & Hemmingsson, T. Educational attainment and cardiovascular disease among middle-aged Swedish men: a study of potential confounding from factors in childhood and adolescence. Submitted.

CONTENTS

LIST OF ABBREVIATIONS

AMI	Acute myocardial infarction
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HR	Hazard ratio
ICD	International Classification of Diseases
SBP	Systolic blood pressure
SEP	Socioeconomic position

1 BACKGROUND

CARDIOVASCULAR DISEASE AND THE SOCIAL GRADIENT

Cardiovascular disease (CVD) is a major global health burden and gets relatively more important with increasing level of economic development (1). In Sweden, cardiovascular disease (including stroke) still is the most common cause of death among both men and women, although cardiovascular mortality has been decreasing continuously during the last decades (2). Tobacco smoking, high blood pressure, and high concentration of blood cholesterol are the major risk factors of CVD, relating to the development of atherosclerosis (3). Obesity, importantly determined by diet and physical inactivity, is associated with high levels of blood pressure and cholesterol (4).

The occurrence of CVD increases gradually in relation to descending socioeconomic position; persons in lower social classes have increased relative risks of CVD as compared to persons in higher social classes. Moreover, this social gradient in CVD is seen also if level of education or income is used to indicate socioeconomic position (5). Risk factors such as tobacco smoking, high blood pressure, and high concentration of blood cholesterol have been found to account for less than half of the relative differences in CVD between socioeconomic positions (6). A substantial relationship between socioeconomic position and CVD thus remains to be explained, as do the different prevalence of the major risk factors in different socioeconomic positions.

The implicit assumption of social status and rank in social class has lead to the idea that psychosocial stress may be important to explain social differences in CVD (6). It may do so through an effect on behaviours, such as smoking, unhealthy dietary choices, and physical inactivity, but it may as well have a direct effect in the aetiology of CVD. No unifying definition of the psychosocial stress mechanism related to socioeconomic position has been reached, however. Stressful work conditions that may vary between socioeconomic positions have been suggested as potentially important (6). But also differences in social status and general control over life, not restricted to work, have been used as a description of the psychosocial mechanism (7).

Explanations of individual and social differences in CVD have been dominated by a focus on risk factors in adult persons, be it biological, behavioural or psychosocial risk factors. This perspective was criticised by George Davey Smith and others (8) for being too occupied with isolated "proximal causes", missing a historical perspective on disease development. In effect, they said, epidemiological studies of chronic diseases such as CVD may have overestimated the importance of risk factors in adulthood and, more generally, may have promoted a de-contextualised perception of chronic diseases. Disappointing results on changes in coronary heart disease (CHD) associated with a focus on risk factors (health education, behaviour modification), contrasting with the dramatic impact of secular changes in social circumstances on declines in CHD in populations, also was said to emphasise the limitations of a de-contextualised approach to chronic diseases (8, 9).

THE LIFE COURSE APPROACH TO CHRONIC DISEASE

The life course approach to chronic disease, also called "life course epidemiology", has subsequently been established. Its aim has been to contribute with contextualisation in epidemiological studies, based on evidence that development of disease risks in populations has important links to historical and societal circumstances. It is argued that biological and social factors from early life and onwards work together to produce health and disease in populations (10, 11, 12). Within life course epidemiology, hypothetical models of relations between exposures over the lifespan and health outcomes are investigated. A useful typology of hypothetical models has been developed during recent years (13, 14). Three main models are shown in figure 1.
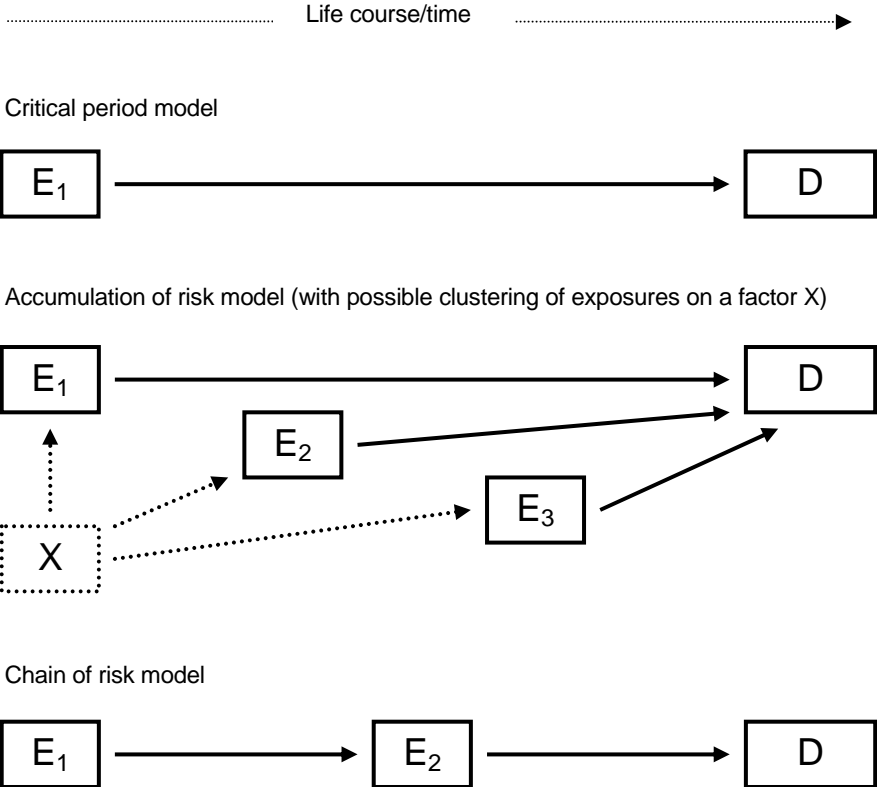
Figure 1. Life course epidemiological models of exposure (E) – disease (D) relationships.

A *critical period model* postulates that some period early in life may have a critical role in the determination of long-term health. Exposure to environmental factors such as malnutrition during a critical period may have consequences it otherwise would not have. Hypothetically, effects of exposure during a critical period on long-term health outcomes may be dependent on circumstances later in life. An *accumulation of risk model* proposes that long-term health risks are explained by accumulated exposures over the life course. Basically, the amount of negative events throughout life could be more important than the timing of such events. The accumulated exposures may be independent of each other or somehow clustered. Finally, a *chain of risk model*

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postulates that a series of events from early life and onwards affect the likeliness of persons to end up in a life situation that is the main explanation of disease development. In this model, early life events have a relation to risks of disease through their effect on future living conditions, but are not themselves causes of disease.

These three life course models may be combined and are to some extent overlapping. At the same time, they are to some extent competing explanatory models. The explanatory power of one hypothetical model over other models may also depend on what specific health outcome is being studied. Investigations of various proposed life course models of health risks require time related study designs, in which data are collected over the life course of individuals.

ORIGINS OF THE LIFE COURSE APPROACH IN EPIDEMIOLOGY

The life course approach to cardiovascular diseases was motivated by previous research that provided evidence of relationships between childhood disadvantage and increased occurrence of CVD. The Norwegian researcher Anders Forsdahl found in the 1970's that geographical areas in which men had higher incidence of CVD tended to have had increased levels of infant mortality when these men were born. In other words, he demonstrated an ecological association between infant mortality and risk of CVD in Norwegian men. Based on his findings he postulated that persons with experiences of poverty in childhood could be at increased risks of CVD when living in affluence as adults (15, 16). Due to these research findings, further investigations were carried out in the 1980's by the British researcher David Barker and his colleagues (17). Barker's findings confirmed the association between infant mortality and later incidence of CVD, and also showed associations between low birth weight and increased risk of CVD in individuals. Barker, like Forsdahl, made the interpretation that early life disadvantage followed by affluent conditions in adulthood could cause CVD. Unlike Forsdahl, however, Barker suggested that disadvantageous conditions may have their impact on future CVD risk during the gestational period rather than in childhood. Barker made the interpretation that environmental factors during the prenatal period could affect development of the fetus and in this way biologically "program" individual risk of future CVD (18). He also suggested that this may contribute to explain the social distribution of CVD among adults. Barker's hypothesis was presented as an alternative to the dominating view in which behaviours were assumed to explain large parts of CVD rates among adults (19, 20).

SOCIAL CIRCUMSTANCES OVER THE LIFE COURSE AND CARDIOVASCULAR DISEASE

A number of studies have subsequently demonstrated that childhood social disadvantage is associated with increased risks of CVD later in life (21, 22). However, childhood social disadvantage also increases the risk of subsequent accumulation of negative factors among individuals, which complicates causal inference (23). Childhood social disadvantage may be causally related to CVD among adults, in

accordance with Forsdahl's and Barker's suggestions, but may as well have an association with CVD explained by exposure to disadvantage during adulthood.

Research on relationships between social disadvantage in childhood and adolescence and risks of disease and mortality in adults has been limited. Appropriate materials have been scarce, although they are now growing in number. This research is even more limited for populations born in the post World War II era, characterised by increased economic growth and lower levels of poverty in industrialised nations. Nevertheless, various types of studies have been used in attempts to investigate relationships.

First, socioeconomic circumstances in childhood have been investigated in relation to prevalence of risk factors of CVD in a number of studies. Cross-sectional studies have shown that low SEP in childhood may be associated with, for instance, short stature and smoking (24, 25). Further, some studies have been based on the British birth cohorts of 1946 and 1958, i.e. study populations specifically aimed for longitudinal studies of childhood conditions and their long-term consequences. These studies have shown that persons born into low SEP families may have significantly increased risks of exposure to potentially negative circumstances during youth and young adulthood (26, 27). Moreover, they have provided evidence that overweight and obesity are more prevalent in men whose fathers were manual workers (26, 27, 28), and that other risk factors, for instance high cholesterol concentration, also are associated with childhood circumstances (29, 30).

Second, associations between childhood social circumstances and disease/mortality outcomes have been examined, although yet with limited numbers of cases. In the British birth cohort of 1946, which is relatively small, total and cause-specific mortality between ages 25 and 50 have been demonstrated to be inversely associated with childhood SEP independently of subjects' adulthood SEP (31). The association between childhood SEP and mortality appeared to be particularly strong for cardiovascular mortality. Further, several studies have used retrospectively collected information on childhood conditions and investigated this in relation to follow-ups on disease and mortality among adult persons. Among these studies, some have found childhood SEP to be associated with increased risks of CVD and total mortality while other studies have not found such associations (22). However, studies based on recall of childhood conditions may be less reliable, since associations with disease and mortality are more likely to be underestimated.

In register-based studies, using information from censuses to study potential relationships between SEP, in childhood as well as in adulthood, and mortality, the weakness of retrospectively gathered information could be avoided (32, 33). Claussen et al (32) demonstrated with such data that CVD mortality may have a stronger association with SEP in childhood than in adulthood whereas violent causes of death may have a relatively stronger association with SEP in adulthood. This finding was interpreted as to support cause-specificity in relations between social disadvantage over the life course and disease later in life, as opposed to the hypothesis of "general susceptibility" (34). From the latter proposition would be expected similar associations between SEP and different causes of death.

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HEALTH-RELATED SELECTION TO SOCIOECONOMIC POSITIONS

Vågerö and Leon had previously showed an association between childhood SEP and future mortality, independent of adulthood SEP, in register-based data (33). With regard to interpretations, however, these authors pointed to the limited possibility to disentangle effects of social circumstances in childhood and adulthood, respectively, in such data. Persons who change socioeconomic positions between childhood and adulthood may have experienced circumstances during childhood and adolescence that differed from those of socioeconomically stable persons. Therefore, SEP in adulthood may be a reflection of experiences from early life and onwards, and, consequently, findings of associations between SEP in adulthood and disease outcomes may have been confounded by the variation in such experiences, not captured by a measure of SEP in childhood. Health-related selection to socioeconomic positions may thus be present, in the sense that there could be factors in early life that are associated both with achievement of SEP and with later-life health.

Whether distributions of risk factors of CVD that appear in adult populations are determined mainly by concurrent circumstances or circumstances earlier in life is also uncertain (35). Smoking, lack of physical activity, and overweight have in several studies been shown to be relatively more common in lower socioeconomic strata, and differences in lifestyle may have been the usual explanation of the social gradient in CVD (36). As said previously, however, such an explanation referring to lifestyles has been criticised of being too narrow, neglecting reasons for lifestyle differences (29). The higher prevalence of unhealthy behaviours among persons with lower SEP may be interpreted as an adverse response to material disadvantage (37). Moreover, several studies have shown that unhealthy behaviours and lifestyles, which tend to be established relatively early in life, predict lower future SEP (25, 38, 39).

The effect of health-related selection to explanations of socioeconomic differences in CVD later in life has not been investigated much. The interpretation of the present evidence may be that the contribution of health-related selection to socioeconomic differences in health is likely to be small (40). However, Patrick West argued early that the issue of health-related selection was dismissed too easily by researchers on social differences in health, which may have resulted in neglect of discriminatory societal patterns (41). A previous study of the 1969 conscription cohort, which is the cohort used in the present thesis, showed that intergenerational social mobility associated with risk factors may increase the difference in mortality between manual workers and non-manual workers in early middle age (42). Risk factors of premature death, already established in late adolescence, were found to be much more prevalent among men who became manual workers, independently of their socioeconomic origin.

EDUCATION, OCCUPATION, AND CARDIOVASCULAR DISEASE

In a study by Davey-Smith et al (43) it was found that educational level had a stronger association with mortality due to CVD than had occupation-based social class, whereas the latter had a stronger association with other causes of death than CVD. The

interpretation was made that education may function as "an index of socioeconomic circumstances in early life", which in previous research had appeared to be of particular importance for CVD. Already in 1968, Hinkle et al (44) reported results of a 5-year prospective survey of the association between occupation/education and coronary heart disease, carried out among 270 000 men employed by the Bell System throughout the US. Findings contradicted a common belief at that time, which said that heart attacks were more frequent among men holding higher occupational (class) positions than among men holding lower positions. Instead, an inverse relationship between occupational position and CHD was found. However, findings also indicated a possible importance of selection. Men who entered the organisation with a college education were shown to have a lower incidence and death rate from CHD, as compared to men without a college education, independently of their position within the organisation. The college educated men also were found to report more favourable circumstances during their upbringing and, based on this, the authors speculated that differences in risk of CHD associated with level of education and occupational position may possibly be linked to these early life differences.

RATIONALE FOR THE STUDIES (I-IV)

Thus, behaviour-related factors such as smoking, unhealthy diet, and physical inactivity, as well indicators of lower socioeconomic position, have been shown among adults to be important predictors of subsequent risk of CVD. On the other hand, unhealthy behaviours are generally adopted before adulthood and may be reflections of social disadvantage in childhood. Risk factors of CVD such as overweight and elevated blood pressure could be established early, although their health consequences are manifest only later in life, and since these risk factors are possibly related to past social disadvantage, they may also be affected by continued social disadvantage. In the present thesis, therefore, risk factors established early (BMI and blood pressure measured at 18-20 years of age) and childhood social circumstances were studied in relation to CHD and stroke followed in middle age. They were also used, along with other early-measured factors, for a study of the association between educational attainment and risk of CHD and stroke in middle age.

BMI in late adolescence and CHD/stroke in middle age (I)

High body mass index (BMI) in adolescence has been found to be strongly related to future coronary heart disease (45), while associations have appeared to be weaker or non-existent with BMI measured either in early childhood or in middle age (46, 47, 48, 49, 50). The significance of BMI in adolescence in relation to cardiovascular disease has been indicated also in autopsies of adolescents and young adults, where a relationship between obesity and coronary atherosclerosis has been found (51, 52). The previous studies of the association between adolescent overweight and obesity and future CVD are nevertheless few.

Socioeconomic conditions in childhood as well as adulthood may be confounders of the relationship between overweight in adolescence and CVD in middle age. Social class in childhood has been shown to predict overweight (28, 53) as well as future

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cardiovascular disease (54). Further, subjects with an early-established overweight seem to obtain less advantageous social positions in adulthood (55, 56, 57) and show an increased risk of future disability pension (58, 59). Disadvantaged socioeconomic positions in adult life may in turn affect the risk of CVD negatively, e.g. through an uneven distribution of psychosocial risk factors at work and their negative effect on health related behaviours (60).

Blood pressure in late adolescence and CHD/stroke before age 55 (II)

High blood pressure affects a considerable part of the middle-aged and older populations of high income countries (61, 62) and is well recognised as a major risk factor in adults for cardiovascular disease (63). However, individual differences in BP appear already in childhood and adolescence, and track into middle and old age (64, 65). Two previous studies have shown that increased blood pressure measured at about 20 years of age predicts cardiovascular mortality in middle age and onwards (66, 67, 68). In the 1960s, Paffenbarger et al reported that elevated systolic blood pressure (SBP) and diastolic blood pressure (DBP) in 19 year old male students, who entered the Harvard and Pennsylvania universities between 1916 and 1950, both were associated with increased risk of coronary heart disease (CHD) and stroke during a follow-up over 10-50 years (67, 68). More recently, associations between blood pressure in similarly aged male students at Glasgow University during the years 1948-1968 and subsequent cardiovascular mortality were reported, with some differences in how SBP and DBP affected specific CVD outcomes (66).

Other cardiovascular risk factors such as cholesterol levels (69), smoking (70), and body mass index measured in adolescence or early adulthood have also been found to predict long-term risk of CVD (45, 47, 71). It is possible that BP and other risk factors measured early are interdependent and also related to CVD via the same causal mechanisms, e.g. atherosclerosis (72). Moreover, clustering of cardiovascular risk factors already in adolescence has been found, particularly in subjects with low socioeconomic backgrounds and low cognitive ability (73). Some young subjects may have a poorer capacity both to prevent and later to manage cardiovascular risk factors, such as high BP, and disease (74). An association also between low socioeconomic position in adulthood and higher BP has been shown (75). Hypothetically, stressful circumstances related to socioeconomic position might affect BP and risk of CVD (76, 77, 78).

Childhood socioeconomic position and CHD/stroke in middle age (III)

Cardiovascular disease is a major contributor to the inverse relationship between socioeconomic circumstances in childhood and mortality risk (54, 79). Robust inverse associations have been found in most studies on socioeconomic circumstances in childhood and their relation to CVD (80). Kuh and co-authors (81) proposed some major hypotheses, which may help to explain associations between childhood socioeconomic circumstances and CVD later in life: (A) Childhood socioeconomic environment may affect biological development from gestation to adolescence, which determines health and resilience to environmental insults in adulthood; (B) Childhood

socioeconomic environment may shape enduring behaviours associated with disease risks in adulthood. (C) Childhood socioeconomic position (SEP) influences socioeconomic circumstances in adulthood (via educational and occupational opportunities) and, through this, negative exposures and disease risks. These hypothetical pathways are clearly not mutually excluding explanations.

Previous studies of associations between childhood socioeconomic circumstances and CVD outcomes have not provided conclusive empirical evidence against any of the hypotheses above. In several studies, socioeconomic status and cardiovascular risk factors in adulthood have contributed to explain associations between socioeconomic circumstances in childhood and CVD (21, 22, 82). Childhood SEP has also been shown to predict risk factor prevalence in adolescence and early adulthood, thus indicating the importance of pre-adulthood in explaining the relationship (24, 73, 83). Furthermore, significant associations between childhood social circumstances and CVD have remained after multivariable adjustment, particularly when stroke has been studied (21, 22). Early life conditions, behaviours through life, and social circumstances in adulthood (A, B and C) all are explanations of the association between childhood social circumstances and disease/mortality to some extent compatible with the empirical findings.

Many studies of the relationship between socioeconomic circumstances in childhood and later CVD have been register-based, with advantages of large size, prospectively gathered information, and minimised SEP misclassification (84, 85, 86). However, registerbased studies have often lacked information on potentially important behaviour-related factors such as smoking, overweight, and high blood pressure. The few previous studies on Swedish data containing analyses of associations between childhood SEP and CVD have not included information on cardiovascular risk factors (42, 79, 87).

Educational attainment and CHD/stroke in middle age (IV)

Lower incidence of cardiovascular disease (CVD) in higher educated persons has by now been demonstrated across the industrialised world (5, 88, 89, 90, 91). Appropriate strategies for reducing differences in CVD between educational groups depend on knowledge of how these differences arise (92, 93, 94). There are several possible mechanisms that could contribute to explain the association between educational attainment and CVD. Three main hypotheses may be proposed, based on previous literature and research. First, associations between educational attainment and long-term health outcomes, such as CVD, could be confounded by various factors from childhood and adolescence, e.g. socioeconomic circumstances, family environment, cognitive ability, behaviour-related risk factors, and health (38, 39, 95, 96, 97). Second, associations between educational attainment and CVD could be mediated by socioeconomic circumstances in adulthood. Material and/or psychosocial factors, linked to occupations with different qualifications, may hypothetically contribute to differences in risk of CVD between educational groups (95, 98, 99, 100). Third, a higher education has been suggested to benefit sense of control and development of healthier behaviours in adulthood (95).

Studies on education and health-related factors/behaviours examined in adolescence or early adulthood suggest that there may be considerable confounding in the relationship between educational attainment and CVD (38, 39, 96). Previous studies of associations between education and CVD during follow-up have found that multivariable adjustment for cardiovascular risk factors, social class, and psychosocial work characteristics attenuate associations to varying degrees (98, 99, 100, 101, 102, 103, 104, 105). However, explanatory factors in the latter studies have been measured in adulthood only, and, consequently, meditation and confounding have not been separated.

2 AIMS OF THE THESIS

The general aim of the thesis was to investigate how socioeconomic and behaviour-related factors measured in childhood, late adolescence, or adulthood are related to coronary heart disease and stroke in middle age among Swedish men. The life course approach was central to the aim, and the potential impact of socioeconomic differences in adulthood among the men was considered throughout.

The following specific questions were addressed:

Is BMI in late adolescence related to CHD and stroke in middle-age among Swedish men? If so, is the association confounded by social disadvantage in childhood and/or risk factors measured in late adolescence? Is the relationship mediated by socioeconomic position in adulthood?

Is blood pressure measured in late adolescence related to CHD and stroke before 55 years of age in Swedish men? Can effect modification or confounding by socioeconomic positions in childhood and adulthood, and/or behaviour-related factors measured in late adolescence be demonstrated for associations between BP and these CVD outcomes?

Is childhood socioeconomic position related to CHD and stroke in middle age among Swedish men? If so, how may social circumstances in childhood, behaviour-related risk factors measured in late adolescence, and socioeconomic circumstances in adulthood contribute to explain the relationship?

Is educational attainment associated with coronary heart disease and stroke, respectively, in middle-aged Swedish men? If so: Are associations confounded by indicators of socioeconomic circumstances in childhood and behaviour-related risk factors measured in late adolescence? Are associations mediated by indicators of socioeconomic circumstances and job control measured at about 40 years of age?

3 MATERIAL AND METHOD

THE CONSCRIPTION EXAMINATION IN 1969/70

All four studies within the thesis were based on "the 1969 conscription cohort". The cohort are based on data from a nationwide survey of young Swedish men who were enlisted for compulsory military service in 1969/70 (fall/spring). Only 2–3 percent of all Swedish men were exempted from conscription during that period, in most cases due to severe handicaps or congenital disorders. The 49 321 men included in the cohort were all born in 1949-1951 and accounted for 97.7% of all conscripts in 1969/70. The remaining 2.3 percent were born before 1949.

At any of seven regional conscription centres in Sweden the young men went through an extensive health examination. A number of physiological factors were measured, such as height, weight, and blood pressure used in the present thesis. All conscripts were seen by a physician who diagnosed any disorders according to the Swedish version of ICD, 8th revision (ICD-8). Conscripts reporting or presenting psychiatric symptoms, according to the physician, were seen by a psychiatrist and any diagnoses were also recorded according to ICD8.

The young men were seen by a psychologist for a structured interview. Assessment of cognitive ability (intelligence) was performed using psychometric tests (see description below). Assessment of emotional control and a few other predetermined scales were also performed. The psychologists' ratings were regularly checked for inter-rater reliability.

During the conscription the young men were asked to complete two questionnaires. The first contained 67 questions of a general nature, concerning social background, behaviour and adjustment, psychological factors, health etc. The second contained 37 questions that dealt specifically with substance use, e.g. tobacco smoking.

A number of variables based on the conscription data were used for analyses within study I-IV. These variables were chosen since they were known from the previous literature to be potential risk factors/predictors of CVD in middle-aged men, and also to be potential explanatory factors in relationships between indicators of social position (SEP, education) and CVD.

Measurements of body height and weight of each conscript were used to calculate body mass index (BMI), an indicator of body fatness (106). BMI was calculated using body weight (kg) divided by height (m) squared. A variable with six categories was constructed: 1) BMI < 18.50, 2) BMI 18.50-20.99 (reference), 3) BMI 21-22.99, 4) BMI 23-24.99, 5) BMI 25-29.99, and 6) ≥ BMI 30. This categorisation is in agreement with established definitions of underweight (<18.50), normal weight (18.50-24.99), overweight (25-29.99), and obesity (≥ 30) (107); the normal weight category was divided into three categories to refine analyses in study I.

BP measurements were made on the first day of the conscription examination, after 5-10 minutes of rest. Only one measurement was made, unless SBP exceeded 145 mm Hg or DBP was outside the interval of 50-85 mm Hg. In that case a second measurement was made on the day after and the resulting value registered. Practices of rounding in registered blood pressures have been reported for later conscription examinations (108) and were seen also in the present material. Both SBP and DBP seem to have been rounded to the nearest 5 or 10 mm Hg, throughout the range of blood pressures. Indications of some variation between conscription centres with regard to BP recording also have been reported for more recent conscription examinations (108). However, adjustments for conscription centre (in study II) did not significantly affect the estimates in the study and were not included in the tables.

In study II, systolic and diastolic blood pressure were analysed as either continuous or categorical variables. Associations between continuous BP variables and the disease outcomes were reported per standard deviation (SD) mm Hg of SBP and DBP. Mean arterial pressure (MAP) and pulse pressure (PP) were also analysed in study II (results are shown in the journal article). Both measures are calculated on the basis of SBP and DBP: PP=SBP-DBP and MAP=1/3*SBP+2/3*DBP. For study II, we analysed SBP and DBP as divided into four categories to assess the shape of associations. The levels of SBP (mm Hg) were the following: <115, 115 to <125, 125 to <135, and ≥135. Levels of DBP (mm Hg) were: <65, 65 to <75, 75 to <85, and ≥85.

Variations in body height was utilised as an indicator of early life conditions, in accordance with previous suggestions (109). Body height was measured at the conscription examination.

Information on cognitive ability/intelligence from conscription was included in analyses within study II and IV. (This variable has previously been studied in relation to health behaviours and outcomes (110, 111, 112).) The intelligence tests performed at conscription included tests of logic/general intelligence, verbal tests of synonym detection, and further tests of visuospatial/geometric perception, and technical/mechanical skills on the basis of mathematics/physics problems. The outcome of each test was ranked 1 to 9. The standard-nine values were transformed into a composite standard-nine scale to measure general ability, corresponding to approximate IQ bands of <74, 74 to 81, 82 to 89, 90 to 95, 96 to 104, 105 to 110, 111 to 118, 119 to 126, >126.

Smoking was reported at conscription in the questionnaire that dealt specifically with substance use, including tobacco. There was only one question on cigarette smoking ("How many cigarettes do you smoke per day?") and the men were asked to report their smoking at one of five levels: non-smoker, 1–5 cigarettes per day, 6–10 cigarettes per day, 11–20 cigarettes per day, >20 cigarettes per day.

REGISTER-BASED INFORMATION

The potential impact of differences between the men as adults in their positions within the social structure was assessed in all four studies. In the research on social

inequalities in health, several indicators of social position have been used; occupational class, educational level, and level of income may be the most common indicators. Whether they could be treated as interchangeable or not in health research has been a matter of discussion (113, 114). For instance, education may be more closely related to social status/rank than income is in West European countries, because higher education has a stronger association with cultural participation (115) than income has. Occupation-based class position is in theory suggested to be a fundamental factor behind the distribution of power/control among individuals (115), and is strongly related to both education and income. In the present thesis, the occupation based indicator "socioeconomic position" (SEP) was used in all studies, while educational attainment was used in addition to SEP in study III and income was used in addition to SEP in study IV[*].

Information on adulthood socioeconomic position for each conscript was obtained by record linkage with the National Population and Housing Census of 1990 held by Statistics Sweden. This census had a response rate of over 98%. The classification into the following eight socioeconomic groups in 1990 was conducted at Statistics Sweden and is based on information on occupation and the educational level required for the occupations:

- Unskilled workers (occupations normally requiring less than two years of post-compulsory school education)
- Skilled workers (occupations normally requiring two years or more of post-compulsory school education)
- Assistant non-manual employees (occupations normally requiring two, but not three, years of post-compulsory school education)
- Intermediate level non-manual employees (occupations normally requiring three, but not six, years of post-compulsory school education)
- Higher level non-manual employees (occupations normally requiring at least six years of post-compulsory school education)

- Farmers
- Self-employed
- Those for whom no occupation was reported (e.g. unemployed, early retired, or disabled)

Information on educational attainment was used in study III and IV. Conscription data were linked to the Longitudinal Database of Education, Income and Occupation (LOUISE) of 1990-2002 held by Statistics Sweden, in order to receive educational information for each member of the study population. Educational attainment is derived from information on education in a number of registers and coded according to Swedish standards ("Svensk utbildningsnomenklatur"). There are imperfections in the reporting of completed educations to registers, mostly at lower levels of education, that produces some underestimation of educational attainment (116). In study IV,

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[*] Among the men who were either manual workers or non-manual employees in 1990, educational level and income level in 1990 had a weaker correlation (0.39; p<0.0001) than had educational level and occupation-based SEP in 1990 (0.63; p<0.0001) and occupation-based SEP in 1990 and income in 1990 (0.52; p<0.0001).

educational attainment was divided into four categories in the analyses: ≤9 years of education, 10-11 years, 12 years, and ≥13 years. Largely, this categorisation corresponds to Swedish compulsory education (7-16 years of age), vocational secondary education, pre-academic secondary education, and university education.

Income in adulthood was used in analyses in study IV. Also for income information, the conscription data were linked to the Longitudinal Database of Education, Income and Occupation (LOUISE) of 1990-2002 held by Statistics Sweden. The register includes information on gross annual income based on any taxable income, also including, for instance, sickness allowances and disability pensions. Income was analysed as divided into income quartiles in study IV.

"Job control" was included in study IV as a potential explanatory factor in the relationship between educational attainment and CHD/stroke (although excluded from the final analyses reported in tables). Information on job control was obtained indirectly by means of a job exposure matrix, which has been created to rate all occupations on a 10-digit scale for control over work, demand of job tasks, and social support in jobs and is based on the Swedish Work Environment Surveys 1989-1997 (117). This job exposure matrix has been used in a previous study of the 1969 conscription cohort (118). The use of a job exposure matrix to measure individual variation in job control has been shown to be valid (119). In study IV, the men were classified as having high, middle-high, middle-low, or low job control.

In study III, parental SEP was used as the focal indicator of socioeconomic circumstances in childhood. In study I, II and IV it was analysed as a potential confounding factor. Information on parental SEP was obtained from the National Population and Housing Census of 1960 (response rate 99%), i.e. when the subjects were 9–11 years old. At Statistics Sweden, the men were linked to their biological parents (or any other head of the household) through their personal identification numbers. A "dominance approach" was applied when assigning the men to a childhood SEP, i.e. occupations held by fathers (when present) were used to define SEP of households. The use of this approach in epidemiological studies has been shown to be valid (120). More than 80 percent of the men lived as children in a household headed by their biological fathers. A classification into six socioeconomic groups was used, based on information on the occupation of the head of the household:

- Unskilled workers
- Skilled workers
- Assistant non-manual employees
- Non-manual employees at intermediate or higher level
- Farmers
- Those that could not be classified into a socioeconomic position

Self-employed people were not possible to identify in the 1960 census and instead classified according to occupation. For 2.2% of the men information on childhood socioeconomic position was missing.

From the National Population and Housing Census of 1960 we also received information from parents on crowded housing in childhood. In the census, > 2 people/room - kitchen not included - was classified as crowded. Crowded housing has been used in previous research (54, 121) and was assumed to indicate material conditions that may vary within socioeconomic positions (122, 123).

Early death in a parent was used in study III as an indicator of adverse circumstances in childhood, in accordance with previous studies (Marmot, Shipley, Brunner, & Hemingway, 2001). Information on early death, i.e. all-cause mortality before 65 years of age, was obtained from the National Cause of Death Register (administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden).

Early death in CVD in a parent (or both) was used as a control variable in study I. Information on this variable was also obtained from the National Cause of Death Register. Parents were followed with regard to CVD mortality before age 65 between 1961 and 2002 (International Classification of Diseases [ICD code], 7th Revision [ICD-7: 400-468], 8th Revision [ICD-8: 390-458], 9th Revision [ICD-9: 390-459] and 10th Revision [ICD-10: I00–I99]).

INFORMATION ON OUTCOMES

Coronary heart disease and stroke were outcomes analysed in all four studies within the thesis. Occurrence of fatal and non-fatal cases were followed among the men between 1991 and 2004 in study I, between 1971 and 2004 in study II, and between 1991 and 2007 in study III and IV.

In study II, acute myocardial infarction, ischemic stroke, and hemorrhagic stroke were analysed as subcategories of CHD and stroke. Additionally, a follow-up on all-cause mortality between 1971 and 2003 was included in that study.

Information on coronary heart disease (CHD), acute myocardial infarction (AMI), all stroke, ischemic stroke, and hemorrhagic stroke was obtained by record linkage with the National Hospital Discharge Register (HDR), administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden. From 1987 HDR covers all public in-patient care in Sweden. For earlier years it does not cover the whole country, but in 1984 reporting to HDR was decided compulsory and most country councils reported all in-patient care at that time. Only a few cases of CHD and stroke could be missed due to this in the follow-up from 1971 (study II), since the incidence prior to age 35 (=1985) was low. Personal records were also linked to the National Cause of Death Register 1971–2006 for information on fatal CHD and stroke (and all-cause mortality in study II).

Codes according to International Classification of Diseases (ICD code) were as follows: 8th Revision (ICD-8): CHD: 410-414; AMI: 410; all strokes: 430-438; ischemic stroke: 433-434; hemorrhagic stroke: 431; 9th Revision (ICD-9): CHD: 410–414; AMI: 410; all strokes: 430-438; ischemic stroke: 434; hemorrhagic stroke: 431-432; and 10th

Revision (ICD-10): CHD: I20-I25; AMI: I21; all strokes: I60-I69; ischemic stroke: I63; hemorrhagic stroke: I61-I62.

STATISTICAL ANALYSES

In all four studies, an "exposure" variable was examined in relation to a number of potential confounding or mediating factors. Prevalence of CVD predictors, measured in childhood, late adolescence or adulthood, were calculated for categories of body mass index, blood pressure, childhood socioeconomic position, and educational attainment. Test for trends over categories was conducted according the Cochran-Armitage trendtest using the FREQ-procedure in the SAS computer package. For continuous variables, e.g. systolic and diastolic blood pressure, the corresponding measure was obtained by using the REG-procedure (linear regression).

Possible associations between "exposure" variables and CHD and stroke, respectively, during follow-up periods, were analysed using the PHREG/TPHREG procedures (Cox proportional-hazards regression) in the SAS computer package 9.1 (SAS Institute, Cary, North Carolina, USA). Cox proportional-hazards regression makes it possible to account for person-years at risk that vary between subjects. Hazard ratios during follow-up should be proportional between exposure categories, for instance between men with different levels of blood pressure, and assumptions of proportional hazards were checked with the LIFETEST procedure (Kaplan-Meier survival curves).

Hazard ratios (with 95% confidence intervals) in crude and adjusted models of associations between exposures and outcomes (CHD, AMI, total stroke, hemorrhagic stroke, ischemic stroke, all-cause mortality) were estimated. In study III and IV, percentage reductions of associations (hazard ratios) in adjusted models were calculated as $100\% * (HRcrude-HRadj.)/(1-HRcrude)$ based on the hazard ratios of CHD and stroke, respectively, in different categories of childhood socioeconomic position or educational attainment.

In study IV, the job control variable was excluded from the final analyses, since 4593 men (and >13% cases of CHD and stroke) would be lost due to missing information (no occupation in 1990).

Men who emigrated at about 35 years of age or after were censored on the day of first emigration regardless of any remigration during follow-up, however. In study II, where CHD, AMI, total stroke, hemorrhagic stroke, ischemic stroke, all-cause mortality were followed between ages 20 to 55, men who both emigrated and returned before 35 years of age were included. Most of these early emigrations were brief and the occurrence of CHD and stroke prior to age 35 was very low (~20 cases).

4 RESULTS

BMI in late adolescence and CHD/stroke in middle age

In study I, the following questions were addressed: *Is BMI in late adolescence related to CHD and stroke in middle-age among Swedish men? If so, is the association confounded by social disadvantage in childhood and/or risk factors measured in late adolescence? Is the relationship mediated by socioeconomic position in adulthood?*

Higher BMI in late adolescence was found to be associated with a higher likeliness of having a father who was manual worker and having experienced crowded housing in childhood. Higher BMI was also associated with an increased likeliness of becoming a manual worker.

It was found that BMI measured in late adolescence was associated with both CHD and stroke during the follow-up period, between age 40 and 55. The relative risk of CHD increased significantly for each BMI category above the reference category (BMI=18.50-20.99). The increased relative risk of stroke was somewhat smaller and increased significantly from BMI=23.00 and above. This BMI gradient in relation to CDH and stroke from 40 to 55 years of age was still present in the multivariable models, although adjustment for cardiovascular risk factors (smoking, systolic and diastolic blood pressure at ages 18–20 years, and parents' death by CVD before age 65 years) somewhat attenuated the associations. Adjustments for socioeconomic position and crowded housing in childhood or socioeconomic position in adulthood did not attenuate the associations significantly. In men who had a BMI≥30 in late adolescence, the adjustment relative risk of CHD before 55 years of age was 3.1 (CI=2.2-4.4) and the relative risk of stroke was 2.0 (1.1-3.8).

Since men with higher BMI in adolescence were found to be more likely to become manual workers in adulthood, it was of interest to see whether BMI measured at 18-20 years of age contributed to explain the association between SEP at ~40 years of age and subsequent risk of CHD and stroke (results not shown in the journal article). Multivariable adjustment for BMI measured in late adolescence attenuated the increased relative risks of CHD in lower SEP strata with ~13% and the increased relative risks of stroke in lower SEP strata with ~7%. The contributing (albeit limited) role of higher BMI in adolescence for adult socioeconomic differences in CVD was indicated also in study IV, focusing on educational differences and CVD (see below).

Blood pressure in late adolescence and CHD/stroke before age 55

In study II, the following questions were addressed: *Is blood pressure measured in late adolescence related to CHD and stroke before 55 years of age in Swedish men? Can effect modification or confounding by socioeconomic positions in childhood and adulthood, and/or behaviour-related factors measured in late adolescence be demonstrated for associations between BP and these CVD outcomes?*

On average, men with higher blood pressure levels (systolic and diastolic) in late adolescence were characterised by lower childhood SEP, lower cognitive ability in late adolescence, and (as expected) higher BMI in late adolescence. However, higher blood pressure levels in late adolescence were associated with a lower likeliness of smoking at the same age among the men.

Associations between measures of BP[*] collected at the conscription examination, and incidence of fatal and non-fatal cases of CHD, AMI, all stroke, hemorrhagic stroke, and ischemic stroke between 1971 and 2004 were analysed, along with all-cause mortality during the same period.

Blood pressure measured in late adolescence was found to predict subsequent cardiovascular disease outcomes followed until 55 years of age in the men. Associations with specific cardiovascular disease outcomes differed between measures of blood pressure. Systolic blood pressure (SBP) was found to be significantly associated with CHD and AMI, but associated with neither of total stroke, ischemic stroke, or hemorrhagic stroke. Diastolic blood pressure (DBP) was associated with all the above outcomes except ischemic stroke. Stratifications by smoking, BMI or cognitive ability at 18–20 years of age did not indicate effect modification (not shown in the journal article). However, adjustment for these factors and childhood SEP attenuated associations between BP measures and the outcomes. In detailed analyses (not shown in the journal article), it was found that the attenuation was mainly attributable to confounding from BMI and cognitive ability whereas smoking appeared to be a 'negative confounder' with considerable strengthening effects on the associations when adjusted for (blood pressure and smoking in late adolescence were inversely associated). Adjustment for adulthood SEP in the multivariate analyses did not affect the associations. When mutual adjustment of SBP and DBP also was performed, the associations between SBP and CHD/AMI, and the associations between DBP and all stroke/hemorrhagic stroke became even more apparent.

All-cause mortality was significantly elevated only among men with SBP 125-135 mm Hg, and after exclusion of CHD and stroke mortality no significant association between BP and all-cause mortality until age 55 was seen.

Childhood socioeconomic position and CHD/stroke in middle age

In study III, the following questions were addressed: *Is childhood socioeconomic position related to CHD and stroke in middle age among Swedish men? If so, how may social circumstances in childhood, behaviour-related risk factors measured in late adolescence, and socioeconomic circumstances in adulthood contribute to explain the relationship?*

Men originating from lower SEP, as compared to men originating from higher SEP, were much more likely to have experienced crowded housing in childhood and were on average shorter in late adolescence. Pre-mature death of a parent was also

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[*] The journal article includes results from analyses of systolic and diastolic blood pressure (SBP/DBP), as well as mean arterial pressure and pulse pressure calculated on the basis of SBP and DBP.

more likely in men originating from lower SEP. Smoking increased in prevalence with lower socioeconomic origin, as did average BMI, but average blood pressure was evenly distributed in relation to socioeconomic origin. Low education and manual work in adulthood were much more likely in men originating from lower SEP, as expected.

Crowded housing in childhood and smoking in late adolescence were particularly frequent among men whose fathers (by which is meant head of households) could not be classified into a SEP. These men also had probabilities of becoming low educated and manual workers (as measured in 1990) similar to the probabilities among men whose fathers were unskilled manual workers. The smoking rate in late adolescence was lowest among men whose fathers were farmers, thus even lower than that among men from high SEP backgrounds, but the probabilities of becoming low educated and manual workers were comparable to those among men whose fathers were manual workers. Details are shown in table 1.

Table 1. Description of potential confounders and mediators measured over the life-course in Swedish men born in 1949-1951, in relation to parental socioeconomic position in 1960: non-manual employees at high or intermediate level (NMH, NMI); non-manual employees at low level (NML); skilled workers (SW); unskilled workers (USW); farmers; or unclassified.

Childhood SEP	NMH, NMI	NML	SW	USW	Farmers	Uncl.	All
N	9949	4658	9828	15107	5088	875	45505
Crowded housing in childhood (%)	7.46	11.23	25.05	29.45	17.79	35.20	20.63
Height at age 18 (mean)	179.27	178.95	177.81	177.60	178.08	177.58	178.20
Death in a parent <65 years (%)	14.54	16.79	17.78	17.66	11.69	15.66	16.21
Smoking at age 18 (%)	54.99	57.49	60.21	61.88	44.98	67.66	58.23
BMI at age 18 (mean)	20.66	20.82	21.06	21.10	21.15	20.68	20.96
DBP[a] at age 18 (mean)	72.86	72.97	72.90	72.96	72.49	73.30	72.88
Education ≤ 9 years (%)	11.65	16.66	27.59	33.97	36.26	32.23	26.16
Manual worker at age 40 (%)	19.54	23.38	42.93	47.16	39.13	47.43	36.88

[a] DBP: diastolic blood pressure

The relative risks of CHD and stroke between 40 and 58 years of age were significantly increased in men originating from manual worker positions. Men whose fathers were farmers had a comparatively low, borderline significant, relative risk of CHD. Adjustment for other indicators of childhood conditions (crowded housing, height, early death in a parent) attenuated relative risks of CHD with 20-40 percent, but they had almost no attenuating effect on the relative risks of stroke. Adjustment for smoking and BMI measured in late adolescence, but not BP, attenuated relative risks. However,

adjustment for smoking increased the relative risk of CHD among men whose fathers were farmers. The increased relative risks of CHD diminished with 40-60 percent in most categories when adjusted for all risk factors measured in childhood and adolescence, but the relative risks of stroke diminished less. Single adjustment for educational attainment attenuated relative risks with approximately 50 percent, while adjustment for SEP in adulthood had a smaller attenuating effect. The attenuating effect from educational attainment and SEP was, however, small or even marginal when these variables were introduced in models in addition to early measured risk factors. Significant increased relative risks of CHD and stroke remained after full adjustment among men whose fathers were unskilled manual. The association between childhood SEP and stroke was somewhat less affected by adjustments as compared to the association with CHD.

Educational attainment and CHD/stroke in middle age

In study IV, the following questions were addressed: *Is educational attainment associated with coronary heart disease and stroke, respectively, in middle-aged Swedish men? If so: Are associations confounded by indicators of socioeconomic circumstances in childhood and behaviour-related risk factors measured in late adolescence? Are associations mediated by indicators of socioeconomic circumstances and job control measured at about 40 years of age?*

Low SEP and crowded housing in childhood, and short stature, i.e. indicators of childhood social disadvantage, were twice as prevalent or more in men who completed less than ten years of education, as compared to the men who would attain a high education. Smoking, lower likeliness of physical activity, and overweight in late adolescence were also more prevalent in men with a low educational attainment than in men who would become high educated. The prevalence of low cognitive ability measured in late adolescence was very high in men who completed less than ten years of education and very low in men who would become high educated. As expected, educational attainment was highly correlated with SEP, job control, and income measured at about age 40.

All three indicators of childhood social circumstances (childhood SEP, crowded housing, and height) had attenuating effects on the associations between educational attainment and risks of CHD and stroke between 40 and 58 years of age. Together they attenuated the increased relative risks with 20-25% among those with the lowest educational attainment. Smoking had a rather strong attenuating effect on the associations, while the effects from BMI and physical activity were smaller and the effect from BP none. Cognitive ability had a strong attenuating effect on the associations between educational attainment and CHD/stroke, but this effect was more modest when cognitive ability was included in a model after adjustment for indicators of childhood social circumstances and risk factors measured in late adolescence. Adjustment for SEP and income in adulthood attenuated the associations somewhat, but there was no attenuating effect from these indicators when they were added to models with factors measured earlier in life already included. Significant association between educational attainment and relative risks of CHD and stroke remained after

full adjustment, although they were much diminished as compared to the unadjusted associations. The full adjustment had somewhat less attenuating effect on the association between education and stroke.

The potential mediating role of job control in adulthood between educational attainment and CHD/stroke was assessed in analyses of those 40279 men with such information (results not shown in tables in the manuscript). Adjustment for job control showed an attenuating effect on the associations between educational attainment and CHD/stroke that was even smaller than the attenuating effects after adjustments for SEP or income in adulthood.

5 DISCUSSION

BMI in late adolescence and CHD/stroke in middle age

In summary, higher BMI measured at age 18-20 was found to be associated with increased relative risks of coronary heart disease and stroke from age 40 to 55. The association with stroke was somewhat weaker than the association with CHD. Adjustments for socioeconomic position and crowded housing in childhood, and socioeconomic position in adulthood, had only minor effects on the associations.

BMI in late adolescence and CVD

In a case-control study by Hoffmans et al. (45), the relative risks of CHD mortality from before 50 years of age, in relation to higher levels of BMI measured at age 18, were similar to our findings. Also in a study of approximately 500 adolescents, who participated in the Harvard Growth Study 1922 to 1935, the relative risk of CHD mortality during 55 years of follow up was similarly increased in relation to higher adolescent BMI (47).

Studies of BMI measured in childhood or middle age appear to have found weaker associations with CVD. In a study of BMI measured in subjects with an average age of ~5 years no association with CHD during follow-up was found, although an association with stroke was indicated (46). In a study of the Boyd Orr cohort (124) an association between BMI, measured in 2 to 14 year old subjects, and CHD during 57 years of follow-up was found. However, subgroup analyses on fewer cases suggested that the association was limited to those who were 8 years and older. Stronger associations with increasing childhood age have been seen also in studies of childhood obesity and indicators of atherosclerosis in adulthood (125, 126). Further, in a small cohort of young men in Glasgow, overweight at age 22 was a better predictor of future CVD mortality than was overweight at age 38 (48). Pre-adult overweight was shown to be a more powerful predictor than overweight later in life also among the approximately 500 participants from the Harvard Growth Study 1922 to 1935 (47). The association between BMI and all cause and CVD mortality among adults appears to be weaker with increasing age (127).

Hence, cardiovascular diseases such as CHD and stroke seems to have a stronger relationship with overweight and obesity if measured in adolescence and young adulthood than if measured in early childhood or in middle age. It may be that those with a high BMI measured in late adolescence are particularly likely to be overweight or obese throughout adult life. This is supported by studies of associations between obesity in childhood and adulthood, where prediction of adult obesity seems to be stronger in older children and adolescents (126, 128, 129). In a study, Freedman et al (125) emphasized the importance of degree and duration of increased BMI in relation to CHD risk. A cumulative effect is further supported by the finding that relations between obesity in childhood/adolescence and increased intima-media thickness (IMT) in adulthood seem to be dependent on adult obesity and that long-term obesity has a particularly strong effect on IMT (125, 126, 130). Moreover, weight gain after

adolescence may also affect the risk of CVD (131). One study suggested an impact of weight gain *per se* on future CVD risk that could be attributed neither to absolute weight in young adulthood nor to levels of risk factors which may have appeared as a result of later weight gain (132). Thus, maintaining ideal weight from childhood onwards may be particularly efficient for lowering the risk of CVD.

Is increased BMI in adolescence an independent risk factor for CVD?

Cardiovascular risk factors such as increased blood pressure and cholesterol have been shown to cluster in young overweight and obese subjects (133, 134). Nevertheless, overweight and obesity may have an independent effect on cardiovascular disease and mortality, even when follow-up periods are long (49, 132). The relationship seems not to have been fully attributable to other cardiovascular risk factors in previous studies (45, 50, 132), and adjustment for risk factors in the present study attenuated associations with coronary heart disease and stroke to a limited extent. It has been hypothesized that cardiovascular diseases, related to BMI, may have a long induction-latency period (135).

The multivariable analyses demonstrated that the associations of BMI in adolescence with CHD and stroke remained strong and only slightly attenuated after adjustment for socioeconomic position and crowded housing in childhood. The multivariable analyses also showed that the associations were unaffected after adjustment for socioeconomic positions in adulthood among the men, i.e. mediation by adult socioeconomic circumstances was not supported. However, men in low socioeconomic position in childhood were more likely to be overweight and obese as adolescents, and men who themselves were manual workers in 1990 were more likely to have been in high BMI categories in adolescence. Associations between early established overweight and relative socioeconomic disadvantage in adulthood have been demonstrated previously (55, 57, 136).

In an analysis excluded from the journal article, BMI were shown to contribute in explaining adult socioeconomic differences in risk of CHD/stroke until age 55, although the contribution might not be more than 10 percent.

Blood pressure in late adolescence and CHD/stroke before age 55

In summary, elevated BP at 18-20 years of age was found to be associated with increased relative risks of CHD, AMI, total stroke, and hemorrhagic stroke during follow-up until 55 years of age. All-cause mortality was not predicted by BP, once CHD and stroke mortality were excluded. Adjustment for childhood socioeconomic position and smoking, BMI, and cognitive ability in late adolescence had an impact on the associations. Adjustment for adult socioeconomic position did not impact on the associations.

Blood pressure in early adulthood and subsequent CVD

Two previous studies have investigated the association between BP in men around 20 years of age and its long-term association with cardiovascular diseases. In the late

1960s, Paffenbarger et al reported, from a study on 50,000 male former students, that increased blood pressure levels recorded at an age of about 19 years were associated with an increased risk of mortality in CHD and stroke during 10-50 years of follow-up (67, 68). More recently, McCarron et al reported that BP levels in a cohort of 9,887 similarly aged male students at Glasgow University between 1948 and 1968 were associated with a risk of cardiovascular mortality during a median follow-up of about 40 years (66, 137).

The present study made significant additions to earlier studies. First, the previous studies were based on university students with, on average, relatively good childhood social circumstances, while the cohort of the present study was highly representative of all men born in Sweden around 1950. Second, the follow-up in the present study regarded outcomes until the year 2004, and thus was based on a more recent cohort than previous studies. Third, since we could include both fatal and non-fatal cases, the number of cases was quite large despite the relatively young age of the men. This allowed us to study subcategories of CHD and stroke. Fourth, unlike previous studies we could assess the potential effect of differences in adult social circumstances on the association between BP in late adolescence and later circulatory outcomes in the present study. Fifth, in the present study it was possible to study whether differences in cognitive ability measured in late adolescence might contribute to explain associations between BP measured early and subsequent CVD, and some confounding from cognitive ability was indicated.

The associations between BP in late adolescence and CHD/stroke during follow-up in the present study were somewhat confounded by BMI, smoking, and cognitive ability at age 18-20 years, but there was no evidence of effect modification by these factors. Some previous studies of middle-aged persons have demonstrated stronger prediction of CVD from hypertension in lean subjects relative to obese, i.e. effect modification has been indicated (138, 139). Smokers were fewer in higher BP categories in the present study, and such an inverse association between smoking and BP has previously been found in several epidemiological studies (140, 141, 142). Paradoxically, smoking is known to cause an acute increase in BP and heart rate (143), but co-variation with body weight/diet make associations between smoking and BP very hard to interpret and no firm conclusions have been reached (144, 145). Even so, relationships between BP and cardiovascular diseases may be considerably underestimated when smoking is not controlled for.

Confounding of the relationship between BP and CHD/stroke by cognitive ability may hypothetically be due to adverse lifestyles and high stress levels among persons with lower cognitive ability (146). That is, cognitive ability in late adolescence may function as a general marker of individual responses and behaviours affecting long-term health risks.

How may blood pressure measured early be important for long-term risk of CVD?

Although a long-term relationship between BP in younger persons and CVD in adulthood has been demonstrated previously, a strong causal effect of early high BP on the risk of CVD in adulthood has been questioned (147). BP levels track over the life

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course and are relatively consistent from about age 20 onwards (65). Thus, high pre-adult BP predicts hypertension in middle age, and the latter may be more important for cardiovascular mortality risk (63). However, BP and other risk factors, such as BMI, smoking, and cholesterol levels, all have been found to be related to advanced atherosclerotic development in pre-adulthood and onwards (52, 72), and long-term associations between BP in adolescence and CVD in adulthood might thus indicate atherosclerotic progression over the life course.

BP levels during the pre-adult years as well as in adulthood seem strongly linked to early life factors such as socioeconomic background, mother's lifestyle during pregnancy, and own lifestyle during childhood (147, 148). Strong tracking of BP from early adulthood and onwards indicates that while high BP in adulthood may be reversible in principle, in practise it is rarely reversed. Hence, preventive strategies with an early life focus may be warranted regarding the association between blood pressure and CVD.

Childhood socioeconomic position and CHD/stroke in middle age

In summary, inverse associations between childhood SEP and risk of CHD and stroke in middle age were found. Indicators of social circumstances in childhood (height, crowded housing and early death in a parent) and cardiovascular risk factors (smoking, BMI, and BP) measured at 18-20 years of age were found to explain about half of the association with between childhood SEP and CHD, and somewhat less of the association with stroke. Additional attenuation after adjustment also for educational attainment and SEP in adulthood was limited.

Socioeconomic position in childhood and CVD in middle age

Most of the several previous studies also reported inverse associations between socioeconomic circumstances in childhood and later CVD outcomes. In a systematic review the authors found that 31 out of 40 studies demonstrated robust inverse associations (22). They concluded that childhood social circumstances generally were found to have stronger associations with stroke than with CHD in most studies that could include both outcomes. Associations between childhood social circumstances and CHD often were diminished by adjustments for adult SEP and risk factors, while associations with stroke were found to be less affected by such adjustments. In a more recent review by the same authors, which also included studies on populations born in the 1950's, this pattern of findings was confirmed (21). Inverse associations between socioeconomic circumstances and CVD were replicated in newer studies, and associations with CHD were more attenuated after adjustment for risk factors as compared to associations with stroke. The results in the present study also replicated this pattern.

Besides demonstrating that significant associations between childhood SEP and cardiovascular outcomes remained after full adjustment, it was found that the associations between childhood SEP and CHD/stroke were attenuated after adjustment for other indicators of childhood social circumstances (height and crowded housing). Although this could be considered as over-adjustment, it helped to investigate to what

extent childhood conditions may contribute to long-term risk of CVD. Height and crowded housing in childhood have been used in previous studies as indicators of childhood socioeconomic circumstances, and both have been shown to be predictors of CVD (22, 149).

We found that childhood SEP was associated with smoking and BMI measured in late adolescence, and also that adjustment for smoking and BMI attenuated the associations between childhood SEP and CHD/stroke. In a review of studies on childhood social circumstances and cardiovascular risk factors in children and young adults, Batty et al concluded that there was evidence of relationships between low childhood SEP, indicated by various measures, and some important risk factors, such as smoking, obesity in early adulthood, aspects of diet, and height (24). Indicators of childhood socioeconomic circumstances also have been shown to be associated with clustering of cardiovascular risk factors in young persons (73, 83).

How may the association between childhood SEP and CVD be explained?

The finding, that associations between childhood SEP and risks of CHD and stroke in middle age remains after multivariable adjustments, is consistent with a proposed hypothetical pathway in which a poor socioeconomic environment in childhood is suggested to affect biological development from gestation to adolescence and, as a consequence of this, increase the risk of disease and premature death in adulthood (81). Indicators of socioeconomic environment, other than childhood SEP, contributed to explain the association between childhood SEP and CHD/stroke in middle age, which is also consistent with such a hypothetical pathway. Independent prediction of CVD from various indicators of childhood social circumstances has been shown in several previous studies (80, 149).

Although poor childhood social circumstances may be an independent risk factor for CVD, this is not the only or even the most important way in which childhood SEP contributes to increase the risk of CVD later in life. In the study, we found evidence of mediation by behaviour-related factors measured in late adolescence (smoking and BMI) in the relationship between childhood SEP and CHD/stroke during middle age. This is consistent with a hypothetical pathway in which childhood socioeconomic environment is suggested to contribute to shape behaviours associated in the long term with disease risks (81). Mediation by cardiovascular risk factors of the association between childhood social circumstances and CVD is supported by findings in several previous studies (21, 24, 73, 80, 81, 83).

A third hypothetical pathway between childhood social circumstances and adult health suggests that childhood SEP influences socioeconomic circumstances in adulthood (via educational and occupational opportunities) and, through this, negative exposures and disease risks (81). This would mean that the relationship between childhood SEP and CVD is mediated by adulthood experiences. We did not find evidence of this as a main explanation in the study. Once social and behaviour-related factors measured in childhood and adolescence had been adjusted for, educational attainment and adult SEP had limited attenuating effects on the associations between childhood SEP and risk of CHD and stroke in middle age. Thus, it was suggested that low education and social

disadvantage in adulthood might not explain the relationship between low childhood SEP and increased risk of CVD as much as has been concluded in previous studies (21, 23, 150, 151, 152). Rather, measures of low status-attainment in adulthood may be markers of negative social experiences and behaviours accumulated from early childhood onwards (39, 42, 153). The latter may be factors actually explaining the relationship between childhood SEP and CVD in middle age.

Our findings showed that early life social disadvantages and behaviour-related risk factors evident prior to adulthood were associated with SEP of origin. Our findings also showed that such factors measured in pre-adulthood may be particularly important to explain why men originating from lower socioeconomic positions are at greater risk of future cardiovascular disease.

Educational attainment and CHD/stroke in middle age

In summary, inverse associations between educational attainment and both CHD and stroke was found. Adjustment for indicators of socioeconomic circumstances in childhood and behaviour-related risk factors measured in late adolescence attenuated these associations considerably. Additional adjustment for SEP, income, and job control in adulthood did not affect the associations.

Comparison with previous studies

We found that indicators of social disadvantage in childhood (parental SEP, crowded housing, and short stature), and low cognitive ability and behaviour-related risk factors in late adolescence increased in prevalence with lower educational level. Evidence of the impact of social background characteristics on educational attainment is large in the social science literature (154). We showed in multivariable analyses that the indicators of social circumstances in childhood confounded associations between educational attainment and CHD/stroke in middle age. Indicators of social disadvantage in childhood have appeared as independent predictors of CVD later in life in a growing literature (21, 22), but very few studies have reported on confounding of the association between education and CVD by childhood social circumstances. A Finnish register-based study on mortality in young men included ~200 cases of CVD and found that adjustment for childhood SEP, but not adjustment for SEP in adulthood, had an attenuating effect on the association between education and CVD (152). For all other causes of death in that study, adjustment for SEP in adulthood, but not childhood SEP, had an attenuating effect.

Cognitive ability had the strongest attenuating effect on the associations between educational attainment and CHD/stroke in our multivariable analyses. Two previous studies, with fewer cases, Batty et al (152, 155, 156) also found considerable attenuation of the association between education and CHD from adjustment for cognitive ability. In our study, it was found that the attenuating effect from cognitive ability was not as strong when indicators of childhood social circumstances and smoking and BMI in late adolescence had already been adjusted for, which also is consistent with Batty et al (156). In a previous study of the association between cognitive ability and CHD in this cohort it was demonstrated that cognitive ability may

have no direct effect on CHD, but that lower cognitive ability may increase risk of CHD partly through adverse behaviours (112).

Smoking, overweight, high blood pressure, and low physical activity measured in late adolescence were found to increase in prevalence with lower educational level in the present study. It has been shown in a few previous studies that adolescents who attain lower educations tend to have various unfavourable health-related behaviours, e.g. more alcohol consumption, more smoking, less physical activity and unhealthier diets, than adolescents who will become higher educated (38, 39). Smoking, and to a lesser extent BMI and physical activity, measured in late adolescence, were demonstrated to confound associations between educational attainment and CHD and stroke, in the present study. Adjustment for cardiovascular risk factors, e.g. smoking, BMI, blood pressure, and cholesterol, have previously been shown to attenuate associations between educational attainment and CVD, although risk factors in these studies generally have been measured later in adulthood (98, 99, 100, 101, 102, 103, 104, 105, 157, 158, 159, 160). Consistent with our results, smoking has in several of the previous studies appeared to be a prominent explanatory factor (98, 100, 102, 103, 104, 157).

Significant associations between educational attainment and risk of CHD and stroke remained in the fully adjusted models within the present study. The remaining associations were markedly diminished as compared to the unadjusted associations. Several of the previous studies also found that associations between educational attainment and CVD remained after adjustments (5, 103, 104, 159, 160). A few smaller studies were inconclusive with regard to the remaining associations (98, 160) while some studies found that adjustments attenuated the associations almost entirely (99, 100, 102, 105). However, adjustment in most previous studies was made for risk factors measured years or decades after educations were completed, and it has not been possible to make inferences about the association between educational attainment and CVD *controlled for confounding*.

Interpretation of the findings

Substantial differences in childhood social circumstances and behaviour-related risk factors for CVD measured in late adolescence between educational groups were suggested to explain large parts of the associations between educational attainment and CHD/stroke in the present study. Yet, the associations between educational attainment and CHD/stroke that remained after adjustments may be even further confounded. Potential confounding factors were not perfectly measured. Furthermore, the associations could be confounded by factors that were unmeasured. Thus, a possible interpretation may be that potential relationships between educational attainment and CVD in middle age are weak. A few recent studies of twins have suggested that associations between educational attainment and CVD-related risk factors examined in early adulthood, such as smoking, BMI, and physical activity, may be explained by strong confounding from childhood family environment and genetic inheritance (96, 97, 161).

Hypothetically, the remaining associations could reflect a relationship between educational attainment and CVD explained by differences in material and/or

psychosocial factors linked to occupations. However, such a hypothesis was not supported by our analyses of SEP, income, and job control at age ~40 as potential mediators. Adjustment for these factors in adulthood attenuated the associations between education and CHD/stroke modestly, and, more importantly, these adjustments had no attenuating effects once associations had been adjusted for indicators of childhood social circumstances and risk factors in late adolescence. The previously mentioned Finnish study (152) also found that the association between educational attainment and CVD was unaffected by adjustment for SEP in adulthood (while confounding by parental SEP was demonstrated). Adjustment for SEP in adulthood did, however, attenuate associations between educational attainment and other causes of death in that study. In contrast, Davey-Smith et al (43) found that adjustment for occupational class attenuated the association between educational attainment and CVD considerably. In addition, a large attenuating effect on the association by adjustment for income in adulthood was seen in van Lenthe et al (100), and some attenuation by adjustment for indicators of adult socioeconomic conditions was seen also in McFadden et al (98) and Wamala et al (87). However, none of these studies included information on early measured predictors of CVD, which we have previously shown also to be predictors of occupational class-position and job control measured in early middle age (42, 118).

The remaining significant associations between educational attainment and CHD/stroke may possibly indicate that a higher educational level has some influence on choices and behaviours beneficial to health, e.g. through a higher sense of control and development of healthier behaviours in adulthood (95). Authors of previous studies (5, 87, 100, 101, 102, 103, 104, 105, 158, 159, 160) have suggested that modifiable behaviour-related risk factors contribute to 'explain' associations between educational attainment and CVD. However, it has not been clarified in these studies whether the explanations refer to confounding or mediation. Yet, this is decisive for the understanding of how differences in CVD between educational groups arise. A general lack of substantial explanations in studies of associations between education and disease endpoints, and the consequent uncertainty in policy implications (whether or not increased education enhance health), has been acknowledged in previous discussions (92, 93, 94).

Interpretation in light of the life course models

In life course epidemiology, three main models have been proposed as hypothetical explanations of relationships between exposures from early life onwards and health outcomes later in life (13, 14). A *critical period model* postulates that some period early in life may have a critical role in the determination of long-term health. Hypothetically, effects of exposure during a critical period on long-term health outcomes may be dependent on circumstances later in life. An *accumulation of risk model* proposes that long-term health risks are explained by accumulated exposures over the life course. The accumulated exposures may be independent of each other or somehow clustered. Finally, a *chain of risk model* postulates that a series of events from early life and onwards affect the likeliness of persons to end up in a life situation that is the main explanation of disease development. In this model, early life events have a relation to

risks of disease through their effect on future living conditions, but are not themselves causes of disease.

It was shown in the studies that higher BMI, higher levels of systolic blood pressure (although not higher levels of diastolic blood pressure), lower body height, lower cognitive ability, smoking, and less likeliness of physical activity, all measured in late adolescence, were more frequent in men of a lower socioeconomic origin. It has been shown in previous studies that childhood social circumstances predict risk factors of CVD that are established in youth or young adulthood (21, 22, 82). Such associations could hypothetically reflect an impact of disadvantage early in life. It could be due to biological mechanisms, for instance "programming" of risk factors as proposed by Barker (18), and it could be due to adverse behavioural responses to disadvantage (29).

Increased levels of BMI and blood pressure in late adolescence were shown, in study I and II, to be significantly associated with CHD and stroke during middle age. BMI, smoking, and body height in late adolescence were shown, in study III, to contribute to explain the associations between childhood socioeconomic position and CHD/stroke in middle age. Possibly, study III also showed that childhood social disadvantage may have an independent long-term effect on CHD and stroke in middle age.

Based on this, it may be suggested that a "critical period model" gets some support from the studies, i.e. a model in which early life may have a critical role in the determination of long-term health. Increased risks of CHD and stroke in middle-aged men could be an effect of disadvantages in childhood, acting through biological and/or behavioural development early in life. Furthermore, a lower socioeconomic position in adulthood may be associated with increased risks of CVD among middle-aged men because it is frequently a reflection of a disadvantaged position in childhood. In study IV it was found that large parts of the associations between educational attainment and CHD/stroke in middle age seemed to be explained by differences in childhood social circumstances, and differences in cognitive ability, and risk factors of CVD already established in late adolescence, and it may help to interpret this finding in terms of a critical period model: the likeliness to end up with a low education and to have an early event of CVD may, to some extent, be codetermined by experiences of disadvantage early in life.

However, the findings may as well be interpreted in support of an "accumulation of risk model". Risks of CVD in middle age may be accumulated in proportion to quantity and duration of exposures, such as social disadvantage, smoking, physical inactivity, overweight, and elevated blood pressure. This risk accumulation would be most prevalent among men born to parents of lower socioeconomic positions and among men who attain lower educational levels. These are the same categories of men who tend to end up in relatively disadvantaged socioeconomic circumstances as adults. Perhaps, risk accumulation could reflect reciprocity between social and biological risk factors (and outcomes) over the life course, in accordance with some previous hypotheses (29, 162). Additionally, risk accumulation could reflect health-related selection, in the sense that early biological outcomes of social disadvantage that are predictors of CVD later in life, e.g. short stature and obesity, may be associated with lower socioeconomic achievement in adulthood.

The findings may not support to a "chain of risk model" in which associations between, on the one hand, childhood disadvantage and risk factors in adolescence, and, on the other hand, cardiovascular disease in middle age could be explained by social status and control over work/life in adulthood. In none of the studies was seen that indicators of socioeconomic circumstances in early middle age importantly contributed, through mediation or modification, to associations between factors measured in childhood/late adolescence and CVD in middle age. Again, the results rather may provide evidence of cardiovascular risk accumulation from childhood and onwards that vary substantially between different social classes of middle-aged men.

METHODOLOGICAL CONSIDERATIONS

Study design

All four studies within this thesis were based on "The 1969 conscription cohort" (described in the Material and methods section above). Thus, all four studies used information on childhood circumstances, risk factor prevalence in late adolescence, adulthood circumstances, and incidence of cardiovascular disease gathered prospectively from the conscription examination in 1969/70 or in national registers. No information used for the studies was based on recall. Many previous studies of associations between circumstances during pre-adulthood, e.g. childhood socioeconomic position, and long-term disease risks relied on information based on recall at some point later in life, which may have generated biased estimations (84, 86). Thus, in the studies within the thesis this important measurement problem likely was minimised.

Systematically missing information, another potentially important methodological problem, also was likely to be minimised in the studies. The 1969 conscription cohort includes almost all men eligible for the conscription in 1969/70, which was compulsory. All information linked to the conscription data was obtained from national registers with very low rates of missing information (see Materials and method section). Thus, it is unlikely that inclusion in the cohort was strongly associated with predictors investigated in the studies, i.e. risk factors measured in late adolescence, socioeconomic position in childhood (or adulthood), and educational attainment. Since follow-ups were based on national in-patient and mortality registers, we also had control over subjects lost due to death, and selective drop-out from the cohort is therefore not likely to have influenced the results significantly.

The extensive information available from the conscription examination cannot be obtained elsewhere, which is why women could not be studied within this thesis. The 1969 conscription cohort provided a rare and powerful material, but the exclusion of women was obviously a limitation. For instance, previous studies of BMI in adolescence or young adulthood and future cardiovascular disease outcomes (45, 48) were also based on male cohorts. It has been indicated that health outcomes as well as social consequences of overweight in adolescence may be dependent on sex (47, 163, 164). During the writing of study II we noted that all previous investigations of

associations between blood pressure in adolescence/young adulthood, as well as BMI, serum cholesterol, and smoking this early in life, and subsequent long-term cardiovascular disease risk were based on male cohorts (47, 66, 69, 70, 71, 165).

The combination of information on potential explanatory factors from pre-adulthood and information from registers on parental SEP, educational attainment, and SEP in adulthood, and follow-up information on incident and fatal CHD and stroke made it possible to contribute to previous research. Early measured factors is helpful when investigating to what extent socioeconomic differences across the life course are causes or consequences of variation in health and health-related factors (166).

Confounding

Confounding is present when an estimated association between a variable X and a variable Y is, to some extent, produced by a third variable Z that influences both X and Y. For instance, potential confounding in the association between education and a health outcome is easy to hypothesise, since there are several factors that may influence both educational achievement and health in adulthood. Childhood social disadvantage and low cognitive ability are examples of such factors.

Information on social circumstances in childhood (register-based data) and cognitive ability/risk factors of CVD in late adolescence (conscription data) made it possible to adjust for potential confounding in the studies. Differences in early life experiences may be an important source of confounding in studies on health determinants in adulthood. The information on such factors is relatively extensive in the 1969 conscription cohort. Nevertheless, the confounding control may have been limited, due to unmeasured confounders as well as imprecise measurement of confounders, and residual confounding cannot be ruled out in the studies. As an example, sports club membership reported at conscription was used in study IV to control for potential confounding from physical activity in the associations between educational attainment and CHD/stroke. Admittedly, the use of sports club membership to measure physical activity was rough and misclassification probably occurred in some of the men. Thus, confounding from physical activity could have been underestimated.

Mediation

The potential mediating role of differences in adult socioeconomic circumstances was analysed in all studies, but was most interesting in study III and IV. Differences in education and occupation-based social position may hypothetically explain (by mediation) associations between childhood socioeconomic circumstances and CVD in middle age. Similarly, differences in occupation-based social position and income may hypothetically explain associations between education and CVD in middle age. However, it is important to consider potential confounding also when studying mediating factors. If an association between a variable X and a variable Y is shown to be "explained" by a hypothetical mediating variable M in a multivariable analysis, this explanation may be spurious nevertheless; the association between M and Y may be confounded too. This was indicated in study III, for instance, where analyses first

showed that adjustment of the association between childhood SEP and CHD/stroke for educational level attenuated relative risks considerably, but then also indicated that the association between educational level and CHD/stroke was confounded by risk factors measured early in life.

Misclassification of conscription data

BMI was calculated based on measurement of height and weight at the conscription examination. It must have been an accurate measurement of individual differences in BMI in late adolescence. However, differences in BMI are used to indicate leanness, overweight, and obesity. As a measure of under- or overweight in late adolescent men in terms of body fatness differences, BMI has limited precision. A high BMI may reflect high muscle mass, and this is particularly so in young men (167). BMI may thus misclassify body fatness and cause an underestimation of associations between body fatness and CVD outcomes. The limitations of BMI pertain to associations with indicators of social status as well (168), for instance by potentially misestimating the explanatory contribution of overweight in associations between social status (SEP, educational attainment, income etc.) and CVD.

BP measurements were made on the first day of the conscription examination, after 5-10 minutes of rest. Only one measurement was made, unless measures were outside a "normal" interval (see Materials and method section). Measurement imprecision with regard to BP might be somewhat larger in the conscription cohort, with single measurements, than in studies where more standardized protocols have been used. Further, practices of rounding in registered blood pressures were apparent in the present material and have been reported for later conscription examinations in Sweden as well (108). Both systolic and diastolic BP seem to have been rounded to the nearest 5 or 10 mm Hg, throughout the range of blood pressures. Non-differential misclassification of BP measures, due to single measurements and practises of rounding, might have resulted in underestimation of associations with CVD outcomes.

The use of information on BMI, BP, smoking, and physical activity, i.e. risk factors of CVD, measured at 18-20 years of age, was not intended to describe the situation in middle age, when most events of CHD and stroke occurred. The intention was to use information from age 18-20 to examine possible long-term relationships between risk factors and CVD in middle age, and the potential importance of these possible relationships when investigating associations between SEP/education and CVD. The distribution of risk factors among the men must to some extent have shifted after conscription in late adolescence. For instance, a number of the men quit smoking in adulthood and, thus, the information on smoking from the conscription examination does not correctly classify level of smoking during follow-up. It has been indicated in a subset of the cohort that higher educational attainment to some extent predicted smoking cessation subsequent to conscription among the men (110).

Misclassification of indicators of childhood social circumstances

Childhood socioeconomic position was used as the focal indicator of social circumstances in childhood in study III. In study I, II and IV it was examined as a potential explanatory factor. Information on childhood SEP, i.e. SEP of the parents when the men were children, was obtained from the National Population and Housing Census of in 1960. The conscripts and their parents (or any other head of the household if different from biological parents) were linked to each other between censuses through their personal identification numbers by Statistics Sweden. Thus, retrospective information was not used. Moreover, childhood SEP of the men in the present study was based on the occupational information from the head of the household in the 1960 census and not limited to information from biological parents. Nevertheless, parental/childhood SEP was based on information from one year only, and childhood SEP could thus have been misclassified in some men as a consequence of changes in SEP during childhood or adolescence. Changes in SEP should not have involved dramatic changes in socioeconomic circumstances in most cases, but could have resulted in some underestimation of childhood SEP as predictor. This pertains to crowded housing in childhood as well, also based on information from the 1960 census.

Misclassification of indicators of adulthood social circumstances

Information on educational attainment was used in study III and IV. Conscription data were linked to the Longitudinal Database of Education, Income and Occupation (LOUISE) of 1990-2002 held by Statistics Sweden, in order to receive educational information for each member of the study population. There are imperfections in the reporting of completed educations to registers, mostly at lower levels of education, that produces some misclassification of educational attainment (116). The association between educational attainment and CHD/stroke may have been somewhat underestimated if the lower educated groups included men who actually had more years in education.

Income in adulthood was used in analyses in study IV. Information on gross annual income in 1990, based on any taxable income (also including, for instance, sickness allowances and disability pensions), was used and the men were classified into income quartiles. A low income at 40 years of age may in some men have reflected a lower health status, but it is unlikely that such reverse causation between cardiovascular disease (which must be undetected) and lower incomes at age 40 was of importance for the results. Since information on SEP in adulthood (used in all studies within the thesis) also was obtained in the 1990 census, when the men were ~40 years of age, this indicator should not either be affected by reverse causation.

Misclassification of outcome data

Outcome data based on information from the National Hospital Discharge Register (HDR) and the National Cause of Death register are frequently used in epidemiological studies in Sweden. A validation study of myocardial infarction diagnoses in the HDR found relatively good correspondence between clinical diagnoses and diagnostic

criteria, although there were some differences between regions, between types of clinic, and between time periods (169).

CONCLUDING REMARKS

The general aim of the thesis was to investigate how socioeconomic and behaviour-related factors measured in childhood, late adolescence, or adulthood are related to coronary heart disease and stroke in middle age among Swedish men. The potential importance of socioeconomic differences in adulthood among the men was considered throughout.

It was found that higher BMI measured in late adolescence may be an important risk factor of coronary heart disease and stroke between 40 and 55 years of age. Men with higher BMI in late adolescence were more likely to be in lower occupation-based socioeconomic positions later in adulthood, but differences among the men in their adult socioeconomic positions did not seem to affect, i.e. mediate or modify, associations between BMI measured early and coronary heart disease/stroke in middle age.

Higher blood pressure measured in late adolescence was found to be associated with increased relative risks of coronary heart disease, acute myocardial infarction, hemorrhagic stroke, and total stroke from age 20 to age 55. Some confounding from childhood socioeconomic position and cognitive ability in adolescence was demonstrated. Differences in adulthood occupation-based socioeconomic position were not found to affect relationships between higher blood pressure in late adolescence and cardiovascular outcomes before age 55.

It was found that men with a low socioeconomic position in childhood had increased relative risks of coronary heart disease and stroke in middle age. However, a large proportion of the associations between socioeconomic position in childhood and coronary heart disease/stroke appeared to be explained by differences in childhood social circumstances and risk factors of cardiovascular disease measured in late adolescence. When these adjustments had been made in the analyses, differences in educational attainment and socioeconomic position in adulthood did not contribute much to explain the associations between childhood socioeconomic position and coronary heart disease/stroke.

Educational attainment was found to be inversely associated with both coronary heart disease and stroke in middle age, as expected. However, differences in childhood social circumstances, cognitive ability in late adolescence, and risk factors measured in late adolescence seemed to explain large parts of the associations between educational attainment and risks of coronary heart disease and stroke in middle age. Differences in socioeconomic positions, income levels, and job control in adulthood seemed not to be mediating factors in the relationship between educational attainment and coronary heart disease/stroke in middle age in the analyses. A significant relationship between education and coronary heart disease/stroke remained in fully adjusted models, which

may possibly indicate that a lower education increases risk of cardiovascular disease in middle age.

The findings showed that cardiovascular diseases in middle age among men may have been importantly determined by circumstances in childhood and adolescence. Risk factors later in life could reflect disadvantaged conditions earlier in life. Strategies to lower the incidence of cardiovascular disease in populations, and in different socioeconomic groups, may benefit from a life course perspective.

6 SAMMANFATTNING (SUMMARY IN SWEDISH)

Det övergripande syftet med avhandlingen var att studera hur socioekonomiska och beteenderelaterade faktorer mätta i barndomen, sena tonåren eller vuxenlivet är förknippade med kranskärlssjukdom och stroke bland medelålders svenska män. Den potentiella betydelsen av sociala skillnader i vuxenlivet undersöktes i alla delstudierna.

Avhandlingen baserades på mönstringskohorten från 1969/70, det vill säga en kohort bestående av nästan 50 000 svenska män som 1969/70 genomgick mönstringsundersökning inför värnpliktstjänstgöringen. Männen var då mellan 18 och 20 år gamla. Information från den fysiologiska undersökningen, intelligenstestning och enkäter användes i kombination med (1) registerbaserade indikatorer på socioekonomiska förhållanden i barndomen och vuxenlivet, samt information om utbildningsnivå, och (2) registerbaserad information om fall av kranskärlssjukdom och stroke mellan 1971 och 2007. Multivariabla regressionsmetoder användes för dataanalyserna.

I studie I och II visades att förhöjda nivåer av BMI och blodtryck i sena tonåren signifikant ökade riskerna för kranskärlssjukdom och stroke före 55 års ålder. Män med högre BMI i tonåren befann sig relativt ofta i lägre socioekonomiska skikt senare i livet, men senare socioekonomiska skillnader tycktes inte påverka sambanden mellan BMI/blodtryck i tonåren och kranskärlssjukdom/stroke i medelåldern.

Skillnader i BMI, rökning och kroppslängd i sena tonåren visades i studie III kunna bidra till att förklara samband mellan barndomsklass och risker för kranskärlssjukdom och stroke i medelåldern. Möjligen visade resultaten också på att ogynnsamma förhållanden i barndomen kan ha en egen långsiktigt verkande effekt på risker för kranskärlssjukdom och stroke i medelåldern. I studie IV visades att samband mellan låg utbildningsnivå och ökad risk för kranskärlssjukdom och stroke i medelåldern till stor del tycktes kunna förklaras av att ogynnsamma barndomsförhållanden och ohälsosamma beteenden etablerade i tonåren var vanligare bland de lågutbildade männen.

Faktorer under barn- och ungdomsåren visades alltså kunna vara särskilt viktiga i förhållande till risken för kranskärlssjukdom och stroke i medelåldern bland männen. De ökade sjukdomsriskerna skulle kunna vara en effekt av sämre förhållanden i barndomen, som verkar på den biologiska och beteendemässiga utvecklingen tidigt i livet. Ogynnsamma förhållanden, och negativa beteendemässiga reaktioner på sådana förhållanden, skulle också kunna påverka sjukdomsriskerna på ett kumulativt sätt genom livet. Studierna visade också att en sådan riskackumulation kan vara vanligast bland män födda i lägre socioekonomiska skikt och bland män som skaffar sig kortare utbildningar, det vill säga samma grupper av män som tenderar att hamna i lägre sociala skikt i vuxenlivet. På så sätt skulle också sociala skillnader i risken för hjärtkärlsjukdom kunna förklaras av att män i lägre sociala skikt oftare har en bakgrund som tidigt börjat påverka hjärtkärlhälsan negativt.

7 ACKNOWLEDGEMENTS

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