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EARLY AND LATER LIFE MECHANISMS IN THE AETIOLOGY OF CARDIOVASCULAR DISEASE

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ABSTRACT

Evidence over the recent decades indicates that susceptibility to cardiovascular disease (CVD) may be established already prenatally and in early childhood, and that the aetiological processes of the disease involve biological and social influences occurring throughout a person's life span. Numerous studies have shown that small size at birth is associated with increased risk of CVD later in life. This finding is suggested to reflect the influence of poor foetal nutrition on the body's organ structure, physiology and metabolism. Surprisingly, there is little empirical evidence available to support the proposed causal mechanisms. The aim of this thesis is to study the mechanisms underlying the inverse association of size at birth with CVD.

Three studies in the thesis are based on Uppsala Birth Cohort Study (UBCoS), a prospective cohort study which includes men and women, who were born at the Uppsala Academic Hospital between 1915 and 1929. Information from birth records, school catalogues, Hospital Discharge Register, Cause of Death Register and Censuses is used. One study is based on Stockholm Heart Epidemiology Program (SHEEP), a population based case-control study of risk factors for acute myocardial infarction (AMI) with study base including all Swedish citizens aged 45-70 years with no prior clinically diagnosed AMI, who lived in Stockholm County during 1992-1994. Data from birth records, questionnaire, health examination and blood sampling is used.

In both data materials small size at birth was associated with increased risk of CVD. Further analyses showed that birth weight for gestational age in men was associated with ischemic heart disease (IHD) mortality within the non-manual class but not among the manual workers, even if the overall mortality rate was higher in the latter. There was no difference in the association by the men's family's social class at birth. For women, social class neither at birth nor in adulthood modified the association between birth weight for gestational age and IHD mortality.

We found that there was a synergistic interaction between low weight for gestational age and overweight in adulthood on risk of AMI.

The simultaneous analysis of foetal growth, cognitive ability and IHD mortality suggested that there is an indirect association between foetal growth and cognitive ability through childhood cognitive ability.

Finally, men with very low and very high birth weight for gestational age had a higher risk of dying after an AMI than men with intermediate birth size. Case fatality in women was not associated with their size at birth.

The results suggest that the effect of poor foetal nutrition on CVD may be modified by social exposures later in life. The synergistic interaction between small size at birth and high adult body mass index with respect to AMI risk supports the thrifty phenotype hypothesis according to which a mismatch between foetal and adult nutrition is causing the disease. The existence of an indirect association between foetal growth and IHD mortality through childhood cognitive ability implies that mechanisms related to brain development are contributing to the association between poor foetal nutrition and IHD, in addition to the effects on physiology and metabolism. As the association of size at birth with case fatality was different from the associations with incidence and mortality, the mechanisms that operate after the AMI event and determine the prognosis might partly be different from the mechanisms that drive the development of the disease.

SAMMANFATTNING (SUMMARY IN SWEDISH)

Forskning från de senaste årtiondena har visat att ökad sårbarhet för hjärt-kärlsjukdomar kan grundläggas redan under fosterlivet och den tidiga barndomen och att både biologiska och sociala förutsättningar under olika skeden i livet påverkar de etiologiska processer som leder till sjukdomen. Många studier har visat att låg vikt vid födseln är kopplad till ökad sjukdomsrisk. Det förklaras med att otillräcklig näringstillförsel i foster-livet påverkar kroppens organstruktur, fysiologi och ämnesomsättning. Överraskande nog finns dock inte mycket empiriskt stöd för de föreslagna mekanismerna. Syftet med denna avhandling är att undersöka mekanismer som kan tänkas ligga bakom sambandet mellan födelsestorlek och kardio-vaskulära sjukdomar.

Tre studier i avhandlingen baseras på *Uppsala Birth Cohort Study* (UBCoS), en longitudinell studie av män och kvinnor som föddes på Akademiska sjukhuset i Uppsala mellan 1915 och 1929. Vi använder uppgifter från förlossningsjournaler, skolregister, Patientregistret, Dödsorsaksregistret och folk- och bostadsräkningar i analyserna. En studie i avhandlingen baseras på *Stockholm Heart Epidemiology Program* (SHEEP), en befolkningsbaserad fall-kontrollstudie om riskfaktorer för hjärtinfarkt. Studiebasen i SHEEP är alla Svenska medborgare som bodde i Stockholms län mellan 1992 och 1994. Vi använder uppgifter från förlossningsjournaler, hälsoundersökningar och enkätundersökningen.

Att vara för liten vid födseln var kopplad till ökad risk för hjärt-kärlsjukdomar i båda datamaterialen. Vidare såg vi att gestationstid-specifik födelsevikt var kopplad till mäns dödlighet i ischemisk hjärt-sjukdom om de var tjänstemän men inte om de var arbetare, trots att de sistnämnda hade en genomsnittligt högre dödlighet. Det fanns emellertid ingen skillnad i detta samband enligt föräldrarnas sociala klass vid födseln. Bland kvinnor påverkade vare sig social klass vid födseln eller i vuxen ålder sambandet mellan födelsestorleken och risken för ischemisk hjärt-sjukdom.

Det fanns en synergistisk interaktion mellan att vara för liten vid födseln och senare övervikt beträffande hjärtinfartrisk.

Då fostertillväxt, kognitiv förmåga och dödlighet i ischemisk hjärtsjukdom analyserades simultant såg vi att det fanns ett indirekt samband mellan fostertillväxt och ischemisk hjärtsjukdom via kognitiv förmåga i barndomen.

Slutligen, män med mycket låg och mycket hög födelsevikt för gestationstiden löpte en högre risk att dö efter ett hjärtinfarktsfall än män med normal storlek vid födseln. Bland kvinnor fanns inget samband mellan storlek vid födseln och risken att dö efter hjärtinfarkt.

Våra resultat talar för att sambandet mellan otillräcklig näringstillförsel under fosterlivet och hjärt-kärlsjukdomar kan skilja sig åt beroende på sociala bestämningsfaktorer senare i livet. Den synergistiska interaktionen mellan låg födelsevikt och senare övervikt beträffande hjärtinfarktrisk stödjer hypotesen om ”sparsam fenotyp” enligt vilken dålig nutrition under fosterlivet, följt av överflöd senare, orsakar sjukdom. Det indirekta sambandet mellan fostertillväxt och ischemisk hjärtsjukdom via kognitiv förmåga tyder på att mekanismer som har med hjärnutveckling att göra bidrar till sambandet mellan näringstillförsel under fosterlivet och hjärt-kärlsjukdomar, utöver inflytandet som näring har på fysiologin och ämnes-omsättningen. Att sambandet mellan födelsestorleken och risken att dö efter ett hjärtinfarktsfall var annorlunda än sambandet med incidensen och dödligheten tyder på att mekanismer som leder till död efter insjuknande delvis kan skilja sig från dem som leder till att sjukdomen utvecklas.

LIST OF PUBLICATIONS

I. Rajaleid K, Manor O, Koupil I. Does the strength of the association between foetal growth rate and ischaemic heart disease mortality differ by social circumstances in early or later life? J Epidemiol Community Health 2008 May;62(5):e6.

II. Rajaleid K, Janszky I, Hallqvist J. Synergistic interaction between small size for gestational age and overweight in adulthood on acute myocardial infraction risk – the SHEEP study. Forthcoming in Epidemiology.

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IV. Rajaleid K, Hallqvist J, Koupil I. The effect of early life factors on 28 day case fatality after acute myocardial infarction. Scand J Public Health 2009;37(7):720-7.

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LIST OF ABBREVIATIONS

AMI	acute myocardial infarction
BMI	body mass index
CI	confidence interval
CHD	coronary heart disease
CVD	cardiovascular disease
HR	hazard ratio
IHD	ischemic heart disease
OR	odds ratio
SD	standard deviation
SEM	structural equation modelling
SHEEP	Stockholm Heart Epidemiology Program
UBCoS	Uppsala Birth Cohort Study
WHR	waist to hip ratio

1 BACKGROUND

Cardiovascular disease (CVD) is the leading cause of chronic illness and death globally and in Sweden and thus a major public health concern.[1,2] It is usually manifested at middle or old age and recognized risk factors for the disease include life-style related factors such as tobacco smoking, physical inactivity, unhealthy diet, high blood pressure, and overweight.[3]

However, evidence over the recent decades indicates that susceptibility to CVD may be established already prenatally and in childhood, and that the aetiological processes of the disease involve both biological and social influences occurring throughout a person's life span.[4] In the 1970's, Anders Forsdahl showed that atherosclerotic heart disease mortality and mean cholesterol values in northern Norway were correlated with infant mortality rates in the same municipalities several decades earlier. He concluded that poverty in childhood and adolescence followed by prosperity in adulthood is a risk factor for morbidity and mortality.[5,6] David Barker observed similar associations in England and Wales and suggested that coronary heart disease (CHD) originates in intrauterine and post neonatal environments.[7,8] After the ecological findings, studies at individual level, the first in 1989,[9] confirmed the association between poor prenatal nutrition as indicated by low birth weight, and later disease. A recent systematic review of currently available studies have established that birth weight is inversely associated with ischemic heart disease (IHD) risk.[10]

The "foetal origins" hypothesis postulates that undernutrition and other adverse influences arising in foetal life or immediately after birth have a permanent effect on the body's organ structure, physiology and metabolism, and raise the risk of chronic disease later in life through an effect on blood pressure, cholesterol and other causal risk factors.[11-13] The related "mismatch" or "thrifty phenotype" hypothesis suggests that the developing organism makes phenotypic modifications in response to the foetal environment by using the current environmental conditions to predict the circumstances it would meet in future. If the prediction is accurate, then the organism is well matched to the environment and will cope adequately. If not, the organism may be more prone to later disease development.[14] In response to foetal undernutrition the body's organ structure and function will be modified in order to maintain long-term metabolic thriftiness. If the organism subsequently is exposed to a nutritionally rich environment, it will not be developmentally matched for this, and will have increased susceptibility to metabolic syndrome and CVD.[15-17] Thus the thrifty phenotype hypothesis does not imply that those exposed to foetal undernutrition are necessarily less healthy than others –

it is the combination of foetal undernutrition with later affluence and overnutrition that is claimed to be harmful with respect to later disease. The hypothesis is schematically presented in Figure 1. In the figure, the arrow pointing on the arrow between poor foetal growth and metabolic syndrome represents an interaction effect, i.e. the modification of the association between poor foetal growth and metabolic syndrome by adult overnutrition.

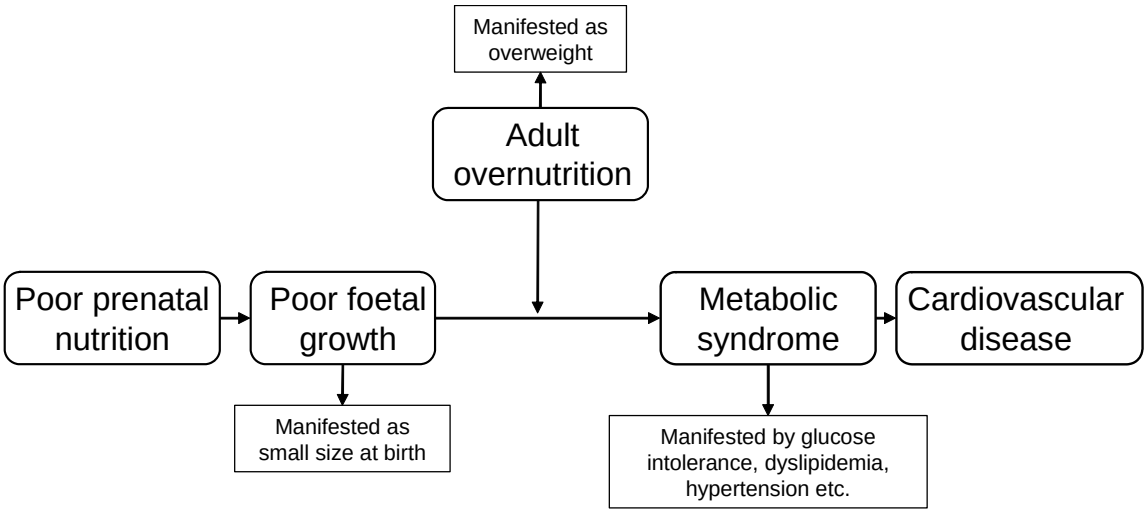

Figure 1. Schematic representation of the thrifty phenotype hypothesis

In line with the mismatch hypothesis it has been suggested that the association of size at birth with CVD may be modified by later factors, and that subgroups of the population with unfavourable profiles of adult risk factors are especially vulnerable to the adverse effects of foetal undernutrition.[10] The effect of poor foetal growth on CHD has been suggested to be increased in those who have low socioeconomic status and low income in adulthood.[18] Generally, little is known about how the proposed biological mechanisms interact with social and economical circumstances.

The association between small size at birth and later CVD is indeed well established, but despite the large number of studies in this field, causal inference remains a challenge.[19] The thrifty phenotype hypothesis plays a major role in the interpretation of the results and is biologically plausible. Surprisingly, there is little empirical evidence available to support the proposed causal mechanism from foetal growth restriction through mismatch to later disease. For example, only a few studies have assessed the combined effect of small size at birth and later overweight, an indicator of overnutrition, on CVD. Some of them,[20-22] but not all[23,24] have found that disease risk is highest in individuals with low weight at birth and high body mass index (BMI) in adulthood.

The studies providing support for the foetal origins hypothesis have been criticized for the possibility of unmeasured confounding by socioeconomic factors, selection bias due to losses to follow-up, and inconsistencies in the hypotheses and analytic procedures.[19,25] Also, alternative explanations for the association between small birth size and later CVD have been proposed such as the "foetal insulin" hypothesis.[26] The latter suggests that the observations linking small size at birth with CVD may be explained by genes that underlie insulin resistance. Insulin has a central role in foetal growth[27] and at the same time, diabetes later in life is a major risk factor for CVD.[3] The finding of an inverse association between size at birth of the offspring and parental CVD risk has been seen as a support for the hypothesis.[28]

During recent years, another field of research called cognitive epidemiology has emerged, focusing on low cognitive ability as a risk factor for later disease.[29,30] Studies in this field have connected low intelligence test scores early in life to all-cause[31,32] and cause-specific mortality, including CVD mortality.[33,34] This association may reflect the fact that cognitive ability is a predictor of educational and socioeconomic attainment[35] both of which are linked to mortality and morbidity;[36] because persons with higher cognitive abilities might better interpret health promotion advice and manage disease than people with lower abilities;[30,37] or because cognitive ability is an indicator of system integrity within the body and the efficiency of information processing in
the nervous system.[37] It has also been suggested that childhood cognitive ability acts as a record of "bodily insults", i.e. the effects of poor prenatal and postnatal nutrition, childhood illnesses and adverse living conditions on the developing brain.[37] In agreement with the latter suggestion, birth weight has been found to be positively associated with cognitive ability in childhood.[38] Thus the effect of poor foetal nutrition on increased disease risk might partly be mediated by cognitive ability. The role of cognition has, however, not been considered within the context of foetal origins hypothesis.

1.1 METHODOLOGICAL ISSUES

Hypotheses that propose pathways linking exposures across the life course to later health outcomes, such as those mentioned above, are a challenge for the design and analysis of epidemiological studies.[39] Such hypotheses may be tested within the framework of life course epidemiology.

Life course epidemiology provides a theoretical model of chronic disease risk that embraces the study of how biological, behavioural and psychosocial pathways operating through a person's life course – from gestation and birth to childhood, adolescence, and adult life – influence the

development of disease.[40,41] It includes efforts aimed to clarify the effects of timing and duration of exposures and whether later favourable or adverse circumstances may modify those effects. Answering such questions may help to understand the underlying disease mechanisms.

Using a life course approach does not merely mean including a number of variables from different stages of the life in the regression model; it emphasizes the importance of considering mutual relationships and temporal ordering of the variables, and taking into account correlated exposures.[42] This can be done with carefully designed regression analyses, but also with path analysis,[43] structural equation modelling (SEM)[44,45] and graphical models that require that the inter-relationships of variables included in the model are explicitly stated.

1.2 DATA AVAILABILITY

Success in testing the theoretical hypotheses is dependent on availability of empirical data. Using a life course approach is only possible if information is available on the proposed exposures and confounders, covering periods that are considered to be important. Longitudinal studies are often limited to one or two exposures acting in a specific time window and lack data on other periods of the life course, thus limiting the possible life course models to be tested.[40] Also, the available data may have low quality. For example, in studies assessing the combined effect of small size at birth and later overweight on CVD, [20-24] none had access to gestational age; self-reported birth weight was used in three studies;[20,21,24] BMI was solely based on recall and self-report in one;[21] outcome included different subgroups of CHD and was in part based on self-report.[24]

Incidence and mortality are alternately used as measures of disease occurrence in studies exploring the association between size at birth and later CVD. Often information on deaths is more easily available than information on incident cases and hospitalisations, thus mortality is used as a proxy for incidence. For example, the systematic review[10] combined fatal and non-fatal IHD to maximize statistical power. In fact, death is a result of a sequence of events leading first to disease development and then to death. Thus mortality rate reflects the rates of component transitions from each stage of the process to the next[46] and using mortality as the outcome in etiologic studies confuses processes of disease development with prognosis. Risk factors for developing a disease and dying from it when diseased need not be the same. Studying case fatality, which is a measure of prognosis,[47] can contribute to an increased understanding of how to interpret differences between incidence and mortality in studies looking at aetiology.

2 AIMS

The aim of this thesis is to study the mechanisms underlying the inverse association of size at birth with CVD.

The following questions are addressed:

Does social background in childhood or adulthood modify the adverse effect of small size at birth on mortality of IHD?

Is the effect of impaired foetal growth on risk of acute myocardial infarction (AMI) conditional on body size in adulthood?

What is the role of cognitive ability in the association between size at birth and IHD mortality?

Is the risk of dying after AMI associated with size at birth or social class in childhood?

3 MATERIALS AND METHODS

3.1 PARTICIPANTS

The studies in this thesis are based on two data materials. Studies I, III and IV use data from Uppsala Birth Cohort Study (UBCoS) and Study II is based on Stockholm Heart Epidemiology Program (SHEEP).

3.1.1 Uppsala Birth Cohort Study (UBCoS)

UBCoS (www.chess.su.se/ubcosmg) is a prospective cohort study. It starts off with detailed birth information on all 14193 live births that were delivered at the Uppsala Academic Hospital between the years 1915 and 1929, covering 75% of births in Uppsala during the period, and 50% of births in surrounding parishes within 20 km from Uppsala.[48] The birth certificates include information on the pregnancy, the newborn baby, and the parents.

Nearly all the individuals have thereafter been successfully traced through parish archives, where information is available on moves within the country, emigrations and deaths for the time before the personal identification number was introduced in Sweden.

Furthermore, the data base has been complemented with information on 10,146 children's school marks and family socioeconomic circumstances from the year they attended 3rd grade. This information was originally recorded by the teachers in the school catalogues and now kept in local archives. By age 10 many of the children had moved from the Uppsala district and school archives all over Sweden have therefore been searched.

Since 1947, every person that has resided in Sweden on a permanent basis is assigned a unique personal identification number.[49] This number has facilitated the identification of the cohort members in different registers including Hospital Discharge Register, Cause of Death Register, and Censuses. In total, 12 168 cohort members alive and residing in Sweden have been identified.

Currently the linkages of the UBCoS members to registers cover the period until 2002.

Moreover, the descendants of the individuals belonging to UBCoS have been linked to the original cohort members through the Swedish Multigeneration Register. This way the Uppsala Multigenerational data base[50] was created. In all, the multigenerational material spans over five

generations: from the parents of the UBCoS cohort (about whom we have information from the birth certificates and school records) to their great grandchildren. By 2002, 35 great great grandchildren had even been identified. This extended material, however, is not used in the current thesis.

The three studies in this thesis that are based on UBCoS make use of somewhat different subsets of the data material, depending on the study question and data needed for the analyses.

The analyses in Study I are based on singletons born at 30 or more completed weeks of gestation who lived in Sweden in 1961 when the Swedish Cause of Death Register was initiated (11 827 individuals). The subjects were followed up from 1961 to 2002 (from ages 31–46 up to 73–88 years). Information was used from the following data sources: birth certificates, the Total Population Register, Census 1960, Census 1970, and Cause of Death Register. People who emigrated from Sweden were censored at the date of the first emigration.

The analyses in Study III are restricted to singleton born children with 30 or more completed weeks of gestation whose school records were available, and who were alive and traced in 1961 (9857 individuals). They were followed in Cause of Death Register from its start on the 1st of January, 1961 until the end of follow-up on the 31st of December, 2002. Additionally, information from linkages to Census 1960 and the Total Population Register was used. People who emigrated from Sweden were censored at the date of the first emigration.

The analyses in Study IV are not based on the whole cohort, but include persons in the cohort who suffered a fatal or non-fatal event of AMI between 1964 and 2002 as registered in the Hospital Discharge Register or Cause of Death Register. Everyone with their first case of AMI was followed 28 days from the date of the case with regard to death from any cause. Thus the individuals constituting the case cohort were collected over almost four decades, but each was followed for four weeks. Multiple births and births with less than 30 completed weeks of gestation were excluded. Five persons who had been living outside Sweden before the case occurred and three persons with unknown vital status 28 days after the case under study (emigrated, had the case less than 28 days before the end of follow-up) were excluded from the analysis. The case cohort included 1776 persons. In addition to the data on circumstances at birth from archived obstetric records, data on social characteristics in adulthood and emigrations were obtained through linkages to Censuses and Total Population Register.

3.1.2 Stockholm Heart Epidemiology Program (SHEEP)

SHEEP is a population based case-control study of risk factors for incident AMI.[51] The study base included all Swedish citizens aged 45-70 years, with no prior clinically diagnosed AMI, living in Stockholm County during 1992-1994.

Cases were defined as nonfatal and fatal first events of AMI from three sources: 1) the coronary and intensive care units at the internal medicine departments at all the emergency hospitals within the Stockholm County area; 2) the Hospital Discharge Register for the Stockholm County area; and 3) death certificates from the Cause of Death Register. The same diagnostic criteria accepted 1991 by the Swedish Society of Cardiology were applied in all the hospitals.

At the time of case incidence, one control per case was randomly selected from the study base after stratification by age, sex and hospital catchment area. If the control did not agree to participate, another one was sampled. Occasionally, however, both controls ended up participating. Also, sometimes the control was already included when the case chose not to participate. Therefore, more controls than cases were finally included in the study.

In total, 2246 cases and 3206 controls were invited to participate in the study and received a questionnaire covering a large set of potential risk factors. For fatal cases the questionnaire was answered by a close relative 6-12 months after the event. The questionnaire response rates were 72% for women and 81% for men among cases, and 70% and 75% among controls, correspondingly. Persons who left part of the questions unanswered were contacted by telephone to fill in the missing answers. In order to estimate the bias introduced by non-response, a short questionnaire was mailed to those who chose not to participate in the study. An extensive amount of register-based information on income, wealth, social circumstances, and health care utilization before and after inclusion in SHEEP has been linked to all participating study subjects.

Non-fatal cases and the respective controls were invited to a physical examination and blood sampling which took place approximately three months after the event (attendance rates 89% and 91% for cases and controls, respectively, without difference between men and women). Waist and hip circumference, height, weight and blood pressure were measured. Blood samples were taken after over night fasting, and stored at -70 ˚C. Each sample was thawed just prior to analysis and assessed in a blinded manner to reduce the possibility of bias. Approximately 25% of the

samples were lost due to freezer break down in 1998 before the measurements of insulin were done.

Archived birth record information for hospital and home deliveries was retrieved for 72% of all Swedish born participants.

In Study II, the analyses are based on Swedish born singletons, in total 1058 cases and 1478 controls. Some of the analyses are restricted to non-fatal cases and corresponding controls (843 and 1085 individuals respectively).

3.2 THE NATIONAL REGISTERS

Information from the following Swedish national registers has been linked to the data materials.

3.2.1 Total Population Register

The Total Population Register is maintained by Statistics Sweden and is the basis for all official population statistics in Sweden. The register includes name, personal identification number, place of birth, civil status, address, dates of immigration and emigration for all Swedish residents.[52]

3.2.2 Cause of Death Register

The Cause of Death Register (http://www.socialstyrelsen.se/register/dodsorsaksregistret) is kept by the National Board of Health and Welfare. It was initiated 1961 and is updated yearly. It includes information on cause of death for all deceased persons residing in Sweden at the time of death.

3.2.3 Hospital Discharge Register

The Hospital Discharge Register (http://www.socialstyrelsen.se/register/-halsodataregister/patientregistret) is kept by the National Board of Health and Welfare. It was initiated in 1964 as an experiment in the Uppsala region and was gradually extended to cover the whole Sweden. In 1983 the register covered about 85% of all hospitalisations and in 1987 it reached complete coverage.[53] It contains information about the patients and the hospital together with administrative and medical data on the disease episode.

3.2.4 Censuses

Information on Censuses is kept by Statistics Sweden (http://www.scb.se/BE0205). Censuses were performed in Sweden every tenth year between 1860 and 1930, and every fifth year (except 1955) thereafter, until 1990.

Since 1960 the censuses included information about the individuals, the households and the apartments. Since 1990 the population statistics is based on registers and Censuses are not organised anymore.

3.3 VARIABLES

3.3.1 Outcome

IHD is the outcome of interest in Studies I and III, and AMI in Studies II and IV.

IHD and AMI belong to the group of disorders of the heart and blood vessels called CVD. The underlying cause of the diseases is atherosclerosis and endothelial dysfunction that will lead to chronic inflammatory processes and result in thickening of the vessel walls and formation of plaque. With IHD, the blood supply to the heart muscle is reduced due to atherosclerosis. AMI is a subtype of IHD and occurs when the blood supply to a part of the heart is interrupted, most commonly due to rupture of an unstable plaque on the vessel wall.

In UBCoS the information on hospitalisations and cause of death was retrieved from the Hospital Discharge Register and the Cause of Death Register. The following diagnostic codes according to the International Classification of Diseases (ICD) were used. For IHD: ICD-7 code 420–422; ICD-8 and ICD-9 code 410–414; ICD-10 code I20–25. For AMI: ICD-7 code 420, ICD-8 and ICD-9 code 410, and ICD-10 code I21.

In SHEEP, the diagnostic criteria for AMI applied in the hospitals were: 1) certain symptoms according to case history information, 2) specified changes in blood levels of the cardiac enzymes, 3) specified electrocardiogram changes, or 4) autopsy findings. The diagnosis of AMI required two of the first three criteria to be met or that autopsy findings showed myocardial necrosis with an age compatible with the time of disease onset. Detailed diagnostic criteria are available as an appendix to Study II.

3.3.2 Incidence, mortality and case fatality

Incidence (in Study II), mortality (in Studies I and III) and case fatality (in Study IV) are used to measure disease occurrence in our studies.

Incidence rate is calculated as the ratio between the number of subjects in the initially disease-free population who develop the disease of interest during the follow-up time, and the total time at risk experienced by the

followed subjects. It measures the occurrence of new cases of the disease per unit of person-time.[54] Incidence rate ratio is the rate among exposed divided by rate among the reference group. Mortality rate is analogous to incidence rate, with the outcome being (cause-specific) death instead of disease onset.

Case fatality is the proportion of people, among those who have developed a disease, who die from the disease. It is an incidence proportion rather than rate and should be measured over a fixed and stated time period.[47] In line with the definition in Swedish National AMI Register[55] and international standard, used among others in the MONICA project,[56] we considered in Study IV all hospital discharges and deaths within 28 days after the event to reflect the same AMI episode.

The relationship between disease incidence, mortality and case fatality is schematically described in Figure 2.

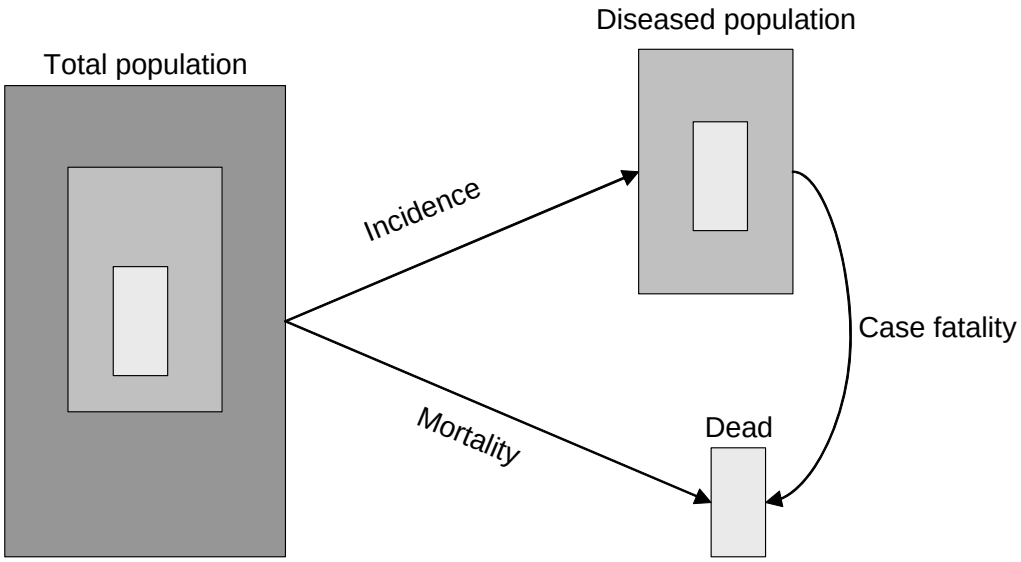

Figure 2. The relationship between disease incidence, mortality and case fatality.

3.3.3 Main exposures

3.3.3.1 Size at birth

In the thesis "size at birth" is used as a general term embracing different measures of the size of a newborn. Small size at birth is seen as an indicator of poor foetal nutrition. Foetal nutrition is determined by

mother's diet and nutrient stores, uterine blood flow and nutrient delivery through the placenta.[57] In a well nourished western population, poor growth may result from inadequate intake of micronutrients[58-60] rather than undernutrition as such.

Birth weight, length and head circumference are absolute measures of size that are routinely recorded at birth. These measures are correlated with many factors including maternal age, parity, weight and height as well as paternal body size,[61,62] but most importantly – gestational age.

The ponderal index is calculated as birth weight in kg/ (birth length in m)^3. It takes into account the weight and the length of the baby simultaneously and is therefore more informative than absolute weight or length per se. It characterises the "chubbiness" of the newborn.

Weight at birth standardised for gestational age is a marker of the growth rate of the foetus in utero. It indicates how well the baby has been growing in utero compared to the expected growth rate. As boys tend to be larger at birth it is calculated separately for boys and girls. It can be calculated when the length of gestation is known, which is often not the case with historical cohorts. By having information on gestational age it is possible to separate between small size due to preterm birth and small size due to growth retardation.

Both UBCoS and SHEEP use archived birth records as the source of information on size at birth. For UBCoS cohort members, according to the cohort definition, all the birth certificates were found in the same place. Individuals included in SHEEP were born all over Sweden and birth certificates were searched in local archives all over the country.

In UBCoS (Studies I, III, IV) the standardisation of birth weight for the analyses was done internally in the cohort, by calculating a z-score = (the individual birth weight - mean birth weight over subjects born within the same week of gestation)/standard deviation of birth weight for the same gestational age. Gestational age was calculated from the date of the last menstruation as recalled by the mother. In Study III, we considered weight, length and head circumference for gestational age being manifestations of an underlying latent variable – foetal growth rate. In SHEEP (Study II), the national reference standard was used for assigning the z-score.[63] Gestational age was based, in the order of preference, on the expected date of delivery, last menstruation, or quickening (the initial motion of the foetus felt by the mother).

We excluded individuals born before the 30th week of gestation from the analyses. During the first half of the 20th century survival rates in preterm births were much lower than today and because they are so few, it is more difficult to establish the expected growth rates in this group. Also, the extremely preterm born babies face different challenges and may be exposed to different disease mechanisms than the babies with size within the normal range who are in focus of our analyses. Also, non-singleton births were excluded from the analyses for similar reasons. Twins are smaller at birth than singletons but do not have higher CHD mortality than the general population.[64,65]

3.3.3.2 Cognitive ability

Cognitive abilities comprise of a wide range of functions related to the selection, storage, manipulation and organisation of information.[30] There are many conceptualisations of intelligence, but the most influential approach is based on psychometric testing.[35] Since Spearman's work in 1904[66] it has been confirmed in a number of studies[67] that all mental tests tend to correlate positively. The underlying factor that explains the inter-correlation is termed 'g' ("general intelligence"). It has been shown that this factor predicts school marks and is correlated with general school achievement.[68]

In Study III, we used school marks in the 3rd grade as realisations of an underlying latent variable reflecting cognitive ability.

3.3.3.3 Socio-demographic characteristics

Socioeconomic position is usually measured by income, occupation or educational attainment and reflects the individual's occupational prestige and access to resources and knowledge.[69] In general increasing social status is associated with better health.[70] The different aspects of socioeconomic position are correlated but may nevertheless have different implications and causes.[71] Occupational class reflects employment status and relations, and the actual work conditions; education is related to cognitive ability and capacity to collect information; income predicts the material conditions.[72] Health differences between social classes may be explained by selection, difference in living and working conditions, life-style and behaviours; unequal access to health care or differing levels of social support.[72]

In UBCoS, data on socioeconomic background at birth and in childhood was derived from the birth records and school registries. Socioeconomic group of the household was based on the father's, and if there was no father, on the mother's occupation. Adult social class was retrieved from

the 1960 Census records. Social class was at all occasions grouped as non-manual, self-employed (including farmers), manual class, and others (no occupation or occupation could not be coded). In Studies I and IV it was analysed as a categorical and in Study III as a continuous variable.

In Study I, we included intergenerational social mobility in the models besides social class at birth and in adulthood. As the self-employed and "other" categories represent small and heterogeneous groups, analyses concerning social mobility were restricted to the non-manual and manual class. Four social trajectories were considered: stable high (non-manual in childhood and in adulthood); stable low (manual in childhood and in adulthood); upward mobile (manual in childhood and non-manual in adulthood) and downward mobile (non-manual in childhood and manual in adulthood).

In Study I, personal earned gross income and household total gross income from the 1970 Census were used as sex-specific quartiles; individuals with zero personal income were treated as a separate group and individuals with zero household income were excluded from the analysis.

In SHEEP (Study II), achieved education as reported in the questionnaire was used as a marker of socioeconomic position. Education rather than occupational social class was used because of better data coverage and better predictive power.

In Study IV, we used marital status from the last Census before the AMI incidence as an additional indicator of social circumstances. It was categorised as married or cohabiting; divorced, separated or widowed; or never married.

In Studies I and IV socioeconomic status was analysed as one of the exposures of interest. In Studies II and III the analyses were adjusted for socioeconomic indicators.

3.3.3.4 Adult body size

BMI, calculated as weight in kg/ (length in m)^2, is a widely used measure of body proportions that is positively correlated with total body fat.[73] It does not, however, characterize the distribution of body fat, and may thus fail to identify individuals with excess abdominal fatness. Such individuals are at higher risk of adverse health consequences of obesity.[74] Waist to hip ratio (WHR) is considered a better indicator of abdominal fat accumulation and CVD risk than BMI.[75]

In Study II, we used BMI from three occasions in adulthood: at the age of 20, the life time maximum (together with the age when it occurred) and at the time of the AMI incidence. The BMI was calculated using current weight and measured, self-reported or recalled weight, preferring the measured values whenever available. Additionally, WHR was calculated based on measurements taken on the health examination. The number of persons with high BMI was small and we were forced, consistently with previous studies on SHEEP,[76] to choose relatively low cut-points to define overweight. We dichotomised BMI with cut-off point 24 at the age of 20, and with cut-off point 28 at maximum and at inclusion. The three BMI measures were used one at a time in the initial analyses and combined to a life-time trajectory at a later stage. WHR was dichotomised at 0.90 for men and 0.8 for women.[77]

3.3.4 Other variables

In addition to the exposures of interest the following variables were added in the models.

All the analyses in the thesis take the subjects' **age** into account. For many diseases including CVD age is the single strongest risk factor. It is also correlated with many exposures. In the analyses based on UBCoS we additionally stratified the cohort by birth year in 5-year intervals. This way we controlled for possible **cohort** effects or, equivalently, the **calendar time** and thus trends in the disease incidence and treatment routines that could confound the associations of interest.

All the analyses were initially stratified by **sex**. The estimates were then pooled where the associations were similar in men and women (Study II, parts of Study IV).

Gestational age was used when calculating standardised birth weight for gestational age. In Study II we added gestational age as a possible confounder when analysing the association between birth weight and AMI incidence.

Parity is the number of live born children a woman has delivered. It was added as a confounder in the models. Also, the analyses were adjusted for other **characteristics of the mother** at the child's birth such as her marital status and age. This information was derived from the birth records.

Metabolic syndrome is clustering of risk factors that increase risk for CVD.[78] There are different definitions for metabolic syndrome,[79] but most of them include abdominal obesity (manifested as increased waist circum-

ference), dyslipidemia (raised triglycerides and low concentration of HDL cholesterol), elevated blood pressure and insulin resistance. According to the thrifty phenotype hypothesis metabolic syndrome is a mediator of the effect of foetal undernutrition on CVD.[17]

In Study II, we used high WHR, elevated blood pressure, insulin resistance, LDL/HDL cholesterol ratio and increased triglycerides as indicators of metabolic syndrome. This information was available for non-fatal cases and their controls who attended the health examination.

3.4 STATISTICAL ANALYSIS

3.4.1 Study I

We used Cox's proportional hazards model with age as the time scale to estimate hazard ratios of IHD mortality. All the analyses were controlled for period of birth in 5-year intervals. Statistical interaction was assessed by adding a multiplicative interaction term in the model.

3.4.2 Study II

We used logistic regression modelling to estimate odds ratios (OR's) of incident AMI. Because incidence density sampling was used for selecting the controls, the OR's from analysing this case-control study estimate incidence rate ratios. All the analyses were adjusted for the design variables, i.e. age and hospital catchment area. Additional adjustments were made for social background at birth and in adulthood as well as for established cardiovascular risk factors. We used latent class growth analysis[80] to identify homogeneous classes within the population with respect to life time BMI trajectory.

Population attributable fraction was calculated as $P_{exp}(OR-1)/[1+P_{exp}(OR-1)]$ where P_{exp} is the proportion exposed to small birth size, and OR is the relative risk for AMI in this group compared to those with normal birth size. Attributable fraction quantifies the proportion of cases that can be attributed to a certain risk factor and help assessing a potential impact of preventive interventions on population health.[81]

We assessed the departure from additivity of risks and thus the presence of biological interaction with synergy index.[54] It was calculated as $S = (OR_{11} - 1)/[(OR_{01} - 1)+(OR_{10} – 1)]$ where OR_{11} is the relative risk for the doubly exposed compared to the non-exposed group, and OR_{10} and OR_{01} are the relative risks for the groups exposed only to the first or second exposure, respectively.

3.4.3 Study III

Structural equation modelling including Cox proportional hazards model was used to simultaneously consider the relationships between the variables, in accordance with the assumed causal structure. Foetal growth and cognitive ability were included as latent variables indicated by different measures of size at birth and school marks, respectively.

3.4.4 Study IV

Logistic regression analysis was used to study 28 day case fatality of AMI. All the analyses were adjusted for period of hospitalisation and age at hospitalisation, and stratified by or adjusted for sex. Additional adjustments were made for biological and social characteristics at birth and social characteristics in adulthood.

3.5 ETHICAL CONSIDERATIONS

UBCoS and SHEEP have received a full approval from the regional Ethics committee:

UBCoS dnr 03-117, 04-944T, 2009/1115-32;

SHEEP dnr 91:259, 97-094, 01-097, 02-486.

4 RESULTS

4.1 STUDY I: EVIDENCE OF A DIFFERENT ASSOCIATION BETWEEN FOETAL GROWTH RATE AND IHD MORTALITY BY SOCIAL CIRCUMSTANCES

In Study I we explored whether the strength of the association of size at birth with mortality from IHD in men and women differs by social circumstances at birth or in adulthood. The aim was to study whether the biological susceptibility to disease is altered by socioeconomic environment at different stages of the life course.

Birth weight for gestational age was inversely associated with the risk of IHD death in men and women: hazard ratio HR = 0.91 with 95% confidence interval (CI) 0.85 to 0.96 per 1 standard deviation (SD) increase in men and HR = 0.88 with 95% CI 0.80 to 0.98 in women. The ponderal index and social class in childhood were not statistically significantly associated with IHD mortality. Lower social class in adulthood and lower personal earned gross income and household total gross income in adulthood were associated with a higher risk of IHD death in men. Lower household income in adulthood was associated with a higher risk of IHD death in women.

The association of size at birth with IHD mortality was not modified by social class at birth. In men, there was an interaction between size at birth and adult social class so that birth weight for gestational age only predicted IHD mortality within the higher social class, i.e. non-manual workers (HR = 0.84 with 95% CI 0.75 to 0.93 per 1 SD weight for gestational age), but not in the manual class. The trend in IHD mortality over quartiles of personal income in adulthood was stronger in men who were thin at birth (ponderal index less than 26) as compared to those with the ponderal index 26 or more. No evidence of an interaction between size at birth and social mobility was found in the data.

4.2 STUDY II: SYNERGISTIC INTERACTION BETWEEN BIRTH WEIGHT FOR GESTATIONAL AGE AND OVERWEIGHT IN ADULTHOOD ON AMI RISK

In Study II we assessed the interaction between size at birth and overweight in adulthood in predicting incident AMI. The aim was to assess the biological mechanism underlying the inverse relationship of size

at birth with risk of CVD, as suggested by the thrifty phenotype hypothesis.

Men and women who belonged to the 5% smallest with respect to birth weight for gestational age, compared to the rest of 95% births, had increased risk of AMI (OR = 2.0 with 95% CI 1.4 to 2.9, attributable fraction 5%).

Size at birth was positively associated with adult BMI so that those who were small at birth tended, on average, to remain relatively lean throughout adulthood. Individuals who were small at birth and however developed high BMI later in life ran a high risk of AMI. For example, people having low birth weight for gestational age in combination with high BMI at the time of the AMI had OR = 10.8 with 95% CI 3.6 to 31.8 as compared to those with normal birth size and normal BMI. This was a synergistic interaction exceeding additivity of combined exposure, synergy index 6.5 with 95% CI 1.8 to 24.0 for the interaction.

4.3 STUDY III: AN INDIRECT ASSOCIATION BETWEEN FOETAL GROWTH AND IHD THROUGH COGNITIVE ABILITY

In Study III we simultaneously analysed the associations between foetal growth, cognitive ability and IHD mortality, taking into consideration possible confounding and mediating factors. The main aim was to assess whether there is an indirect association between foetal growth and IHD mortality through cognitive ability in childhood.

In the analyses, weight, length and head circumference at birth were used to measure latent foetal growth rate, and school marks in the 3rd grade were considered as indicators of latent cognitive ability. The study confirmed a positive association of foetal growth with childhood cognitive ability, and negative associations of foetal growth and childhood cognitive ability with IHD mortality in men and women in a simultaneous analysis. The results suggest that there is an indirect association between foetal growth and IHD mortality through cognitive ability, and cognitive ability is linked to IHD mortality partly through achieved education and adult social class.

4.4 STUDY IV: BIRTH WEIGHT FOR GESTATIONAL AGE AND SOCIAL CLASS AT BIRTH ARE ASSOCIATED WITH CASE FATALITY OF AMI

In Study IV we explored the influence of standardised birth weight for gestational age and social class at birth on 28 day case fatality of AMI. The main aim was to gain knowledge about early life predictors of AMI case fatality, and thus the link between incidence and mortality.

There was a U-shaped association between standardised birth weight for gestational age and case fatality of AMI in men (p = 0.045 for age and period adjusted quadratic trend over quintiles of standardised birth weight): men with very low or very high birth weight for gestational age had a higher risk of dying after AMI than men with intermediate birth size. The U-shape was especially strong in cases of AMI occurring during the early years of follow-up, i.e. among younger men. We found no association between birth weight for gestational age and case fatality of AMI in women. There was a suggestion of increased case fatality of AMI for manual social class at birth and in adulthood compared to non-manual class, as well as a suggested inverse association of AMI case fatality with household income in adulthood in the cohort. Never married men had higher case fatality than married and divorced men.

5 DISCUSSION

5.1 MAIN FINDINGS

In this thesis we studied the mechanisms underlying the inverse association between size at birth and CVD. To begin with, small size at birth was associated with an increased risk of disease in both data materials, UBCoS and SHEEP.

Further analyses showed that birth weight for gestational age was associated with IHD mortality in men within the non-manual class but not among the manual workers, although the overall mortality rate was higher in the latter. There was no difference in the association by the men's family's social class at birth. For women, neither social class at birth nor in adulthood modified the association between birth weight for gestational age and IHD mortality.

We found that there was a synergistic interaction between low weight for gestational age and overweight in adulthood on risk of AMI.

The simultaneous analysis of foetal growth, cognitive ability and IHD mortality suggested that there is, besides a direct association between foetal growth and IHD mortality, an indirect association through childhood cognitive ability.

Finally, men with very low and very high birth weight for gestational age had a higher AMI case fatality than men with intermediate birth size. Case fatality in women was not associated with their size at birth.

5.2 INTERPRETATION OF THE RESULTS

5.2.1 Study I

We found that birth weight for gestational age in men was associated with IHD mortality within the non-manual class but not among the manual workers. This finding was unexpected as previous studies suggest that small babies are less resilient to adverse exposures later in life.[18] Thus a stronger association with size at birth would be expected among those in the more disadvantaged socioeconomic position. Our main explanation to these result is that the effect of size at birth may be less pronounced in the lower adult social class because other cardiovascular risk factors are more prominent, thus rendering the effect of size at birth relatively unimportant in that group. This is plausible as the overall mortality rate was higher in

the lower class. On the other hand, the mismatch hypothesis states that foetal undernutrition in the meeting with later affluence causes the disease. In the 1960's, at the beginning of follow-up, prevalence of risk factors such as diet high in fat may have been relatively high in higher classes. For example, CHD was more prevalent in higher social class than in lower in USA at that time even if incidence in the both classes was almost equal suggesting an ongoing shift.[82] In Sweden around the same time a shift in the social gradient of alcohol consumption[83] and smoking[84] took place so that the consumption level for manual workers became equal to or exceeded the level for non-manuals. As a consequence, the social gradient in the degree of mismatch between early and late nutrition changed during the follow-up and the effects are difficult to disentangle. Different indicators of exposures may have different implications and their role should be more thoroughly explored in further studies.

5.2.2 Study II

The synergistic interaction suggests that there is a causal interdependence between small size at birth and high adult BMI with respect to AMI risk. This result supports the thrifty phenotype hypothesis according to which a mismatch between foetal and adult nutrition is causing the disease. The public health relevance of this mechanism, on the other hand, seems to be limited with only a small portion of cases originating through this biologically plausible mechanism. This is in line with arguments presented by Kramer who suggests that restricted foetal growth plays a minor role in the aetiology of adult chronic disease.[85] In another population with a different pattern of exposure and with a different degree of mismatch, nevertheless, this mechanism could underlie a larger proportion of cases.

5.2.3 Study III

The existence of an indirect association between foetal growth and IHD mortality through childhood cognitive ability, besides the direct association, suggests that mechanisms related to brain development are contributing to the association between poor foetal nutrition and IHD. According to the foetal programming and thrifty phenotype hypotheses the association is generated by an effect on organ structure, physiology and metabolism. Our results imply that foetal nutrition also has an effect on cognition, and the association with IHD involves pathways, through which cognitive ability is assumed to affect chronic disease development, such as educational and socioeconomic attainment, or ability to understand health promotion messages and manage disease. At the same time, childhood cognitive ability is not determined by foetal nutrition alone and other factors play a role in the development of cognitive skills. Thus cognitive

ability has an independent effect on IHD mortality, beyond that explained by foetal nutrition.

5.2.4 Study IV

The results in the case fatality analysis in Study IV suggest that mechanisms operating after the AMI event that determine the prognosis might partly be different from the mechanisms that drive the development of the disease. The U-shaped association may reflect the important role of co-morbidities such as diabetes, which is known to affect the prognosis after AMI,[86-88] and at the same time is more frequent in individuals with very small or very big size at birth.[89-91] Besides biological severity and susceptibility of the case, the mechanisms for 28 day case fatality are also linked to factors influencing getting to the hospital and in-hospital treatment. These are probably related to socioeconomic circumstances – the strong association with marital status supports this suggestion. However, socioeconomic background may be indirectly influenced by foetal exposures, for instance through the effect on cognitive ability as found in Study III. An association between foetal growth and subsequent marital status for men has been found in UBCoS,[92] Helsinki and Hertfordshire.[93]

5.3 ASSOCIATIONS WITH SIZE AT BIRTH

Among others, the systematic review that was mentioned earlier,[10] and a recent book by Gluckman and Hanson[15] propose that that there is no absolute birth weight under which the risk for CVD is increased; rather, there is a monotonic inverse association with disease risk over the whole range of normal birth size. This is explained by the fact that size at birth does not precisely reflect the actual conditions experienced prenatally. A newborn may be small because of a lower innate growth potential despite an optimal foetal environment; conversely, a large baby could still have suffered from foetal malnutrition that prevented it from reaching its full growth potential.[94] Misclassification of the exposure – poor foetal nutrition – is thus inevitable. Even if ponderal index and birth weight standardised for gestational age are more informative measures than the absolute birth weight, they are still only crude measures of how foetal nutrition has affected body composition, so the true size of the effect of foetal growth on later disease is hard to measure.[95]

In UBCoS, the relationship between standardised birth weight for gestational age and IHD mortality was well approximated by a linear model. In SHEEP which includes individuals who were born later and during a longer period than in UBCoS, on the other hand, the association of size at birth with incident AMI seemed to be confined to the smallest 5% of newborns – this was particularly apparent for men. The threshold

effect in women was less clear and increasing absolute birth weight and birth weight for gestational age seemed to be associated with somewhat decreased disease risk even within the highest 95%. However, there was a clear difference in the level of risks between the lowest 5% and the rest of the birth size distribution that was not captured by a linear trend. Also the interaction effect with later overweight was detected among those with smallest birth size only.

The somewhat different shape of the association in the two materials need not be a contradiction. Under the same biological mechanism the strength and the shape of the observed association may differ in different samples, depending e.g. on the distribution of exposure, without contradicting the biological hypothesis.[96]

The association between birth weight for gestational age and AMI case fatality has not been studied before. The suggested mechanism of the association through diabetes or other comorbidities is plausible, but should be confirmed in other studies where the role of these factors can be explored.

5.4 CONTRIBUTION OF SOCIOECONOMIC FACTORS

Associations with indicators of socioeconomic position were analysed in Studies I and IV. In both men and women, less advantaged childhood social class was associated with a marginally higher risk of IHD death and AMI case fatality. Similar associations were found for adult social class and income. The interaction between standardised birth weight and adult social class on IHD mortality was only present in men.

In Studies II and III socioeconomic indicators were analysed as confounders or intermediate variables. Adjustments for social background at birth and in adulthood had only minor effect on the estimates in Study II. In Study III, social class at birth was associated with foetal growth and cognitive ability, and cognitive ability was indirectly associated with IHD mortality through achieved education and adult social class.

The indicators were crude and most probably did not capture all relevant aspects of socioeconomic position or socioeconomic circumstances. For example, social class derived from father's occupation may not adequately describe the environmental influences on the developing child.[97] In Studies I and IV, measurement of social class gathered at a later point during the childhood might have been a better indicator of social circumstances during the course of up-bringing than social class at birth. Adult social class and income were assessed at the censuses and may not reflect the circumstances throughout adult life. Misclassification is possible, especial-

ly for women and for older individuals, but is supposedly independent of the outcome. To conclude, the role of socioeconomic factors is certainly underestimated in our analyses. However, our results are consistent with the suggestion that childhood socioeconomic environment is associated with exposures relevant for adult disease,[98] and with the idea of social chains of risk operating through education and adult socioeconomic circumstances.[99] Where size at birth and early social characteristics were included in the same models and thus mutually adjusted for, both still had an independent association with the outcome. This indicates that they represent two partly different pathways to CVD.

5.5 DIFFERENCES BETWEEN MEN AND WOMEN

Absolute risk of CVD is lower for women than for men, but relative risks associated with classical adult risk factors such as smoking, hypertension, obesity and physical inactivity are similar[100] in both genders or possibly higher[51] in women. There are some differences in the relative contribution of risk factors, but reduced foetal growth, poor socioeconomic conditions and adult life style factors are consistently associated with CVD in both genders.[100-102]

Even if formal comparisons between men and women were not performed (as this was not the focus of the thesis), we noticed that there were some differences in the associations. The associations of size at birth with AMI incidence and IHD mortality were similar in men and women, but the association with AMI case fatality was present in men only. The associations with indicators of socioeconomic position tended to be stronger in men than in women. All the estimates were less precise in women due to smaller number of cases.

Some differences between men and women in the association of size at birth with later disease have been found,[103-105] and it has been suggested that women are more resilient to intrauterine undernutrition than men.[106,107] Our results are however consistent with the analyses in the systematic review referred to above that did not indicate any significant sex differences in the relative risks for IHD.[10]

The weaker associations with adult socioeconomic circumstances in women were at least partly due to misclassification. Misclassification of adult social class was supposedly independent of the outcome, but different in men and women. At the time of Census 1960, over 60% of the women in UBCoS were not in gainful employment and were assigned their husband's social class. Husband's class may however even better reflect the women's living conditions than their own. This suggestion is

supported by the finding of an association between household but not personal income with IHD mortality among women in Study I.

Misclassification of social circumstances in childhood is most probably unrelated to the children's sex. The associations with social class at birth and the child's birth order with foetal growth, and the association of foetal growth with cognitive ability were almost identical in boys and girls in Study III, indicating that similar biological mechanisms might operate in both genders.

5.6 METHODOLOGICAL CONSIDERATIONS

5.6.1 Study design

The analyses in this thesis were based on two data materials.

UBCoS is a prospective cohort study including extensive biological information recorded at the time of the cohort members' birth; data on school marks and social background from the time they went to school; and comprehensive register-based social information throughout the individuals' life course. The morbidity and mortality follow-up is done through linkages to the Swedish national registers that are known to hold a good quality. The follow-up in the registers starts before the ages when CVD becomes a frequent cause of morbidity, and ends when the cohort members have reached old age.

SHEEP is a population based case-control study where information on possible risk factors of AMI was gathered through questionnaire, blood sampling and health examination shortly after the AMI incidence. These data were complemented with information recorded at birth certificates at the time of birth.

UBCoS and SHEEP provide a valuable source of data to life course studies of disease aetiology and are appropriate for the aim of the thesis. The available information allowed considering biological and social risk factors of later disease and investigating pathways from early exposures to adult health. We were able to integrate foetal origins and cognitive epidemiology in the life course approach.

5.6.2 Possible sources of bias

There are possible sources of bias in the studies. Bias in epidemiological studies can broadly be divided into selection bias, information bias and confounding.[54] Selection bias occurs when there is a systematic difference between the characteristics of those selected for the study and those who

are not, for example when the exposure status of cases or controls influences the likelihood that they are entered into the case-control study. Information bias arises due to random and non-random misclassification of data.[108]

5.6.2.1 Selection bias

UBCoS

UBCoS only includes hospital births. This might have an effect on the generalizability of the results as for example single mothers were overrepresented among women giving birth in the hospital. Nevertheless, the cohort is representative of the Uppsala region and Sweden in 1915–1929 in terms of infant mortality.[109,110] Also, as our analyses in SHEEP did not reveal any differences in the associations found in home deliveries compared to hospital deliveries, we think we can assume that the same applies to births in Uppsala region.

School records were found for about 80% of the children. The records were less often found for children to unmarried mothers. Probably many of the unmarried women got married later and changed their names which made tracing their children difficult. They also moved more frequently, and some may only have come to Uppsala in order to give birth.[111] Also, children from families of high social class were slightly underrepresented because they more often attended private schools where school records were less well preserved than at state schools. However, under 5% of the children attended private schools at this time.[112]

Follow-up of the cohort members in national registers was practically complete. The proportion of missing data was small and those with missing information on some variables in our studies did not differ significantly from the rest of the cohort with respect to social characteristics at birth, birth weight or IHD mortality. The exclusion of a small proportion of men and women who did not participate in the censuses is unlikely to bias the results notably.

In Study IV we missed hospitalised cases of AMI in cohort members residing in regions that were not included in the Hospital Discharge Register before it covered the whole country. We also restricted the inclusion of cases from Cause of Death Register to the time periods when each administrative area was covered by the Hospital Discharge Register. By doing this we avoided overrepresentation of fatal cases and thus bias. There is also a possibility that we missed some first cases which occurred before start of registering and counted recurrent cases as first cases.

However, as the cohort was relatively young during 1960's and 1970's and coverage by Hospital Discharge Register increased with time, the number of missed cases is probably small. Furthermore, a large part of the cohort never moved away from Uppsala where the registering has been complete since 1964.[53] There is no comparable information available about AMI case fatality rates in the general population for the follow-up period. As our aim was to study the relative case fatality rates, rather than the incidence or the absolute case fatality, we believe that the analysis based on the registered cases within our cohort is reliable.

SHEEP

Participation rate in SHEEP study was around 75%. It was higher among men and non-fatal cases, but without differences across age groups or hospital catchment areas. Thus the bias due to factors correlated with age or area of residence should be minimised.[51]

We restricted the analysis to subjects born in Sweden because birth records could not be searched for people born outside the country. As a result, one tenth of people were removed from the analysis. This is a restriction of the study base. Similarly, including only singleton births in the study is a restriction of the study base and not a source of bias.

Birth information was available for more than 70% for the eligible subjects. The missingness due to unavailability of birth records does probably not impede generalization or create any large bias as the records were sought from all of Sweden and missingness was foremost due to archive routines at smaller health care units. These were scattered around the country implying less influence on generalizability. There was a slight decrease in availability of birth information with increasing age; birth records were less often found for those who were born to a farmer's family than for other social class groups. However, there were no differences between the study subjects with and without birth information with respect to sex, case status, BMI at any time, or any of the measurements at the physical examination.

Health examination and blood laboratory was only done for the non-fatal portion of SHEEP. Participation rate was 90% and did not differ between men and women, cases and controls. Non-participation here could be selective but this only affected those secondary analyses in which we used this data for adjustments. There was a loss of blood (about 25% of samples) for laboratory analyses because of a freezer brake-down in 1998 but supposedly this affected the blood samples completely at random.

To sum up, a quarter of the initially eligible participants were lost due to non-participation, a tenth due to restrictions made, and a fifth due to non-available information presumably random to case status and exposure. A flow chart describing the losses is available as an appendix to Study II. In the extended analyses there were further losses due to loss of blood samples. On the other hand it is worth noting that item non-response was very low in the material as participants with partial non-response were contacted by telephone in order to make the questionnaire complete.

5.6.2.2 Information bias

UBCoS

In UBCoS, all information is based on records made at the time of the cohort members' birth and school attendance and in contemporary registers, and no information is based on recall. Thus misclassification of the data, both the historical and that recorded in the registers, can be assumed to be non-differential with respect to exposures or outcome. As discussed earlier, it is possible that there was a degree of misclassification in the adult social characteristics of the study subjects, or that the social class recorded at a census is a poor indicator of the actual circumstances the individuals experienced.

During the follow-up period the diagnostic criteria and tools as well as treatment techniques have changed. Therefore there could be some misclassification in both Hospital Discharge Register and Cause of Death Register that could bias the results. It is known that the diagnostics of AMI between 1987 and 1995 varied regionally but were independent of patients' age and gender.[113]

SHEEP

The cases in SHEEP were identified during a short period and the diagnosis was based on rigorous diagnostic criteria that were identical in all participating hospitals. In Stockholm area, diagnostic quality of AMI is high and coverage by Hospital Discharge and Cause of Death Register is considered practically complete.[114] Comparisons of the SHEEP material with population based registers indicate close to complete ascertainment of all first AMIs. Outcome ascertainment had nearly perfect specificity and sensitivity and the possibility of misclassification is minimised.

It is likely that bias was introduced in the results due to information based on recall. For example, two of the three BMI measurements used in our

analyses were based on recall. Also, the fraction of missing values was higher among fatal cases than other groups. However, substantial differences in the levels of BMI would be needed to cause serious bias. Current weight and height were both measured at the health examination and self-reported in the questionnaire by a majority of the participants. Self-reports were highly consistent with measured values, but we were still careful when interpreting the results and avoided putting emphasis on the actual values of the OR's; rather we compared the magnitude and consistency of the estimates.

Bias could also occur due to answers from relatives to fatal cases. To analyse the quality of answers attained this way, 296 partners to non-fatal cases were asked to fill in the same questionnaire as the cases (response rate 82%). Comparisons showed that answers given by the cases and by their partners were highly consistent regarding hypertension, diabetes, overweight and smoking; the quality was lower for physical inactivity.

The health examination was done by trained personnel and blood samples were analysed in a blinded manner in order to reduce the possibility of bias. The examination was undertaken at least 3 months after the AMI onset, when metabolic stability should have been attained. People who have had AMI are commonly advised to make preventive changes in lifestyle that may alter levels of biomarkers. As a result the cases may have become more similar to the controls than they were when the AMI occurred and we might underestimate the influence of biomarkers on the estimates.

5.6.2.3 Confounding

Many important possible confounders were included in our analyses. The available data allowed adjustments for factors from several time points through the life course in all the analyses. We had access to information on biological and social exposures. Residual confounding nevertheless remains possible depending on how the variables were measured. For example, social class was very crudely measured and probably did not capture all aspects of socioeconomic position. There are also potential unmeasured confounders such as maternal smoking and hypertension, and anthropologic measurements of the parents that might be associated with birth weight and later disease risk of the child. In order to cause serious bias the unmeasured confounders should, however, be related to both the exposures and the outcome, and not be associated with the other variables included in the analyses.

In UBCoS we relied on register-based information and did not have any data on health behaviours or markers of disease in adulthood. However,

these factors probably lie on the causal pathway leading to the disease and are thus not confounders.

5.6.3 Choice of method

In Study I we analysed the data with Cox proportional hazards regression and adjusted all models for age and period of birth. We assessed statistical interaction by adding an interaction term in the model. Inclusion of an interaction term in a multiplicative model implies that the investigated relation is not multiplicative, but it does not imply biological interacion.[115] We tried to disentangle the observed associations further by exploring the effect measure modification by social mobility.

In Study II the main analyses were done with logistic regression. By using synergy index we assessed biologic (additive) interaction of exposures, relying on the relative risk estimates from the multiplicative model. When calculating synergy index based on OR there is a risk for bias, depending on the baseline incidence of the outcome.[116] There is no such risk in our analyses because controls were selected from the study base by incidence density sampling and the OR's thus estimate incidence rate ratio irrespectively of the frequency of the outcome.

We complemented the analyses with latent class growth curve analysis. Limiting the analyses to only one BMI measure at a time would have been under utilizing the richness of the data. We thus sought to include the three BMI measurements into the analysis simultaneously and classify the study subjects according to their life time BMI trajectories. The aim of this part of the analysis was latent class analysis rather than growth modelling, thus a relatively simple method was used. Unfortunately, the results of the three classes provided somewhat limited additional information to the results already obtained with previous analyses. However, the question was adequate and we think it is informative in itself that we were not able to single out exposure categories that would allow us to really test the effect of timing of an increased BMI.

In Study III we used SEM that included Cox proportional hazards model. By using SEM, we explicitly stated the temporal ordering and inter-relationships of the variables, both directly and through potential intermediate variables. Including Cox proportional hazards model within the SEM allowed taking time at risk and censored observations into account. Yet, caution is needed when using SEM, because the specified inter-relationships in the model are based on a hypothesised structure and SEM cannot prove that the hypothesis holds. On the other hand, the time sequence of the events in a person's life reduces the possibility of incorrectly specified paths in our analysis.

In Study IV we applied logistic regression. The follow-up for each case was only 28 days and there were no losses or censoring as we excluded the few persons with unknown vital status at the end of follow-up. The main study question and the focus of our analysis was in whether a person died or not during the four weeks period after the AMI event, i.e. we considered it of relatively less importance to describe when during the period the death occurred. Thus it was not necessary to use a method that would take the time at risk into account. Moreover, having 28 days of follow-up and several hundred cases means that we would face the problem of tied observations when using Cox regression, and instead of gaining precision we could have introduced bias in our estimates.[117,118] Considering these arguments logistic regression was an adequate choice of method. For longer periods of follow up it would be preferable to use an approach that considers the time at risk for each individual.

We are aware of risks with adjusting for intermediate variables in regression analysis. For example, according to the thrifty phenotype hypothesis components of metabolic syndrome in Study II lie on the pathway leading to AMI (see Figure 1). Adjustment for these indicators reduced the OR estimates. In order to interpret this as evidence for mediation, some assumptions should hold, namely that there is no confounding between the intermediate variables and the outcome, and that the exposure and intermediate variables do not interact to cause the outcome.[119-121] These assumptions are not verifiable from observed data;[121] it is moreover plausible that they are violated. If this is the case, adjustments may lead to diminution of the estimate even when no mediation is present, or vice versa – no diminution of the estimate occurs even if there is complete mediation.[119] However, our main aim was to study the causal interaction between small birth size and adult overweight. The analyses including intermediate variables were only secondary to the main analysis and an attempt to find out about the details of the interaction mechanism. We emphasize that the effects of these adjustment should be interpreted with caution.

In contrast, we did not see adult BMI as a mediator of the effect of small size at birth on AMI, which would motivate using other techniques such as marginal structural models when analysing the interaction.[122] We observed in our material, consistent with earlier studies, that small birth size predicted low rather than high adult BMI and that it was the small proportion of low birth weight babies that nevertheless developed high BMI in adulthood, probably due to exposure to overnutrition, who had increased risk of AMI.

It could also be argued that adult social class is an intermediate variable in the association of birth weight and childhood socioeconomic circumstances with later disease. On the other hand, adult social class can also be viewed as a marker of earlier social circumstances and full adjustment for confounding by social class therefore needs to include measures from both childhood and adult life. We have in our analyses in Studies II and IV given the reader an opportunity to judge the possibility of some mediation by introducing different factors sequentially in the models and including adult social characteristics only at the final stage.

5.7 CONCLUSIONS

In this thesis we studied mechanisms underlying the well established inverse association of size at birth with CVD risk.

We found that birth weight for gestational age in men was associated with IHD mortality within the non-manual class but not among the manual workers. There was no difference in the association by the men's family's social class at birth. For women, social class neither at birth nor in adulthood modified the association.

There was a synergistic interaction and thus a causal interdependence between low weight for gestational age and overweight in adulthood on risk of AMI. This finding supports the thrifty phenotype hypothesis which states that a mismatch between foetal and adult nutrition is causing CVD.

The simultaneous analysis of foetal growth, cognitive ability and IHD mortality revealed that there is, besides a direct association between foetal growth and IHD mortality, an indirect association through childhood cognitive ability, implying that mechanisms related to brain development are contributing to the association between poor foetal nutrition and IHD.

Men with very low and very high birth weight for gestational age had a higher AMI case fatality than men with intermediate birth size. Thus mechanisms that determine the prognosis after the AMI event might partly be different from the mechanisms that drive the development of the disease. Case fatality in women was not associated with size at birth. There was a suggestion of increased case fatality of AMI for manual social class at birth in both genders.

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