INEQUALITIES IN HEALTH – SOCIAL, BIOLOGICAL, ETHNIC AND LIFE COURSE PERSPECTIVES

Amal Khanolkar

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ABSTRACT

There is an unmistakable consistency in differences in risks for morbidity and mortality between social
groups. The more advantaged, whether measured in terms of income, education, class, status or ethnicity
in general fare better when compared to others, emphasizing the importance of the social environment in
determining health in all stages of life. The early stages of life; infancy, childhood, and adolescence are
particularly vulnerable – exposures and health in these and later periods of life are dependent on both
concurrent social environments and on previous parental life experiences and intergenerational
influences. This stresses the need to investigate the development of risk factors and disease across the life
course. Affluent and high-income countries are increasingly characterized by widening inequalities in
health. Less is known about health differences in ethnic minorities in Sweden compared to similar high-
income countries with large immigrant and ethnic minority groups.

The importance of intergenerational mechanisms and the psychosocial environment in predicting
childhood health was highlighted in studies in this thesis. Children (aged 5-14 years) of parents with
lower reported levels of physical activity, higher smoking and alcohol consumption had higher mean
BMI and cholesterol levels, independent of parental socioeconomic indicators. Overweight/obese parents
also had substantially higher risks for having overweight/obese children (compared to parents of normal
BMI, an obese mother had an OR of 4.53 (95% CI 1.98–10.38) for having an overweight/obese child.
Similarly, OR for obese fathers was 5.07 (95% CI 2.11–12.20)).

Results from studies included in this thesis show that some immigrant groups are at higher risk for health
outcomes seen in different stages of the life course. Immigrant parents from Poland, Yugoslavia, Iran,
South Asia, East Asia and Sub-Saharan Africa had higher risk for early preterm birth (adjusted RR (95%
CI) 1.76, (1.24-2.50), 1.57, (1.31-1.87), 1.67, (1.30-2.14), 1.52, (1.07-2.16), 1.51, (1.08-2.10) and 2.03,
(1.32-3.12)) respectively). South Asian, Sub-Saharan African and East Asian immigrant groups had a
higher risk for late preterm birth (adjusted RR 1.62 (1.42-1.84), 1.31 (1.08-1.60) and 1.20 (1.06-1.36)
respectively). North African/Middle eastern, Somali, and Ethiopian/Eritrean groups had increased RR for
postterm birth (adjusted RR 1.31, (1.16-1.47), 2.57 (2.31-2.86), 1.85 (1.67-2.04) respectively). Children
aged 4-5 years old, with immigrant parents from Turkey, North Africa, Iran and South America had a
higher risk for overweight or obesity compared to children of Swedish born parents. In both studies,
socioeconomic indicators did not explain the observed increased risk for either non-term birth or
overweight/obesity indicating that other factors that constitute ethnicity may play a role.

On the other hand, young Swedish males (ages 18 years) of immigrant parents had lower systolic blood
pressure when compared to ethnic Swedish males. The established inverse association between foetal
growth and adulthood blood pressure while observed in European-origin men was not seen in non-
Europeans.

While evidence exists to support that certain ethnic groups suffer disproportionately in risk for some of
the adverse health outcomes studied in this thesis, there is also an indication that some ethnic groups are
protected from the same. Contrary to expectation, variation in socioeconomic indicators did not explain
the observed differences in risk. More studies are needed to understand these observed differences in
health and guide better public health intervention for reducing inequalities seen in ethnic minorities.
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<table>
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<tr>
<td>ApoB/ApoA1</td>
<td>ApolipoproteinB/ApolipoproteinA1 ratio</td>
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<td>AOR</td>
<td>Adjusted Odds Ratio</td>
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<td>BP</td>
<td>Blood Pressure</td>
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<td>BW</td>
<td>Birth Weight</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>FGR</td>
<td>Foetal Growth Rate</td>
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<td>HBW</td>
<td>High Birth Weight</td>
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<td>LBW</td>
<td>Low Birth Weight</td>
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<td>LDL/HDL ratio</td>
<td>Low density Lipoprotein/High Density Lipoprotein ratio</td>
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<td>MET</td>
<td>Metabolic Equivalent Task</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PA</td>
<td>Physical Activity</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<td>SEP</td>
<td>Socioeconomic Position</td>
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<td>Social Mobility Database</td>
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<td>UFS</td>
<td>Uppsala Family Study</td>
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<td>ULSAM</td>
<td>Uppsala Longitudinal Study of Adult Men</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1 BACKGROUND

1.1 INTRODUCTION

Health inequities persist in all societies, including high-income nations with very little absolute poverty (1). In fact in some high-income nations, ‘health inequalities’ are widening against a backdrop of increasingly better overall population health (decreasing all-cause mortality and increasing life expectancy) (1, 2). In Sweden, differences in life expectancy between the highest and lowest educated men was 4.9 years in 2000 and this difference increased by 0.4 years by 2010 (similarly, the difference in case of women increased by 0.3 years from 4.4 to 4.7 years between 2000 and 2010) (3).

In modern welfare societies, ‘health inequalities’ are a result of complex mechanisms that can be difficult to decipher. They could include sensitive issues like social stigma and isolation, integration into society, racism, and multiple mechanisms related to ethnicity. Which health inequalities constitute health inequities that warrant public health intervention is equally important. The importance of social determinants of health in contributing to health inequalities both within and between countries was highlighted by the evidence gathered and proposals recommended by the World Health Organization’s (WHO) Commission on Social Determinants of Health (CSDH) (1, 4).

What drives health inequalities in high-income and multicultural societies? Are these health inequalities driven by similar mechanisms which result in the large extremes in inequalities that exist between the poorer and most high-income nations of today? In some of the most egalitarian countries such as Sweden with one of the longest life expectancies at birth, differences in mortality by educational groups are amongst the lowest in the world, but inequalities exist and the differences in life expectancy between the highest and lowest educated groups have been steadily increasing over the past few decades (2, 5). Differences have also been documented for specific health outcomes such as cardiovascular disease (CVD), cancer and injuries (6).

If health inequalities emerge by the way people are born, grow, live, work and age (as the CSDH has concluded and ratified recently by all WHO member nations) (7), an investigation into health inequalities, its mechanisms and how they can be better addressed can only be done using an approach that spans the entire life course. Life course epidemiology addresses interactions between multiple risks, accumulation of risk and effects due to environmental exposures during “sensitive” or critical periods beginning early in life and extending throughout the life span and across generations (8-10). In such a framework, in utero, genetic and/or ethnic factors predisposing to health problems can be considered as a disadvantage that accumulates or interacts with other disadvantages over the life course. Identification of critical periods in early life that predetermine later disease risk is also possible. Inequalities due to ethnicity are complex, as minority groups generally have less wealth (often comparable to lower socioeconomic groups of the majority) face racial barriers like unequal opportunities and health access which can transgress generations. Whether socioeconomic circumstances alone are responsible for differential health among ethnic groups is uncertain and debatable (11).
Using both a cross-sectional and life course approach, we investigated the role of the social (position/class in society at different life stages and ethnicity) and biological (foetal growth, early life factors and genetics) environments in contributing to health inequalities. We examined social and ethnic patterning of selected risk factors that may 

1.2 SIGNIFICANCE

CVD is one of the biggest killers in high-income countries despite its recent decreasing incidence. It will be the one of the largest killers in developing countries in the near future (14). Investigating what drives inequalities in high-income nations will not only help reduce the same but can be transferred to developing countries that are increasingly becoming more multicultural and undergoing the same economic and health transition experienced by high-income countries some decades ago.

Ethnicity is considered by some to be next most important epidemiological variable after age (15, 16). Several high-income countries in Europe and North America are ethnically diverse and more countries in other parts of the world are increasingly becoming so. Future public health policies will need to be shaped and developed taking into account the heterogeneous composition of modern society. While some countries have already made it mandatory for public health policies and similar guidelines to be developed taking into account ethnic diversity, others are still lagging behind in appreciating and understanding the role of ethnicity in determining health.
1.3 ETHICAL CONSIDERATIONS

All published papers and manuscripts included in this thesis were based on studies conducted with necessary local ethical permissions and clearance. Specifically, the ethical permits: Dnr 02-605, Dnr 2006:055, Dnr 2008/367, Dnr 03-466 and Dnr 02-410 issued by regional ethical boards in Stockholm and Uppsala cover all studies carried out as part of this thesis. The personal integrity of subjects was not violated as all studies were carried out using anonymised data.

The definitions of ethnicity, ethnic group, ethnic minority, immigrant, immigrant group, minority and other similarly associated terms may appear confusing to define and often spark considerable debate. What (or who) rightly constitutes an ethnic/immigrant group or ethnic/immigrant minority may not always be agreed upon by everyone. In the course of working on some of the projects included in this thesis, I have often received criticism for the manner in which I classify ethnic /immigrant groups or who I consider to be belonging to an ethnic/immigrant minority. Quite often I have been reproached for using such terminology. On the other hand I have also received considerable support and enthusiasm in pursuing these projects. On several occasions I have even received positive feedback in initiating such discussions and ‘steering’ a debate on the definitions of ethnicity in the Swedish context. Nonetheless, I would like to stress that the usage of the terms ethnicity, immigrant group and similarly associated terms in this thesis are not meant to cause offense to any particular individual or group of individuals. I hope that results from the studies included in this thesis will not only highlight the differences in health observed in some groups of the Swedish population depending on their geographical origin, but will also help encourage further research in this area.

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2 SOCIAL DETERMINANTS OF HEALTH

2.1 BACKGROUND

Considerable research in recent years has helped us better understand and appreciate the sensitivity of health to the social environment (4, 17). Furthermore, research has highlighted the consequences of being exposed to adverse environments and ill health in earlier stages of life which may have both short and long-term effects on health in subsequent stages spanning the entire life course (18). Such long-term consequences are indeed truly ‘long-term’ as these effects may span generations thereby affecting health of individuals for considerable amount of time.

Life expectancy is shorter and diseases are more common in those individuals lower down on the ‘social ladder’ across all societies within and between countries. The sensitivity of an individual’s position on this social ladder is incredible such that even among middle-class office workers, lower ranking staff suffer disproportionately from mortality and morbidity when compared to higher ranking staff (19). Mothers with a Master’s or Doctorate degree are more likely to gain the recommended gestational weight during pregnancy when compared to mothers with a Bachelor’s degree (from on-going research). This indicates that the social gradient in health runs right across society. Figure 1 below shows age-specific mortality rate ratios in Swedish men and women by educational level. It is considered that both material and psychosocial disadvantages contribute to such differences in risk for increased morbidity and mortality. Such disadvantages – whether measured in absolute (family assets, income etc.) or relative (lower education, receiving lower amount of social services, inadequate social networking or social exclusion) terms tend to concentrate in similar groups of people. There can also be an ‘accumulation’ of disadvantage that occurs across the life course substantially increasing risk for ill health and earlier mortality. The sensitivity of health to the social environment was recently explored during the 2008 economic recession which exposed even wider inequities than expected both between and within countries that constitute the WHO European region (2).

Systematic differences in health between social groups that are both avoidable and morally considered to be unjust are collectively referred to as ‘health inequities’. Health inequalities on the other hand, are any sort of differences in health between social groups which may or may not be morally unjust (e.g. differences in rates of breast cancer between men and women, longer life expectancy among women, or higher rates of diabetes in the Indian origin population in the UK ). While health inequities are observed in all societies across the world, the reasons behind these inequities could be very different between countries and regions making comparisons difficult and maybe unfair. Consequently, very different public health policies maybe required to address health inequities in high-, middle- and low-income countries. Countries with vastly different economic resources have equally different priorities including those in the health arena. Thus most research cited in this thesis is based on studies conducted in high-income countries similar to Sweden.

In a recent review commissioned by the WHO to develop a new health policy framework (Health 2020) for the 53 member states of the WHO European region, recommends: 1. Universal health coverage; 2. Addressing health behaviours (smoking, alcohol consumption, diet and physical activity) which are not only causes of
differences health risk and mortality but are also socially patterned; and 3. To address the
causes of the causes; the conditions in which people are born, grow, live, work and age – i.e.
the entire life course (2). The report also calls to address issues related to distribution of
resources, power and money. This highlights that tackling social determinants of health and
reducing health inequities requires an all-inclusive approach that must target the conditions
that effect individuals of all ages and all stages of development which go hand in hand with
human rights and empowerment.

![Figure 1. Age-specific relative mortality ratios for women (left) and men (right) by educational

2.2 INDICATORS OF SOCIAL DETERMINANTS OF HEALTH AND THEIR MEASUREMENT

As discussed above, there is ample evidence that socioeconomic conditions influence health.
An exposure or independent variable must be clearly defined and labelled and must be
measured precisely to reduce bias. There are several ways to measure and describe an
individual’s or groups’ or populations’ socioeconomic conditions. The terms socioeconomic
status (SES), socioeconomic position (SEP), social class, social conditions, and social
stratification are often used interchangeably even if they might have different theoretical
backgrounds or implications. This is problematic (20). In this thesis, I have used the term SEP
to indicate an entity that tries to capture the social and economic conditions of an individual
or group of individuals. In order to understand the use of various socioeconomic indicators in
social epidemiological research, it could be beneficial to understand some of the historical
underlying concepts developed in this field. Many of such concepts were developed by two
social theorists; Karl Marx and Max Weber, both German “thinkers” and philosophers. Marx
hypothesized about the struggle between the workers and employers (21). Social class and
thus an individual’s position in society was intrinsically tied to his or her relation to ‘means of production’ such as land, factories, or other places of work. He further postulated that interactions between different social classes i.e. social relations, were characterised by the friction that arose between upper and lower social classes (such as those between the exploiters who controlled production and the exploited who often worked in factories or on land). This was a structural relationship exogenous to any individual and formed an intrinsic component of the capitalist system (21).

Weber, on the other hand thought society on the whole was structurally and hierarchically stratified along many dimensions, such as the labour market or the state bureaucracy. This creates groups of individuals who often share common interests, goals and positions in society (21). More importantly, they have similar possibilities or ‘chances’ in life. These chances are often created and acted upon by an individual’s circumstances and abilities – for example to use or trade one’s social skills, education and other attributes to better one’s social position (21). It is Weber’s ideas on social stratification that form the bases for today’s use of multiple socioeconomic indicators in epidemiology. It is important to understand that though SEP in epidemiology is most often defined at the individual level, it is partly determined by structural relations between various groups within a society.

Monitoring or describing health inequalities poses challenges. Not only must one strive to have robust indicators of socioeconomic conditions, but these indicators must also measure the same construct and have the same meaning across time, groups (ethnic/immigrant, gender, age etc.) and/or countries. It is not useful to ‘search’ for the best indicator (or indicators) of SEP. A lot of thought must be given to the reasons for choosing a particular indicator (or set of) when designing a research project. Most often our choice of socioeconomic indicators depends on variables that are available or easily accessible, but as Braveman et al concluded in their paper, ‘one size does not fit all’ (22).

Described below are some of the most commonly used socioeconomic indicators:

**Education:** This is very commonly used as an individual level indicator of SEP. In many countries, educational level is routinely collected in National registers. Education is often thought to capture the ‘knowledge-related’ assets of an individual (23). It also strongly determines future employment and thus is an indicator of income and social status of an individual. In the life course epidemiological framework it often measures the transition from childhood SEP to that an individual will attain in adulthood. The educational level finally obtained by an individual also captures to some extent, family influences (such as parental choices, motivation and encouragement, financial resources) on an individual’s educational attainment. Similarly it may also capture society’s influence on an individual’s educational attainment (for example, in the Nordic countries education including university level is free and accessible to all). Education can reflect various non-socioeconomic characteristics of an individual such as problem solving skills, intellect, health-related knowledge, general knowledge, influence over others (at work or at home) and one’s life. Additionally, education is a more ‘stable’ measure of SEP, as most often people obtain their highest educational level in early adulthood and this is less likely to change across the life course as other socioeconomic indicators such as income or occupation.
Occupation: As a socioeconomic indicator, occupation is favoured in the UK where a person’s position in society is often conceptualized based on an individual’s occupation and is recorded in all death certificates (23). It is also a popular indicator of SEP in other western European countries like Sweden, Denmark, Norway, Finland, but is less used in North America. Most often similar levels of occupation are grouped together to form occupational classes. Occupation is considered a robust indicator of a person’s SEP but can be problematic in measuring SEP when it comes to certain groups such as students, retirees, people engaged in the ‘black labour market’ or those mostly working at home. Occupation as an indicator of SEP can capture the generic mechanisms that associate SEP with health irrespective of the scheme used to classify various occupational groups. It may also capture specific issues associated with certain occupations such exposure to toxins or greater physical workload at particular places of work. Furthermore, occupation is directly related to income and thus will capture the relationship between material wealth and health. It also reflects social status or prestige associated with different types of occupation.

Income: These could be considered the indicators that best directly measure material wealth or circumstances (22, 23). The amount of money at an individual’s disposal is not likely to affect health outcomes directly but rather indirectly. This may occur through mechanisms in which money is used to promote better health behaviour (such as access to better quality food, gyms, sports facilities, safer modes of transport, and recreational activities). It will affect health outcomes in the manner in which money and assets are used to provide health promoting environments both at the place of work and at home. It may also determine the speed at which certain people may access services and the quality of the same (such as private health care, education etc.). Higher incomes give people more control or power, better social standing and positions of influence in many societies. Income can be problematic as an indicator of SEP, as it can change quite dramatically in short spans of time. It also changes frequently as people move up (or down) their chosen career paths. There may arise instances such as when a person with poor health will lose his job leading to a decrease in income – an example of reverse causality. Income may be difficult to record as it is considered to be sensitive and personal by some. This is however not a problem in the Nordic countries where individual income and taxes are routinely collected. Income maybe measured both at the individual and household level and both have advantages depending on the research question. Ideally income should take into account money received from work/employment as well as other sources such as social benefits, savings, investments and informal sources of income (could be hard to measure).

Wealth is another indicator of SEP used to measure an individual’s material resources such as house and car ownership, savings, access to financial loans, pension, inheritance etc (23). While income is time specific, wealth is often an indicator of accumulated resources. Wealth was not used as an indicator of SEP in this thesis.

The above indicators are the most commonly used in measuring SEP in epidemiological studies where SEP is the main independent variable of interest and when the effects of SEP are adjusted for (22). It is most beneficial to use a combination of these three indicators to get a better overall measure of SEP. Sometimes researchers are reluctant to use both education and income together in the same model as this may introduce collinearity. However, studies have shown that despite education and income being correlated, the correlations are not strong enough for one to replace the other or be used as a proxy (most often correlations
between education and income are less than 0.5 (22)). Also earnings at similar levels of education can vary considerably especially across different social groups (gender, ethnicity, age amongst others). This suggests that education and income are not interchangeable. A study by Geyer et al showed that despite moderate correlations between education, income and occupational class, these social indicators predicted various health outcomes differently suggesting they cannot be used interchangeably in social epidemiological studies. Further, the authors concluded that these indicators measure different phenomena and possibly highlight different underlying causal pathways (20). Issues arising when assessing the role of SEP in ethnic disparities in health are further addressed in section 4.4 below.

Another indicator of SEP is to use area-level indicators of SEP, when the aim of the analysis is not to investigate individual level differences but those based on geographical differences of SEP. Area-level indicators can be used to specifically study socioeconomic indicators of a particular area in determining health outcomes and socioeconomic health inequalities. Area-level indicators are also of importance in studying health inequalities in addition to those described above, however they are not used in this thesis.

Generally the following is recommended when assessing SEP in health related research (22):

1. Different socioeconomic indicators are not interchangeable, since they tap into different aetiologies (even modest correlations do not indicate reason for multicollinearity or that one can be substituted for the other).
2. Ideally multiple socioeconomic indicators should be included (even if they are correlated). Different forms of each indicator should be considered and tested (categorical, continuous, various ways of categorising the variable such as tertiles, quartiles, indices etc.).
3. Stratified analysis should be considered and tested.
4. Claims to have controlled or adjusted for ‘overall’ SEP/SES should be avoided when just one or two socioeconomic indicators have been used.
5. Justification for using a particular socioeconomic indicator(s) must be included.
6. Potential unmeasured socioeconomic aspects must be considered (more likely to be observed in ethnic differences in health).

2.3 SOCIOECONOMIC POSITION AND CVD AND CVD RISK FACTORS

Cardiovascular disease (CVD), primarily ischemic heart disease (IHD) and stroke are the two top causes of death worldwide. Collectively, CVD was responsible for 17.3 million deaths (of a total of 57 million deaths) in 2008 (14). This corresponds to 3 in every 10 deaths that are attributable to CVD. Of these, according to the WHO, IHD and stroke were responsible for 7 million and 6.2 million deaths respectively (14). This corresponds to 11.2% and 10.6% of global deaths in 2008. With the exception of low-income countries, IHD and stroke were the leading causes of death in lower- and upper-middle income countries as well as in high-income countries (14). The global burden of CVD is projected to only increase in the future, with a major distributional shift towards low- and middle-income countries (14). The decline in CVD in high-income countries is mostly attributed to 1. Successful and sustained reductions/increases in modifiable risk-factors (smoking, physical activity, hypertension, lipidemia, diabetes mellitus) of CVD and 2. Improvements in case-fatality (better interventions
and treatment and survival post event (24). As middle-income countries get wealthier, it is beginning to be apparent that they will go through similar experiences in regards to CVD as previously seen in high-income countries (14). The precise contribution of these two factors in lowering the incidence of CVD mortality in high-income countries is hard to say due to different results from various studies. Hunink et al using a ‘state-transition IHD simulation model’ for the USA concluded that 50% of the decline was due to changes in risk factors and other 50% was due to improvements in case-fatality (25). These figures can be considered as approximately right and were further confirmed by other studies.

The importance of health inequalities and social determinants of health were discussed above. There exists substantial evidence for an association between SEP and CVD, most of which comes from high-income countries (26, 27). The decrease in both CVD incidence and mortality in high-income countries was accompanied by the emergence of social (and ethnic) gradients in the same outcome which are widening with time in many European and North American nations (24). Given the global burden of CVD, and its apparent shift towards middle- and low-income countries (which constitute the vast majority of the world’s population), it is evident that socioeconomic differences in CVD will have to be better tackled in the years to come.

Most evidence for social gradients in both incidence and risk has been gathered for CVD. In a large collaborative study which included data from ten western European nations (not Sweden, but including other Scandinavian countries, Denmark and Norway), the authors reported a combined increased risk for IHD in both men and women of lower SEP compared to their higher SEP counterparts (men aged 30-59: RR 1.55, 95% CI 1.51 to 1.60 and women aged 30-59: RR 2.13, 95% CI 1.98 to 2.29) (28). If people of lower SEP have a higher risk for CVD, one could hypothesize that this is due to 1. A higher level of adverse and modifiable risk factors seen in this stratum of society or 2. The effect of SEP on CVD in people of lower SEP is above the contribution of such risk factors. It could of course also be a combination of the two.

**Modifiable and behavioural/lifestyle risk factors, SEP and CVD** – it is well known that the risk of CVD is strongly linked to several risk factors which are modifiable (29). These include (but are not limited to) smoking, low physical activity, a poor diet, heavy alcohol consumption, which are in turn linked to hypertension, hyperlipidaemia, obesity, and diabetes, all of which contribute to increasing risk for CVD (29). The famous INTERHEART case-control study which analysed data (15,152 cases and 14,820 controls across 8 major ethnic groups) from more than 50 countries found that nine largely modifiable CVD risk factors account for most of the risk for myocardial infarction in both sexes, in all age groups and across all geographic regions (30). These nine risk factors included smoking, ApoB/ApoA1 ratio, hypertension, diabetes, abdominal obesity, psychosocial factors, fruit and vegetable consumption, alcohol intake and exercise (30). Other large cohort studies indicate that 80-85% of coronary heart disease can be attributed to four risk factors: smoking, diabetes, hyperlipidaemia, and hypertension (24).

Studies from high-income countries indicate that underlying social gradients observed in CVD are due to social gradients in these risk factors, i.e. such risk factors tend to cluster in people of lower SEP (29, 31). The effect of several individual risk factors is believed to be multiplicative (rather than additive) thus greatly increasing CVD risk and mortality in lower socioeconomic groups (32). Of more interest is the finding that favourable risk factors profiles (increased leisure time physical activity, lower cholesterol, smoking and blood pressure) are
improving but with increases in relative inequality. On the contrary, obesity and diabetes are increasing all groups with narrowing relative inequalities. However, these ‘classic’ and modifiable risk factors only partially explained the relative socioeconomic gradients in CVD (24). For example results from the first Whitehall study indicated that while classic risk factors (cholesterol, smoking, obesity and blood pressure) did explain the socioeconomic differences in RR of IHD, their contribution was rather small (24). Such studies have been replicated in several study populations in different countries (USA, Sweden, Holland, Norway, and Finland) coming to similar conclusions (24). These studies also indicate that the association between SEP and CVD is that of a dose – response relationship with risk often reducing with every step up the social ladder – the so-called ‘Social gradient’ (24). Also, if conventional or classic risk factors could not explain all of the risk between SEP and CVD, it would indicate that unknown risk factors are yet to be discovered and that interventions centred around reducing such risk factors would not completely obliterate the social gradient observed in CVD risk (24). Nonetheless, the conclusions just specified are controversial with some researchers stating that modifiable risk factors explain all of the association between SEP and CVD (29). Either way, this led to the search for ‘independent effects of SEP on CVD’ (29). Broadly speaking, such independent effects can be grouped into psychosocial factors, residential/neighbourhood environments, and early-life/parental risk factors during childhood and adolescence (24).

Psychosocial factors – These include a range of exposures including stress, low self-esteem, negative emotions, low levels of social support or control at work or home (24). Of these, stress (either acute or chronic or an accumulation of stress over long periods of time) has received considerable attention. Stress can occur both at places of work or at home and primarily increase risk for CVD through their effects on physiological regulation, emotional responses, and maladaptive behaviours (33). These can be socially patterned with lower socioeconomic groups facing increased levels of stress which in turn result in poor coping strategies (such as increased levels of smoking, and alcohol consumption), worsening physiological regulation (increase blood pressure) which leads to increased CVD risk (24, 33). In such a scenario, stress and other psychosocial factors can be considered to be mediators in the relationship between lower SEP and increased risk for CVD risk factors and CVD (24). Nonetheless, recent reviews conclude that the contribution of psychosocial factors to inequalities in CVD is largely inconclusive (16).

Neighbourhood environments – Another possible cause of social patterning of CVD risk factors and CVD is the potential effect of neighbourhood level factors (34). Poorer neighbourhoods are more likely to have greater levels of unemployment, lower levels of income, higher socioeconomic deprivation, worse health services such as access to health, inadequate infrastructure (health clinics/hospitals, recreational facilities), and social capital/cohesion (34). This situation is further complicated with such neighbourhoods in cities of high-income countries often having higher levels of immigrant or ethnic-origin residents. Again, one can hypothesize neighbourhood level factors as being mediators between lower SEP and increased risk for CVD (24).

Early-life socioeconomic factors and CVD and CVD risk factors – A review by Galobardes et al which looked at forty-one studies that analysed associations between childhood SEP and adulthood CVD concluded that SEP during childhood was an important determinant of CVD risk and this association was inverse in nature (35). However, associations between childhood
SEP and CVD differed by specific outcomes with stronger associations for stroke, particularly haemorrhagic stroke than for CHD. More interesting was the finding that associations between childhood SEP and later risk for CVD were independent of adulthood SEP.

If early-life social circumstances are independently associated with CVD risk in adulthood, one can also conclude that they are equally important in determining the development of CVD risk factors as well. Several studies have analysed the associations between childhood social circumstances and CVD risk factors in later adolescence and adulthood (24). Most studies have found consistent evidence for an inverse association between childhood SEP and subsequent increased risk for development of conventional CVD risk factors (blood pressure, overweight/obesity, adverse lipid profile, smoking, low physical activity, and alcohol consumption) (24, 35). But childhood and adulthood SEP are differentially associated with various CVD risk factors. For e.g. while smoking, physical activity, blood pressure and lung function among men were more dependent on adult SEP than on childhood SEP, BMI and triglycerides were found to be more dependent on childhood social circumstances (24, 35). As childhood circumstances improve, one would expect the associations between early SEP and adult CVD and its risk factors to become more favourable. These associations will naturally differ between countries. Nonetheless the finding between childhood SEP and adulthood CVD and its risk factors led researchers to hypothesize and study potential trajectories that underlie the development of CVD risk factors over the life course highlighting the importance of intergenerational factors. This is further discussed in the next section.
3 LIFE COURSE EPIDEMIOLOGY

3.1 BACKGROUND

Life course epidemiology is defined as “the study of long-term biological, behavioural, and psychosocial processes that link adult health and disease risk to physical and/or social exposures acting during gestation, childhood, adolescence, early adulthood or across generations” (36). The origins of life course epidemiology – a series of ecological studies from the 1970s and 1980s found that areas with high rates of infant mortality often had high rates of chronic disease morbidity and mortality (36-39). This led Forsdahl to conclude that ‘the weaker of the cohort probably died in infancy and childhood, while those who survived into adulthood carried with them a lifelong vulnerability to chronic diseases’ (40). This was a result of both exposure to poverty and poor growth in infancy and childhood as well as a result of accumulation of risk across the life course. Further investigations revealed that chronic disease mortality was differentially correlated with various aspects of early life including neonatal mortality, infant mortality, and maternal mortality. This led to a general hypothesis that deprivation in early life, (and as early as prenatal life), childhood and adolescence was associated with higher risk for chronic disease later in life. This deprivation in early life could be in the form of poverty, severe illness, exposure to environmental hazards, or inadequate nutrition. Many such factors are often inter-related and go hand in hand.

Much of this research was pioneered by David Barker and colleagues, whose studies showed clear correlations and associations between markers of early life (such as infant mortality, and low birth weight) and increased risk for various chronic diseases in adulthood including CVD, type 2 diabetes (hereafter diabetes), and increased hypertension (41, 42). This gave rise to the term ‘Foetal origins of adult disease hypothesis.’ Put simply, people who have CVD or diabetes in adulthood grew differently from those who do not have these outcomes. Barker proposed that these associations between small size at birth and later risk for chronic disease in adulthood arose due to maternal/foetal undernutrition. The foetus is dependent on the mother for nutrition and when it experiences a lack of nutrition it tends to ‘spare the brain’ at the expense of development of other organs and tissues (the brain being the most vital organ) (43). Such changes are permanent persisting into adulthood. These changes are also ‘programmed’ as they occur during ‘critical periods’ of development. Further studies demonstrated that inadequate and slow growth in utero could be compensated by ‘catch-up growth’ or a period of rapid growth in infancy and childhood (43). Thus adult diseases were not only linked to prenatal growth but also to post natal growth and early life, the term ‘Foetal origins of health and disease’ was supplanted by ‘Developmental origins of health and disease’ (32).

This hypothesis has been further developed over the recent years with accumulating evidence from both human and animal studies showing that even small changes in the developing environment may induce permanent phenotypic changes in order to adapt an individual’s response to later environmental cues (43). If there is a ‘mismatch’ between the pre- and postnatal environments which leads to the development of risk factors for chronic diseases in later life and these changes may involve epigenetic mechanisms which can have multigenerational effects (32, 44).
However, it must be acknowledged that the seeds of thought that gave rise to the concept of the importance of the environment in early life on later adulthood disease were hypothesized by many scientists in the early 19th century. It was already evident in official public health bodies, that “the health of the adult was dependent upon the health of the child...and the health of the child is dependent upon the health of the infant and its mother (36).” Research to support this idea in the fields of biological sciences, psychoanalysis and behavioural psychology in the early 20th century, also developed the idea of the critical period (36). Researchers realized that adverse events or the lack of appropriate stimuli during critical periods of development of tissues, organs or organs systems during foetal growth and early childhood could have permanent effects on mental and physical development (36).

An alternative hypothesis is that risk factors for CVD often developed in childhood itself and then ‘tracked’ into adulthood (45-48). For example, children/adolescents who smoked were more likely to smoke as adults and obese children were more likely to be obese in adulthood as well. Children with higher levels of cholesterol and blood pressure were more likely to have higher levels of the same risk factors in adulthood because of tracking (46, 49, 50). Such thinking lead to the idea that ‘classic risk factors’ for chronic disease in adulthood, such as lifestyle habits and dietary patterns had to be established in childhood.

Considerable evidence has been accumulated that social circumstances in early life, as early as in utero life and throughout childhood and adolescence have long lasting and often permanent effects on health throughout the life course (51). Not only do early social circumstances determine adulthood health, it also shapes growth and developmental trajectories in childhood both physiologically, biologically and socially, and also influences adulthood social circumstances (achievement in education, higher income, status all of which are linked to adulthood health) – Figure 6 (51, 52).

The interest in understanding underlying biological and social mechanisms that connect exposures in early life with distal outcomes, understanding the role of prenatal and postnatal growth in conjunction with development in childhood, adolescence and early adulthood and intergenerational mechanisms led to the development of the field of life course epidemiology as we know it today (36, 51, 53). This has generated the need for larger population-based and national cohorts with social and biological data on subjects from early life into late adulthood.
3.2 THE LIFE COURSE EPIDEMIOLOGICAL MODELS

Given that different exposures may act in a complex pattern in different periods across the life course or interact with several other exposures in their effect on distal health outcomes, several ‘life course epidemiological models’ were put forth to help explain concepts integral to life course epidemiology and to aid in the designing and explaining of results using a life course epidemiological approach. There are three principle types of models: 1. The Critical Period model and 2. The Accumulation model and 3. The Sensitive Period model.

3.2.1 The Critical Period model:
This type of model postulates that an exposure during a specific period of growth or development called the critical period has a permanent (or lifelong) effect on the development and/or structure and/or function of a particular tissue, organ or body system. This effect results in a health outcome later in life. In order for the exposure to have an effect, it must occur during the critical period. This type of model is also known as the latency model and forms the bases for the ‘foetal origins of adult disease’ hypothesis.

A variation of the Critical Period model is the ‘Critical Period model with later effect modifiers’. Here exposures during critical periods of early life interact with exposures in later life in increasing the effect on the distal outcome.

3.2.2 The Accumulation model:
As the name suggests, the Accumulation model proposes that risks for a particular health outcome accumulate over a period of time or over the life course. Greater the number and duration of exposures, greater is the final effect on the health outcome. There are several variations of the accumulation model:

(The figures for the different models are adapted from Kuh, D and Ben-Shlomo Y. – A life course approach to chronic disease epidemiology – Introduction (54))

A). Independent accumulation model - Different risk factors are independently associated with the outcome.

B). Accumulation model with risk clustering - In this model, a group of risk factors cluster in their effect on the health outcome. Several risk factors might come about because of an individual’s SEP and all of these risk factors are exposures for the health outcome.
C). Chain of risk model – In such a model one exposure must lead to another which is turn leads to a subsequent exposure. The final exposure in this chain causes the health outcome. Each component exposure may also increase the likelihood of the next exposure occurring. The final exposure in the chain is essential for the health outcome to take place and hence this model is also known as the ‘trigger effect’ model.

D). Chain of risk model, additive – When the different exposures in a chain of risk model are also independently associated with the health outcome, the model takes on an additive nature.

3.2.3 The Sensitive Period model:
A sensitive period is a time period when an exposure has a stronger effect on development and hence disease risk than it would at other times; the same exposure outside this time period may still be associated with increased risk but this association is weaker than during the sensitive period (10).
3.3 SIGNIFICANCE – WHAT CAN LIFE COURSE EPIDEMIOLOGY ADD TO WHAT WE ALREADY KNOW?

A life course approach to epidemiological studies offers an interdisciplinary framework to design research that investigates the development of risk factors and disease risk. According to some researchers the aim is to better understand the contributions of the biological, psychosocial, and behavioural mechanisms to the development of diseases over long periods of the life course (53). While the initial ideas behind life course epidemiology arose from the studies that highlighted the contribution of early life factors to the subsequent development of CVD in adulthood, (i.e. biological programming), the idea has now been expanded to include both biological and social factors that operate throughout various periods of development (independently, interactively or accumulatively) to influence the development of risk factors and subsequent disease (or protection from the same) (Figure 6) (53). Thus for example as described in section 3.1, one would study the contribution of early life factors in conjunction with risk factors that track from childhood to adulthood as well take into account behavioural or lifestyle factors in adulthood that contribute to the development of CVD risk. It is important to emphasise that life course epidemiology should aim to study the joint contribution of both biological and social factors to the development of disease instead of drawing false dichotomies between them (53). In this respect, this branch of epidemiology also incorporates social epidemiology as one takes into account social factors or processes (or the ‘social environment’) at different stages of the life course that influence the development of disease. Needless to say, this approach may be applied to a wide variety of health outcomes and diseases processes. It gives us the possibility of not only studying the underlying mechanisms that lead to the development of diseases but also to investigate health inequalities that might arise due to complex networks comprising adverse social and biological factors at different stages of life. The life course approach acknowledges that the associations between adverse social exposures (with or without biological factors) and subsequent poor health may work in both directions.

Figure 6: How childhood circumstances and health affect health in adulthood. Adapted from Graham H. and Power C. – Childhood disadvantage and health inequalities: a framework for policy based on lifecourse research (51).
3.4 LIFE COURSE EPIDEMIOLOGY IN THIS THESIS

The ideal life course epidemiological study which links early life exposures with distal outcomes in adulthood or old age, taking into account social and biological aspects (mediators and confounders) during various stages in the intervening period is not always possible in the because of data limitations. In Scandinavian countries (and many others that have set-up national or smaller births cohorts with long follow-up) it is easier to collect information on individuals through linkages with National registers often using unique social identity numbers. This is not only cost effective but also time saving as the data is often collected as part of routine statistics. Many countries with the ability to do so do not allow such extensive data to be collected for research purposes most often due to historical reasons. National registers in Sweden can be a source of a plethora of data on an individual. This coupled with a rather favourable attitude towards public health research has made Sweden and other similar countries to be ‘an epidemiologist’s paradise’. However, there is often one limitation - the lack of biological data as this is almost never collected at the national level for obvious reasons. But the importance of biological data in such research is clearly evident and there have been several such recent initiatives to collect, for example blood in large nationally representative projects.

The initial idea behind this thesis – to study social patterning of CVD biomarkers with a life course perspective – was understandably a challenge to design. Nonetheless, all the Papers in this thesis can be viewed to be studies of life course epidemiology in some respect (Figures 7-9): 1. The outcomes of interest, such as CVD risk factors are known to track into adulthood contributing to future CVD risk as well as other diseases that form a part of the Metabolic Syndrome or birth outcomes such as preterm and postterm birth that have short-term and long-term consequences of ill health. 2. With the exception of Paper I, the other Papers take into account intergenerational transfer or aspects of health which include direct influences (biological and social) of one generation on the next. It is however in Paper V, where one can see more of a textbook example of a life course epidemiological approach applied in better understanding a possible mechanism that could contribute to the development of increased blood pressure in early adulthood.

![Diagram showing Socioeconomic indicators, Lifestyle factors, CVD risk factors, Parental influences, Intergenerational, Outcomes in offspring.]

*Figure 7: Life course epidemiology in Paper II*
Figure 8: Life course epidemiology in Paper IV

Figure 9: Life course epidemiology in Paper V
4 ETHNICITY AS A DETERMINANT OF HEALTH

4.1 DISCLAIMER

Ethnicity and its role in determining lifestyle, risk behaviour, and health may be a topic of controversy. This is not surprising given that it was not too long ago that ‘race’ was almost entirely used in place of ‘ethnicity’ (15). We are all familiar with the unfortunate consequences that resulted from the perceived associations between certain races and their supposed propensity towards lower IQ, risk behaviour, worse lifestyle, and ill health. It is encouraging to see that ‘race’ is now almost entirely replaced by ‘ethnicity’ in public health and medical research. Nonetheless there continues to be some controversy in the use of the term ethnicity, its definition and how different groups of populations are labelled by it. In my research on ethnicity and health my justification to pursue such research has often been questioned, given the possible negative impact it may have on the prevailing political climate in the country that this research was conducted in. Some often thought that such research could lead to further stigmatisation of ethnic minorities and create a more negative image of immigration in general. I would like to take this opportunity to stress that the word ‘ethnicity’ and all other terms associated with it in this thesis are not used to marginalise, malign, or cause offense to any individual or group of individuals.

4.2 BACKGROUND

After age, ethnicity is considered to be the strongest variable responsible for health inequalities within countries (15, 55). The vast majority of countries have laws and policies (to varying degrees) that dictate and ensure equal access to health care and optimal health for all including ethnic minorities. If one is to ensure equitable health care for all, then the first step would be to identify health inequalities – i.e. differences or the lack of uniformity in health between groups (be it age, gender, SEP, ethnicity/immigrant group etc.). The next step would be to then identify which of these inequalities are in fact ‘inequities’, i.e. those inequalities that are morally unjust or unfair and should be changed. It is thus essential to take into account ethnicity when studying the aetiology and various patterns of diseases if one is to ensure healthy equity across life for the entire spectrum of society (15).

There is considerable variation in the approach to studying and tackling ethnic differences in health between North America and Europe (15, 55). While North America has been a destination for migration for several hundred years, Europe has primarily been a source of emigrants until quite recently. Also, historically institutionalised practises such as slavery and marginalisation have led to tremendous differences in virtually all aspects of life (including health) for Black and Native Americans - many of which are still evident today. As such, the USA has a stronger tradition of producing national statistics on differences in health by ethnic group, initiating research on ethnic differences in health, and a better political and national level debate on racial/ethnic issues (15). A law was even passed in 1993 that made it obligatory for all researchers receiving funding from the National Institutes of Health, to design their research projects taking into account racial/ethnic and gender differences (56). Such measures in Europe are lacking, both at the national and pan-European level. Self-identified ethnicity is not collected in many European countries and research has often relied on country of birth which is more readily available in National registers (15).
Large scale national surveys, randomised control trials and cohort studies which focus on ethnic and immigrant minorities are lacking in European research (15). In 2011, an estimated 1.7 million immigrants from outside the EU27 moved into a country of the European Union (EU 27) (57). As of January 2012, 33 million people born outside of the EU 27 were resident in one of the EU member states (57). They joined the millions of descendants of immigrants already resident in various EU countries. Europe today is clearly much more multicultural than it has ever been and there exists a greater need to study differences in health, and health care access.

4.3 MEASUREMENT AND LABELING OF ETHNICITY

Measuring ethnicity is not straightforward. This is highlighted by the below example I quote from Raj S. Bhopal’s book on Ethnicity, Race, and Health in Multicultural Societies (pages 24-25, Chapter 1)(15):

“I do not see myself as British, or Pakistani, as I am not fully accepted by both. I’m too different to be Pakistani and too different to be British i.e. I don’t speak the language and don’t look the part, in both cultures....

....However, if I had to choose, and have to be pushed to do this, I am a ‘Pakistani’ as this is my origin, but it has to be realised that I do not see myself as Pakistani. I am British by passport and if anything Britain is my home (I don’t feel that any other country is my home, even the ‘Muslim’ countries, as my family is in Britain) but I do not see myself as British, especially not English....however, British has the same connotation for me i.e. British colonial rule etc....
The only label I feel comfortable with is Muslim. This is after a long, long time of being uncomfortable with myself. But, if I had to describe myself as anything, in Britain I am Pakistani, and in Pakistan I’m British. For statistics purposes, I am Pakistani, but it must be realised that I am uncomfortable with being described as British or Pakistani as I am neither!”

There are no official guidelines in Sweden on terminology relating to ethnicity and labelling of ethnic groups. Unlike in the UK or the US where a tradition of categorizing groups by ethnicity has long existed for political discussions and for the purposes of data collection or statistics, this has not been the case in Sweden (58, 59). Labelling of ethnic groups has to be done with much consideration, not only because it can affect research and results and even lead to the wrong conclusions but also because it might hurt the sentiments of the individuals or groups being labelled. The main methods used in practise to identify and label ethnic groups include (15):

1. Skin colour
2. Country of birth
3. Name analysis
4. Family origin
5. Self-identified ethnicity

Of the above five mentioned ways, the last, self-identified ethnicity is considered to be the most appropriate as an individual not only knows best his/her roots and origins but also has the freedom to classify oneself (15). There is also growing consensus that ethnicity is more a concept of how an individual perceives oneself (15). It is a complex combination of various factors that may take into account not only place of origin, but also language, religion,
ancestry, culture and a sense of belonging. Nonetheless even self-identified ethnicity may not be the perfect choice in all circumstances. A person’s self-perceived ethnicity may change even over short periods of time and this differs across ethnic groups (15). There is greater stability is self-identified ethnicity in the White, South Asian, and East Asian ethnic groups. Changes in how a person perceives his or her ethnicity or greater instability is more in the Black, Hispanic, Native American and indigenous populations (15, 60).

Some of the other methods of assessing ethnicity such as skin colour and name analysis rely on observer assessment and are more prone to error (15). Also a person’s visible skin colour may not always truly indicate his/her ethnic group. Assigning a person to an ethnic group based on skin colour alone (or in combination with other physical features such as hair, eye colour etc.) can at the most create very broad groups of classification such as continental and sub-continental. For example, it would be quite hard for an external observer to determine the various ethnic groups that constitute the Indian subcontinent (e.g. Gujurati, Punjabi or Maharashtrian).

Name analysis is increasingly popular in some countries. Names are often distinct and may easily identify a person’s origin (15). For example, Indian names are very distinct often based on region of origin, language, religion and caste. It is becoming more common to use computer based software programs to help identify ethnicity based on names, but this methods has limitations. Often a computer program may be able to identify the ethnicity of one group very well but not others (15). Other issues also include change of name after marriage, followers of some religions share common names regardless of their country of origin (e.g. Indian Christians often have names that are also used by their Western counterparts, and Muslims throughout the world over share a more common naming system) (15). Thus name analysis in such cases may be used to identify ethnic groups based on religion but not country of origin. Again, name analysis seems to be more appropriate to identify larger and more broad-based ethnic groups.

Country of birth is another method to assign ethnicity especially when self-identified ethnicity is missing (55). Country of birth is routinely collected in many countries either in censuses or in National registers which makes this method especially popular in continental Europe and in the Scandinavian countries as the data is often reliable and easily available (55). However, using country of birth also has some drawbacks. Many people can be born abroad where their parents are residing often temporarily for work and other reasons. Also, large numbers of individuals were born abroad during colonial times returned to their home countries as colonial rule ceased. This however is more likely a problem in older populations and in countries with a stronger colonial history. A larger problem with using country of birth to assign ethnicity is that we can’t always capture all major ethnic groups resident in a country. For example, the Kurdish people identify themselves as a distinct ethnic group and are a fairly large ethnic population in Sweden. Kurds originate from a region called Kurdistan that spans several countries including Turkey, Iran, Iraq and Syria. It is however impossible to identify members of this ethnic group resident in Sweden using country of birth alone. Another disadvantage with using country of birth is that one cannot identify the several distinct ethnic groups that may constitute a country (e.g. India is considered to be highly heterogeneous with several hundred distinct ethnic groups with well-established differing lifestyles and health patterns). Another issue with using country of birth in identifying ethnicity is that it gets
diluted with time. As immigrants have children and subsequent generations develop country of birth can become obsolete in identifying people of ethnic minorities.

In Sweden, self-identified ethnicity is not collected as part of national statistics. The only way to identify the various ethnic groups in the large population based registers is to use country of birth. This is the method that we have employed in all projects that investigate ethnicity as a determinant of health.

4.4 SOCIOECONOMIC POSITION & ETHNIC DIFFERENCES IN HEALTH

It is not uncommon that immigrants and ethnic minorities often belong to lower socioeconomic groups in their country of adoption (15). This is especially evident among newly arrived immigrants who often tend to live in neighbourhoods with cheaper housing and often take on lower paid jobs. Such neighbourhoods often already have higher numbers of immigrants and are viewed as ‘low status’ neighbourhoods less desirable in the prevailing housing market (15). Recently arrived immigrants often go through a period of adjustment in their new country before they are familiar with the system and are able to get jobs that are worthy of their qualifications. An exception to this are immigrants who are selected into a country because of their skills and expertise to fill labour shortage gaps (15).

Immigration policies differ substantially between countries which often determine not only the type of immigrants that are allowed in but also the kind that it attracts (15). Thus different immigrant groups may fare differently depending on their country of adoption, its policies on immigration, integration and access to the labour market amongst others. It is not necessary for the same immigrant group to experience the same level of integration/acculturation and ‘success’ in different countries of adoption (15).

It is also well established that some ethnic minorities long resident in a country may belong to lower socioeconomic groups often because of a history of institutionalised discrimination. A well-researched example in public health literature is the disparity between the smaller Black and Native American populations and the majority white population in the USA (15). An immigrant or ethnic group that is disproportionately of a lower SEP will be more likely to suffer and report ill health regardless of whether it is relatively newly arrived or long established in a society (15).

Traditionally, differences between ‘racial’ and ethnic/immigrant groups have often thought to be because of biological (or genetic) differences (61). Such reasoning helped fuel the ideology that some groups were ‘racially inferior’ to others (15, 61). Fortunately, most of this ‘research’ and ideology is of the past. There is no doubt today, that all human populations belong to the same species. All populations and population clusters overlap when single genes are considered and more importantly all alleles are present in almost all populations but with varying degrees of frequency (62). And to make the argument against the concept of race even stronger, the genetic variation within populations is far greater than that between populations (62). Today, research on differences in health between ethnic/immigrant groups tend to take into account aspects other than those biological or ‘racial’. These aspects will also include the various components that go into defining the construct that we call ethnicity; language, religion, lifestyle, diet, genetics and socioeconomic indicators (15). Researchers now
give increasing importance to the role of SEP in explaining the differences in health between various ethnic groups that we see today.

Given the strong association between ethnicity and SEP, it is apparent that ethnic differences in health outcomes must be controlled for SEP (63-65). It is evident from prior studies that controlling for differences in SEP sometimes eliminated but almost always explained some amount of the observed differences in health between ethnic groups (11, 63, 65). This suggests that even when SEP indicators are held constant between ethnic groups, ethnicity still has an effect on health (31). It is quite common to conclude that the remaining effect seen on health is often due to unmeasured or residual confounding such as lifestyle factors, diet or genetics or even racism which are often difficult to measure especially in large population based studies. Nonetheless, some studies showed that when the associations of interest were instead stratified by SEP some ethnic groups still had worse health even within each level of SEP (66). This was observed in studies on differences between Black and White groups in the US which showed that Blacks still fared worse than their White counterparts even in higher levels of SEP (66). This highlights the fact that merely ‘adjusting’ or controlling for SEP in trying to understand ethnic differences in health is not enough. It is also important to stratify by levels of SEP. Others argue that adjusting for SEP is sequentially wrong, as SEP is often determined after one’s ethnicity, and such statistical adjustment for SEP leads to ‘over-adjustment’ as in this case SEP is more likely to be a mediator in the association between ethnicity and health. Others still argue that it is fine to adjust for SEP in investigating ethnic differences in health, but it is necessary to follow-up by stratifying the associations by levels of SEP and test for potential interactions between ethnic and SEP groups (11, 15, 63).

Another issue is the measurement of SEP when analysing its role in trying to explain ethnic differences in health (22, 63). Most often three or more indicators are considered to be ideal in measuring SEP (22, 23). Using just one measure of SEP such as educational or income level could be problematic especially in newly arrived immigrants (15). New émigrés often do not hold jobs that are equivalent to their educational qualifications and may have lower income levels (15). Despite the widely accepted consensus that SEP is a multidimensional construct, the literature is abound with studies that often just use one indicator for SEP (63). There is considerable evidence showing that associations between SEP and various health outcomes vary by the indicator(s) used for SEP and the health outcome under study. This is further complicated when one analyses the role of SEP in explaining ethnic disparities in health. As shown clearly in a study by Braveman et al, conclusions about the role SEP in explaining ethnic disparities in maternal health varied to a great extent by the socioeconomic indicator used (63). One could have drawn different or even opposite conclusions regarding the role of SEP in explaining ethnic differences in a range of maternal outcomes based on which socioeconomic indicator was being used. The authors also showed that correlations between educational level and income were rather modest and one could not be replaced by the other (22, 63). The authors suggest using several SEP indicators (‘multiple dimensions’), and to test each indicator in different ways, such as categorical, continuous, quartiles amongst others. The authors further recommend that observed ethnic differences in health by SEP must acknowledge the potential role of unmeasured socioeconomic aspects such as institutionalised and individual racism. Without measuring all relevant aspects of SEP (education, income, wealth, occupation) supposedly observed ethnic differences in a particular health outcome should not be considered to be ‘independent’ of SEP.
4.5 ETHNIC INEQUALITIES IN HEALTH & HEALTH CARE

Discrimination in access to public health care services and to good quality health care has been documented by a large body of research (67-70). A substantial portion of this research originates from the USA. Ethnic minorities receive lower quality and intensity of healthcare, and these disparities cover a wide range of services and diseases. Findings in the USA are highly consistent and robust with only a handful (of several hundreds) of studies not finding any associations between ethnic minority status and worse health care. In many studies which examined associations between ethnic minority status and worse health care, controlling for insurance status often attenuated these associations, but did not completely obliterate them (69). After reviewing a remarkably large number of studies in the USA Smedly et al, concluded that ethnic disparities in healthcare exist independently of insurance status (i.e. private, public or none), education or income levels across a wide range of diseases (69).

In the UK, ethnic disparities in health care access, quality and service appear to be less of a problem. This research field is less developed in the UK when compared to the USA, and a relatively recent study indicated that there was no evidence for ethnic disparities in use of primary and secondary health care (67). The authors did not find any evidence for inequalities in care of three common health outcomes (hypertension, raised cholesterol and diabetes) between Indian, Pakistani and Bangladeshi residents when compared to their White counterparts (67). There was fairly strong evidence for ethnic inequalities in use of dental care and access to hospital services. Is it possible that universal public health care may explain the large differences seen in ethnic disparities of health care between the USA and UK? The authors conclude that a publically funded health care system reduces ethnic disparities in health care considerably (67).

One could expect a similar effect in Sweden, which also has a universal public health care system financed primarily through taxes. The health care system is structured on three levels: the national (under central government), regional (under the county councils) and the local (under the municipalities). Research on ethnic and immigrant disparities in health care in Sweden is rather limited. Nonetheless, there is evidence that shows immigrants have significantly poorer health compared to native Swedes. Various cross-sectional surveys have shown that Non-European immigrants report higher levels of worse self-rated health and in some instances this could be explained by socioeconomic indicators, language barriers, poor social networking and discrimination (71-73). In addition, immigrants are less likely to utilise health care services compared to natives Swedes (74). It is also reported that standard and ‘well-documented’ medical treatments for heart attacks, strokes, and chronic obstructive pulmonary disease are less utilised among immigrants compared to native Swedes. This is in contradiction to a study from 2001 that reported ‘no gross pattern of inequity in access to care for ethnic minorities in Sweden’ (75). This study did not examine specific disease-associated outcomes and was conducted before the larger influx of non-European immigrants who have come to Sweden since 2001. However, differences in access to dental care and dental health were found between immigrants and native Swedes (76). Differences in attitudes including cultural perceptions, stereotyping, miscommunication, language barriers, possible discrimination, and differences in educational levels have been thought to explain some of the differences in maternal and pregnancy health between immigrant and Swedish born mothers.
4.6 IMMIGRATION IN SWEDEN

Research on ethnicity/immigrant group and health in Sweden is relatively new. This might seem surprising given that Sweden has been receiving immigrants from countries around the world for many decades now. Sweden has a long history of recording of emigration/immigration which started in the 1850s (Figure 10 below shows the pattern of emigration/immigration between 1851 and 2007) (3). Sweden has changed from a country which had net emigration in the 1930s to a country with net immigration from the Second World War onwards. Following the Second World War, most immigrants were refugees from the Baltic countries but the 1940s also marked the beginning of a long period of labour immigration that lasted well into the 1970s (3). Since then Sweden has received a mix of refugees and labour immigrants. The last two decades have witnessed a significant influx of non-European immigration with large numbers of people from Iraq, and Somalia moving to the country. Sweden received its highest number of immigrants in 2009 with a total of 102,280 people entering the country (3). The proportion of foreign-born residents in Sweden today has more than doubled from 6.7% as recorded in 1970. As of 31 December 2011, 1,427,296 people resident in Sweden were recorded as being born abroad. In addition, 430,253 were recorded as being born in Sweden to foreign-born parents (3). This corresponds to 15.1 and 4.5% of the total population, respectively, that could be considered to be of ‘non-ethnic Swedish or immigrant-origin’. Of the 15.1% recorded as being born abroad and resident in Sweden in 2011, 18.2% were from other Nordic countries (Denmark, Norway, Iceland and Finland), 19.5% from one of the EU27 nations (excluding the Nordic countries), 8.6% from Africa, 2.3% from North America, 4.6% from South America and 30.1% from Asia (Figure 11) (3). The top fourteen countries of origin (including those born abroad and those born in Sweden to foreign-born parents) as of 2011 in descending order are: Finland, Iraq, the former Yugoslavia, Poland, Iran, Turkey, Bosnia and Herzegovina, Germany, Denmark, Somalia, Norway, Lebanon, Syria and Chile (3). With almost 20% of its population considered as of foreign origin, one would assume that research on ethnic differences in health would be given more importance but this has not been the case. This might appear especially amiss given the vast amount of other kinds of data available on the population and the established fact that ethnicity is a significant determinant of health. The lack of research on ethnicity and health when compared to other countries could be due to various reasons. The government does not collect any data on ethnicity or ethnic origin as it is considered to be sensitive. Nonetheless, data on country of origin is readily accessible and as discussed earlier is a reliable proxy for ethnic origin.
Figure 10. Pattern of immigration and emigration in Sweden between 1851 and 2007. Reproduced with permission from Statistics Sweden
Figure 11. Number of foreign born residents in Sweden by region of origin as of December 2011. Source of data: Statistics Sweden (3). *EU27: Belgium, Bulgaria, Czech Republic, Germany, Estonia, Ireland, Greece, Spain, France, Croatia, Italy, Cyprus, Latvia, Lithuania, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovakia, & United Kingdom (here excluding the Nordic countries).
5 SPECIFIC AIMS OF THIS THESIS

1. Is socioeconomic position (SEP) associated with common cardiovascular disease (CVD) biomarkers in an ageing population? Do these associations change with age?

2. Are there intergenerational mechanisms in the transfer of cardiovascular risk factors? Do parents influence the development of CVD risk factors in their children through their SEP and lifestyle?

3. Are offspring of immigrant parents at a higher risk for preterm and postterm birth and impaired foetal growth compared to those of Swedish-born parents? Are these associations mediated by maternal SEP and other risk factors?

4. Can differences in overweight and obesity by ethnic/immigrant origin be detected as early as 4 and 5 years age? If yes, can these differences be explained by parental SEP and other factors such as maternal characteristics (smoking, BMI and breast feeding)?

5. Does the pattern of association between foetal growth rate and blood pressure/obesity differ between young adults born to immigrant parents and those born to Swedish parents?

6. Can the above associations contribute to health inequalities amongst second generation immigrants in Sweden?
6 DATASETS USED IN THIS THESIS

6.1 UPPSALA LONGITUDINAL STUDY OF ADULT MEN (ULSAM)

As the name aptly indicates, the Uppsala Longitudinal Study of Adult Health (ULSAM) is a longitudinal study of men resident in Uppsala County, Sweden. The study was first initiated as the ‘Uppsala Primary Preventive Study’, when all men born between 1920 and 1924 and resident in Uppsala county in 1970 were first invited to participate (78, 79). This first investigation included 2,322 men (participation rate of 81.7%). The investigation was extensive including a medical and lifestyle questionnaire, interview, anthropometric measurements, blood and urine sampling, blood pressure and glucose tolerance tests as well as chest x-rays, ECG recording and pure tone audiometry.

The initial sample of men were re-invited to take part in a second investigation conducted between 1980 and 1984, giving rise to the longitudinal aspect of the study. This second investigation was similar to the first one and included 1,860 men of an eligible 2,130 men. Subsequent investigations took place when the men were 70, 77, 82 and 88 years of age. All medical procedures in subsequent investigations were carried out in a manner as similar as possible to the first one so as to enable comparisons. Figure 12 below shows the sequence of investigations with the corresponding number of participants as well as the number of men lost to follow-up between investigations. As the men aged, those unable to physically attend the examinations at the clinic were visited at home by a nurse. The last and final investigation took place in 2008-2009 when the men were 87-89 years old and consisted of 354 participants (58% of those eligible).

In addition to the extensive medical data collected at each investigation and information on medical history, and lifestyle from questionnaires, detailed information on other medical aspects as well as SEP, housing conditions, origin and family status were collected through linkage with various national registers. These included the Medical Birth register, the Cancer register, the Hospital discharge and Cause-of-Death registers, the Census register and from a later date the Drug prescription register. Linkage was done using the unique personal identification numbers given to all residents in the country.
6.2 THE UPPSALA FAMILY STUDY

Also set in Uppsala County, Sweden, the Uppsala Family Study (UFS) is newer than the ULSAM. The study was conducted over an 18 month period starting in March 2000. As the name suggests this was a family study initially designed to investigate the associations between birth weight and blood pressure (80). Six hundred and two families agreed to participate (31% of the total number of families eligible). In order for a family to be eligible, it had to comprise of two full siblings that were delivered between 1987 and 1995 at the University Academic hospital in Uppsala. Another rather unique eligibility criterion was that the two siblings had to be highly concordant or highly discordant in their birth weights, i.e. the two siblings had birth weights that were both at one end of the birth weight distribution (concordant) or were highly different in their birth weights - located at either end of the birth weight distribution (discordant). Data on mothers resident in Uppsala that gave birth to consecutive singletons within 36 months of each other and delivered at 38-41 weeks of gestation was obtained from the Swedish Medical Birth register. This gave rise to a ‘sampling frame’ of 5,226 women and their 10,452 children, from which 602 families eventually participated in the investigation. In instances where mothers that had more than 2 consecutive singleton children the oldest two were included in the medical examinations. Ninety-five percent of the families were examined on the same occasion. All four members of the family were examined (parents and their children). The data collected included detailed anthropometry including various skinfold measurements, blood pressure, blood sampling and DNA extraction. Each parent was also requested to answer a detailed questionnaire on household, medical history, education, employment, lifestyle and their respective parents’ medical history. Parents were also requested to answer shorter questionnaires on the medical history of their children.

Figure 12. A schematic representation of the Uppsala Longitudinal Study of Adult Men (ULSAM)
6.3 THE UPPSALA YOUNG CHILDREN’S COHORT - DATA COLLECTED AT THE CHILD HEALTH CARE CLINICS IN UPPSALA COUNTY, SWEDEN

This is an on-going study that comprises all children born in Uppsala County from 1997 onwards (81). The study sample was drawn from a total population of 20,520 infants, born 2000-2004, and registered as residents in the county of Uppsala on the 31 December of their birth year. The sample was defined by a subgroup of 13,796 children [aged 4 years (born 2004, N=3,169) and 5 years old (born 2000-2003, N=10,741)]. Using personal identification numbers and linkage with national registries, data on parental socioeconomic variables, including disposable income, country of birth, and family circumstances were accessed. Information on birth weight, maternal BMI and smoking habits were retrieved from the MBR. Information on breast feeding habits and anthropometric measurements of children (height and weight – used to compute BMI) were recorded by nurses when subjects attended an annual examination at local paediatric clinics.

6.4 SWEDISH INITIATIVE FOR RESEARCH ON MICRODATA IN THE SOCIAL AND MEDICAL SCIENCES (SIMSAM) & THE SOCIAL MOBILITY DATABASE (SMD)

This database comprises all individuals included in any Swedish census conducted in 1960, 1970, 1980 and 1990 and those individuals registered in the Swedish Multi-Generation Register born 1932-2002 including their parents, representing the entire Swedish population from 1960 onwards (approximately 13 million individuals) with family membership identified through linkage. Figure 13 illustrates this database.

The census registers comprise data from the various censuses and include information on sex, family/cohabitation status, place of residence, occupation, and other socioeconomic variables. Data on circumstances around delivery and pregnancy-related issues is available from the Medical Birth register. The Medical Birth register was initiated in 1973, and includes information on maternal social, demographic, anthropometric, lifestyle and other pregnancy-related variables and anthropometric data on the new-born. Data on educational levels are obtained from the Education register. Information on country of birth and date of immigration/emigration is obtained from the Emigration register. Other registers also linked to this database include the Cancer, In-patient, Out-patient, National Diabetes, Drug Prescription, National Crime, Cause of Death and Military Conscription registers. The latter register provides detailed information from Military Conscription examinations attended by Swedish men when they are approximately 18 years of age and include data on anthropometry, blood pressure, muscle strength, and IQ tests.
Figure 13. A schematic representation of the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) and the Social Mobility Database (SMD).
7 PAPERS I & II – INVESTIGATING SOCIOECONOMIC DIFFERENCES IN CVD BIOMARKERS

7.1 BACKGROUND
The main aim in Papers I & II was to study social patterning of CVD biomarkers in the Swedish population. For this purpose we used both the ULSAM and the UFS, which allowed us to study social patterning of CVD biomarkers at different ages and in both genders. As the ULSAM is longitudinal in design, we were able to study the change in CVD biomarkers with age as a secondary aim in Paper I. In the UFS, we analysed social patterning of CVD biomarkers in children. This gave rise to an intergenerational aspect to study which assessed if parents influence CVD biomarkers in their children.

7.2 CARDIOVASCULAR DISEASE – THE BURDEN
Cardiovascular disease is the leading cause of death worldwide. Statistics from 2008 showed that globally 17.3 million people died as a result of CVD, representing 30% of all global deaths (14). CVD includes a wide range of diseases including coronary heart disease (that affecting blood vessels connected to the heart), cerebrovascular disease (that affecting blood vessels that are connected to the brain), peripheral arterial disease (that affecting blood vessels in the arms and legs), rheumatic heart disease (when heart muscles get damaged, most often caused by infection due to streptococcal bacteria), congenital heart disease (malformations of the heart that are already present at birth) and deep vein thrombosis and pulmonary embolism (clotting of veins most often in the legs that could then cause subsequent damage to the heart and lungs) (14). Of these, coronary heart disease and stroke are responsible for more than 78% of all deaths attributed to CVD (14).

While CVD mortality has been decreasing in high income countries, its incidence is increasing in middle and low income countries (14). The decrease in CVD mortality in high income countries is mostly attributed to public health intervention – that is greater awareness and better handling of the risk factors of CVD and to a lesser extent, the increase in prevalence of other diseases such as cancer (24).

CVD is generally a disease that afflicts older people (18). However, its antecedents may begin much earlier in life (18). CVD can be prevented to a large extent by modifiable risk factors mostly concerning lifestyle, such as a better diet, greater physical activity, not smoking, low alcohol consumption, and maintaining a healthy and recommended BMI (14). These behaviours in turn affect other risk factors of CVD such as increased blood pressure or hypertension, insulin resistance, obesity, raised lipids, diabetes and atherosclerosis. Other risk factors of CVD include low SEP, ethnicity, increased urbanization, ageing populations, and genetic factors which are commonly referred to as ‘the causes of causes’, as many of these underlying factors are interlinked with the above mentioned lifestyle and risk factors of CVD. CVD will continue to remain the leading cause of global death in the future. It is projected to kill 23.3 million people by 2030 (14). Low and middle income countries will continue to be disproportionately affected (14).
7.3 LIFE COURSE EPIDEMIOLOGY OF CVD

For a long time it was thought that the aetiology of CVD risk was largely accounted for by adult lifestyle factors which are intrinsically linked to other CVD risk factors such as hypertension and obesity (24, 29). However, atherosclerosis (the thickening of the arterial walls due to excessive deposition of fatty materials like cholesterol and triglycerides) occurs much earlier in life and as early as childhood (18). Other risk factors such as obesity, higher lipid profile, blood pressure, or even lifestyle habits such as smoking or low physical activity can be seen in childhood and track into adulthood thereby increasing the risk for CVD (46, 49, 50, 82).

Several studies from the last few decades have investigated the possible associations between so called ‘pre-adult influences’ on later ‘adulthood CVD risk’ (including some its risk factors) (18). One such ‘pre-adult influence’ which has been studied in much detail is that concerning the associations between markers of impaired foetal growth and increased risk for CVD in adulthood (18, 83, 84). Several studies in many countries have shown a consistent and inverse association between birth weight and increased risk for CVD (18). This inverse association was also shown for other anthropometric measures of birth size such as ponderal index and birth length (18) as well as gestational age (85). These associations were independent of confounding factors such as SEP and smoking. Later studies suggested that this inverse association was in fact ‘U’ or reversed ‘J’ shaped with even very high birth weights having an increased CVD risk in adulthood (18). Studies have also found inverse associations with birth size and stroke. Associations between birth size and atherosclerosis however have been less consistent (18).

Some of the principle explanations put forth to explain the birth size – adulthood CVD risk include: foetal and maternal nutrition, genetic mechanisms, transgenerational associations and post natal catch-up growth (36, 86).
7.4 AIMS
To investigate the relationship between SEP and common CVD biomarkers in Swedish men and to assess if these associations change with age.
To investigate if parental SEP, lifestyle factors (smoking, alcohol consumption and physical activity) and CVD biomarkers determine CVD biomarkers in their children.

7.5 METHODS

7.5.1 Data sources, datasets & study populations
For Paper I, we used data from the ULSAM. We accessed data from two of the six investigations: those at ages 50 and 70. Of all men invited to participate at the first investigation at age 50, N=2,841, 82% or N=2,322 agreed to participate. During the 20 years between the age 50 and age 70 investigations, 422 men died and 219 moved out of Uppsala. Of the 1,681 men invited for the reinvestigation at age 70, N=1,221 or 73% participated. In addition to detailed anthropometric, blood pressure, glucose, insulin measurements, and blood analysis, information on the sociodemographic profile of the participants was also collected through linkage with various National registers. Data on occupational group and the education was obtained from the 1960 and 1970 census respectively, stored in the Census register. Information on men who emigrated from Sweden was obtained from the Emigration register. Information on the participants’ lifestyle habits such smoking, and physical activity (both during spare time – recreational and at work) was collected from questionnaires.

As one of our main aims was to assess if social variation in biomarkers changed with age, it was essential that measurements at the two examinations at ages 50 & 70 should be comparable. The subsequent examinations were carried out in a manner as closely as possible to the first age 50 examination. In addition, lipid measurements were ‘Monarch adjusted’ to enable comparison between the different examinations.

For Paper II, all data on socioeconomic characteristics; education and occupation of parents in the UFS were obtained from questionnaires. Information on lifestyle factors were also obtained from questionnaires.

7.6 OUTCOMES

7.6.1 Cholesterol & LDL/HDL ratio
Serum cholesterol, LDL and HDL were measured by routine laboratory analysis. Even though the first age 50 investigation occurred in 1970-73, serum cholesterol was measured in 1981-82 using blood stored in liquid nitrogen from the first investigation. Serum cholesterol and triglyceride levels were determined using a Technicon Auto Analyser type II. HDL cholesterol was assayed in the supernatant after precipitation with a heparin/manganese chloride solution. LDL cholesterol levels were calculated using Friedewald’s formula: LDL = serum cholesterol - HDL (0.45 × serum triglycerides’ level). The lipid measurements from the age 50 examination were multiplied by these conversion factors: 1.06 for LDL cholesterol and serum cholesterol, 1.17 for HDL cholesterol and 0.9 for serum and HDL triglycerides. This permits comparison with lipid measurements from subsequent examinations (Monarch adjustment).

At the age 70 examination, serum cholesterol was measured by enzymatic techniques using a Monarch apparatus (Instrumentation Laboratories, Lexington, USA). The method employed was IL Test Cholesterol Trinder’s Method. As above, HDL cholesterol was precipitated with
magnesium chloride/phosphotungstate. As previously, LDL cholesterol was calculated using Friedewald’s formula (see above).

7.6.2 ApoB/ApoA1 ratio

ApoB and ApoA1 were measured in 1988 also using blood samples stored in liquid nitrogen since original sampling at the age 50 examination. ApoB was measured by a two-site immunoradiometric assay and ApoA1 by a competitive radioimmunoassay using commercial kits from Pharmacia (Uppsala, Sweden). At the age 70 examination, ApoB and ApoA1 were measured by turbidimetry in a Monarch apparatus (Instrumentation Laboratories, Lexington, USA) using monospecific polyclonal antibodies against ApoB and ApoA1.

7.6.3 Adiponectin

Serum adiponectin was measured only at the age 70 examination, using a validated in-house time-resolved immunofluorometric assay. This was based on commercial reagents from R & D Systems, UK.

Procedures for measurements of CVD biomarkers in the UFS children; serum cholesterol, ApoA1, Apob, adiponectin, and leptin are mentioned below in section 7B.3.3.

7.6.4 Body Mass Index (BMI) & overweight and Obesity

In the ULSAM, standing height and weight measured at both examinations was used to calculate BMI (weight in kilograms/height in metres²). Using the WHO’s classification of BMI, men were grouped into normal, overweight and obese groups. In the case of ULSAM, and Paper I, BMI and its classification were only used as confounders in statistical analysis.

In the UFS, BMI (continuous) and overweight/obesity in the children were outcomes. For children, we used the sex and age specific classification for normal, overweight and obese groups as devised by the International Obesity Task Force (87). Due to the smaller size of the study sample, we combined overweight and obese children into one group.

7.6.5 Blood pressure - Systolic & diastolic blood pressure (SBP/DBP)

SBP and DBP were outcomes in Paper II. Blood pressure was measured with a Dinamap "Compact T" Monitor (Critikon Ltd). Three measurements were taken using the left arm with the subject in a sitting position. There was an interval of 1-2 minutes between each reading. Based on the recommendations of the 1987 Task Force on Blood Pressure Control in Children, the following cuff sizes were used on subjects based on their arm circumference: <20.0 cm, "child" cuff (approximate width 8.5 cm); 20.0 - 27.5 cm, "small adult" cuff (approximate width 11.5 cm); 27.6 - 35.0 cm, "adult" cuff (approximate width 14.5 cm); >35.0 cm, "large adult" cuff (approximate width 17.5 cm). The mean of the three readings were used in analysis.

7.6.6 Cardiovascular disease mortality

For Paper I, we obtained information on mortality due to CVD from the Cause of Death Register. Identification of those men who died due to a cardiovascular event was done using the relevant ICD codes; ICD 9:390-459 or ICD 10:I00-I99.
7.7 PREDICTORS

7.7.1 Occupational class & educational level

Between 1960 and 1990, Sweden conducted a compulsory housing and population census every 5 years. Data collected included information on individuals’ education and occupation as well as housing conditions (type of dwelling; own or rented, and number of individuals in a household). In ULSAM information on both the participant’s highest educational level and occupational group were obtained from the census register. Men were grouped into primary education (<9 years), secondary education (9-12 years) and post-secondary education (>12 years). A majority of the men (N=1,651, or 71%) completed <9 years of primary schooling with no further education. Based on occupation, the men were divided into the following four social classes: manuals, non-manuals, self-employed and not working/unknown. The majority belonged to the manual (44%) and non-manual (43%) classes.

In the UFS, educational level and occupational status were obtained from questionnaires. Mothers and fathers received separate questionnaires which they answered on site. Parents were classified into six occupational classes: higher/intermediate non-manuals, lower non-manuals, skilled workers, unskilled workers, entrepreneurs/farmers and unknown. This was done by collapsing the original sixteen occupational groups as specified by Statistics Sweden. Educational groups comprised the following: university, secondary school or equivalent, and ‘other’ (<9 years of compulsory schooling).

7.7.2 Parental lifestyle factors

This section is only concerned with Paper II. Information on parental lifestyle factors was obtained from questionnaires answered by parents in the UFS. A separate section in the questionnaire (Section B) was dedicated to aspects of lifestyle.

Smoking
Parental smoking status was assessed with the following questions: 1. Have you ever been a smoker? and 2. Have you stopped smoking now? Parents were classified into ‘never’, ‘former’ and ‘current’ smokers.

Alcohol consumption
Alcohol consumption by parents was assessed by frequency of drinking. Parents were given the option for one of the following choices: 1. Never drink alcohol, 2. Seldom drink alcohol (less than once a week), 3. Drink now and then (at least once a week), 4. 1-2 glasses nearly every day, 5. 3-9 glasses every day, 6. At least 10 glasses a day and 7. Don’t know. Based on how they answered, parents were categorised as 1. Teetotalers, 2. Drinking less than once per week, 3. Drinking once a week and 4. Drinking more than once a week.

Physical activity
Assessment of physical activity was more complex. We constructed two variables that assessed extent of physical activity. Parents were asked about the number of hours per week they spent on 1. Gentle exercise, 2. Moderately demanding exercise, and 3. Demanding exercise. We then calculated the total intensity of physical exercise for each parent in Metabolic Equivalent Task (MET). This was done by multiplying the number of hours per week of moderately demanding and very demanding (vigorous) by 4.5 and 6 MET respectively and using the sum of these products. We then classified mothers and fathers into tertiles of low,
moderate and high physical activity. Parents were given an idea of what sorts of activities were considered as moderately demanding; scrubbing floors, chopping wood, dancing, golfing, cycling and swimming for leisure and very demanding/vigorous physical activity; running and sports activities like tennis or squash.

The second measurement of physical activity was based on criteria recommended by the WHO. The WHO recommends a minimum 75 minutes of vigorous physical activity per week and 150 minutes of vigorous physical activity per week for ‘additional health benefits’. The assessment of vigorous physical activity per week in minutes was categorised as none, ≤75 minutes/week, 76-150 minutes/week, and <150 minutes/week in mothers, and ≤30 minutes/week, 60 minutes/week, 90-120 minutes/week, 150-360 minutes/week and >360 minutes/week in fathers. However, data coverage on vigorous physical activity in parents was low; 56% in case of fathers and 61% in case of mothers.

7.7.3 Parental cardiovascular risk factors

CVD biomarkers including serum cholesterol, ApoA1, ApoB, adiponectin and leptin were measured using routine laboratory methods. The Architect Ci8200 analyser (Abbot Laboratories, Abbot Park, USA) was used to measure serum cholesterol and apolipoproteins A1 and B. Adiponectin and leptin were measured using commercially available ELISA kits (R & D Systems, MN, USA).

Body weight and height was measured three times and the mean was used. As above BMI was calculated by dividing body weight in kg by height in metres squared (kg/m²). Parents were grouped into normal, overweight and obese groups based on the WHO’s classification for BMI.

The procedure for measurement of SBP and DBP in parents is described above in section 7.8.5.

7.8 STATISTICAL ANALYSIS

7.8.1 Linear regression

Linear regression is used when we assume that a certain change in the predictor X variable leads directly to a change in the Y outcome or dependent variable provided certain assumptions are met. Linear regression was used in instances when the main outcome of interest is continuous. Assumptions of linearity for continuous variables and constant variance of the standardised residuals were done by plotting the residuals against the fitted values. Log-transformed values were used for those variables that had skewed distributions (e.g. adiponectin in Paper I and parental BMI and adiponectin in Paper II). Coefficient estimates of log transformed variables were converted to the original scale and are interpreted as relative differences (in percentages) in the outcome variable in comparison to the reference category. Linear regression models also included potential confounders that were associated with both the predictor and outcome of interest.

We used linear regression modelling to investigate the social patterning of CVD biomarkers in: (i) all men with information available at age 50 to provide data on a representative, population based sample of men from 1970 (N=2,115); and (ii) the longitudinal sample of men restricted to those who attended both investigations at ages 50 and 70 to allow an unbiased comparison of differences in strength of the associations in same group of men (N=1,220). We controlled for known covariates that might mediate or confound the relationship between SEP and the...
outcomes of interest. We built four linear regression models: adjusted for age (continuous in years) (model 1), with additional adjustments for BMI (continuous in kg/m²) (model 2), BMI and physical activity in spare time (categorical) (model 3), and BMI, physical activity in spare time, and physical activity at work (categorical) (model 4). We used formal tests for interaction to compare the strength of associations of SEP with cardiovascular biomarkers at age 50 between the longitudinal sample and men who were lost from the study after age 50.

In Paper II, linear regression was used to analyse associations between Parental SEP/CVD biomarkers/lifestyle factors and CVD biomarkers (except overweight/obesity) in their children. Analyses were adjusted for age, gender and pubertal stage of the children. Models with diastolic and systolic blood pressure were additionally adjusted for children’s height. Robust standard errors allowing for clustering of children within families were used for all regression models. We also ran stratified analysis by gender which was formally tested for interaction.

7.8.2 Cox regression & Kaplan-Meir survival curves

The Cox proportional hazards model enables us to model the instantaneous hazard (event or outcome) as the dependent variable as it is the change in this that ultimately predicts survival time. The Cox model links the instantaneous hazard to an individual at time to a baseline hazard. This model also measures relative survival or hazards and not absolute values. We used the Cox model in Paper I where we wanted to compare the hazard rates (HR) for CVD mortality between the different educational groups over 37 years of follow-up (1970–2007). The Cox regression models were adjusted for potential confounders (age and BMI). We also ran the cox model by splitting this period of follow-up into two: 1970–90 and 1991–2007. Subjects exited from risk on their date of first emigration, death, or end of follow up, whichever was first.

Kaplan–Meier survival curves for plotted for the above described longer 37 years of follow-up and the two shorter periods as well.

7.8.3 Logistic regression

Logistic regression is useful when the dependent variable or outcome of interest can take only one of two options, most often coded 1 or 0. Multivariate logistic regression which enables inclusion of more than one predictor and hence adjustment for potential confounders was used in some of the analysis in Paper II when the outcome of interest was binary. This was used to compute the odds for a child to be OW/OB by parental exposures taking into account potential confounders. All logistic regression models were additionally adjusted for confounders, took into account family clustering, and analysed for gender differences as described in section 7.8.4.1 above.

7.9 RESULTS

7.9.1 Associations between socioeconomic indicators and CVD biomarkers

In Swedish men of the ULSAM, mean values of all outcomes fell between ages 50 and 70. Analysis for BMI showed that the proportion of overweight and obese subjects was higher in the self-employed and ‘not working’ groups. Non-manuals had the lowest proportion of obese subjects. A decreasing trend of borderline statistical significance was observed with BMI across educational groups, with the highest educated men (postsecondary-education) subjects having the lowest BMI. At age 50, a higher proportion of non-manual workers reported ‘high’ physical activity in leisure time (55%) as compared to manual workers (45%). For physical activity at work, men in the highest educational group and non-manuals reported the least
physically demanding jobs (79% and 61%, respectively) while the lowest educational group and manual workers included greater proportions reporting ‘heavy’ and ‘demanding’ physical activity at work.

We found a statistically significant association between occupation and cholesterol at age 50 even after adjustment for BMI and physical activity (Paper I - Table 2). We also found a statistically significant inverse association of education with cholesterol (Paper I - Table 3). The fully adjusted difference in cholesterol level between subjects with the highest education (post-secondary) compared to the reference group of <9 years of education (elementary) was 0.5 mmol/l (95% CI 0.3–0.7 mmol/l) (Paper I - model 4, Table 3). We also found significantly lower LDL/HDL and ApoB/ApoA1 ratios in the highest educational group, both before and after adjustment for BMI and physical activity. We did not find any statistically significant association with either measure of SEP and any of the CVD outcomes studied at age 70 (with the exception of higher ApoB/ApoA1 ratio in ‘not-working’ men (Paper I - tables 2 and 3). Figure 14 shows differences in mean cholesterol by educational level for men who attended both Age 50 and Age 70 investigations and visually summarises the main findings of this study. Regression models of adiponectin at age 70 suggests a possible inverse association with education in age-adjusted analysis (Paper I - model 1) that became statistically non-significant when adjusted for BMI and physical activity in spare time. This suggests that these covariates partly mediated the influence of education on adiponectin. Differences in adiponectin levels at age 70 across occupational classes were minor and insignificant.

In models that were restricted to men who attended both age 50 and 70 investigations, N=1,220 (Paper I - Table 4), only the non-manual and the highest educated men had statistically significantly lower cholesterol levels (-0.24mmol/l, 95%CI -0.40, -0.09 and -0.60mmol/l, 95%CI -0.81, -0.38, respectively) at age 50. As before, no statistically significant associations were detected at age 70. We found no evidence for statistical interaction between SEP and participation group when we tested for bias that might arise due to drop-outs between the age 50 and age 70 examinations, (i.e. those who participated at both ages 50 & 70 vs. those who participated at age 50 only) in their effect on cholesterol and LDL/HDL ratio. This suggests that results reported in Tables 2 and 3 in Paper I are not severely biased by drop outs after age 50.

We found little evidence for associations between parental socioeconomic indicators (occupational group and educational level) and CVD biomarkers in their children in the UFS (Paper II). Most of the evidence was limited to mean BMI, overweight/obesity and SBP. For example, children of lower educated parents (mothers with less than university education or father with <9 years compulsory schooling, Paper II – Table 2) had higher mean BMI levels. Compared with children of fathers from the highest SEP groups, children of fathers who were skilled manual workers or had low education had higher mean systolic BP levels. Children of mothers classified as unskilled and farmers/entrepreneurs had higher mean BMI levels and children of farmer mothers had higher mean cholesterol levels (Paper II – Table 2). Logistic regression modelling showed significant associations between parental SEP and OW/OB only in children of lowest educated mothers and fathers who had a 75–107% increased risk of OW/OB respectively.
Figure 14. Mean cholesterol levels by education, for the Uppsala Longitudinal Study of Adult Men (ULSAM) who attended both ages 50 and 70 investigations (N = 1220).

7.9.2 Associations between socioeconomic indicators and CVD mortality

In the approximately 37 years of follow-up (between 1970 and 2007), 1499 men had died of various causes of which 681 died due to CVD. We found that men with the highest levels of education had a significantly decreased risk of CVD mortality compared to men with the lowest level of education (age-adjusted HR 0.68, 95% CI 0.54–0.86, age- and BMI-adjusted HR 0.72, 95% CI 0.57–0.91). We however did not find any difference between the lowest and middle educational groups.

Kaplan–Meier survival curves for death due to CVD showed a distinctly lower rate of mortality for men with the highest education, while the differences between men belonging to the middle and lowest levels of education were minor with the curves running almost concurrently (Paper I - Figure 1).

When the analysis was run by splitting the follow-up time into two periods (Figures 15 & 16): 1. 1970–90 (213 deaths due to CVD), the HRs for men with the highest compared to lowest education were 0.54, 95% CI 0.34–0.86 (age adjusted) and 0.59, 95% CI 0.37–0.94 (age and BMI adjusted).

2. 1991-2007 (468 deaths due to CVD), the HRs were 0.74, 95% CI 0.57–0.97 (age adjusted) and 0.78, 95% CI 0.59–1.02 (age and BMI adjusted).

Differences in survival curves between manual and non-manual workers were distinct with the curves running parallel to each other from around 1988 onwards. However, the differences in mortality by occupational classes were smaller in comparison to those by educational groups (Figure 17 - manuals and non-manuals only - not included in Paper I due to lack of space). As can be seen, non-manuals (blue line) had a consistently lower rate for death due to CVD mortality compared to manuals.
Figure 15. Kaplan-Meier survival curves for cardiovascular disease mortality by educational groups in the ULSAM, 1970-1990.

7.9.3 Associations between parental lifestyle factor/CVD biomarkers and CVD biomarkers in their offspring

We found more consistent associations between parental lifestyle habits and CVD risk factors in children (Paper II - Table 3). Fathers and mothers classified as current smokers had children with higher mean BMI corresponding to an increase of 4% and 3%, respectively, when coefficient estimates were converted to original scale. We also found a 27% increase in leptin levels of children of current smoker fathers. Those fathers that reported drinking alcohol more than once a week had children with an average of 0.35 mmol/l (95% CI 0.05–0.65) higher cholesterol and 0.26 (95% CI 0.09–0.44) higher (log) adiponectin levels compared with children of teetotaller fathers. In contrast, children of teetotaller fathers had 0.04 (95% CI 0.00–0.08) higher mean ApoB/ApoA1 ratio levels. Increased alcohol consumption among mothers – once/week – was associated with increased mean BMI (0.03 (log)BMI or a 3% increase) and cholesterol levels (0.18 mmol/l) in children compared to those of teetotaling mothers (Paper II - Table 3).

Consistently strong associations were found between PA, especially among mothers, and several CVD risk factors in children. Fathers who reported ≥90 min vigorous PA per week had children with significantly lower mean BMI. Children of mothers reporting vigorous PA had lower mean BMI, cholesterol and leptin and decreased odds for overweight/obesity (the latter with a possible dose response effect). Compared to mothers reporting no vigorous PA, mothers with up to 75 min weekly vigorous PA had a 43% (95% CI 0.22–0.89) lower odds of having an OW/OB child. The corresponding effect in mothers reporting vigorous activity between 76-150 min per week was 72% (0.14–0.60) (Paper II – Table 3). Children of fathers who reported vigorous PA had decreased odds for OW/OB as well, though these findings were not statistically significant.
The second measurement of PA in parents – total moderate and vigorous PA combined into MET hours per week, had almost no significant associations with CVD risk factors in children. An exception was lower mean BMI and cholesterol levels in children of mothers who reported greater number of total MET hours per week of PA (Paper II - Table 3). However, in sensitivity analysis restricting these regression models to mothers who had information on vigorous PA revealed strong and significant associations between total MET hours per week and BMI, cholesterol and ApoB/ApoA1 ratio levels in children. Similar sensitivity analysis in fathers did not reveal any significant associations with CVD outcomes in children. The associations between parental lifestyle factors and CVD risk factors in children were additionally adjusted for parental SEP (Paper I - Table 3), which only marginally affected the estimates. (For regression models unadjusted for parental SEP, see Paper II - Supplementary digital table S1).

CVD biomarkers in parents were strongly associated with their children’s CVD biomarker levels (Paper II - Table 4). All CVD biomarker outcomes in the children were statistically significantly associated with the respective CVD biomarkers in their parents. Additional adjustment for parental SEP and parental lifestyle habits (smoking, alcohol consumption and PA) did not appreciably change these associations, but a significantly stronger association was found between father’s and child’s BMI and odds of OW/OB in children. The change in regression estimates of studied outcomes was greater in the case of the mother for cholesterol and ApoB/ApoA1 ratio. For systolic BP, the father’s biomarker levels seem to play a greater determining role (Paper II – Table 4).

We did not find any systematic differences in the associations between the three sets of parental exposures and CVD biomarkers in children when the regression models were run separately for boys and girls. Tests for interaction were statistically significant for only paternal ApoB/ApoA1 ratio, indicating that father’s played a greater role in determining the level of this biomarker in their daughters compared to their sons ($p$ for interaction = 0.03). Interaction tests between all parental exposures studied and pubertal stage in children were statistically non-significant suggesting that pubertal development does modify any of the associations studied in this particular study sample.
7.10 BACKGROUND

The main aims of Papers III, IV, and V were to analyse ethnic differences in various health outcomes in the Swedish population and to assess if such differences if any could be mediated by important covariates including socioeconomic indicators. We analysed: ethnic differences in overweight/obesity (OW/OB) in Swedish children aged 4-5 years, and ethnic differences in risk for early preterm, late preterm and postterm birth. We also reinvestigated the established association between reduced foetal growth and increased risk for higher systolic blood pressure in adulthood and if this association could differ between major ethnic groups in Sweden.

7.10.1 Ethnic differences in overweight & obesity in children

As explained previously immigrants and ethnic minorities in high-income countries often belong to lower socioeconomic groups and have higher rates of chronic diseases, report worse self-reported health and higher infant mortality (61, 88-90). Poor health in immigrants and ethnic minorities are reported in all age groups; the elderly, adults, children and their descendants. Differences in health vary considerably by country of origin, destination, time since immigration, acculturation and disease/health outcome (6). Also not all immigrant or ethnic minority groups are at increased risk for disease or ill health. Some groups might also fare better when compared to other immigrant/ethnic groups or the majority population. Phenomena such as the ‘Hispanic Paradox’ and Healthy Migrant effect have been described (15, 91-94).

The overweight/obesity epidemic in children is a major health concern in both high and low income countries. In 2011, more than 40 million children under 5 years of age were overweight worldwide (95). The recent decades have witnessed a significant rise in obesity levels in children across the world, with children of lower SEP being the worse affected in high income countries (96-100). OW/OB in childhood can track into adulthood, posing greater health risks (50, 101). Socioeconomic, cultural, ethnic and/or genetic factors may contribute to obesity in childhood (102). Numerous studies, reports and data from national statistics in many countries show that ethnic minority children are disproportionately affected. In the USA, black and Hispanic children have much higher rates of OW/OB compared to their white counterparts (103, 104). Data from the latest 2009-2010 National Health and Nutrition Examination Survey (NHANES) which reports sex-, age- and ethnic- specific prevalence and trends in OW/OB in both infants (birth to 2 years of age) and children (2-18 years of age) in the USA, showed strong ethnic differences in weight for recumbent length already in infants (105). Hispanic and Mexican infants had almost twice the prevalence of high weight for recumbent length (14.8 and 15.7% respectively compared to 8.4% for Whites). More discouraging was the finding that all ethnic minorities sampled (Hispanic, Mexican-American, and non-Hispanic Black) had higher prevalence of high mean BMI (at both above the ≥85th and ≥95th percentiles of BMI) in all age groups compared to non-Hispanic White children (105). However, ethnic-specific analysis of trends in obesity over a 12 year period from 1999 to 2010 showed an increasing trend in obesity for only Black male children. The NHANES unfortunately does not
include Asian children. In the UK, ethnic minorities such as South Asians and Blacks of both African and Caribbean ancestry have been shown to be disadvantaged in regards to OW/OB (103).

There are differences in the associations between ‘nativity’ and ‘ethnicity’ in their association with OW/OB (106). For example in the USA, Latino immigrants have a lower rate of obesity compared to their native born-counterparts, but this ‘immigrant advantage’ (probably due to healthy immigrant selection in some migrant groups) tends to fade with time with acculturation (107). If this apparent ‘immigrant advantage’ actually extends to children of immigrants is not very clear and studies in the US have found mixed results (108). This is relatively understudied in other countries. Studies from the USA, UK, Sweden and elsewhere have shown that immigrant mothers from some countries tend to have better health behaviour patterns such as lower rates of smoking and higher rates of breast feeding (which protect against low birth weight) (81). This is not surprising as relatively newly arrived immigrants will bring lifestyle practices from their home country.

Some have proposed the concept of an ‘obesogenic environment’, where ‘obesogenicity’ is defined as ‘the sum of influences that the surroundings, opportunities, or conditions of life have on promoting obesity in individuals or populations’ (109). This is often dependent on four environments: the economic, social, cultural and political. Lofink showed that Bangladeshi adolescents residing in a socially deprived neighbourhood in London were more exposed to an obesogenic environment because of the cheap and easy access to high energy dense and fast food, cultural traditions relating to diet in their ethnic community and low neighbourhood SEP which all contributed to higher prevalence of OW/OB (110). This has been further exemplified in other studies, which have shown that low socioeconomic neighbourhoods with higher proportions of immigrants and/or ethnic minorities often have greater access to cheap and energy dense foods that contribute to increasingly higher prevalence in overweight/obesity in ethnic minority children (111).

Are ethnic minority children disproportionately affected by OW/OB solely due to “ethnic differences” between groups - cultural differences in diet, lifestyle, physical activity, perceptions of obesity, genetic predisposition, or other intergenerational factors like family history of obesity, breastfeeding and maternal smoking? Or is it largely driven by socioeconomic factors or a combination of these? The answer is more likely to be the latter, but nonetheless there remains scope for intervention on several fronts.

As discussed previously, the role of socioeconomic factors in the health of immigrants and ethnic minorities is debated. Some but not all studies have found that these factors partly explain ethnic differences in certain health outcomes (112-114). The role of parental socioeconomic factors in creating differences in the proportions of children who are OW/OB between immigrant groups needs further investigation.

A ‘levelling-off’ in the obesity epidemic has been reported but this might be country and region specific, and it is generally the more affluent that have benefited from this trend (115, 116). In a study which analysed data from nine countries around the world (including regional data from Sweden), the authors concluded that the OW/OB epidemic was indeed plateauing and the media had sensationalised the issue to a large extent (117). They also hypothesised the reasons behind this plateauing including successful public health interventions, and a
saturation-equilibrium theory. The latter means that those children who could become OW/OB have done so and the remaining ones are ‘resilient’ to this condition. Nonetheless, it still remains that overweight/obesity levels are still much higher than they were a couple of decades back and several groups are probably worse affected by this condition. The WHO on the other hand predicts the number of OW/OB children will increase to 60 million by 2020 (118). In Sweden, nationally representative data for trends in OW/OB in children are lacking. Studies are conducted on regionally representative data often with small sample sizes, and results indicate that OW/OB levels in children are falling but socioeconomic and gender differences still exist, at least in urban areas (119-123). Community-based interventions were shown to reduce obesity, and promote healthier behaviours in low SEP groups in the Swedish context (124). Less is known if such differences actually permeate the various ethnic/immigrant groups in the country.

In the adult Swedish population, there has been an overall increase in the prevalence of being OW/OB. The prevalence of OW/OB increased from 35% in 1980 to 53% in 2009 among men and 26% to 37% among women for the same years (125). The number of ‘foreign-born’ residents in Sweden has doubled over the past four decades and number of residents with ‘both parents born abroad’ have been increasing continuously (13.4% and 17.34% respectively in 2007) (125).

Our research aims in Paper III were: To investigate (i) if ethnicity by mother’s country of birth was associated with odds of being OW/OB in children born in Sweden aged 4-5, (ii) if this association could be explained by differences in parental SEP and/or health behaviours and early life factors (breastfeeding, maternal smoking, maternal BMI and birth weight) and (iii) if the association differed by gender. The conceptual model outlining this study is shown in Figure 21. While this figure explains the reasoning behind our analysis, we acknowledge that it could be drawn in different ways which would suggest different analytical approaches.

7.10.2 Ethnic differences in preterm and postterm birth

According to the WHO, 15 million babies are born premature every year (i.e. <37 weeks of completed gestation). Of these, one million die of complications arising from prematurity. This makes preterm birth one of the global leading causes of infant mortality (death of a baby less one year of age) (126). It is also the second largest cause of childhood mortality (death below the age of 5 years) with only pneumonia killing more (126). The rate of preterm birth differs markedly by country, with rates ranging from 5% to 18% (126). In a 2010 WHO bulletin based on data collected between 1997 and 2007, the authors showed that despite the absolute numbers of preterm births being the highest in South Asia and Africa, the highest rates of preterm birth were actually in Africa (11.9%) and North America (10.6%) and the overall global rate for preterm birth in 2005 was 9.6% of all births (127, 128). There is a strong correlation between economic development and the rate of preterm births across countries (127). The vast majority of deaths due to preterm birth can now be saved (up to three-fourths of all deaths) but the aetiology of preterm birth continues to remain largely elusive (129). Despite the significant progress in care for premature infants, reducing its prevalence has been more challenging (129). Rates of preterm births have also increased in some regions (127, 130). Preterm birth has both short- and long-term consequences for the infant (129). Short-term consequences of preterm birth include respiratory distress, apnoea, hypoglycemia, jaundice, feeding difficulties, and rehospitalisations (127, 131). Long-term sequelae of preterm birth
include cerebral palsy, mental retardation and visual and hearing impairments (127). Children and adolescents born very preterm have higher rates of behavioural issues, and slower academic progress (131). Several risk factors for preterm birth have been identified including short maternal stature, higher maternal age, undernutrition, genital infections, smoking, substance use, short intervals between subsequent pregnancies, previously induced abortions, and stress (127, 132, 133). Higher or lower rates of preterm birth are also found in certain ethnic or immigrant groups as well as in lower socioeconomic groups and single mothers (129, 134-142).

Less is known about the causes of postterm birth (defined as birth at gestational age of 42 weeks and greater). Previous postterm births, male foetal sex, genetic predisposition, nulliparity and obesity are some of the risk factors for postterm birth (143). It is normal to induce labour in postterm pregnancies when there is potential harm to either the infant or the mother. In some countries such as Canada, it is routine to induce labour once mothers have crossed 42 weeks of completed gestation (verbal communication). In these cases it can be difficult to estimate the actual length of postterm pregnancies and if they differ by ethnic and/or socioeconomic groups. A few studies have been conducted on postterm birth and the health risks it poses in the infant. Postterm birth has been linked to increased risk for infant death, still birth, convulsions, meconium aspiration and Apgar scores <4 (144). It has also been linked to long-term consequences such as increased risk for behavioural and emotional problems in early childhood and greater risk for both OW/OB in adolescent males (144, 145). However, little evidence is available on the relationship between ethnicity and the risk for postterm birth in literature reviews that I have conducted.

Ethnic differences in risk for postterm birth are well studied with ethnic minorities at consistently higher risk for this adverse birth outcome (134, 141, 146). One previous study that analysed the risk for preterm birth and low birth weight among immigrant and Swedish women found little difference in rates for either outcome (147). Since the time of this study, the pattern and composition of immigration to Sweden has undergone a drastic change. The country is far more diverse and multicultural with larger numbers of non-European immigrants. Today, almost 20% of the Swedish population was either born abroad or has one parent that is foreign-born (125). It is likely that greater differences exist today in maternal and perinatal health between Swedish and immigrant mothers, than previously.

Maternal health and birth outcomes vary by both socioeconomic position and/or ethnic group in high-income nations (148-151). A previous study in the USA showed that non-Western and ethnic minority women in an high-income country were at higher risk of receiving suboptimal maternal care (138). In many instances certain immigrant groups are more likely to belong to lower socioeconomic groups and live in neighbourhoods with higher deprivation and/or segregation (15).

There have been a lot of advances in our understanding of the intricate molecular machinery that lies behind the progression and timing of pregnancy and birth (152). For the most part of gestation, the foetus cannot survive outside the uterus, and thus the timing of birth is critical and must be coordinated with the rate of development of the foetus. Two factors can go wrong and affect this delicate biological clock having direct consequences on the foetus and pregnancy outcome: the rate of foetal growth and maturation is altered but the duration of
gestation remains normal (an example would be the case of gestational diabetes) or the more common scenario, where foetal maturation is normal, but the timing of birth is altered resulting is either an early or late delivery (152). The duration of pregnancy is maintained and relies heavily on the inhibition (or delay) of events that could result in contractions and delivery. Both foetal and maternal developmental and physiological changes and events have been identified which must come together in bringing about a delay in contractility until it is time for parturition, usually between 37 to 40 weeks of gestation in humans. In pathological conditions, changes occur in intricate biochemical pathways (such as hormonal disturbances in oestrogen/progesterone/corticotropin-releasing hormone – all essential in maintaining pregnancy and timing of birth and delivery) that alter the environmental milieu of the uterus resulting in the cascade of events that ultimately lead to an early or later delivery (152). Not much is known about the nature of these intricate timings and processes.

Using the Swedish Medical Birth Register which includes all births in the country, our aim was to study the risk for early preterm, late preterm and postterm birth among offspring of ethnic minority parents compared to Swedish born parents and if differences could be explained or mediated by commonly measured confounders.

<table>
<thead>
<tr>
<th>Gestational age in completed weeks</th>
<th>Birth outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;28</td>
<td>Extremely preterm</td>
</tr>
<tr>
<td>28 to 31</td>
<td>Very preterm</td>
</tr>
<tr>
<td>32 to 36</td>
<td>Moderate to late preterm</td>
</tr>
<tr>
<td>37 to 42</td>
<td>Term</td>
</tr>
<tr>
<td>&gt;42</td>
<td>Postterm</td>
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</tbody>
</table>

Table 1. Classification of infants based on gestational age according to the WHO (153).

### 7.10.3 Ethnic differences in blood pressure

High blood pressure is a major risk factor for cardiovascular disease as well as stroke, chronic renal failure and thus premature mortality (154). Blood pressure (BP) is the ‘force’ with which it flows through the arteries as a result of the pumping action of the heart. It is measured by two ‘pressures’, the systolic blood pressure (SBP) which is the pressure in millimetre of mercury (mmHg) when the heart beats while pumping blood and diastolic blood pressure (DBP) which is the pressure when the heart is at rest between beats. BP of a person is expressed in terms of the systolic pressure over the diastolic pressure. Persistent high BP or hypertension is dangerous and is considered to be equivalent to SBP values >119mmHG and DBP values >79mmHG. Low BP is equivalent to SBP and DBP values of <90mmHG and <60mmHG respectively. Values in between these are considered to be desirable. According to the WHO the number of people with hypertension will reach 1.5 billion by 2020 (155).

High BP has been thought to be a condition of middle and later life often brought about by several risk factors such as alcohol consumption, body build, low physical activity and poor diet (high salt intake) (156). More recent studies have now shown that high BP may also have
some of its origins much earlier in life, such as in childhood or even during foetal growth (156-159). Several studies using a life course epidemiological design have tried to investigate at what stages in life BP actually becomes an independent risk factor for future chronic disease (156). Some studies have shown independent contributions of BP from childhood and adolescence on adulthood CVD risk but these have been rather modest (156). Many such studies often were unable to control for BP in later adult life, i.e. closer to the adverse event such as CVD.

BP is known to track throughout life and this has been studied in populations around the world (82). Strong differences in BP have been found in various ages between populations residing in different countries. Studies have also concluded that the variation or patterning of BP in middle age is already visible in young adulthood.

Geographic or ethnic differences in BP may be attributed to differences in lifestyle (diet, physical activity, alcohol consumption) and body size, genetics and socioeconomic differences. Nonetheless both ethnic and socioeconomic differences in BP are discernible in early adulthood and to a lesser extent in childhood as well (160-162). Studies on migration and its effect on BP have shown that migrants quickly achieve the BP of the local population of the host country (156). Studies on ethnic differences in BP within countries have shown inconsistent results. In a Swedish study which compared SBP levels between ethnic Swedes, ethnic Swedish adoptees and international adoptees using data on military conscripts found that regardless of geographic origin, all international adoptees had lower SBP compared to their ethnic Swedish counterparts and these differences were partly explained by differences in height and BMI. (163). As international adoptees arrived in Sweden at a very young age (mean age 7 months), differences in SBP could be attributed to genetics and differences in foetal growth, early life and pregnancy. Studies from the US and UK have shown that African origin men have higher rates of BP compared to Whites (164, 165). Results are often contradictory and inconsistencies between studies can be attributed to study design, study population size and body composition. Other studies investigating ethnic differences in BP within the same country have found inconsistent or mixed results but many studies show higher rates of hypertension in Black compared to white populations though such differences are more limited in younger populations (164, 166).

7.10.4 The association between birth weight and later adulthood blood pressure

Several studies from different populations around the world have shown that LBW (including other indicators of impaired development such as short gestational age) is associated with higher BP in adulthood (167-171). More than 40 studies have demonstrated this association, more so for SBP (172). The association has been demonstrated in children, adolescents and adults (156, 167, 173). The mechanism responsible for this association is thought to be the foetal origins hypothesis – that maternal undernutrition in pregnancy hampers foetal growth (often measured by BW) thereby disrupting biological function which has an impact on later adulthood BP (158). This association stands even after adjustment for several factors strongly associated with BW including SEP, maternal smoking, and alcohol consumption. The association is also thought to be independent of maternal BP.
There has been considerable discussion about the adjustment for adult body size (most often measured by BMI) in the study of BW in its association with subsequent BP (174). The effect is often stronger after adjustment for adulthood BMI and many argue this introduces a bias (174, 175). The unadjusted estimate for the association between BW and adulthood BP is inverse but small and weak. This unadjusted estimate is thought to provide the best indicator of the overall association between BW and adulthood BP. In a well cited meta-analysis – the first to comprehensively study the BW – BP association taking into account 55 studies, the authors found that the estimate for the association depended on the size of the study (174). It was of the order of the magnitude of -1.9mmHg per kg BW in studies with <1000 subjects and the estimate decreased to -0.6mmHg per kg BW in studies with >3000 participants. Further the authors concluded that the association of interest ‘may chiefly reflect the impact of random error, selective emphasis of particular results and inappropriate adjustment for current weight and for confounding factors’. Nonetheless, even when taking into account the larger estimate of the strength of association into consideration – a difference of 1.9mmHg – would represent a change in BP equivalent to 0.2 SD for a rather large change in BW (2 SD).

The inverse association between BW and BP in children is found only after adjustment for concurrent body size. Adjustment for current body size in estimating BW – BP associations in children is considered to be more appropriate, especially adjusting for current height. This is because both height and weight-for-height are associated with BW and are strong determinants of childhood BP. While height is an important determinant of BP in childhood, it is less predictive of BP in adulthood (156).

Gestational age is also shown to be inversely associated with subsequent SBP in offspring however, these studies are fewer in number (170, 176, 177). Studies have not analysed if this association differs across ethnic groups.

There continues to be sustained interest in the association between BW and subsequent BP despite it being a weak association. This is primarily because the exposure could be imprecisely measured especially if BW (often used to measure foetal development) does not really capture all aspects of prenatal development that might be associated with later adulthood BP. The association could be more pronounced in a particular subset of the population. A Swedish study showed that the BW – BP association was stronger in middle aged men with higher BMI (178). However, this interaction was not replicated successfully in other studies. It is also likely that the association between BW – BP may become stronger with age in subsequent generations and may also differ between ethnic groups.

Studies have tried to analyse ethnic differences in the association between BW and later BP both between and within countries. Using the large INTERSALT study (which has BW, infant mortality and SBP data from 32 countries), Owen et al. hypothesized that those countries with lower mean BW and higher rates of infant mortality would also have higher mean BP (179). The authors found to the contrary that mean SBP was inversely correlated with infant mortality and positively correlated with BW suggesting that foetal growth was not an important determinant high mean SBP in adulthood. Nonetheless ethnic disparities in the association between BW and adulthood BP were shown in other studies, many of which were based on smaller study samples, and focus on differences between African-American and white populations in the US where the ethnic differences in hypertension are larger (173, 180-182). Hemachandra et al demonstrated that BW was positively associated with SBP and DBP in
Black children but not in White children and remained significant for SBP after adjustment for SEP, and anaemia in pregnancy (167). The direction of the association between markers of foetal growth and subsequent BP thus probably differs between ethnic groups and at different ages (being positive in children and inverse in adulthood).

7.11 METHODS

7.11.1 Data sources & datasets

For Paper III, the study sample was drawn from a population of children born 2000-2004, registered as residents in Uppsala county, Sweden (N=20,520) when they were 4-5 years old (Paper III - Figure 1) (45). Of these, 19,123 were born in Sweden and had data on birth weight (obtained from the Swedish Medical Birth register, (MBR)). The study sample was first restricted to singletons, (N=18,555), and then to children who attended annual routine examinations at child health care centres when anthropometric measurements (height and weight – used to compute BMI) were recorded and whose valid BMI at age 5 or 4 was available. For children who had not yet completed the examination at age 5, measurements from the examination at age 4 years were included. Thus 10,509 children with age 5 BMI (born 2000-2003) and 4,331 children with age 4 BMI (born 2000-2004 and had BMI at age 5 missing) were included. Of the 14,840 children with valid BMI data, 10,628 had complete data on all covariates (parental socioeconomic variables – educational level, disposable income and occupation, maternal BMI, smoking during pregnancy and breastfeeding).

For Papers IV & V, the study sample was first drawn from all infants registered in the MBR and then further restricted in number based on the time period, main exposures and covariates of interest. In Paper IV, our main aim was to analyse ethnic differences in risk for preterm and postterm birth. We could have included all births in Sweden (approximately 3.2 million births between 1973-2002), but our sample was restricted by the availability of data on maternal cohabitation status and smoking which we considered to be important confounders and recorded only from 1982 onwards. The final study sample included 1,766,026 (86%) of 2,044,208 eligible infants born in Sweden 1982-2002 with data on all covariates.

For Paper V, the above study sample was further restricted to all those infants born in Sweden and in the MBR who eventually attended the military conscription examinations when they reached 18-19 years of age. 590,909 men were eligible to be included (born 1973-1990 and who attended the military conscription medical examinations between 1990 and 2009). The final sample included 406,833 men with data on all covariates.

Variables including maternal age at offspring birth, parity, pre-pregnancy BMI (calculated from height weight measured at the first antenatal check-up) and height, smoking habits in early pregnancy, year of birth, birth weight, gestational age and infant sex were obtained from the MBR. According to WHO criteria women were classified into underweight (<18.5kg/m²), normal (18.5kg/m²-24.9kg/m²), overweight (25kg/m²-29.9kg/m²) and obese (≥30kg/m²). Mothers were asked about their smoking habits (generally reflecting habits during the first trimester) and were grouped into a) Nonsmokers, and those who smoked b) <10 cigarettes/day and c) ≥10 cigarettes/day. Women with hypertension during pregnancy were identified using the relevant ICD 8, 9 and 10 codes as recorded in the MBR.

88.1.1. Child health care centres

The child health care centres (or barnhälsovårdcentraler in Swedish) provide free annual check-ups for all infants and children registered as residents in the local counties. The child health care centres receive children between the ages of one and five. In Uppsala County,
height and weight measurements were also collected enabling calculation of BMI. Parents answered detailed questionnaires administered by a nurse.

**8B.1.2. Military conscription register**

The Swedish Military Conscription register includes all information recorded at the conscript medical examinations. Conscription was mandatory by law for all Swedish males except those with severe disabilities or chronic diseases until the year 2000. After 2000, the register only includes information on those conscripts accepted for military service and is thus more selective. Other variables recorded at the conscript examination and used in analysis in Paper V include age, and conscription office. Men were expected to attend the examination at the conscription office closest to their registered address. Controlling for conscription office adjusts for any difference in methods used for measuring BP and anthropometry. Mean age of men at conscript examinations was 18.20 years (range 17 - 25 years).

**8B.1.2. Other registers**

For all three papers, data on socioeconomic indicators (education, disposable income, occupation and marital status) were obtained from the Education and Census Registers. Maternal education was based on the highest level achieved and recorded in the register 7.11.2 Outcomes

**7.11.2.1 BMI & OW/OB**

As described previously, we used the age- and sex-specific cut-offs proposed by the International Obesity Task Force (IOTF) to classify children into overweight or obese groups. As the study sample was small, we combined overweight and obese groups into one group.

**7.11.2.2 Preterm birth and postterm birth**

We used length of pregnancy (gestational age at birth - defined as the time from last menstrual period to birth and/or from ultrasound assessment of gestational age) to group infants into early preterm (<32 weeks), late preterm (32-36 weeks), term (37-41 weeks) and postterm (>42 weeks) births, based on cut-offs as recommended by the WHO.

**7.11.2.3 SBP**

Both SBP and DBP were recorded at the conscript examinations. Blood pressure was measured in the supine position after 5-10 minutes of rest. We were unable to use diastolic BP measurements due to heaping of values to the nearest 10mmHg. This was not a problem for systolic BP (SBP), which tended to be rounded-off to the nearest 2mmHg.

**7.11.3 Predictors**

**7.11.3.1 Ethnicity**

Ethnicity is the main predictor variable in Papers III & IV. We determined ethnicity based on country on birth as recorded in the Total Population Register. This register also provides information on the dates of first and subsequent immigration or entry into Sweden. This was used to calculate the duration of residence (in years) in Sweden.

In Paper V, analysis was stratified by ethnicity.
In Paper III, we used maternal ethnicity to determine the ethnicity of a child. As the study population was smaller (compared to that in Paper IV), we had a broader classification of ethnic groups and fewer countries as their own categories. Countries were first grouped into the following regions: i). Sweden (reference); ii). Western Europe and North America; iii). South America; iv). East Europe; v). North Africa; vi). East Asia; and vii). Middle East. Those countries that had sufficient numbers (a minimum of \(N=80\)) were excluded from the above regional groupings and classified as separate categories. This included Iran, Finland and Turkey. One hundred and thirty eight children whose parents were born in South Asia (India, Pakistan, Bangladesh and Sri Lanka) and Africa (except Northern Africa) were excluded due to insufficient numbers.

In Paper IV, ethnicity of an infant (included in the Swedish Medical Birth register) was based on the ethnicity of both parents (determined by their country of birth). Parents not born in Sweden were considered to be non-Swedish ethnicity. Only infants with parents of the same nativity were considered to belong to a particular ethnic group. Infants of mixed ethnicity, i.e. parents born in two different countries were classified into one of three groups as follows: i). Swedish born mothers and non-Swedish born fathers; ii). Swedish born fathers and non-Swedish born mothers; and iii). Non-Swedish born mothers and non-Swedish born fathers of differing nativity. Countries were grouped into the following regions: Sweden (reference group), Western Europe and North America, Eastern Europe, Former Yugoslavia, North Africa and Middle East, South Asia, Ethiopia and Eritrea, East Asia, Latin America, Sub-Saharan Africa, Finland, Poland, Iraq, Lebanon, Somalia, Syria, Turkey, Iran, and Chile. These nine countries had sufficient number of subjects (a minimum of \(N=3000\)) to be classified as their own categories.

The above ethnicity variable was re-categorised into three groups for analysis in Paper V as follows: 1. Swedish, 2. Europeans and 3. Non-Europeans. This was meant to roughly reflect differences between Caucasian and non-Caucasian groups. The three groups of mixed ethnicities described above were not included.

7.11.3.2 Foetal Growth Rate (FGR)

FGR is both an outcome and predictor in Paper V. Birth weights were converted into z scores representing birth weight standardised to gestational age (birth weight z scores), calculated as birth weight minus mean birth weight divided by the SD, (using gestational age-specific birth weight means and SDs from the MBR as an internal standard). This was used a measure of FGR (independent of gestational age) and to analyse if there were any differences in this measure between various ethnic groups.

7.11.3.3 Gestational Age

Gestational age (in completed weeks) was estimated from first day of last menstrual period or by ultrasound where available. Men were grouped into preterm (<37 completed gestational weeks), term (37-41 completed gestational weeks) and postterm (>41 completed gestational weeks) birth. Gestational age was used both as a continuous predictor (in weeks) and categorised as described above.

7.11.4 Statistical analysis

7.11.4.1 Logistic regression

In Paper III, multivariable logistic regression models were fitted with the child’s OW/OB status as outcome and the child’s maternal ethnicity as the primary exposure. Four models were run as follows: Model 1: adjusted for child’s age and sex. Subsequent models were fitted by grouping covariates into socioeconomic factors and lifestyle/early life factors. Model 2:
Model 1 covariates + adjustment for socioeconomic factors; income and education of both parents and father’s family status. Model 3: Model 2 covariates + adjustment for breastfeeding, maternal smoking, and birth weight. Model 4: Model 3 covariates + adjustment for maternal BMI. In a separate analysis (model 5), model 4 was run with the addition of father’s ethnicity (categorised in the same way as mother’s nativity variable). We also ran the same logistic regression models stratified by sex of the child. Differences in the nativity – OW/OB associations between males and females were tested formally using interactions. Robust standard errors allowing for clustering of children within families were used for all logistic regression models.

7.11.4.2 Multinomial logistic regression

This is a type of regression model generalises logistic regression by allowing more than two discrete outcomes (i.e. a categorical or nominal outcome with a set of categories which cannot be ordered in any meaningful way). Some of the assumptions in this type of modelling include: that the data are case specific (i.e. each independent variable has a single value for each case), the dependent variable cannot be perfectly predicted from the independent variables for any case, and collinearity is assumed to be fairly low. Multinomial logistic regression uses the maximum likelihood estimation method and requires large sample sizes. In multinomial logistic regression, one of the categories of the dependent variable is chosen as the reference. Separate odds ratios are determined for all independent variables for each category of the dependent variable with the exception of the reference category (which is omitted from the analysis). The exponential beta coefficient represents the change in the odds of the dependent variable being in a particular category vs. the reference category, associated with a one unit change of the corresponding independent variable. The Relative Risk Ratio (RRR) is the estimate produced in statistical software such as STATA when multinomial logistical regression is the chosen modelling method. The RRR is essentially ‘the ratio of two ratios’ (or of two probabilities) as is interpreted by some researchers as ‘relative risk’ (RR).

We used multinomial multivariate logistic regression to estimate the RR for early preterm, late preterm and postterm birth relative to term birth in different ethnic groups in Paper IV. We first tested each independent covariate (maternal age, parity, education, smoking status, gestational hypertension and period of residence) separately with the outcome of interest. Those covariates found to be statistically significantly predictive of the outcome variable were included in the final multivariable logistic regression model. Five models with sequential adjustment for confounders were constructed as follows: Model 1 – minimally adjusted for infant’s sex & birth year, Model 2 – additionally adjusted for maternal age and parity, Model 3 – additionally adjusted for maternal SEP, Model 4 – additionally adjusted for smoking and Model 5 – additionally adjusted for hypertension during pregnancy.

We additionally tested a model adjusted for duration of residence in Sweden, comprising a smaller sample of 221,245 immigrant women only. This model was run adjusted for sex and birth year only and again adjusted for all covariates as described for model 5 above. Robust standard errors allowing for clustering of children within families were used for all regression models.

7.11.4.3 Linear regression

Multivariable linear regression was used in the first part of statistical analysis in Paper V to investigate the associations between: 1. Ethnicity and SBP 2. FGR and SBP stratified by ethnic group and 3. Gestational age and SBP stratified by ethnic group. 2 and 3 were further tested with formal tests for interaction. All above regression models were run adjusted for age at conscription, birth year, and conscription office (model 1). The ethnic-origin – SBP models were additionally adjusted in subsequent models for concurrent BMI (model 2), concurrent
height (model 3), maternal education (model 4), foetal growth rate (model 5) and gestational age (model 6). The FGR-SBP and gestational age-SBP models stratified by ethnicity were adjusted for conscription, birth year, and conscription office (model 1) and additionally for concurrent BMI and height, maternal education, and FGR/gestational age (model 2). Robust standard errors allowing for clustering of conscripts within families were used for all regression models. All models described above were run to assess if there were any differences in associations of interest between Caucasian and non-Caucasian groups.

7.11.4.4 Structural equation modelling (SEM) & path analysis

We used path analysis to investigate the relationships between foetal growth, concurrent adulthood BMI and SBP in Swedish conscripts stratified by ethnic groups. Path analysis (183) (which is an extension of regression analysis) allows the simultaneous modelling of several interrelated regression relationships while taking into account adjustment for confounders. Thus a variable which is dependent in one relationship, maybe independent in another (184). For example in this study, adulthood BMI is the dependent variable in the regression association between foetal growth and adulthood BMI, but it is the independent variable in the regression association between adulthood BMI and SBP. Path analysis can be considered as a special case of structural equation modelling (SEM), where the structural model but not the measurement model is specified. Path analyses enable us to assess both direct and indirect (and thus total) effects of one variable on another (for example, we are able to assess the direct effect of foetal growth on SBP as well and the indirect effect that goes via BMI. The sum total of these two direct and indirect effects will give us the total effect from foetal growth to SBP).

The standard errors of the estimated effects and the model fit indices were calculated taking into account the non-independence of observations due to clustering on conscription office. All error terms were set to be uncorrelated throughout this paper. Models were fitted using full information maximum likelihood (FIML) which allows all subjects who have data for at least one of the variables in the path model to contribute to the analysis under the assumption of data being missing at random (MAR).

Path coefficients in path analyses (or SEM analyses) are frequently reported in two different ways: non-standardised and standardised. Non-standardised path coefficients are interpreted in the same way as conventional regression coefficients – as the estimated increase in the outcome variable associated with a one unit increase in the explanatory variable. Standardised coefficients, however, represent the estimated number of standard deviations the outcome variable increases for a one standard deviation increase in the explanatory variable.
7.12 RESULTS

7.12.1 Associations between parental ethnicity & offspring overweight/obesity

Prevalence of OW/OB in children varied statistically significantly by maternal ethnicity, with North African, South American and Turkish mothers having the highest proportions of OW/OB children (28%, 32% and 31%, respectively). The Finns had the lowest proportion of OW/OB children (11%), whereas Swedish and Western European mothers had 16% and 19%, respectively, of their children classified as OW/OB (Paper III - Supplemental Table 1). This was further reflected in all logistic regression models, where we observed statistically significant differences in odds for children being OW/OB between Swedish born mothers and those born in other countries: North Africa, Finland, South America and Turkey (OR 1.96, 95% CI (1.20-3.17), 0.60 (0.37-0.98) 2.53 (1.60-4.02), and 2.31 (1.41-3.80), respectively). These were statistically significant in all four models and the strength of the associations increased marginally on adjustment for covariates (Paper III – Table 3 and Figure 19).

Adjustment for socioeconomic covariates (Model 2) did not change the OR materially for any of the above four ethnic groups. Additional adjustment for breastfeeding, maternal smoking and birth weight (early life factors) led to an increase in the OR by 20-40% in those groups that already had significantly increased odds for OW/OB. Additional adjustment for maternal BMI (Model 4) slightly increased the strength of the associations, with stronger effects in the North African and Turkish groups. Children of Iranian mothers had increased odds of being OW/OB but only on adjustment for early life factors and maternal BMI (seen in Models 3 and 4).
When we used father’s ethnicity as the principle exposure, we found that children of North African, Middle Eastern, South American and Turkish born fathers had increased odds for being OW/OB after adjusting for all covariates (Paper III – Table 4). The increased odds for being OW/OB previously observed for Iranian children (according to mother’s ethnicity) lost statistical significance. However, when both maternal and paternal ethnicity were included as covariates in the same model, there was statistically significant evidence of an independent association with overweight/obesity for maternal (p<0.0001), but not for paternal ethnicity (p=0.70).

In analyses stratified by sex, the significantly increased ORs for being OW/OB in North African and Turkish children were observed only in boys (Paper III - Supplemental Table 2). However, both South American boys and girls had significantly increased OR for OW/OB though the OR were consistently higher for boys. Finnish girls but not boys had a significantly decreased OR for OW/OB. However, formal tests for interaction were non-significant.

**Figure 19.** Odds ratios (unadjusted and adjusted) and corresponding 95% CI for overweight and obesity combined by ethnic group in Swedish children aged 4-5 and resident in Uppsala County, Sweden. Odds ratios are adjusted for child’s age and sex, socioeconomic factors (income and education of parents and father’s family status), breastfeeding, maternal smoking, birth weight and maternal BMI.

7.12.2 Associations between parental ethnicity & preterm & postterm birth in their offspring

Results indicated differences in prevalence of several risk factors for preterm and postterm birth between the reference Swedish and ethnic groups (Paper IV – Table 1). Swedish mothers were the tallest and along with other Western European/North American, Eastern European, Polish and East Asian mothers, had the highest proportions of mothers with normal BMI. The highest proportions of OW/OB were found in mothers from the North African/Middle eastern,
Iraqi, Somali and Sub-Saharan African countries (overweight ≥30%/obesity≥8%). North African/Middle eastern, Lebanese, Somali, Syrian, and East Asian groups had the highest number of mothers with the lowest levels of education. Western European/North American, Eastern European, Polish, and Iranian groups had the largest proportions of mothers that were highly educated (≥20%). Smoking habits also differed markedly by immigrant group; Finnish mothers smoked the most (19%) whereas mothers from the North African/Middle Eastern, Iraqi, Somali, South Asian, East Asian, Ethiopian, and African groups smoked the least (≤3% of the total population).

In models adjusted for sex and birth year only (model 1), Polish, Former Yugoslavian, Iranian, and Sub-Saharan African groups had higher risk of early preterm birth compared to Swedish-born parents (RR 1.76, (1.25-2.50), 1.48, (1.24-1.76), 1.46, (1.14-1.87) and 1.81, (1.18-2.78) respectively) (Table 2). We also found that that bi-ethnic couples composed of Swedish born mothers with non-Swedish born fathers and parents of two different immigrant groups were at a higher risk for early preterm birth (unadjusted RR 1.67 (95% CI 1.56-1.80) and 1.51 (1.32-1.73) respectively). The Chilean group was the only group that had a statistically significant decreased risk for early preterm birth (RR 0.55 (0.31-0.94) in minimally adjusted model 1). Besides marginal differences in change of RR, additional adjustment for confounders did not explain the differences in RR for postterm birth in the above groups compared to Swedish born parents (Table 2 and Figure 1).

We found a different risk pattern for late preterm birth. South Asian, Sub-Saharan African and East Asian immigrant groups (latter group no longer significant after adjustment for maternal SEP) had a higher risk for late preterm birth compared to Swedish-born parents (unadjusted RR 1.52 (1.33-1.73), 1.26 (1.03-1.53) and 1.16 (1.03-1.31), respectively) (Paper IV – Table 2 and Figure 1). We did not find any substantial increase in risk for late preterm birth in the groups of mixed ethnicity. Former Yugoslavian, Lebanese, Somali, and Syrian ethnic groups had a decreased risk for late preterm birth after adjustment for all confounders.

We found increased risks for postterm birth in parents from North African and Middle Eastern countries (North African/Middle Eastern, Somali, and Ethiopian/Eritrean - unadjusted RR 1.27, (1.13-1.43), 2.34 (2.11-2.60), 1.83 (1.66-2.03) respectively) compared to infants of Swedish born parents (Paper IV – Table 2 and Figure 20). Several immigrant groups had decreased RR for postterm birth including Eastern Europeans, Polish, Iraqi, Syrian, Iranian, South Asian, East Asian, Latin American and Chilean (Paper IV – Table 2 and Figure 1). Additional adjustment for covariates did not mediate either the increase or decrease in RR for postterm birth in the above groups compared to Swedish born parents.

In preliminary additional analysis including 1,312,923 mothers in the Swedish MBR, we found that obese mothers (BMI ≥30kg/m²) were at increased risk for both early preterm (RR 1.18, 1.08-1.30) and postterm (RR 1.50, 1.46-1.54) birth (model adjusted for sex, birth year, maternal age, parity, education, marital status, smoking, gestational hypertension and ethnicity).
Figure 20. Risk ratios with corresponding 95% confidence intervals for postterm birth by select ethnic groups in Sweden. Estimates are adjusted for infant sex, birth year, maternal age, parity, education, cohabitation status, smoking, and gestational hypertension. Term birth is a reference category.
7.12.3

Associations between parental ethnicity & offspring preterm & postterm birth – a note on the role of duration of residence in Sweden

Our analysis revealed, that after adjustment for all covariates, immigrant mothers resident in Sweden for <3 years had an increased risk for early preterm birth compared to immigrant mothers resident in the country for >10 years. Both mothers resident for <3 years and those resident for 3-10 years had increased risk for postterm birth. These results are summarised in the supplementary table in Paper IV.

Some additional results:

7.12.4 A note on the associations between parental ethnicity & offspring foetal growth rate

We also ran an analysis to investigate potential differences in foetal growth rate (FGR – using birth weight Z scores standardised to gestational age) between ethnic groups and if these differences were independent of important covariates. Our a priori theory was that FGR would differ across ethnic groups and could partially be explained by covariates such as maternal education, cohabitation status, gestational diabetes and hypertension, smoking, prepregnancy BMI, and parity. We used the same ethnicity variable as used in Paper IV and described above in section 7.12.3.1 Ethnic differences in FGR were analysed using multivariable linear regression modeling with subsequent adjustment for covariates as follows:

Model 1 – adjusted for child's sex & birth year, Model 2 – additionally adjusted for maternal age and parity, Model 3 – additionally adjusted for maternal SEP; education, & family status, Model 4 – additionally adjusted for gestational age, Model 5 – additionally adjusted for maternal smoking, Model 6 – additionally adjusted for hypertension in pregnancy, Model 7 – additionally adjusted for gestational diabetes and Model 8 – additionally adjusted for maternal prepregnancy BMI & height.

The study sample was smaller (N=1,269,500) than that in Paper IV, as we restricted the sample to those mothers with information on prepregnancy BMI and height which was missing for substantial proportion of mothers.

Our results indicate that compared to infants of Swedish parents, infants of all other ethnic groups had reduced FGR. The only exception was Finnish infants where differences in FGR were minor. The largest difference in FGR was observed in infants born to South Asian parents (adjusted for sex and birth year only -0.58, 95% CI -0.62 to -0.55). Large differences in FGR were also seen in infants born to East Asian (-0.46, -0.49 to -0.43), African (-0.45, -0.50 to -0.40), Somali (-0.45, -0.48 to -0.41), Ethiopian and Eritrean (-0.37, -0.41 to -0.34), Iraqi (-0.37, -0.40 to -0.35) and Lebanese (-0.34, -0.36 to -0.31) parents.

Adjustment for covariates explained relatively small differences observed in FGR in the different ethnic groups. Adjustment for maternal age and parity marginally increased the differences in FGR in North African/Middle Eastern, Iraqi, Lebanese, Somali, Syrian, Turkish, Ethiopian and Eritrean, Latin American and African groups. Further adjustment for maternal socioeconomic indicators explained some of the differences observed in FGR for most ethnic
groups. However, adjustment for maternal smoking increased the differences in FGR for almost all ethnic groups compared to the Swedish group. Thus maternal smoking could be considered to be a negative confounder and is probably indicative of larger effects of smoking on FGR in the Swedish group compared to other ethnic groups especially if most other non-Swedish mothers smoke less (and as observed in this dataset). Adjustment for smoking only explained the relatively minor differences in FGR between Finnish and Swedish infants and this is probably attributable to Finnish mothers having the highest prevalence of smokers. However, it was adjustment for maternal BMI and height which explained a substantial amount of the observed differences in FGR in infants of North African/Middle Eastern, Lebanese, Iraqi, Syrian, Turkish, Iranian, South Asian, Ethiopian and Eritrean, East Asian, and Latin American parents. Adjustment for maternal BMI did not change the coefficients for FGR differences in infants of Swedish born mothers with non-Swedish-born fathers.

7.12.5 Ethnicity modifies the effect of maternal smoking on offspring BW and FGR

Additionally we analysed if the effects of maternal smoking on offspring birth weight and FGR differed between Swedish, European and non-European groups.

Using data on 1,144,571 infants with data on all covariates, we analysed associations between maternal smoking and i). birth weight and ii). FGR using multivariate linear regression. Models were stratified by ethnicity in order to compare the effect sizes between the three ethnic groups. Two models were run, the first adjusted for birth year and infant sex only and the second additionally adjusted for maternal age, education, cohabitation status, prepregnancy BMI and gestational age. Differences in the associations of maternal smoking on BW between ethnic groups were formally tested for interaction. All covariates adjusted for are previously described in this chapter.

Swedish and European mothers had similar and higher proportions of smokers compared to non-Europeans and give birth to heavier babies and had a lower mean BMI (data not shown). Regardless of ethnic group, all mothers who smoked gave birth to lighter babies (Table 2). Adjustment for potential confounders explained approximately 15% of the effect of smoking on BW in the two European ethnic-origin groups (Table 2). Adjustment for covariates in model 2 reduced the estimates by approximately 30g in the Swedish and European groups but not in the non-European group. Interaction tests were statistically significant indicating that the effect of smoking on birth weight differed between the ethnic groups.
Table 2: Multivariate linear regression analyses of the effect of maternal smoking on offspring BW and FGR stratified by ethnic group.
(Std. dev.= standard deviation) *Adjusted for infant sex and birth year only. **Additionally adjusted for maternal age, education, cohabitation status, prepregnancy BMI and gestational age.

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<th>Model 2**</th>
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7.12.6 Ethnic differences in the association between foetal growth rate and systolic blood pressure

7.12.6.1 Ethnic-origin differences in SBP

We found significant differences both height and BMI by ethnic group in military conscripts. Ethnic Swedish conscripts were the tallest (180.10 cm), whereas non-Europeans were the shortest (175.71cm), (Paper V – Table 1). We observed differences in mean BMI between ethnic groups; non-Europeans had the highest mean BMI (23.15kg/m²) compared to Swedes (22.37kg/m²). Non-Europeans also had the lowest mean birth weight. There was little variation in age at conscription (Table 1).

Differences in mean SBP between European and Swedish men was small (-0.27mmHg, (-0.49, -0.05) and statistically significant only after adjustment for concurrent BMI. Conscripts of non-European origin had significantly lower mean SBP compared to conscripts of Swedish-origin (-3.75mmHg 95% CI (-4.18, -3.32)).
Adjustment for confounders explained only a small part of the observed differences in mean SBP, primarily seen after adjustment for current BMI and height. Adjustment for maternal education did not change the coefficients in any ethnic group (Paper 5 – Table 2).

7.12.6.2 Ethnic differences in the association between FGR and SBP

Ethnic-origin differences in the association between FGR and SBP

FGR was inversely associated with SBP in Swedish and European conscripts (-0.65 mmHg, -0.70 to -0.62 and -0.42 mmHg, -0.65 to -0.20 respectively after adjustment for all covariates including concurrent BMI and height). This association was not statistically significant in the non-European group (-0.31 mmHg, -0.78 to 0.16 after adjustment for all covariates). Test for interaction to assess if ethnic-origin modified the FGR-SBP association between groups of Swedish, European and non-European origin was statistically significant in both unadjusted (P<0.001) and adjusted models (P<0.05), Table 3.

7.12.6.3 Ethnic-origin differences in the association between gestational age and SBP

Associations with gestational age showed a pattern similar to that seen with FGR above. Gestational age was also inversely associated with SBP in all three ethnic groups but the association was not statistically significant in non-Europeans. Adjustment for confounders slightly strengthened these associations (Table 3). In stratified analysis, we found an increased in SBP in Swedish conscripts that were born preterm (1.55mmHg, 1.38 to 1.72, after adjustment). No similar association was found in European and non-European conscripts born preterm (Table 3). Decreased SBP was observed in Swedish (-0.84mmHg, -0.94 to -0.72, after adjustment) and European conscripts (-0.93mmHg, -1.64 to -0.22 after adjustment) born postterm but not in non-Europeans (Table 3). Tests for interaction with ethnic-origin were statistically significant in both unadjusted and adjusted models (P<0.001 for both).

7.12.6.4 Structural equation modelling

FGR was inversely associated with SBP in all three ethnic groups (‘direct effect’ - Path C in Figure 1 – Paper V), but the association was statistically insignificant in non-Europeans. FGR was positively and similarly associated with concurrent BMI (Path A in Figure 1 – Paper V) in all three groups, (Swedish 0.09kg/m^2, (0.08-0.09), European 0.11kg/m^2,( 0.09-0.12), and non-European 0.09kg/m^2, (0.06-0.12)).The association between concurrent BMI and SBP (Path B in Figure 1 – Paper V) was also similar in all three groups, but marginally stronger in non-Europeans (0.20mmHg vs. 0.16mmHg per SD change in BMI in non-European and Europeans respectively – Table 5 – Paper V).

Maternal educational level was inversely and weakly associated with conscript BMI in all three ethnic groups, with conscripts of mothers with highest education (post-secondary) having the lowest mean BMI. The association between maternal education and FGR was positive in the Swedish group with foetal growth rate increasing with higher levels of maternal education. We did not observe a similar effect in the European and non-European groups where the association between maternal education and foetal growth rate was negative and did not reach statistical significance in all educational categories (Table 5 – Paper V).
7.12.6.5 Direct & indirect effects

The total indirect effect of FGR on SBP via BMI (i.e. the product of the estimates of the two linear regressions of FGR on BMI and BMI on SBP – Path A*Path B in Figure 1 – Paper V) was similar and statistically significant in all three ethnic groups. For one SD increase in FGR, the effect of FGR on SBP that was mediated by BMI was equivalent to an increase of 0.015mmHg, 0.018mmHg and 0.018mmHg in the Swedish, European and non-European groups. However, the total effect from FGR to SBP (Path A*Path B + Path C) while negative in the Swedish and Europeans, it was zero in Non-Europeans (Paper V – Table 5).
8 DISCUSSION

8.1 MAIN CONCLUSIONS:

Based on the analyses of associations between ethnicity, socioeconomic position (SEP), birth outcome and common cardiovascular disease (CVD) biomarkers at different stages of the life course in the Swedish population, the main conclusions from this thesis are:

1. Adulthood SEP, while inversely associated with CVD risk factors in mid-life in Swedish men, is no longer associated with the same risk factors at an older age. Adulthood SEP is also inversely associated with CVD mortality in older ages. This could indicate persistence in the effect of adult SEP on CVD mortality in later life.

2. There is considerable evidence for intergenerational mechanisms in the transfer of CVD risk factors from parents to children. Parental influences on CVD risk factors in their children in ethnic Swedes appear to be more determined by their lifestyle and less so by their SEP.

3. Certain ethnic minority groups in Sweden are at higher risk for early-, and late-preterm and postterm birth as well as reduced foetal growth. Differences in risk for these outcomes by ethnic origin appeared to be independent of SEP and did not appear to be mediated by covariates considered. Immigrant women with short duration of residence in Sweden were at higher risk for preterm and postterm birth compared to immigrant women with long duration of residence.

4. Children of some ethnic minority groups in Sweden are at higher risk for overweight/obesity compared to children of Swedish ethnicity. These differences in risk for OW/OB could not be explained by parental SEP, or early life and maternal factors.

5. The association between foetal growth rate and adulthood blood pressure is modified by ethnic origin. While the association is found in Swedish and European-origin men it is not observable in men of non-European origin.

Some additional conclusions:

6. Differences in health by ethnic origin are already evident from an early age in the Swedish population and are also observed in ethnic minorities born in Sweden (i.e. Swedish children born to immigrant parents).

7. SEP did not seem to mediate the observed differences in health by ethnic origin despite many ethnic groups having lower levels of income and education. It is possible that the indicators of SEP were not robust enough or may be SEP isn’t as important as other factors for the health outcomes studied here in some ethnic groups. We might have also had insufficient power in some studies.
8. Results indicate that combining many ethnic/immigrant groups into larger groups should be avoided, if possible. Strong differences in health outcomes were found for immigrants from individual countries which might have gone unnoticed if only ‘regional groupings’ had been used. This could better help in designing public health policies.

9. Often overlooked groups when analysing ethnic differences in health are those of mixed ethnic origins. We found that these groups have health risks that fall between those of the ethnic majority and those of ethnic minority origin.

10. More prospective studies are required to investigate growth and development of CVD risk factors and both by parental SEP and ethnic origin. One must consider additional factors not taken into account in the studies here such as the possible role of institutionalised racism or discrimination or miscommunication/misunderstandings, role of lifestyle including diet and cultural differences especially when investigating differences in health between ethnic groups.

8.2 CVD RISK FACTORS IN CHILDREN AND ADOLESCENTS AND THEIR PREDICTORS

Summary of the most recent literature and comparisons with results from this thesis

Several clinical, epidemiological, pathological, metabolic, genetic, and randomized clinical trials have demonstrated strong evidence that the origins of atherosclerosis and CVD risk factors begin in childhood (185, 186). The following key points are some of the main conclusions drawn from this large body of evidence: A. Atherosclerosis, which is the pathogenic basis of CVD, has its origins in childhood, B. Risk factors for the development of atherosclerosis (and consequentially CVD) can be identified in childhood, C. The development of atherosclerosis is clearly associated with the number and intensity of risk factors in childhood, D. There is clear evidence for tracking of several of these risk factors from childhood to adolescence and E. Interventions which can help reduce these risk factors exist, and have been tried and tested (186). This had led to recommendations that treatment to reduce the prevalence of CVD risk factors and in turn prevent the development of atherosclerosis in childhood should begin early in life (186). This should have natural consequences in reducing the burden of CVD in adulthood.

Results from Paper II showed associations between 1. Parental behaviours and CVD risk factors in their children and 2. Parental CVD risk factors and CVD risk factors in their children. Associations between parental SEP (education and income of both parents) and CVD risk factors in their children were less evident. This is in line with most studies that investigated similar associations. It is hard to draw concrete conclusions based on comparisons with similar studies as many are limited to analysing BMI, overweight/obesity or other measures of adiposity (a justification to conduct this study as data was available on a wider range of CVD risk factors). Also, comparisons are difficult due to the different ways in which parental SEP is measured and how socioeconomic indicators are classified. Finally, comparison is hampered
by the fact that there is a large inconsistency is results especially in regard to parental SEP – offspring CVD risk factors.

In a report recently published by an ‘expert panel’ to develop integrated guidelines for cardiovascular health and risk reduction in children in the USA, the authors conclude “However, evidence is not adequate for the recommendations provided in this report to be specific to racial or ethnic or socioeconomic status” (186). The authors acknowledge that low SEP confers an increased risk for CVD risk factors but the evidence wasn’t conclusive enough. A very recent and quite exhaustive review by Slopen et al compared results from thirty-seven studies that specifically looked at associations between parental socioeconomic indicators (and stressors) and cardiometabolic risk in youth (185). The authors concluded that studies were too few in number and inconsistent in their results to come to strong conclusions on associations between SEP and CVD risk factors, specifically biomarkers in youth. Again, most studies analysed associations with central adiposity (as it is more easily available and easier to measure). Paper II was included in this review and considered to be of higher quality. While most of these studies were cross-sectional in design, the few that were prospective should more consistent associations between lower SEP and higher CVD risk factors in children.

This is not to say that childhood socioeconomic circumstances are not important for subsequent health (indeed the evidence for the same is overwhelming specially in determining adulthood health (187)) but rather the evidence is more limited specifically for CVD biomarkers in childhood and adolescence.

8.3 ETHNIC DIFFERENCES IN HEALTH

A difficult to measure but an important mechanism which could explain some of the differences observed in health between Swedish and non-Swedish groups, is institutionalized racism/discrimination in access to health care or differences in quality of health care, misunderstanding or miscommunication that might arise due to language barriers and/or differences in other aspects of ethnicity such as cultural attitudes, and lifestyle differences including diet. While there is some evidence for this in the Swedish context we were unable to investigate for the same in any of our studies which is a limitation (74, 77).

8.3.1 Overweight/obesity in children:

Summary of the most recent literature and comparisons with results from this thesis

A recent study investigated if parental SEP, early life factors during pregnancy and in infancy and early childhood could explain the differences in obesity in children between different ethnic groups found rather different results from those in Paper III (188). The authors found that adjusting for obesity-related factors in early life (rapid weight gain in infancy, non-exclusive breast feeding, early introduction of solid foods, higher intake of sugar-sweetened beverages, sleeping <12 hrs/day, presence of a television in the child’s room) attenuated the observed BMI – Z score differences between Blacks and reference whites by 69% and between Hispanics and whites by as much as 83%. This study points to lifestyle-related factors that can be targeted to help reduce ethnic differences in childhood obesity. We were unable to control for several of these risk factors due to lack of data. Another finding of the study in contrast to ours was that adjustment for parental SEP also attenuated some of the observed ethnic differences in childhood obesity. While the ethnic composition of the study sample in Paper III
was quite different to that in the above cited paper, it is likely that some of these risk factors may also play a role in explaining the increased risk for overweight/obesity that we observed. More detailed studies are needed which take into account a wider range of early life risk factors for overweight/obesity.

Most of such information cannot be obtained from routine registers and specific pre-births cohorts need to be set-up to investigate the role of pre and post-pregnancy factors in explaining potential mechanisms in ethnic differences in overweight/obesity in Swedish children.

**Why doesn’t SEP explain some of the observed ethnic differences in overweight/obesity in Swedish children?**

The role of parental SEP in trying to explain ethnic differences in child obesity is difficult to decipher because of the lack of consistency in results and potential difficulties in using standard socioeconomic indicators as measures of SEP in ethnic minorities and immigrants (189). It is known that lower SEP groups have higher levels of obesity and higher mean BMI (189). Some studies show that parental SEP partly explains the differences in obesity in children by ethnic origin while others show contradictory results. Caprio et al discusses the ‘limited nature’ of using parental education and household income as markers of SEP as they may not fully capture a child’s access to resources or the family SEP (65). In Paper III the inability of SEP to explain observed ethnic differences in childhood obesity could be a mix of two reasons: the inability to capture family SEP in the different ethnic minority groups (for e.g. education of immigrants is reported to be underestimated in Sweden) and the smaller size of some of the ethnic minority groups.

Cultural differences between ethnic groups on what constitutes a ‘healthy’ child could partially explain the observed differences but data on this was lacking (189).

**8.3.2 Preterm and postterm birth:**

Controlling of maternal indicators of SEP did not explain ethnic differences in the risk for preterm and postterm birth (Paper IV) and the inability of these indicators to capture SEP as described above could be problematic here as well. Similar to several other studies from different countries, results from Paper IV found that South Asian and East Asian groups are at higher risk for preterm birth. Ethnic differences in postterm birth have not been previously described so direct comparisons are difficult but results are consistent with other studies that showed Somali, Ethiopian, Eritrean and Arabic mothers to be at higher risk for pregnancy-related outcomes some of which could potentially be linked to postterm birth (higher prevalence of obesity, higher rates of C-section, and induction and lower risk for preterm birth etc). An interesting finding in Paper IV was that a short duration of residence in Sweden (<3 years) was associated with higher risk for early preterm and postterm birth. Duration of residence is a crude marker of acculturation (190). In line with other studies, one could hypothesize that recently immigrated women face higher risks for non-term birth potentially associated with complex issues including stress, acculturation, cultural differences in lifestyle and pregnancy health (134).
Summary of the most recent literature and comparisons with results from this thesis

Despite the innumerable studies that have confirmed ethnic differences in risk for preterm birth, this area of research continues to generate sustained interest. Several studies have been published in the last two years alone (191-195). A very recent review by Schaaf et al summarizes the results from forty-five studies that analysed ethnic differences in risk for preterm birth (191). The study found significantly increased risk for preterm birth (pooled estimate) in black mothers but not in Hispanic or Asian mothers. More importantly, the authors conclude that “currently recognized confounders do not appear to explain the increased risk of preterm birth among black women” (191). This conclusion is similar to that in Paper IV where adjusting for several commonly recognised risk factors did not explain increased risks associated with non-term birth in ethnic groups. However, the vast majority of studies included in this review were from the USA making international comparisons difficult. This is a major motivation for Paper IV – as clearly more knowledge is needed on ethnic differences in non-term birth outside of North America. An interesting finding from our study was the shift in gestational age distributions in some ethnic groups; the distribution was shifted to the left in South Asians and East Asians (probably due to physiological and genetic causes) and to the right in Somalis (more likely due to lifestyle and pregnancy related issues). Different gestational age distributions by ethnic origin could imply that we need to develop ethnic-specific cut-offs for preterm and postterm birth.

A potential link between results from Papers III & IV:

An interesting link that one could hypothesize from the results of Papers III & IV is an underlying mechanism that could lead to increased risk of overweight/obesity is children of North African and Arabic ethnicities. Given that maternal overweight/obesity is a risk factor for postterm birth in this study population (as described in section 17.4.2), and that postterm birth in turn is a risk factor for subsequent overweight/obesity in adolescence (145) one could hypothesize a link between maternal and offspring obesity via postterm birth (Figure 21). Immigrant mothers of from North Africa and Arabic countries had higher rates of being overweight and obese compared to mothers of other ethnic backgrounds. North African and Arabic mothers also had higher risks for postterm birth. And as found in Paper III children of mothers from these same regions had higher risks for being overweight/obese.

Figure 21: A potential pathway between ethnicity and overweight/obesity in children that is mediated via obesity and postterm pregnancy in mothers.
8.3.3 Associations between FGR and subsequent BP:

Despite the discussion on methodological issues that arise when investigating the association between BW and subsequent BP (as regression estimates for the same become apparent or are accentuated upon adjustment for current weight or BMI), this research question continues to generate interest not only because low BW (a marker for impaired foetal growth) may contribute to the epidemic in hypertension but also as addressing the methodological issues here will help solve several other research questions of a similar nature – if it is appropriate to condition on intermediate variables that lie on the pathway between the exposure and outcome of interest (196).

Summary of the most recent literature and comparisons with results from this thesis

In the past two years some reviews and meta-analysis have tried to re-analyse the BW and subsequent BP associations. A review by Mu et al which considered 20 articles that investigated BW and subsequent BP at different ages concluded that the association primarily exists for SBP – pooled OR for hypertension were 1.21 (1.13-1.30) for LBW (compared to HBW) and 0.78 (0.71-0.86) for HBW (compared to LBW) respectively (197). Another review by Edvardsson et al that considered only studies that included children concluded that BP percentiles would be a better measure than absolute BP (as BP is gender, age and body stature dependent) (198). The authors also suggest that postnatal growth be included in studies as it strongly associated with subsequent BP (especially in those born with LBW). The most recent review by Zhang et al specifically analysed associations between HBW and subsequent BP (at all ages) using data from thirty-one studies (199). The authors found that while the association between HBW and subsequent BP in childhood was positive, it becomes inverse in adulthood – i.e. HBW has contrasting effects on BP in younger compared to older subjects.

Paper V is the first to analyse possible ethnic differences in the association between measures of FGR (BW and gestational age) and subsequent BP using the path analysis. As discussed and recommended by Chiolero et al DAGs were used to help frame the conceptual idea behind the hypothesis before testing direct and indirect pathways between measures of FGR, adulthood BMI and BP (196). Results from both ‘traditional’ statistical regression modelling and path analysis came to the same conclusion: that the association between measures of FGR and subsequent SBP while present in European men was absent in Non-Europeans.

8.4 LIFE COURSE EPIDEMIOLOGICAL PERSPECTIVES

The studies included in this thesis do not have the life span approach to studying associations between exposures in early life and outcomes in adulthood with several in between measurements of potential confounders and/or mediators that are more common in life course epidemiological studies. The common link to all studies in this thesis (except the first one) is the intergenerational aspect – i.e. the transfer of risk factors or risk for future disease from parents to their children. The risk factors studied here; CVD biomarkers, overweight/obesity, and high SBP have potentially long term serious consequences in adulthood. Non-term birth while considered to be a maternal outcome is nonetheless associated with several adverse health outcomes in mothers, infants and children some of which may have long term consequences.
One of the main aims of life course epidemiology is to study the joint contributions of both the biological and social environments to the development of disease. As the results indicate, there was less evidence for the importance of the social environment in contributing to the development of the outcomes as far as socioeconomic indicators are considered – both in the ethnic and non-ethnic Swedish populations (Papers II – V). There was stronger evidence for ethnic differences in health – and ethnicity is a complex variable which incorporates SEP. The effects of the indicators of SEP could be hidden by the larger effects of ethnicity.

One approach would be to try and sequentially link the results from the different studies together across the life course as shown in the simplified figure below. For e.g. one could hypothesize that (Figure 22) 1. Some non-Swedish ethnic groups are at higher risk for preterm birth which is linked to post-natal catch-up growth (not measured in our studies) and subsequent obesity in childhood and adolescence. 2. These ethnic groups would then be at higher risk for SBP in adulthood due to FGR restriction, post-natal catch-up growth and obesity in childhood and adolescence. However, the first part described above was true for many non-ethnic Swedish groups. The second part was not, as the non-ethnic Swedish group actually had lower mean SBP compared to ethnic Swedes in adulthood. One could hypothesize different versions of the diagram below.

![Diagram](image)

**Figure 22.** A possible hypothesized link between results from different papers in this thesis (Dashed box indicates a variable not studied in this thesis).

### 8.5 STRENGTH AND LIMITATIONS:

A strength of this thesis was the use of nation-wide registers as data sources of identification of study populations (Papers III & IV), exposures (ethnicity in Papers III-V, SEP in Papers I & II and BW and FGR in Paper V), outcomes (gestational age in Paper IV) as well as several
confounders and mediators. Registers as sources of information on socioeconomic indicators, country of birth, medical diagnoses, mortality, immigration/emigration, family linkages are often better sources than self-reported data (200). National registers also help to achieve adequate statistical power and reduce selection bias due to nonresponders (200). Register-based research is non-invasive and helps to protect personal integrity (200). In register-based studies, exposures can be measured before outcomes. This helps with designing life course epidemiological studies which ideally need data to be collected prospectively and also helps limit recall bias.

Selection bias

In Paper I, there is possibility of selection bias (Self-selection) as men opted to take part in the ULSAM study. There could also be selection bias, as the healthier men would have more likely survived till the end of the follow-up (between ages 50 and 70). There is a risk for selection bias in Paper II as the UFS only included those families that agreed to participate (self-selection (201)). These families could be of higher SEP and thus also have higher levels of healthy behaviours affecting the composition of the exposures categories. This could cause an underestimation of the association between families SEP and CVD risk factor profile.

On the other hand in Paper IV, all mothers who delivered in Sweden between 1982-2002 were eligible to be included in the study minimizing selection bias due to non-responders. The MBR includes 99% of all deliveries in Sweden and having a non-term birth does not influence inclusion in this register.

In Paper V, non-European origin men had lower rates of attendance at military conscription examinations compared to European-origin and Swedish men. It is possible that healthier men were more likely to attend the military conscription examinations in both the Swedish and non-Swedish groups. However, we do not have detailed knowledge as to how strong such selection might have been.

We did not take into account area-level indicators which could also potentially mediate the observed health differences between ethnic groups.

Information bias

As ethnicity is based on country of birth, it is possible that some people could be misclassified.

Inaccurate recall of physical activity, alcohol consumption and smoking by parents in the UFS could cause misclassification of exposure in Paper II leading to bias in the results.

Gestational age distributions might differ by ethnicity (202) causing misclassification of gestational age in women of some ethnic groups. Thus, proportions of preterm and postterm births might be either underestimated or overestimated in these ethnic groups. However, in the absence of ethnic-specific cut-offs for non-term birth this is unavoidable.

Maternal smoking habits as recorded in the MBR reflect smoking patterns during the time immediately preceding the antenatal check-up and should not be subjected to recall bias. However, some women might under-report their smoking habits and the degree of under-reporting might differ across SEP and ethnic groups. This might cause bias in adjusted analysis.
Educational level of immigrants have higher chances of misclassification in Sweden (203). Inaccurate information on confounders and mediators could hamper the ability to control for them appropriately in analysis (201). Even if data on several covariates were obtained from registers, there is always possibility for some degree of misclassification contributing to potential bias in adjusted analysis.

External validity

As the subjects in Paper I are from a much older cohort (born 1920-24) it could be difficult to generalize the results to men aged 50 and 70 and alive today as the distribution of SEP has changed in men of these ages. More men today are likely to have higher levels of education as compared to those born 1920-24. Also, results from this paper cannot be generalized to women.

Results from Paper II are from a relatively recent cohort but are generalizable only to the ethnic Swedish population. Results from Papers III & IV should be generalizable to the Swedish population as the subjects belonged to contemporary cohorts. It could be more difficult to generalize the results on ethnic differences in health to immigrant and ethnic minorities outside Scandinavia as ethnic minority compositions differ greatly between countries. Reasons for immigration of particular groups into Sweden might also be quite specific. Also, policies related to immigration and integration are country specific and change quite often. Unfortunately, as military conscription was not mandatory for women, the results from Paper V cannot be generalised to them.

Missing data

There were considerable problems with missing data in Papers III-V. In all three papers, analyses were restricted to those with complete information on all covariates (complete case analysis - CC). CC analysis gives valid results if the probability of being a CC is independent of the outcome given the model covariates (204). This is plausible in the studies here (for example missing data on maternal smoking, breast feeding habits and maternal BMI should be independent of a child’s OW/OB status in Paper III implying validity of CC analysis).

Another issue is if data is missing at random or not. Data not missing at random could be a source of potential bias. For example, in Paper III the finding that children of Finnish mothers had decreased risk for OW/OB was partly explained by nonrandom missingness in maternal BMI. In contrast to the children of Swedish ethnicity, the risk of being OW/OB for children of Finnish ethnicity with maternal BMI available was lower than the risk for those with missing maternal BMI, such that in the CCs, children of Finnish maternal nativity had lower risk of OW/OB.

In Paper V, Models were fit using a full information maximum likelihood estimation which allows all subjects who have data for at least one of the variables in the path model to contribute to the analysis under the assumption of data being missing at random (MAR). This helped address missing data to some extent.

‘Mutually adjusted models’ – recently attention has been drawn to interpretation of regression models which are mutually adjusted for several covariates including both confounders and mediators (205). Researchers claim that it is difficult to interpret the results from such models and instead one must have a series of models informed by a priori
knowledge of the structure of data. For example in Paper IV one could have had a series of models for each ethnic group that only adjusts for covariates appropriate for the specific association and ethnic group in question. Thus, the ‘mutually adjusted’ models should be interpreted with caution.

8.6 FUTURE DIRECTIONS

It would be beneficial to investigate whether the increased risks for OW/OB and non-term birth observed in the ethnic minority groups changes with time. It is important to also identify other risk factors which could explain the increased risk for OW/OB, and non-term birth in ethnic groups such as dietary habits and genetic factors. Such detailed studies will need additional data not available in routine registers. In order to study trends, longitudinal studies which repeated measures of CVD risk factors with adequate sample sizes are essential. It would be informative to re-investigate the associations studied in Papers II-IV using SEM to better understand the relationship between confounders and mediators and compare the results with those already obtained.

8.7 FINAL CONCLUSIONS

We found evidence for increased risk for different health outcomes in some ethnic minority populations resident in Sweden, not previously described or investigated in such detail. Previous studies that did investigate some of the outcomes came to contrary conclusions that ethnic differences were absent. Ethnic disparities were also found in second generation ethnic minorities born and raised in Sweden. Results also provide evidence for intergenerational transfer of risk factors and poorer health in both ethnic minorities and the majority ethnic Swedish population. Nonetheless, the evidence for intergenerational transfer of risk factors in the ethnic Swedish population studied here is probably of less clinical significance compared to those in ethnic minorities. More prospective studies are needed to better understand the underlying mechanisms that lead to increased risk in these health outcomes and to understand the differences in risk between ethnic minority and majority populations. These studies must take into account factors not collected in the routine registers such as lifestyle, cultural differences, genetic factors and their respective interactions in addition to institutionalised racism and factors associated with acculturation, and access to good quality health care amongst others.
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10 REFERENCES


38. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *British journal of preventive & social medicine* 1977;31(2):91-5.


111. Patterson R, Risby A, Chan MY. Consumption of takeaway and fast food in a deprived inner London Borough: are they associated with childhood obesity? *Bmj Open* 2012;2(3).


118. de Onis M, Blossner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* 2010;92(5):1257-64.


165. Leon DA, Johansson M, Rasmussen F. Gestational age and growth rate of fetal mass are inversely associated with systolic blood pressure in young adults: An


Social determinants of cardiac disease biomarkers: investigating a Swedish male cohort at ages 50 and 70

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Social determinants of cardiac disease biomarkers: investigating a Swedish male cohort at ages 50 and 70

Amal Khanolkar¹,², Denny Vågerö¹ and Ilona Koupil¹

Abstract

Background: Social status is associated with cardiovascular disease (CVD) prevalence and incidence.
Aims: to investigate relationships between socioeconomic position (SEP) and common CVD biomarkers including adiponectin not previously investigated in a Swedish-population sample, and to assess if these associations changed with age.
Methods: A total of 2322 men attended an investigation at age 50 of which 1221 attended a reinvestigation at age 70. Association between SEP and CVD biomarkers [cholesterol, low-density lipoprotein/high-density lipoprotein (LDL/HDL), apolipoprotein (Apo) ApoB/ApoA1, and adiponectin] were analysed by linear regression (adjusted for age, body mass index, and physical activity). SEP was measured as occupational class and educational level. CVD mortality over 36 years of follow-up was analysed by Cox regression.
Results: At age 50, we found a significant inverse association of education with cholesterol level, LDL/HDL ratio and ApoB/ApoA1 ratio. Cholesterol was also associated with occupational class, statistically significant after adjustment for all covariates. At age 70, no significant associations were found between either measurement of SEP and any of the biomarkers studied. Highest educated men had decreased risk for CVD mortality during follow-up.
Conclusions: Associations of SEP with cholesterol levels and LDL/HDL ratio that exist at age 50 are no longer apparent in the same group of men at age 70. We found no significant association between SEP and adiponectin levels at age 70.

Keywords
Adiponectin, apolipoproteins, biomarkers, cardiovascular disease, cholesterol, HDL cholesterol, LDL cholesterol, socioeconomic position

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Introduction

Socioeconomic characteristics including income, education, and occupation are recognized influences on cardiovascular disease (CVD).¹² In high-income countries the relationship between socioeconomic position (SEP) and CVD morbidity and mortality is inverse, with those poorest in society the most susceptible. This relationship has generally an opposite direction in middle- and low-income countries where higher SEP tends to be associated with a higher risk.¹ In high-income countries, improvements in cardiovascular health have been observed first and foremost among the wealthier and better educated people, and the once frequently used term that dubbed CVD as a ‘disease of affluence’ is now obsolete. However, improvements in cardiovascular health among people with lower SEP and education have been slower.³ Earlier studies have explored associations between SEP and CVD biomarkers, including cholesterol, other blood lipids, glucose levels, C-reactive protein, fibrinogen, and tumour necrosis factor-α amongst others.⁴⁻⁶ Most studies from high-income countries

¹Centre for Health Equity Studies, (CHESS), Stockholm University/ Karolinska Institute, 106 91 Stockholm, Sweden.
²Institute of Environmental Medicine, Karolinska Institutet, 171 77 Stockholm, Sweden.
Corresponding author: Amal Khanolkar, Centre for Health Equity Studies, 106 91 Stockholm, Sweden Email: Amal.khanolkar@ki.se
found a negative association between SEP and cardiovascular biomarkers. Results were particularly strong for blood lipids but contradictory for other CVD biomarkers.5,6 Panagiotakos et al.11 reported significant negative associations between socioeconomic index and C-reactive protein, interleukin-6, fibrinogen, homocysteine, and tumour necrosis factor-α in a Greek study.8 A study conducted on the Uppsala Longitudinal Study of Adult Men (ULSAM) (the subjects included in our study) showed inverse relationships between education and mortality from CVD and between education and cholesterol, blood pressure, and body mass index (BMI).7

Apolipoproteins (Apo) A1 and B, cholesterol, and adiponectin are clinically associated with CVD and insulin sensitivity/type 2 diabetes. Elevated levels of ApoB and ApoA containing lipoproteins are used in estimation for CVD risk, both as independent markers and together as a ratio.8,9 Studies indicate that ApoB/ApoA1 ratio not only is an accurate predictor of CVD risk but also a good measurement for evaluating treatment.10 Low-density lipoprotein/high-density lipoprotein (LDL/HDL) cholesterol ratio is included in standard blood lipid profile tests and studies suggest that this ratio is an excellent predictor of CVD risk and an accurate outcome for monitoring success of lipid-lowering therapies.10 Blood serum levels of the hormone adiponectin are inversely proportional to BMI and adiponectin is used as a clinical marker for obesity and type 2 diabetes.11,12 An earlier study of the ULSAM men showed that independent of established cardiac risk factors, elevated levels of adiponectin were associated with lower risk for CVD.13 Numerous studies reported significant associations between various indicators of SEP and BMI, overweight, and obesity.7,14,15

Few studies have explored associations between SEP and CVD biological risk factors in adulthood in Sweden.16,17 Sweden is renowned for its social welfare system and relatively low health inequalities.18 Despite the country’s strong emphasis on social welfare, health inequalities persist, affecting the whole population.19,20 In this study we investigate if CVD biomarkers including serum cholesterol (hereafter cholesterol), LDL, HDL, LDL/HDL ratio, ApoB/ApoA1 ratio, and adiponectin are associated with SEP and if these associations change with age by following a unique longitudinal cohort of men with more than 36 years of follow-up.

Methods

The ULSAM cohort, based on the ‘Uppsala Primary Preventive Study’, comprises 2322 men born 1920–24, resident in Uppsala county, Sweden, in 1970–73 and followed up from 1970 to 2007.21 Of all men invited (n = 2841) for an investigation, 82% (n = 2322) participated.22 At the first examination at around age 50, anthropometric data and blood samples were collected.23 The men answered questionnaires on medical history and lifestyle habits including physical activity. The men were subsequently reinvestigated at age 70.24

Investigated measurements

Data for occupation and education were obtained from the national census of 1960 and 1970, respectively. The men were divided into three educational groups: primary education (<9 years), secondary education (9–12 years), and post-secondary education (>12 years). A majority of the men (n = 1651, 71%) completed <9 years of primary schooling with no further education. Based on occupation, the men were divided into four social classes; manuals, non-manuals, self-employed and not working/unknown. The majority belonged to the classes manual (44%) and non-manual (43%).

Cholesterol, including LDL and HDL, and ApoB and ApoA1 were measured by routine laboratory analysis using blood samples collected during the first investigation (ages 48–51). During the 20 years between the first and third investigations, 422 men died and 219 moved out of Uppsala. Of 1681 men invited for the reinvestigation at age 70, 460 declined to participate. Thus 1221 (73% of the eligible) men participated in this investigation conducted 1991–94 (ages 69–74), when adiponectin levels were measured by routine laboratory analysis. All measurements and laboratory analyses at subsequent investigations were as similar as possible to those used in the first investigation at age 50.21

At age 50, cholesterol was measured in a Technicon Auto Analyzer type II in 1981–82 in serum samples that had been stored in liquid nitrogen since 1970–73. High-density lipoprotein (HDL) was assayed in the supernatant after precipitation with a heparin/manganese chloride solution. LDL-cholesterol was calculated using Friedewald’s formula: LDL = serum cholesterol – HDL – (0.45 × serum triglycerides). Lipid measurements are ‘Monarch adjusted’ to enable comparison with lipid measurements taken at age 70, i.e. values were multiplied by the following conversion factors: 1.06 for LDL and serum cholesterol, 1.17 for HDL cholesterol, and 0.9 for serum and HDL triglycerides.

ApoB and ApoA1 were measured in 1988 by a two-site immunoradiometric assay and a competitive radioimmunoassay, respectively, using commercial kits (Pharmacia, Sweden), in samples that had been stored in liquid nitrogen since the original sampling in 1970–73.

At age 70, cholesterol was measured by enzymatic techniques (IL Test Cholesterol Trinder’s Method) using a Monarch apparatus (Instrumentation Laboratories, Lexington, USA). HDL particles were
separated by precipitation with magnesium chloride/ phosphotungstate. LDL-cholesterol was calculated using Friedewald’s formula (as above). Apolipoproteins were analysed in a random subsample of 550 men. ApoB and ApoA1 concentrations were determined by turbidimetry in a Monarch apparatus (Instrumentation Laboratories, Lexington, USA), using monospecific polyclonal antibodies against ApoB and A1.21

Serum adiponectin was analysed using a validated in-house time-resolved immunofluorometric assay based on commercial reagents from R & D Systems (UK).21

Standing height and weight measured at ages 50 and 70 were used to calculate BMI by dividing weight in kilograms by height in metres squared. BMI was divided into three categories according to the World Health Organization criteria with ‘overweight’ defined as BMI between 25–29.99 kg/m² and ‘obesity’ as BMI ≥30 kg/m².24

The men answered detailed questions regarding their physical activity at work at age 50 and during leisure time at ages 50 and 70. Physical activity at work was classified as sedentary, light, heavy, and demanding based on the number of minutes and mode of transportation to the place of work and the nature of physical activity the subject’s occupation demanded, i.e. if it was mostly sedentary or involved a lot of time standing, walking, lifting, and carrying heavy objects. Subjects were asked if they exercised regularly, engaged in other activities such as gardening or sports, and if they cycled or walked for pleasure during the week and on the weekends in order to assess physical activity during their spare time, which was classified as high, medium, and low.

At age 50, cholesterol was measured for all study participants. Measurements for other outcomes are available for about 78% of the men. At age 70, cholesterol, LDL, HDL, and adiponectin measurements are available for about 78% of the men. At age 70, cholesterol, LDL, HDL, and adiponectin measurements are available for about 78% of the men, but coverage for ApoA1 and ApoB was lower at 45%.

The National Cause of Death Registry (CDR) was used to obtain information on men who died due to any cause and CVD in specific during the follow-up. Death was attributed to CVD if the men died due to a cause corresponding to ICD 9 codes 390–459 (or ICD 10 codes, I00–I99). Information on men who emigrated from Sweden was obtained from routine registers.

Statistical analysis

All statistical analysis was done using STATA 10 (College Station, Texas, USA). Continuous variables are presented as mean± one standard deviation and categorical variables as frequencies. Assumptions of linearity for continuous variables and constant variance of standardized residuals were assessed through plotting residuals against fitted values. Log-transformed values were used for adiponectin in regression analysis due to its skewed distribution. To control for known covariates that might mediate or confound the relationship between SEP and the outcomes under study, we built four linear regression models. All models were adjusted for age (continuous in years), with additional adjustments for BMI (continuous in kg/m²) (model 2), BMI and physical activity in spare time (categorical) (model 3), and BMI, physical activity in spare time, and physical activity at work (categorical) (model 4). Crude and adjusted analyses were always performed in subsamples of men with complete data on all covariates included in the respective models and the number of subjects is given in the tables.

We investigated social patterning of CVD biomarkers in: (i) all men with information available at age 50 to provide data on representative, population-based sample of men from 1970 (n = 2115); and (ii) the longitudinal sample of men restricted to those who attended both investigations at ages 50 and 70 to allow an unbiased comparison of differences in strength of the associations in same group of men (n = 1220). We performed formal tests for interaction, comparing the strength of associations in subsamples of men, with and without cardiovascular biomarkers at age 50 between the longitudinal sample and men who were lost from the study after age 50.

Kaplan–Meier survival curves and multivariate Cox regression analyses were performed (age- and BMI-adjusted) to determine risk for mortality due to CVD in the subjects between 1970–2007 and by splitting this period into two: 1970–90 and 1991–2007. Subjects exited from risk on their date of first emigration, death, or end of follow up, whichever was first. The study was approved by the regional ethics committee in Uppsala.

Results

A comparison of men who attended both investigations at ages 50 and 70 with those who attended the investigation at age 50 only, showed statistically significant differences for age, BMI, and ApoB/ApoA1 ratio. Compared to men who attended the investigation at age 50 only, men investigated on both occasions were older and had lower BMI and ApoB/ApoA1 ratio at age 50. However, these differences were small (Table 1). At age 50, 2172 (93%) of the 2322 men had mean levels of cholesterol above the clinical cut-off point of 5.12 mmol/l. Mean levels of cholesterol, ApoB/ApoA1, and LDL/HDL ratios were 6.87 mmol/l, 0.89, and 4.23, respectively. Mean values of all outcomes fell between...
ages 50 and 70. For mean values of each outcome by both exposures at ages 50 and 70, see Supplemental Digital Content 1 and 2. Mean of adiponectin at age 70 was 10.35 ng/ml. As expected, adiponectin exhibited a strong linear inverse association with BMI. Overweight and obese subjects were less likely to have adiponectin values above the cut-off point of 18 ng/ml (data not shown).

Analysis for BMI revealed that the proportion of overweight and obese subjects was higher in self-employed and ‘not working’ groups. Non-manuals had the lowest proportion of obese subjects. For BMI, a decreasing trend of borderline statistical significance was seen across educational groups, with post-secondary-educated subjects having the lowest BMI (Supplemental Digital Content 1).

At age 50, a higher proportion of non-manual workers reported ‘high’ physical activity in leisure time (55%) as compared to manual workers (45%). Regarding physical activity at work, men in the highest educational group and manual workers included greater proportions reporting ‘heavy’ and ‘demanding’ physical activity at work (data not shown).

Supplemental Digital Content 1 includes analyses of social patterning in proportion of men with increased levels of biomarkers, and shows an inverse association of SEP with cholesterol and ApoB/ApoA1 ratio at age 70. In similar analyses of biomarker at age 70, SEP was not significantly associated with any of the studied biomarkers (Supplemental Digital Content 2).

The association of occupation with cholesterol at age 50 remained statistically significant after adjustment for BMI and physical activity (Table 2). We also found a statistically significant inverse association of education with cholesterol (Table 3). The fully adjusted difference in cholesterol level between subjects with the highest education (post-secondary) compared to the reference group of <9 years of education (elementary) was 0.5 mmol/l (95% CI 0.3–0.7 mmol/l) (model 4, Table 3). The highest education group also had significantly lower LDL/HDL and ApoB/ApoA1 ratios, both before and after adjustment for BMI and physical activity. Differences in adiponectin levels at age 70 across occupational classes were minor and insignificant.

### Table 1. Comparison of men from the Uppsala Longitudinal Study of Adult Men who attended both investigations at ages 50 and 70 with those who attended only the age 50 investigation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Men present at age 50 and 70 investigations</th>
<th>Men present only at age 50 investigation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean, n)</td>
<td>49.80 (1221)</td>
<td>49.44 (1101)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²) (mean, n)</td>
<td>24.86 (1221)</td>
<td>25.20 (1101)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol (mean, mmol/l) (n)</td>
<td>6.90 (1221)</td>
<td>6.84 (1101)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cholesterol ≤5.12 mmol/l (n, %)</td>
<td>73 (6)</td>
<td>79 (7)</td>
<td>0.24</td>
</tr>
<tr>
<td>LDL/HDL ratio (mean, n)</td>
<td>4.17 (999)</td>
<td>4.31 (881)</td>
<td>0.07</td>
</tr>
<tr>
<td>ApoB/ApoA1 ratio (mean, n)</td>
<td>0.87 (968)</td>
<td>0.90 (858)</td>
<td>0.01</td>
</tr>
<tr>
<td>Occupational class: (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>557 (42)</td>
<td>461 (43)</td>
<td>0.15</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>515 (46)</td>
<td>476 (42)</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>98 (8)</td>
<td>105 (10)</td>
<td></td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>51 (4)</td>
<td>59 (5)</td>
<td></td>
</tr>
<tr>
<td>Education level (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>887 (73)</td>
<td>767 (70)</td>
<td>0.23</td>
</tr>
<tr>
<td>Secondary</td>
<td>161 (13)</td>
<td>153 (14)</td>
<td></td>
</tr>
<tr>
<td>Post-secondary</td>
<td>173 (14)</td>
<td>181 (16)</td>
<td></td>
</tr>
</tbody>
</table>

Means and percentages recorded at age 50. The numbers of subjects (n) differ due to missing information on the various characteristics. BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
Table 2. Differences in cholesterol, LDL/HDL ratio, ApoB/ApoA1 ratio and adiponectin between occupational classes in the Uppsala Longitudinal Study of Adult Men at age 50 and age 70, with manuals as the reference group.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Age 50</th>
<th>Age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>-0.30 (-0.41 to -0.18)</td>
<td>-0.29 (-0.41 to -0.17)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>-0.34 (-0.54 to -0.13)</td>
<td>-0.36 (-0.56 to -0.15)</td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>-0.37 (-0.65 to -0.08)</td>
<td>-0.36 (-0.64 to -0.08)</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>-0.14 (-0.31 to 0.00)</td>
<td>-0.14 (-0.31 to 0.00)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>-0.08 (-0.40 to 0.22)</td>
<td>-0.16 (-0.47 to 0.14)</td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>-0.27 (-0.70 to 0.15)</td>
<td>-0.24 (-0.66 to 0.18)</td>
</tr>
<tr>
<td>ApoB/ApoA1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.00 (0.00 to 0.00)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>0.00 (0.04 to 0.00)</td>
<td>0.00 (0.05 to 0.04)</td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>0.00 (0.06 to 0.06)</td>
<td>0.00 (0.06 to 0.06)</td>
</tr>
<tr>
<td>Adiponectin (ng/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>-0.04 (-0.03 to 0.00)</td>
<td>-0.03 (-0.02 to 0.02)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>-0.05 (-0.04 to 0.00)</td>
<td>-0.06 (-0.05 to 0.04)</td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>-0.06 (-0.06 to 0.06)</td>
<td>-0.06 (-0.06 to 0.06)</td>
</tr>
</tbody>
</table>

Values are coefficient (95% CI). Results in bold indicate statistical significance at p < 0.05 level. Model 1, adjusted for age only. Model 2, adjusted for age and body mass index. Model 3, adjusted for age, body mass index and spare time physical activity. Model 4, adjusted for age, body mass index, spare time physical activity and physical activity at work. At age 70, the subjects were retired and data on physical activity at work is absent, thus only three models are presented. Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Log-transformed values only.
Table 3. Differences in cholesterol, LDL/HDL ratio, ApoB/ApoA1 ratio and adiponectin between educational groups in the Uppsala Longitudinal Study of Adult Men at age 50 and age 70, with primary education as the reference group

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Age 50</th>
<th>Age 70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>0.21 (0.22 to 0.22)</td>
<td>0.21 (0.21 to 0.21)</td>
</tr>
<tr>
<td>p-value trend</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>0.10 (0.10 to 0.10)</td>
<td>0.10 (0.10 to 0.10)</td>
</tr>
<tr>
<td>p-value trend</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.00 (0.00 to 0.00)</td>
</tr>
<tr>
<td>ApoB/ApoA1</td>
<td>0.06 (0.05 to 0.05)</td>
<td>0.05 (0.04 to 0.04)</td>
</tr>
<tr>
<td>p-value trend</td>
<td>0.00 (0.00 to 0.00)</td>
<td>0.00 (0.00 to 0.00)</td>
</tr>
<tr>
<td>Adiponectin (ng/l)*</td>
<td>0.04 (0.04 to 0.04)</td>
<td>0.05 (0.05 to 0.05)</td>
</tr>
</tbody>
</table>

Values are coefficient (95% CI). Results in bold indicate statistical significance at p < 0.05 level. Model 1, adjusted for age only; Model 2, adjusted for age and body mass index; Model 3, adjusted for age, body mass index and spare time physical activity; Model 4, adjusted for age, body mass index, spare time physical activity and physical activity at work. At age 70, the subjects were retired and data on physical activity at work is absent, thus only three models are presented. Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Log-transformed values.
Regression analyses restricted to 1220 men who attended both investigations (age 50 and age 70) are presented in Table 4 (age-adjusted only). In this group of men, non-manuals and the highest educated have significantly lower cholesterol levels (−0.24 mmol/l, 95% CI −0.40, −0.09 and −0.60 mmol/l, 95% CI −0.81, −0.38, respectively) at age 50. No significant associations were detected at age 70 (Table 4).

Supplemental Digital Content 4 illustrates the pattern of change in cholesterol level between age 50 and 70 by educational group. Differences in mean cholesterol levels between the three educational groups observed at age 50 were no longer apparent at age 70. The strength of associations between education and cholesterol and education and LDL/HDL ratio were generally comparable in the group of men investigated at both ages 50 and 70 and in men examined at age 50 only. There was a suggestion of a possibly stronger association between occupational class and cholesterol in men investigated at age 50 only (Supplemental Digital Content 3). We tested for statistical interactions between SEP and participation group (those who participated at both ages 50 & 70 vs. those who participated at ages 50 only) in their effect on cholesterol and LDL/HDL ratio. None of these tests indicated a statistically significant interaction (p-values shown in Supplemental Digital Content 3). This suggests that associations presented in Table 4 (age-adjusted only) are not severely biased by drop outs after age 50.

At the end of 2007, approximately 37 years of follow up since first enrolment, 1499 men had died of various causes and 681 had died due to CVD. Men with the highest education had a significantly decreased risk of mortality due to CVD compared to men with lowest education (age-adjusted HR 0.68, 95% CI 0.54–0.86, age- and BMI-adjusted HR 0.72, 95% CI 0.57–0.91) from 1970 until end of follow up in 2007, but the latter did not differ from middle educational group.

Kaplan–Meier survival curves for death due to CVD revealed a distinctly lower rate of mortality for men with highest education, while differences between men belonging to middle and lowest level of education were small and the curves ran almost concurrently (Figure 1). Differences in survival curves between manual and non-manual workers were distinct with the curves running parallel to each other from around 1988 onwards (data not shown), however, the differences in mortality by occupational classes were smaller in comparison to those by educational groups.

We re-ran the analysis by splitting the follow-up into two time periods. During 1970–90 (213 deaths due to CVD), the HRs for men with the highest compared to lowest education were 0.54, 95% CI 0.34–0.86 (age-adjusted) and 0.59, 95% CI 0.37–0.94 (age-and BMI-adjusted). For the second time-period, 1991–2007 (468 deaths due to CVD), the HRs were 0.74, 95% CI 0.57–0.97 (age-adjusted) and 0.78, 95% CI 0.59–1.02 (age- and BMI-adjusted).

Discussion

We investigated the relationship between SEP ( quantified as educational level and occupation in midlife) and clinical biomarkers for CVD in a population of Swedish men born 1920–24. After controlling for potential confounders, we found that in midlife, manual workers and subjects with lowest education (<9 years) had the highest levels of cholesterol. Men with lowest education had highest LDL/HDL and ApoB/ApoA1 ratios. Mean levels of cholesterol, LDL/HDL and ApoB/ApoA1 ratios reduced with age. Interestingly, no significant associations were found between SEP and cholesterol, LDL/HDL or ApoB/ApoA1 ratios in the same cohort of men when examined at age 70. No association was found between SEP and adiponectin at age 70.

A recent study reported mean cholesterol levels of 5.39 mmol/l for American Caucasian men aged between 50 and 60 years, which is lower than 6.9 mmol/l for our subjects.25 Previous studies reported decreasing levels of cholesterol after 65 years of age.26 Our study is consistent with others in observing associations of lower SEP with higher levels of cholesterol and blood lipids.4–6,27,28 The association of SEP with cholesterol and LDL/HDL ratio observed in our study subjects at age 50 that is no longer significant at age 70 is a unique finding. This is especially interesting in the context of marked social differences in CVD mortality seen in our study beyond age 70. In contrast to our findings at age 50, results from the Whitehall II study showed no gradient in cholesterol by social position but a significant inverse gradient with ApoB/ApoA1 ratio was observed.29 Our results are consistent with the Whitehall II study in that we also saw a clear gradient in ApoB/ApoA1 over educational categories at age 50.

Mortality across all educational categories has decreased in western Europe and other industrialized countries in recent decades.30 A steady decrease in CVD across all groups of education level has been observed in Sweden between 1991–2005. However despite this decrease, health inequalities in CVD between different educational groups remain fairly strong.19 Mortality among Swedish men decreased across all occupational classes, except manual workers between the 1950s and the 1980s, and Swedish men aged 30–74 with only primary education are still at twice the risk for mortality compared to men with higher levels of education.18

As the outcomes were measured in a manner as consistent as possible at each subsequent investigation (i.e.
Table 4. Comparison of results of linear regression analysis for the association of occupational class and education (independent) with CVD biomarkers (dependent), age adjusted for only those men who attended both investigations (ages 50 and 70) in the Uppsala Longitudinal Study of Adult Men

<table>
<thead>
<tr>
<th>Socioeconomic group</th>
<th>Cholesterol (mmol/l)</th>
<th>LDL/HDL</th>
<th>ApoB/ApoA1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 50 (n = 1220)</td>
<td>Age 70 (n = 1220)*</td>
<td>Age 50 (n = 992)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manuals</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-manuals</td>
<td>-0.24</td>
<td>-0.01</td>
<td>-0.21</td>
</tr>
<tr>
<td>(−0.40 to −0.09)</td>
<td>(−0.13 to 0.10)</td>
<td>(−0.43 to 0.01)</td>
<td>(−0.11 to 0.16)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>-0.13</td>
<td>0.11</td>
<td>-0.09</td>
</tr>
<tr>
<td>(−0.42 to 0.14)</td>
<td>(−0.29 to 0.33)</td>
<td>(−0.51 to 0.32)</td>
<td>(−0.30 to 0.23)</td>
</tr>
<tr>
<td>Not working/unknown</td>
<td>-0.11</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>(−0.50 to 0.26)</td>
<td>(−0.30 to 0.27)</td>
<td>(−0.55 to 0.53)</td>
<td>(−0.36 to 0.32)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary education</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary education</td>
<td>-0.19 (0.41 to 0.03)</td>
<td>0.06</td>
<td>-0.19</td>
</tr>
<tr>
<td>(−0.20 to 0.12)</td>
<td>(−0.51 to 0.12)</td>
<td>(−0.08 to 0.32)</td>
<td>(−0.06 to 0.06)</td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>-0.06</td>
<td>-0.04</td>
<td>-0.54</td>
</tr>
<tr>
<td>(−0.81 to −0.38)</td>
<td>(−0.20 to 0.12)</td>
<td>(−0.85 to −0.24)</td>
<td>(−0.18 to 0.20)</td>
</tr>
</tbody>
</table>

Values are coefficient (95% CI). Results in bold indicate statistical significance at p < 0.05 level. Apo, apolipoprotein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*a n differs from those reported for age 70 analyses in Tables 2 & 3 as analyses reported in this table are not adjusted for body mass index and physical activity.
using same validated laboratory protocols), misclassification of the outcome is an unlikely explanation for an apparent reduction in social differences in cardiac disease biomarkers between ages 50 and 70. One possible explanation could be misclassification of exposure. SEP at age 70 is considered to be the same as that used for the analysis at age 50, i.e. occupation from the 1960 national census, when the subjects were around 40 years old and education achieved by the men as recorded in the 1970 national census. Change of occupational class would tend to dilute any association measured at age 70. At this time most men are also retired. Irrespective of their previous occupational class or education level, it is likely that men who survived to age 70 have a more similar situation and quality of life as pensioners than previously. It is possible that this similarity will reduce the previous associations seen between SEP and CVD biomarkers by age 70. The absence of statistically significant associations between SEP and CVD biomarkers (seen at age 50) at age 70 and the continuing influence of SEP on risk of CVD death in old age calls for further explanation. Perhaps the socially determined excess mortality at old age is mediated by other major risk factors, not captured by these biomarkers, like smoking, risky alcohol consumption, psychosocial stress (e.g. from the loss of a partner), or differences in health care.

Our study was conducted on an aging population of men first investigated at age 50 and followed thereafter with a reinvestigation at age 70. As these men get older, clinical parameters including those investigated here are expected to decrease naturally with age. As seen in Table 1, a majority of the men at age 50 already had high levels of total cholesterol above today's clinical cut-off of 5.12 mmol/l.22 Subjects in this cohort are Swedish men, thus results from this study are gender specific and generalization to other ethnic groups is limited.

Our cohort is well defined and has been investigated several times in relation to CVD, and its determinants. Age is an important determinant of CVD and several of its risk indicators, thus a standardized age at baseline as in this cohort can be seen as a strength. On the other hand, the cohort design of our study and the relatively narrow age range of the study subjects at the start of the study does not allow for a distinction between period effects (changes in screening policies or availabil-

ity of effective treatments over time) as compared to effects of ageing as such.

In conclusion, both occupation and education showed strong inverse associations with cholesterol levels and LDL/HDL ratio at age 50 that were not mediated by BMI or physical activity. Education was also weakly associated with ApoB/ApoA1 at age 50.

The cumulative effect of decades of high cholesterol values or LDL/HDL ratio can still contribute to differences in mortality risk by occupation and education in later life. Our analysis of CVD mortality differences by occupation and education level from 1970 to 2007 confirmed that such differences exist in the ULSAM cohort post age 70, despite the similar profile of CVD biomarkers at this age (Figure 1). At the same time, the smaller social gradient in mortality in the period 1994–2007, when the subjects are older, than in 1970–90 is perhaps influenced by the smaller or non-existent social gradient in biomarkers at age 70.

Both analyses of association between SEP and biomarkers in all ULSAM men with data available and in the longitudinal cohort of men investigated both at age 50 and 70, yielded consistent results and suggested a weakening or disappearance of social gradients in cardiovascular biomarkers by age 70. The absence of statistically significant associations between SEP and CVD biomarkers (seen at age 50) at age 70 and the continuing influence of SEP on risk of CVD death in old age calls for further explanation. Perhaps the socially determined excess mortality at old age is mediated by other major risk factors, not captured by these biomarkers, like smoking, risky alcohol consumption, psychosocial stress (e.g. from the loss of a partner), or differences in health care.

Our study was conducted on an aging population of men first investigated at age 50 and followed thereafter with a reinvestigation at age 70. As these men get older, clinical parameters including those investigated here are expected to decrease naturally with age. As seen in Table 1, a majority of the men at age 50 already had high levels of total cholesterol above today’s clinical cut-off of 5.12 mmol/l. Subjects in this cohort are Swedish men, thus results from this study are gender specific and generalization to other ethnic groups is limited.

Our cohort is well defined and has been investigated several times in relation to CVD, and its determinants. Age is an important determinant of CVD and several of its risk indicators, thus a standardized age at baseline as in this cohort can be seen as a strength. On the other hand, the cohort design of our study and the relatively narrow age range of the study subjects at the start of the study does not allow for a distinction between period effects (changes in screening policies or availability of effective treatments over time) as compared to effects of ageing as such.

In conclusion, both occupation and education showed strong inverse associations with cholesterol levels and LDL/HDL ratio at age 50 that were not mediated by BMI or physical activity. Education was also weakly associated with ApoB/ApoA1 at age 50.

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In conclusion, both occupation and education showed strong inverse associations with cholesterol levels and LDL/HDL ratio at age 50 that were not mediated by BMI or physical activity. Education was also weakly associated with ApoB/ApoA1 at age 50.
Despite a continuing effect of education and occupational class on CVD mortality after age 70, no associations between measures of SEP and lipid levels measured at age 70 were seen in our material.

Acknowledgements
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References
Parental influences on cardiovascular risk factors in Swedish children aged 5–14 years

Amal R. Khanolkar,1,2, Liisa Byberg,3, Ilona Koupil1

1 Centre for Health Equity Studies, Stockholm University/Karolinska Institutet, Stockholm, Sweden
2 Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
3 Department of Surgical Sciences, Section of Orthopaedics, Uppsala University

Correspondence: Amal Khanolkar, Centre for Health Equity Studies (CHESS), Stockholm University/Karolinska Institutet, 106 91 Stockholm, Sweden, tel: +46 (0)8 162584+46 (0)73 0899409, Fax: +46(0)8 16 26 00, e-mail: amal.khanolkar@ki.se

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Background: Precursors of cardiovascular diseases (CVD) originate in childhood. We investigated relationships of children’s CVD risk factors with parents’ socio-economic position (SEP) and lifestyle and how CVD risk factors correlate within families.

Methods: We studied 602 families with 2141 individuals comprising two full sibs; aged 5–14 years, and their biological parents (Uppsala Family Study). Parental SEP (occupational class and education) and lifestyle habits [smoking, physical activity (PA), alcohol consumption] were taken from questionnaires. Associations with cholesterol, ApoB/ApoA1, leptin, adiponectin, blood pressure, body mass index (BMI) and overweight/obesity (OW/OB) were analysed by linear/logistic regression. Results were adjusted for child’s age, gender, pubertal stage and family clustering. Results: We observed no consistent associations between parental SEP and children’s CVD risk factors. Parental lifestyle had stronger effects, independent of parental SEP. Children of smoking fathers had higher BMI (4%, 95% CI 1–7%) and leptin levels (27%, 95% CI 1.00–61.60%). Children of mothers reporting vigorous PA had lower BMI, cholesterol and decreased odds for OW/OB with a possible dose effect. Compared with mothers reporting no vigorous activity, mothers with >75 min and 76–150 min/week of vigorous activity had 43% (OR 0.57, 95% CI 0.22–0.89) and 72% (OR 0.28, 95% CI 0.14–0.60) lower risk of having an OW/OB child, respectively, after adjustment for confounders. Independent, consistently stronger and significant associations were found between all studied parents’ and children’s CVD risk factors. Conclusion: Parental behaviours: smoking, alcohol consumption, low PA are associated with higher levels of CVD risk factors (BMI, OW/OB, cholesterol) in children. Strong correlations in CVD risk factors within families not related to parental SEP/lifestyle suggest a role of genetics in influencing children’s CVD risk factors. Public health policies should target families with unhealthy lifestyles.

Introduction

Cardiovascular disease (CVD) continues to be the deadliest killer accounting for 17.5 million deaths globally each year.1 Socio-economic position (SEP)—measured by occupational group and highest educational level achieved—is strongly associated with risk for CVD disease in adults.2,3 The extent of socio-economic and psychosocial influences on the development of CVD risk factors in early life and childhood remains debatable and controversial. Several studies provide evidence that the precursors of CVD begin in early childhood.4,5 Longitudinal studies show that early recognizable risk factors including obesity (OB), hypercholesterolemia, hypertension, physical activity (PA) and smoking during childhood track into adulthood.4,6 While numerous studies have concluded that parental influence on the development of cardiovascular risk in their offspring goes beyond that of just biological, other studies show that social influences in childhood are modest.4,6–10 Most studies investigating intergenerational effects of parental socio-economic characteristics on child health study childhood body mass index (BMI) as the outcome with often conflicting results.5,11–12 Few studies in Europe looked specifically at possible effects on CVD biomarkers in children, showing that children of lower manual parents and farmers and lower educated mothers had higher total and LDL cholesterol, leptin, C-reactive protein, interleukin-6 and higher blood pressure (BP).13,14 Lack of associations between parental SEP and their children’s CVD risk factors have also been reported.14,15

In comparison to previous studies, we investigated three possible determinants of CVD risk factors in childhood [children aged 5–14 years] that could contribute to accumulation of risk that tracks into adulthood: (i) parental SEP; (ii) parental lifestyle (smoking, alcohol consumption and PA); and (iii) parental CVD risk factors. We also studied a wider range of CVD risk factors in children in addition to BMI, including cholesterol, ApoB/ApoA1 ratio, leptin, adiponectin and BP. Early identification of determinants of CVD could be effective in reducing that part of adulthood CVD risk that originates in childhood. We hypothesized that parental SEP is inversely associated with their children’s cardiovascular risk factors such that children from lower SEP families have generally higher levels of CVD risk factors. We also hypothesized that parental lifestyle would be reflected in their children’s lifestyle, which in turn influences the latter’s cardiovascular risk factors. To our knowledge, no study in Sweden has investigated the effects of parental social characteristics and lifestyle on children’s CVD risk factors other than BMI.

Methods

The Uppsala Family Study (UFS), initiated to study associations of birthweight with BP in children, is described in detail elsewhere.16 Briefly, in 2000–01, we investigated 602 families (of 1967 eligible families invited) comprising two full sibs aged 5–14 years, and their biological parents (in all 2141 individuals). For >95% of the families, all four family members were examined on the same occasion by trained nurses. Laboratory, lifestyle and socio-economic data were available for the 592 mothers, 559 fathers, 509 older children and 481 younger children who were included in this study.

The parents’ questionnaire assessed occupational status, education and lifestyle habits including smoking, alcohol consumption and PA. SEP was determined by occupational status
and highest education achieved. Occupation was coded using the socio-economic classification devised by Statistics Sweden24 collapsing the original 16 groups into six occupational classes: higher/intermediate non-manuals, lower non-manuals, skilled workers, unskilled workers, entrepreneurs/farmers and unknown, as used here. Education was divided into three groups: university, secondary school or equivalent, and other (<5 years of compulsory schooling). In all analyses, the higher/intermediate non-manual occupational and university education groups were the reference.

We calculated the total intensity of physical exercise for each parent in Metabolic Equivalent Task (MET) by multiplying the number of hours per week of moderately demanding (e.g., scrubbing floors, chopping wood, dancing, golfing, cycling, leisure swimming) and very demanding/vigorous PA (e.g., running, sports activities like tennis, squash) by 4.5 and 6 MET, respectively, and using the sum of these products25,26. Mothers and fathers were grouped into tertiles of low, moderate and high PA. As a second PA exposure, we defined vigorous exercise, based on criteria recommended by the WHO, i.e., a minimum of 75 min of vigorous PA per week and 150 min of vigorous PA per week for additional health benefits.27 Vigorous exercise by minutes per week was categorized as non, ≤75 min/week, 76–150 min/week and >150 min/week in mothers and; ≤30 min/week, 60 min/week, 90–120 min/week, 150–360 min/week and >360 min/week in fathers. Data on vigorous PA was available for only 56% of fathers and 61% of mothers.

Parents’ smoking habits were classified as ‘never’, ‘former’ and ‘current’ smokers. Alcohol consumption was assessed by frequency per week and was categorized as teetotallers, less than once per week, once a week and more than once a week. Height and weight were measured three times (to the nearest 0.1 cm and 0.1 kg, respectively) for all four family members in undergarments only and the means were used. BMI was calculated as weight (in kilograms) divided by height (in metres) squared. Overweight (OW) and OB in children was determined by using age- and sex-specific cut-offs proposed by the International Obesity Task Force.28

BP and pulse rate were measured using a Dinamap ‘Compact T’ Monitor (Critikon Ltd). Three measurements were taken with the subject in a sitting position, on the left arm with an interval of about 1–2 min between each reading and the mean of the three readings were used in the analyses.22 Serum cholesterol, apolipoproteins (Apo) A1 and B were measured using an Architect Ci8200 analyser (Abbott Laboratories, Abbott Park, USA). Adiponectin and leptin levels were analyzed using commercially available ELISA kits (R & D Systems, MN, USA).

Pubertal stage was determined by visual examination of pubic hair growth (boys and girls) conducted by the nurses, and the children were assigned to one of the five stages on the Tanner scale.22

Statistical analysis

Statistical analyses were performed using STATA 11 (College Station, USA).

Continuous variables are presented as mean values, with standard deviations and categorical variables as frequencies. Differences in mean values of continuous variables and comparison of categorical variables (between boys and girls; mothers and fathers) were analysed using t-tests and chi-square tests, respectively. In linear regression analyses, assumptions of linearity for continuous variables and constant variance of the standardized residuals were assessed through plotting the residuals against the fitted values. Log-transformed values were used for BMI and adiponectin (parents and children) due to skewed distributions. Coefficient estimates of log transformed variables were converted to the original scale and are interpreted as relative differences (in percentages) in the outcome variable in comparison to the reference category.28 Multiple logistic regression (with the binary outcome of normal BMI and OW/OB) was used to compute odds ratios for OW/OB in children by parental exposures. Age, gender and pubertal stage of children were considered potential confounders and controlled for in all analyses. Analyses of diastolic and systolic BP were additionally adjusted for children’s height. Analyses of associations between parental lifestyle habits and children’s outcomes were additionally adjusted for parental SEP. The ‘cluster’ option in STATA was used in all regression analyses to account for the family structure of the cohort. Gender differences were analysed in stratified analyses and with formal tests for statistical interaction. We also ran all analyses by stratification for pubertal development using a binary indicator (pre-pubertal or Tanner scores 1 vs. pubertal or Tanner scores 2–4).

Differences between the associations of the respective parental exposure and child’s outcome between the two pubertal groups were tested using formal tests for statistical interaction.

Our study was approved by the Regional Ethics Committee in Uppsala.

Results

Characteristics of children and parents are presented in Table 1. Girls had higher levels of cholesterol, ApoA1, leptin, adiponectin, ApoB/ApoA1 ratio, systolic and diastolic BP than boys but lower ApoA1 levels. No statistically significant differences between genders were found for age and BMI. A majority of children (77% boys and 69% girls) were at a pre-puberty stage at the time of examination (Tanner stage 1). A total of 12% of boys and 14% of girls were OW and 4% of boys and 5% of girls were OB in our sample.

Smoking patterns were similar among mothers and fathers with 10–12% current and 24–26% former smokers. Frequency of alcohol consumption differed between the parents with a generally lower alcohol consumption in mothers (Table 1).

Analyses of parental SEP and CVD risk factors in children revealed few significant and consistent associations (Table 2). Children of lowest educated parents (mothers with less than university education or father with ≤9 years compulsory schooling) had higher mean BMI levels. Compared with children of fathers from the highest SEP groups, children of fathers who were skilled manual workers or had low education had higher mean systolic BP levels. Children of mothers classified as unskilled and farmers/entrepreneurs had increased mean BMI levels and children of farmer mothers had higher mean cholesterol levels (Table 2). Logistic regression modelling showed significant associations between parental SEP and OW/OB only in children of lowest educated mothers and fathers who had a 75–107% increased risk of OW/OB (Tanner score 1 vs. pubertal or Tanner scores 2–4).

We detected specific associations between parental lifestyle habits and CVD risk factors in children (Table 3). Children of fathers and mothers classified as current smokers had a higher mean BMI corresponding to an increase of 4% and 3%, respectively, when coefficient estimates are converted to original scale. We also observed a 27% increase (coefficient converted to original scale) in leptin levels of children of current smoker fathers. Children of fathers who reported drinking alcohol more than once a week had on average 0.35 mmol/l (95% CI 0.05–0.65) higher cholesterol and 0.26 (95% CI 0.09–0.44) higher (log) adiponectin levels compared with children of teetotallers.
The latter estimate corresponds to an increase of 30% in mean adiponectin levels in children when compared with those of the reference group, i.e. children of teetotaller fathers. In contrast, children of teetotallers had 0.04 (95% CI 0.00–0.08) higher mean ApoB/ApoA1 ratio levels. Increased alcohol consumption among mothers was associated with increased mean BMI and cholesterol levels [0.03 (log)BMI or 3% increase and 0.18 mmol/l, respectively] in children of mothers who reported drinking 1/week and 0.03 increase in ApoB/ApoA1 ratios levels in children of mothers who reported drinking <1/week compared with those of teetotaller mothers (table 3).

Vigorous PA, especially among mothers, showed association with several of the CVD risk factors among children. Fathers reporting ≥90 min vigorous PA per week had children with significantly lower BMI. Children of mothers reporting vigorous PA had lower BMI, cholesterol and leptin and decreased odds for OW/OB with a possible dose response effect. Compared to mothers reporting no vigorous activity, mothers with up to 75 min weekly vigorous activity had a 43% (95% CI 0.22–0.89) lower odds of having an OW/OB child. The corresponding effect in mothers reporting vigorous activity between 76 and 150 min per week was 72% (0.14–0.60) (table 3). Children of fathers who reported vigorous PA had decreased odds for OW/OB, even though these findings were not statistically significant.

In contrast to parents' amount of vigorous PA, we detected almost no significant associations between CVD risk factors in

### Table 1: Characteristics of children and their parents in the UFS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Boys, n = 620</th>
<th>Girls, n = 584</th>
<th>P*</th>
<th>Fathers, n = 569</th>
<th>Mothers, n = 602</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>10.04 (1.76)</td>
<td>10.06 (1.75)</td>
<td>0.84</td>
<td>41.07 (5.10)</td>
<td>38.70 (4.31)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>17.60 (2.75)</td>
<td>17.88 (2.87)</td>
<td>0.09</td>
<td>25.95 (5.26)</td>
<td>24.61 (4.07)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/l)</strong></td>
<td>4.25 (0.65)</td>
<td>4.33 (0.67)</td>
<td>0.06</td>
<td>5.32 (0.99)</td>
<td>4.86 (0.83)</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>ApoA1 (g/l)</strong></td>
<td>1.41 (0.22)</td>
<td>1.35 (0.17)</td>
<td>&lt;0.01</td>
<td>1.36 (0.20)</td>
<td>1.50 (0.23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>ApoB/ApoA1 ratio</strong></td>
<td>0.61 (0.13)</td>
<td>0.66 (0.15)</td>
<td>&lt;0.01</td>
<td>0.90 (0.21)</td>
<td>0.76 (0.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Leptin (pg/ml)</strong></td>
<td>6601 (2311)</td>
<td>6921 (2395)</td>
<td>0.03</td>
<td>4089 (1895)</td>
<td>5604 (2508)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>ApoB/ApoA1 ratio</strong></td>
<td>0.44 (0.11)</td>
<td>0.50 (0.13)</td>
<td>&lt;0.01</td>
<td>0.67 (0.20)</td>
<td>0.51 (0.16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Diastolic BP (mmHg)</strong></td>
<td>61 (7)</td>
<td>62 (6)</td>
<td>&lt;0.01</td>
<td>79 (10)</td>
<td>75 (9)</td>
<td>&lt;0.01</td>
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<tr>
<td><strong>Overweight (%)</strong></td>
<td>72 (12)</td>
<td>84 (14)</td>
<td></td>
<td>272 (46)</td>
<td>156 (26)</td>
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<tr>
<td><strong>Obese (%)</strong></td>
<td>23 (4)</td>
<td>28 (5)</td>
<td></td>
<td>61 (11)</td>
<td>61 (10)</td>
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<tr>
<td><strong>Pubertal stage</strong></td>
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<tr>
<td>Stage 1</td>
<td>477 (77)</td>
<td>404 (65)</td>
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<tr>
<td>Stage 2</td>
<td>112 (18)</td>
<td>120 (20)</td>
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<td>Stage 3</td>
<td>22 (3)</td>
<td>46 (8)</td>
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<td>Stage 4</td>
<td>9 (2)</td>
<td>14 (3)</td>
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<tr>
<td><strong>Total</strong></td>
<td>620</td>
<td>584</td>
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<tr>
<td><strong>Parents</strong></td>
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<tr>
<td>Higher and intermediate non-manual</td>
<td>253 (46)</td>
<td>257 (44)</td>
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<td>Lower non-manual</td>
<td>65 (12)</td>
<td>99 (16)</td>
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<td>Skilled workers</td>
<td>126 (23)</td>
<td>87 (15)</td>
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<tr>
<td>Unskilled workers</td>
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<td>115 (19)</td>
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<td>Entrepreneur/farmer</td>
<td>26 (4)</td>
<td>16 (3)</td>
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<tr>
<td>Unknown</td>
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<td>18 (3)</td>
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<tr>
<td><strong>Total</strong></td>
<td>552</td>
<td>581</td>
<td></td>
<td>&lt;0.01</td>
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<td><strong>Educational group</strong></td>
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<td>292 (50)</td>
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<td>Secondary school</td>
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<td>232 (40)</td>
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<td>Other</td>
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<td>57 (10)</td>
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<td>&lt;0.05</td>
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<tr>
<td><strong>Total</strong></td>
<td>552</td>
<td>581</td>
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<tr>
<td>Never</td>
<td>350 (64)</td>
<td>367 (64)</td>
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<td>Former</td>
<td>144 (26)</td>
<td>138 (24)</td>
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<tr>
<td>Current</td>
<td>55 (10)</td>
<td>71 (12)</td>
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<td>&lt;0.01</td>
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<tr>
<td><strong>Total</strong></td>
<td>549</td>
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<td>&lt;1/week</td>
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<td>326 (57)</td>
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<td>1/week</td>
<td>266 (48)</td>
<td>209 (36)</td>
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<tr>
<td>&gt;1/week</td>
<td>18 (3)</td>
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<td>&lt;0.01</td>
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<tr>
<td><strong>Total</strong></td>
<td>547</td>
<td>578</td>
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<tr>
<td><strong>Physical activity: Fathers/mothers</strong></td>
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<td>&lt;10 min/week (never)</td>
<td>51 (15)</td>
<td>28 (8)</td>
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<tr>
<td>1 h/week (&lt;1.15 h/week)</td>
<td>83 (25)</td>
<td>124 (54)</td>
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<tr>
<td>1.5–2 h/week (1.15–2.43 h/week)</td>
<td>85 (25)</td>
<td>116 (32)</td>
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<tr>
<td>2.5–6 h/week (≥2.5 h/week)</td>
<td>100 (30)</td>
<td>97 (26)</td>
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<tr>
<td>&gt;6 h/week</td>
<td>18 (5)</td>
<td></td>
<td>&lt;0.01</td>
<td></td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>337</td>
<td>365</td>
<td></td>
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</tr>
</tbody>
</table>

Values are means (SD or percentages).

*P*-value for difference in means between male and female children. 
*P*-value for difference in means between mothers and fathers.

a: Pubertal stage determined by visual inspection of pubic hair growth and classified according to the Tanner scale.

Cardiovascular risk factors in Swedish children
Table 2: Differences in the UFS children’s CVD biomarkers (outcome) by parental socio-economic position (occupational and educational group), adjusted for child’s age, gender, pubertal stage and family clustering

<table>
<thead>
<tr>
<th>Parental socio-economic position</th>
<th>Child’s outcome</th>
<th>Log (BMI) Coefficient (95% CI)</th>
<th>Overweight or OB Odds ratio (95% CI)</th>
<th>Cholesterol (mmol/l) Coefficient (95% CI)</th>
<th>ApoB/ApoA1 Ratio Coefficient (95% CI)</th>
<th>Log (Adiponectin) Coefficient (95% CI)</th>
<th>Systolic BP (mm/Hg)* Coefficient (95% CI)</th>
<th>Diastolic BP (mm/Hg)* Coefficient (95% CI)</th>
<th>Log (Leptin) Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent’s occupational class</td>
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<td></td>
<td></td>
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<tr>
<td>Father’s occupational class</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Higher non-manual</td>
<td>Reference group</td>
<td>0.00 (-0.03 to 0.03)</td>
<td>1.01 (0.55 to 1.86)</td>
<td>-0.15 (-0.30 to 0.00)</td>
<td>-0.03 (-0.06 to 0.00)</td>
<td>-0.02 (-0.10 to 0.06)</td>
<td>1.68 (-0.61 to 3.98)</td>
<td>0.06 (-1.90 to 1.63)</td>
<td>-0.04 (-0.30 to 0.21)</td>
</tr>
<tr>
<td>Lower non-manual</td>
<td>Reference group</td>
<td>0.01 (-0.01 to 0.04)</td>
<td>1.24 (0.80 to 1.95)</td>
<td>-0.03 (-0.16 to 0.08)</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>-0.01 (-0.07 to 0.05)</td>
<td>3.04 (1.05 to 8.03)</td>
<td>0.97 (-0.10 to 2.09)</td>
<td>0.16 (-0.01 to 0.34)</td>
</tr>
<tr>
<td>Skilled worker</td>
<td>Reference group</td>
<td>0.02 (-0.01 to 0.05)</td>
<td>1.18 (0.70 to 2.00)</td>
<td>-0.07 (-0.22 to 0.07)</td>
<td>-0.01 (-0.04 to 0.01)</td>
<td>0.05 (-0.02 to 0.13)</td>
<td>1.96 (-0.38 to 4.30)</td>
<td>0.86 (-1.15 to 1.38)</td>
<td>0.05 (-0.16 to 0.26)</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>Reference group</td>
<td>0.03 (-0.02 to 0.09)</td>
<td>1.31 (0.57 to 2.98)</td>
<td>-0.20 (-0.39 to 0.01)</td>
<td>-0.08 (-0.07 to 0.00)</td>
<td>-0.05 (-0.14 to 0.03)</td>
<td>0.92 (-1.85 to 3.70)</td>
<td>0.45 (-1.70 to 2.60)</td>
<td>0.00 (-0.31 to 0.32)</td>
</tr>
<tr>
<td>Farmers/entrepreneur</td>
<td>Reference group</td>
<td>0.04 (-0.00 to 0.07)</td>
<td>2.07 (1.21 to 3.55)</td>
<td>0.00 (-0.15 to 0.15)</td>
<td>-0.01 (-0.04 to 0.02)</td>
<td>0.02 (-0.05 to 0.10)</td>
<td>2.72 (0.11 to 5.33)</td>
<td>0.44 (-0.92 to 1.80)</td>
<td>0.20 (-0.03 to 0.44)</td>
</tr>
<tr>
<td>Parent’s educational group</td>
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</tr>
<tr>
<td>University</td>
<td>Reference group</td>
<td>0.01 (0.00 to 0.03)</td>
<td>1.25 (0.85 to 1.87)</td>
<td>0.02 (-0.08 to 0.13)</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>0.04 (0.00 to 0.10)</td>
<td>1.11 (-0.42 to 3.65)</td>
<td>0.51 (-0.40 to 1.42)</td>
<td>0.11 (-0.04 to 0.27)</td>
</tr>
<tr>
<td>Other</td>
<td>Reference group</td>
<td>0.04 (0.00 to 0.07)</td>
<td>2.07 (1.21 to 3.55)</td>
<td>0.00 (-0.15 to 0.15)</td>
<td>-0.01 (-0.04 to 0.02)</td>
<td>0.02 (-0.05 to 0.10)</td>
<td>2.72 (0.11 to 5.33)</td>
<td>0.44 (-0.92 to 1.80)</td>
<td>0.20 (-0.03 to 0.44)</td>
</tr>
<tr>
<td>Mother’s occupational class</td>
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<td></td>
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<tr>
<td>Father’s occupational class</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher non-manual</td>
<td>Reference group</td>
<td>0.00 (-0.03 to 0.02)</td>
<td>1.01 (0.60 to 1.73)</td>
<td>0.03 (-0.10 to 0.16)</td>
<td>0.01 (-0.01 to 0.04)</td>
<td>0.04 (-0.02 to 0.11)</td>
<td>0.43 (-1.78 to 2.65)</td>
<td>-0.27 (-1.64 to 1.06)</td>
<td>-0.02 (-0.24 to 0.20)</td>
</tr>
<tr>
<td>Lower non-manual</td>
<td>Reference group</td>
<td>0.01 (-0.01 to 0.04)</td>
<td>1.37 (0.82 to 2.28)</td>
<td>0.00 (-0.15 to 0.15)</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>0.00 (-0.06 to 0.08)</td>
<td>1.68 (-0.62 to 3.98)</td>
<td>0.45 (-0.75 to 1.65)</td>
<td>-0.09 (-0.28 to 0.10)</td>
</tr>
<tr>
<td>Skilled worker</td>
<td>Reference group</td>
<td>0.02 (0.00 to 0.05)</td>
<td>1.44 (0.90 to 2.20)</td>
<td>-0.04 (-0.17 to 0.08)</td>
<td>0.00 (-0.02 to 0.02)</td>
<td>0.00 (-0.06 to 0.07)</td>
<td>0.50 (-1.30 to 2.27)</td>
<td>0.20 (-0.88 to 1.30)</td>
<td>0.08 (-0.10 to 0.27)</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>Reference group</td>
<td>0.03 (0.03 to 0.20)</td>
<td>1.34 (0.64 to 2.79)</td>
<td>0.30 (0.05 to 0.54)</td>
<td>0.02 (-0.02 to 0.06)</td>
<td>0.08 (-0.07 to 0.25)</td>
<td>2.28 (-0.03 to 3.70)</td>
<td>1.10 (-0.73 to 3.21)</td>
<td>0.64 (0.28 to 1.03)</td>
</tr>
<tr>
<td>Farmers/entrepreneur</td>
<td>Reference group</td>
<td>0.10 (0.03 to 0.20)</td>
<td>3.42 (1.48 to 7.94)</td>
<td>0.30 (0.05 to 0.54)</td>
<td>0.02 (-0.02 to 0.06)</td>
<td>0.08 (-0.07 to 0.25)</td>
<td>2.28 (-0.03 to 3.70)</td>
<td>1.10 (-0.73 to 3.21)</td>
<td>0.64 (0.28 to 1.03)</td>
</tr>
<tr>
<td>Mother’s educational group</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>Reference group</td>
<td>0.01 (0.00 to 0.03)</td>
<td>1.23 (0.85 to 1.78)</td>
<td>0.07 (-0.02 to 0.18)</td>
<td>0.01 (-0.01 to 0.03)</td>
<td>0.00 (-0.06 to 0.04)</td>
<td>2.17 (0.63 to 3.70)</td>
<td>1.37 (0.47 to 2.27)</td>
<td>0.09 (-0.06 to 0.24)</td>
</tr>
<tr>
<td>Other</td>
<td>Reference group</td>
<td>0.03 (0.00 to 0.07)</td>
<td>1.75 (1.00 to 3.13)</td>
<td>0.16 (-0.11 to 0.23)</td>
<td>0.01 (-0.01 to 0.05)</td>
<td>-0.05 (-0.13 to 0.03)</td>
<td>2.18 (-0.05 to 4.42)</td>
<td>0.88 (-0.42 to 2.28)</td>
<td>0.09 (-0.20 to 0.37)</td>
</tr>
</tbody>
</table>

Text in bold indicates statistical significance at $P<0.05$ level. OR for OW and OB in children computed by logistic regression.

a: Systolic BP and diastolic BP adjusted additionally for children’s height.
Table 3 Differences in the US children’s CVD biomarker (outcomes) by parental lifestyle habits (smoking, alcohol consumption and PA), adjusted for child’s age, gender, pubertal stage, family clustering and parental socio-economic group (education and occupation)

<table>
<thead>
<tr>
<th>Parental Lifestyle</th>
<th>Child’s outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log (BMI) Coefficient (95% CI)</td>
</tr>
<tr>
<td>Father’s smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>Reference group</td>
</tr>
<tr>
<td>Former</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Father’s Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
</tr>
<tr>
<td>&lt;1/week</td>
<td></td>
</tr>
<tr>
<td>1/week</td>
<td></td>
</tr>
<tr>
<td>&gt;1/week</td>
<td></td>
</tr>
<tr>
<td>Father’s PA</td>
<td></td>
</tr>
<tr>
<td>Total MET h/week</td>
<td></td>
</tr>
<tr>
<td>≤75</td>
<td></td>
</tr>
<tr>
<td>&gt;75</td>
<td></td>
</tr>
<tr>
<td>Total hours of vigorous PA/Week</td>
<td></td>
</tr>
<tr>
<td>None or &lt;30 min/week</td>
<td></td>
</tr>
<tr>
<td>60–120 min/week</td>
<td></td>
</tr>
<tr>
<td>120–360 min/week</td>
<td></td>
</tr>
<tr>
<td>&gt;360 min/week</td>
<td></td>
</tr>
<tr>
<td>Mother’s smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td></td>
</tr>
<tr>
<td>Mother’s Alcohol consumption</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
</tr>
<tr>
<td>&lt;1/week</td>
<td></td>
</tr>
<tr>
<td>1/week</td>
<td></td>
</tr>
<tr>
<td>&gt;1/week</td>
<td></td>
</tr>
<tr>
<td>Mother’s PA</td>
<td></td>
</tr>
<tr>
<td>Total MET h/week</td>
<td></td>
</tr>
<tr>
<td>≤20.25</td>
<td></td>
</tr>
<tr>
<td>&gt;20.25</td>
<td></td>
</tr>
<tr>
<td>Total hours of vigorous PA/Week</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>&lt;1/week</td>
<td></td>
</tr>
<tr>
<td>1/week</td>
<td></td>
</tr>
<tr>
<td>&gt;1/week</td>
<td></td>
</tr>
</tbody>
</table>

a: Total MET h/week is calculated as a product of moderate and vigorous PA in hours per week (multiplied by 4.5 and 6 respectively) as reported by each parent.
b: 2.5 h/week of vigorous PA is the minimum criteria recommended by the WHO for ‘additional health benefits’.
c: Systolic BP and diastolic BP adjusted additionally for children’s height. Text in bold indicates statistical significance at P<0.05 level. OR: odds ratio for OW and OB combined in children computed by logistic regression.
Test run (72), <5% were statistically significant which is the number expected to be due to chance.

Discussion

What have we shown?

In this study, we investigated intergenerational transfer of cardiovascular risk factors by studying associations between parents and children. While we found some evidence of associations between parental SEP and children's CVD risk factors, parental lifestyle habits seem to play an important role in determining levels of this CVD biomarker in their children. We found significant associations of children's CVD risk factors with all three aspects of parental lifestyle: mother's and father's PA, alcohol consumption and smoking status. Adjustment for parental SEP in these regression models only marginally affected the regression estimates suggesting that parental SEP does not confound the associations studied. Statistically strongest and most consistent associations were found between parent’s own CVD risk factors and those of their children (statistically significant for all CVD risk factors studied). We speculate that strong associations between parental and children’s biomarkers, independent of SEP and lifestyle, indicate shared genetics/inheritance. Our results possibly indicate that vigorous PA as an exposure in fathers might be a more important determinant of the studied outcomes in children than moderate PA. In the case of mother for cholesterol and ApoB/ApoA1 ratio. For systolic BP, the father's biomarker levels seem to play a greater determining role (table 4).

In regression analyses stratified by gender of the children, no systematic differences were observed in the strength of effects of mother's or father's CVD risk factors on children’s CVD risk factors, indicating no differences by gender except for paternal ApoB/ApoA1 ratio. These stratified analyses were adjusted for child's age, gender and pubertal stage and parental SEP.

Strengths

The UFS has the advantage of being a 'contemporary' cohort, comprising families of Nordic ethnicity residing in Uppsala County at the time of examination, and only includes children who are full siblings born within a 3-year interval and who lived together at the time of the examination. Children in this study cohort were born 1987–95 and results from analyses would in all probability be applicable to public health interventions in the near future. Laboratory analyses and physical examinations were performed in laboratories and physical examinations were performed in Stockholms Universitet on December 14, 2011.
conducted with optimal and valid methods available at the time of examination. We analysed BMI in children both as continuous and categorical outcomes enabling interpretation for risk of childhood OW/OB. Gender and pubertal differences in children were taken into account enabling speculation of increased or decreased risk from one parent to only sons or daughters; pre-pubertal or pubertal children.

Weaknesses
This family study is modest in size and its possible lack of power could be a reason for lack of associations between parental exposures and children’s outcomes. Another possibility is a limited variation in SEP among the parents since most families probably had a fairly high and similar standard of living. Recent studies in both Sweden and elsewhere in children of comparable ages show clearly that the OW and OB trends are levelling off, and that it is only the lower SEP children that have not benefitted from this new phenomenon. Those families are probably under-represented in our study as well as those of divorced/single parents and immigrant families. This, together with the recruitment of families with two children in a narrow age range might limit generalization of our results to other family structures and other populations.

Despite the fact that parental and child characteristics were measured simultaneously in our study, we believe that our results are unlikely to be driven by ‘reverse causality’ (children’s CVD risk factors influencing lifestyle or social position of parents) in our population based sample of generally healthy children. We did, however, lack information on the children’s lifestyle and were thus unable to study associations between parental and children’s lifestyle habits. Misclassification of some parental lifestyle exposures could have diluted the results. Alcohol consumption is a sensitive issue and it is possible that not all parents reported their true alcohol consumption. However, despite this, we still found statistically significant associations between parental alcohol consumption and children’s BMI and cholesterol levels. Lack of dietary information on family members and breastfeeding habits meant we were unable to account for other potentially important determinants of CVD risk factors like BMI or cholesterol in children. We also do not have information on PA in children which could be a strong determinant of both BMI and cholesterol levels. On the other hand, it can be quite difficult to measure PA in children as young as 5–10 years of age. Furthermore, we cannot exclude residual confounding by socio-economic factors that we were unable to capture with our measurement of SEP.

A majority of the children (73%) in our study sample are pre-pubertal (i.e. assigned a Tanner score of 1) and pubertal children are underrepresented. It is possible that as children enter puberty, the associations under investigation here undergo a change which we were unable to capture in our analyses due to a lack of power. Despite being a smaller cohort with fewer children as compared with other studies that investigated similar associations, we still found consistently significant results in regards to all three lifestyle habits in parents as well as strong associations between CVD risk factors in both parents and children aged 5–14 years. This indicates a predilection for increased levels of some CVD risk factors that start fairly early in life.

Comparison with similar studies
To our knowledge, this is the first study in Sweden to investigate parental social and lifestyle influences on children’s CVD risk factors. Few studies from the Nordic countries have investigated similar associations in older cohorts of children and reported contradictory findings. While Letón et al found significantly lower total and LDL cholesterol levels in children of lower manual and farmer parents, Byckling et al found no differences in a range of CVD risk factors including those used here. The authors conclude that social and economic equalization of families with children is the main reason behind the findings; a rationale that we are inclined to believe is the reason for our results as far as socio-economic indicators are concerned. These two Nordic studies only use occupation of fathers as the socio-economic exposure, whereas we use parental education as well, and investigate associations with both mother’s and father’s SEP. We also have the advantage of using parental lifestyle and parental CVD biomarkers as exposures. We go further by investigating associations between parental and children’s CVD risk factors.

Possibilities for the future
As immigrants are likely to belong to lower socio-economic groups, it is important to study the role of parental SEP in relation to CVD risk factors in children of non-Nordic ethnicity in future studies. Possible gender differences of the parental effects and effects over the life course in these associations would be possible to explore in larger studies and databases with repeated observations for both children and parents.

Contribution from a public health perspective
Our results indicate that shared environments and lifestyles are important in setting early trends in some cardiovascular risk factors in children. Children can benefit if their parents adopt a healthy lifestyle. Furthermore, it is also plausible that children brought up in a home exposed to a healthy lifestyle (or an unhealthy one) will be likely to continue the same habits later in life and the effects of parental lifestyle will further increase with age of children. This also means that public health interventions targeting parental lifestyle can benefit whole families and help reduce accumulation of risk factors over the life time of the offspring. On the other hand, we speculate that in addition to the effects of shared wider environment and shared lifestyle, strong associations observed between parental and children’s CVD risk factors are partly driven by shared genetic factors.

Conclusion
Our study indicates that BMI and common CVD risk factors like cholesterol in children aged 5–14 years are more strongly related to parental lifestyle factors than to parental SEP in a contemporary Swedish cohort. Strong associations between parental and children’s CVD risk factors possibly indicate further contribution of common genetics. Multiple and potentially interrelating pathways like social, behavioural and genetic appear to contribute to CVD risk factors in children. Families with unhealthy lifestyles should be targeted with public health interventions that not only highlight the negative consequences in children but also help in initiating better lifestyle patterns.

Supplementary Data
Supplementary Data are available at Eurpub online.

Acknowledgements
We would like to thank Dr Ulla Sovio, London School of Hygiene and Tropical Medicine, UK, for advice on statistical analysis and Johanna K. Sandling, Department of Medical Sciences, Molecular Medicine, Uppsala University, Sweden for help with laboratory analyses.
Funding
This work was supported by the Swedish Council for Working Life and Social Research (grant number 2006-1518), the Swedish Research Council (grant 2006-7468) and Uppsala University.

Conflicts of interest: None declared.

Key points
- We found evidence that SEP of parents measured by occupation and education is associated with CVD biomarkers like BMI, OW/OB and systolic BP in their children.
- Unhealthy parental lifestyle habits (lack of vigorous PA, higher alcohol consumption and smoking) show clear associations with increased CVD risk factor levels in children.
- CVD biomarkers in children were most strongly related to their parents’ biomarker levels, independent of parental SEP and lifestyle suggesting that genetic associations play an important role in these associations.
- Public health policies specifically targeting whole families and children of parents with unhealthy lifestyles might help to reduce future CVD risk in children.

References
Socioeconomic and early-life factors and risk of being overweight or obese in children of Swedish- and foreign-born parents

Amal R. Khanolkar1,2, Ulla Sovio1,3, Jonathan W. Bartlett3, Thomas Wallby4 and Ilona Koupil1

BACKGROUND: Ethnic minorities/immigrants have differential health as compared with natives. The epidemic in child overweight/obesity (OW/OB) in Sweden is leveling off, but lower socioeconomic groups and immigrants/ethnic minorities may not have benefited equally from this trend. We investigated whether nonethnic Swedish children are at increased risk for being OW/OB and whether these associations are mediated by parental socioeconomic position (SEP) and/or early-life factors such as birth weight, maternal smoking, BMI, and breastfeeding.

METHODS: Data on 10,628 singleton children (51% boys, mean age: 4.8 y, born during the period 2000–2004) residing in Uppsala were analyzed. OW/OB was computed using the International Obesity Task Force’s sex- and age-specific cutoffs. The mother’s nativity was used as proxy for ethnicity. Logistic regression was used to analyze ethnicity–OW/OB associations.

RESULTS: Children of North African, Iranian, South American, and Turkish ethnicity had increased odds for being overweight/obese as compared with children of Swedish ethnicity (adjusted odds ratio (OR): 2.60 (95% confidence interval (CI): 1.37–4.27), 1.67 (1.03–2.72), 3.00 (1.86–4.80), and 2.90 (1.73–4.88), respectively). Finnish children had decreased odds for being overweight/obese (adjusted OR 0.53 (0.32–0.90)).

CONCLUSION: Ethnic differences in a child’s risk for OW/OB exist in Sweden that cannot be explained by SEP or maternal or birth factors. As OW/OB often tracks into adulthood, more effective public health policies that intervene at an early age are needed.

Immigrants and ethnic minorities in high-income countries often belong to lower socioeconomic groups and have higher rates of chronic diseases, worse self-reported health, and higher infant mortality (1–3). Poor health in immigrants and ethnic minorities is reported in adults and children and their descendants; however, differences in health vary considerably by country of origin, destination, time of immigration, acculturation, and disease (4). Immigrants of lower socioeconomic position (SEP) may be predisposed to certain negative health outcomes by virtue of their position in society as well as by ethnic susceptibility resulting from genetic differences and/or mechanisms related to developmental origins of disease (4).

Ethnic differences in levels of child overweight and obesity (OW/OB) and its risk factors, such as unhealthy diet, genetic predisposition, breastfeeding, and maternal smoking, have been substantial enough in some countries to warrant concern (5,6). Becoming overweight/obese may start in childhood and track into adulthood, posing health risks (7). In 2010, nearly 43 million children younger than 5 y of age were overweight worldwide (8). The recent decades have witnessed a significant rise in obesity levels in children across the world with children of lower SEP and ethnic minorities being the worst affected in industrialized nations (5,9–13). Some studies have reported a “leveling off” in the obesity epidemic, which might be country and region specific, but it is generally the more affluent that have benefited from this trend (14,15). In Sweden, nationally representative data for trends in OW/OB in children are lacking. Studies are conducted on regionally representative data often with small sample sizes, and results indicate that OW/OB levels in children are falling, but socioeconomic differences still exist, at least in urban areas (16–20).

In the adult Swedish population, there has been an overall increase in the prevalence of being overweight/obese. The prevalence of OW/OB increased from 35% in 1980 to 53% in 2009 among men, and from 26 to 37% among women for the same years (21).

The role of socioeconomic factors (education, family income, and occupation, among others) in the health of immigrants and ethnic minorities is debated. Some, but not all, studies have found that these factors partly explain ethnic differences in certain health outcomes (22–24). The role of parental socioeconomic factors in creating differences in the proportions of children who are overweight/obese between immigrant groups needs further investigation.

The number of “foreign-born” residents in Sweden has doubled over the past four decades and the number of residents with “both parents born abroad” has been increasing continuously (13.4 and 17.34%, respectively, in 2007) (21).
We investigated (i) if ethnicity by mother’s country of birth was associated with the odds of being overweight/obese in children born in Sweden aged 4–5 y, (ii) if this association could be explained by differences in parental SEP and/or health behaviors and early-life factors (breastfeeding, maternal smoking, maternal BMI, and birth weight), and (iii) if the association differed by gender. Identification of immigrant groups at increased risk for being overweight/obese can help in designing public health interventions that target high-risk children at an early age, preferably before the onset of OW/OB.

RESULTS
Descriptive Analyses
Characteristics of the children and their parents (n = 10,628) are summarized in Tables 1 and 2. Mean BMI of all children was 16.11 kg/m² (56th percentile). Boys had slightly higher mean BMI than girls. A higher percentage of girls (19%) than boys (14%) were overweight/obese, with the overall prevalence being 16.5%. The distribution of number of children per mother was as follows: 7,618 mothers (84%) had 1 child each, 1,448 mothers (16%) had 2 children, and 38 mothers (0.5%) had 3 children.

Differences between maternal and paternal characteristics are presented in Table 2.

Unadjusted Associations Between Parental Characteristics and Odds of Being OW/OB
Increasing levels of parental education were associated with lower risk of being overweight/obese in children (those with research degree had the lowest proportions of overweight/obese children relative to the least educated parents (≤9 y of education)—13 vs. 20% and 13 vs. 19% for fathers and mothers, respectively, P < 0.001 for either parent) (Supplementary Table S1 online). Statistically significant differences were found in proportions for OW/OB by family status, breastfeeding, and maternal smoking. Single parents had higher proportions of overweight/obese children than married parents. Mothers who exclusively breastfed for 6 mo had the lowest proportion of overweight/obese children as compared with those who partly breastfed/did not breastfeed. Mothers who reported smoking had a greater proportion of overweight/obese children as compared with nonsmokers. Detailed results on unadjusted analyses can be seen in the Supplementary Table S1 online.
Associations Between Socioeconomic Characteristics and Odds of Being OW/OB

Children of parents with ≥3 y of college and research degree had decreased odds for being overweight/obese as compared with children of parents with ≤9 y of education (odds ratio (OR): 0.72, 95% confidence interval (CI): 0.59–0.88, 0.63, 0.44–0.89, respectively, for mothers and OR: 0.63, 95% CI: 0.52–0.77, 0.58, 0.44–0.77, respectively, for fathers, adjusted for the child’s age and gender). However, after adjustment for maternal BMI, there was no evidence of an association between education and odds of being overweight/obese. Parental income was not significantly associated with the odds of a child being overweight/obese (data not shown).

Associations Between Nativity and Odds of Being OW/OB

Prevalence of OW/OB in children varied statistically significantly according to maternal nativity, with North African, South American, and Turkish mothers having the highest proportions of overweight/obese children (28, 32, and 31%, respectively). The Finns had the lowest proportion of overweight/obese children (11%), whereas Swedish and Western European mothers had 16 and 19%, respectively, of their children classified as overweight/obese (Supplementary Table S1 online).

In all logistic regression models we found statistically significant differences in odds for children being overweight/obese between Swedish born mothers and those born in other countries: North Africa, Finland, South America, and Turkey (unadjusted OR: 1.96 (95% CI: 1.20–3.17), 0.60 (0.37–0.98), 2.53 (1.60–4.02), and 2.31 (1.41–3.80), respectively). These were statistically significant in models 1–4, and the strength of the associations increased marginally on adjustment for covariates (Table 3).

Addition of socioeconomic covariates (model 2) did not change the OR materially for any of the four groups. Additional adjustment for breastfeeding, maternal smoking, and birth weight (early-life factors) led to an increase in the OR by 20–40% in those groups that already had significantly increased odds for OW/OB. Additional adjustment for maternal BMI (model 4) slightly increased the strength of the associations, with stronger effects in the North African and Turkish groups. Children of Iranian mothers also had increased odds of being overweight/obese but only in models adjusted for early-life factors and maternal BMI (models 3 and 4).

When father’s nativity was instead the principle exposure, children of North African–, Middle Eastern–, South American–, and Turkish-born fathers had increased odds for being overweight/obese after adjusting for all covariates (Table 4). The increased odds for being overweight/obese previously observed for Iranian children (according to mother’s country of birth) lost their statistical significance. When both maternal and paternal nativity were included as covariates, there was statistically significant evidence of an independent association with OW/OB for maternal (P < 0.0001), but not for paternal (P = 0.70), nativity.

In analyses stratified by sex, the significantly increased ORs for being overweight/obese in North African and Turkish children were observed only in boys (Supplementary Table S2 online). However, both South American boys and girls had significantly increased ORs for OW/OB, although the ORs were consistently higher for boys. Finnish girls but not boys had a significantly decreased OR for OW/OB. However, formal tests for interaction were nonsignificant.

DISCUSSION

Main Findings of the Study

Our study reveals that Swedish children aged 4–5 y belonging to certain maternal nativity groups—North African, Iranian, South American, and Turkish—have increased

### Table 3.

<table>
<thead>
<tr>
<th>Mother’s country of birth</th>
<th>Model 1a</th>
<th>Model 2b</th>
<th>Model 3c</th>
<th>Model 4d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
<td>OR 95% CI</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.00 —</td>
<td>1.00 —</td>
<td>1.00 —</td>
<td>1.00 —</td>
</tr>
<tr>
<td>North Africa</td>
<td>1.96 1.20–3.17 1.95 1.20–3.14 2.40 1.47–3.93 2.60 1.57–4.27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td>1.22 0.77–1.94 1.31 0.80–2.11 1.67 1.00–2.71 1.67 1.03–2.72</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>0.87 0.54–1.37 0.90 0.55–1.42 1.12 0.70–1.78 1.28 0.80–2.06</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle East</td>
<td>1.01 0.72–1.43 1.00 0.70–1.45 1.20 0.83–1.72 1.17 0.81–1.68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>0.60 0.37–0.98 0.60 0.37–0.98 0.58 0.35–0.96 0.53 0.32–0.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>1.18 0.80–1.76 1.32 0.88–1.98 1.33 0.88–2.01 1.37 0.90–2.10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South America</td>
<td>2.53 1.60–4.02 2.58 1.61–4.13 2.90 1.81–4.65 3.00 1.86–4.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>0.90 0.58–1.40 0.97 0.62–1.51 1.00 0.63–1.62 1.11 0.70–1.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkey</td>
<td>2.31 1.41–3.80 2.17 1.31–3.60 2.54 1.52–4.26 2.90 1.73–4.88</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Values in bold indicate statistical significance at the P ≤ 0.05 level.
2CI, confidence interval; OR, odds ratio; OW/OB, overweight/obesity.
3Model 1: adjusted for age and sex of child, and family clustering. Model 2: model 1 + adjustment for socioeconomic factors: income and education of both parents and father’s family status. Model 3: model 2 + adjustment for breastfeeding, maternal smoking, and birth weight. Model 4: model 3 + adjustment for maternal BMI.
risk for being overweight/obese that cannot be explained by parental SEP or by early-life factors. Our results suggest that the mother’s nativity, used as a proxy for ethnicity, may be more strongly associated with a child’s OW/OB than the father’s nativity.

### Comparison With Similar Studies

As this is the first study in Sweden to investigate ethnicity and OW/OB in childhood in detail (using regional/country-specific categorization of parental nativity, and accounting for early-life factors), we cannot make any direct comparisons to previous studies.

### Table 4. Logistic regression analysis results for the association between maternal and paternal nativity (ethnicity) and child’s OW/OB at the age of 4–5 y (N = 10,588)

<table>
<thead>
<tr>
<th>Country of birth for both parents included in the model</th>
<th>Mother’s country of birth only OR 95% CI</th>
<th>Father’s country of birth only OR 95% CI</th>
<th>P value heterogeneity (10 d.f.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>1.00</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>North Africa</td>
<td><strong>2.60</strong> 1.58–4.29</td>
<td><strong>2.16</strong> 1.35–3.43</td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td><strong>1.68</strong> 1.03–2.72</td>
<td>1.26 0.81–1.96</td>
<td>0.83–4.25</td>
</tr>
<tr>
<td>East Asia</td>
<td><strong>1.24</strong> 0.77–2.01</td>
<td><strong>1.37</strong> 0.61–2.05</td>
<td>0.75–2.00</td>
</tr>
<tr>
<td>Middle East</td>
<td><strong>1.17</strong> 0.82–1.69</td>
<td><strong>1.42</strong> 1.01–1.98</td>
<td>0.38–1.30</td>
</tr>
<tr>
<td>Finland</td>
<td><strong>0.53</strong> 0.32–0.90</td>
<td>0.90 0.56–1.45</td>
<td>0.31–0.90</td>
</tr>
<tr>
<td>Western Europe and North America</td>
<td><strong>1.38</strong> 0.90–2.10</td>
<td><strong>1.14</strong> 0.80–1.60</td>
<td>0.90–2.04</td>
</tr>
<tr>
<td>South America</td>
<td><strong>3.00</strong> 1.86–4.82</td>
<td><strong>1.87</strong> 1.00–3.47</td>
<td>1.71–4.60</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td><strong>1.12</strong> 0.70–1.80</td>
<td><strong>1.12</strong> 0.70–1.82</td>
<td>0.62–1.78</td>
</tr>
<tr>
<td>Turkey</td>
<td><strong>2.92</strong> 1.74–4.90</td>
<td><strong>2.46</strong> 1.51–4.00</td>
<td>1.00–3.89</td>
</tr>
</tbody>
</table>

1. OR included in this analysis differs from that in Tables 1–3 because it is restricted to complete cases with data on nativity of both parents. Values in bold indicate statistical significance at the P ≤ 0.05 level. All models adjusted for socioeconomic factors (income and education of both parents and father’s family status), breastfeeding, maternal smoking, maternal BMI, birth weight, and family clustering.

CI, confidence interval; df, degrees of freedom; OR, odds ratio; OW/OB, overweight/obesity.
Ethnicity and overweight/obesity

Articles

other studies. One Swedish study that investigated ethnic differences in OW/OB in children used a smaller study sample \( n = 2,306 \) and classified subjects only into “Nordic” and “non-Nordic” origin (25). The authors found a higher proportion of overweight among non-Nordic children.

Several studies have investigated the association of ethnicity and OW/OB in children in high-income countries with large populations of immigrants and ethnic minorities. Almost all showed increased risks for certain ethnic groups. In studies conducted in the United States, Hispanic and African-American children generally have increased risks for being overweight/obese (23,26). Similarly, studies from the United Kingdom, Holland, Germany, and Norway also showed increased risks for being overweight/obese or higher mean BMI in ethnic minority children (11,27,28).

An interesting finding from our study was that key socioeconomic indicators could not explain the association between nativity and OW/OB (additional adjustment for parental SEP did not change the odds for OW/OB in nativity groups in this study sample). Other studies show inconsistent results in this regard. Studies from the United States and United Kingdom—one using a cruder indicator of SEP (eligibility for free lunch in schools) and the others using several indicators including free lunch eligibility, crowding index, and parental employment—found that SEP did not explain the association between ethnicity and BMI or OW/OB in children (26,29). By contrast, German and other American studies found that parental SEP partly explained the crude association between ethnicity and OW/OB in children (5,12).

As in other similar studies, we also observed clearly different effect sizes by gender, but interaction tests were statistically nonsignificant, possibly due to small numbers in some of the strata.

Strengths and Weaknesses of the Study

The study subjects were born recently (2000–2004), making this a “contemporary” cohort, and results are applicable for future public health interventions. The large sample size included a large proportion of children aged 4–5 living in Uppsala, making the study sample representative of this county.

Results from our study may apply to other regions in Sweden because community services including health care are relatively similar across the country.

The proportion of foreign-born parents included in our study population of 10,628 is 13%, similar to the 14.3% proportion of foreign-born residents in Sweden in 2009. Uppsala has a large university and levels of education are probably higher than the national average. Immigrant/ethnic minority groups residing in Uppsala are likely to have higher educational levels than immigrant/ethnic groups in other parts of the country. This could be why socioeconomic indicators used in this study did not explain the ethnicity–OW/OB associations. The associations between nativity/ethnicity and OW/OB in other regions of the country are more likely to be stronger and explained by socioeconomic indicators where immigrant/ethnic groups have lower SEP.

BMI is only a crude measure of body fat, but it is argued to be one of the best single measures for use in large-scale epidemiological studies and is more acceptable than skin-fold measures in children. The widely used International Obesity Task Force’s cutoffs for OW/OB in children are based on internationally pooled data from six countries, none of which are well represented in our study sample (30). Nonetheless, the International Obesity Task Force’s cutoffs are based on sex-specific growth curves and account appropriately for both age and sex. Our estimates for obesity should not be biased in this regard.

Height and weight used to calculate BMI could be misclassified because they are measured by different nurses at various clinics as part of routine examinations. However, we do not believe this will bias our results, as we do not believe that this misclassification is differentially based on a child belonging to an ethnic/immigrant minority or being ethnic Swedish.

The loss of study participants due to missing data, primarily in childhood OW/OB, maternal breastfeeding, and maternal BMI, is a weakness. Our complete case (CC) results for each model are valid provided missingness is independent of the outcome (OW/OB) after adjusting for the model’s covariates. This assumption cannot be verified from the data, but we believe it is plausible, particularly for the models that—in addition to ethnicity, age, and sex—also adjust for socioeconomic factors: income, education, and father’s family status.

Educational levels of immigrants are systematically underestimated and significant associations seen between parents’ education and OW/OB in children could be slightly overestimated (31).

Few studies have addressed groups of mixed ethnicities. Children of mixed ethnic heritage may have different risks for OW/OB as compared with single-ethnicity groups. In our study sample, 13% of subjects are of mixed nativity, which was not similar across the different nativity groups, indicating that people of certain nativities are more likely to marry Swedes or people belonging to their own/similar nativity groups and backgrounds. For example, more Finns and immigrants from other Western European countries were likely to be married to Swedes as compared with immigrants from the Middle Eastern countries and Iran, who were likely to be married to people from their regions of origin. We were unable to examine this group of mixed nativity separately due to insufficient numbers.

Given the young age of children in the study, we speculate that mothers play a greater role in determining their children’s diet (which is closely tied to ethnic traditions and perceptions (6)) than fathers. Therefore, we focused on the mother’s nativity (the proxy for her ethnicity) instead of the father’s. In the additional regression model 5, adjustment for paternal nativity only marginally reduced the statistically significant associations between maternal nativity and odds of being overweight/obese, indicating that maternal nativity had an effect largely independent of paternal nativity.

Another strength is inclusion of two well-established indicators of SEP, previously shown to partly explain the crude influence in the association between ethnicity and childhood risk of being overweight/obese.
Using country of birth/nativity as a proxy for ethnicity has limitations. Not all people born in a country necessarily have the ethnicity associated with it. However, we believe that only a minority of people born in a particular country would have an ethnicity associated with another. Those who do are more likely to be from neighboring countries with similar cultural and ethnic origins. Nonetheless, we did not have sufficient numbers to categorize subjects solely by country of origin, and in most instances we had to use regional groupings of countries based on geographical locations widely used in similar studies on ethnicity and health. Ethnicity is not recorded in any of the routine registers, and country of birth is the only available variable for identifying ethnicity. Another weakness is exclusion of nativity groups with small numbers (South Asians and Africans).

It is possible that the association between nativity and OW/ OB in childhood is mediated by factors not measured in this study, such as genetic predisposition or diet, which significantly affects body fat composition and BMI. Other early-life factors previously shown to vary by ethnicity and to increase risk for childhood obesity include maternal depression, infant sleep, television watching, physical activity, and weight gain during infancy, for which we lacked data (32,33).

**Interpretation**

We speculate that the increased risk for OW/OB in certain maternal nativity groups of children is primarily due to differences in genetics and culture (which in part constitute ethnicity). The importance of genetic susceptibility to becoming overweight was highlighted in a Swedish study that showed adoptees from South America, specifically Chile, had increased OR for being overweight as compared with native Swedish children. These children grew up in Swedish households with a Swedish lifestyle including diet (34). Our results also indicate that children of South American descent are more vulnerable because they had the highest OR for OW/OB, consistent across all models regardless of adjustments, and in sex-stratified analysis. A substantial proportion of children in our study classified as South American had parents born in Chile (n = 37 or 40% of all South Americans). The observed estimated OR marginally increased on adjustment for early-life factors including birth weight, maternal BMI, breastfeeding, which capture maternal nutrition and genetics to some extent. SEP varies by ethnicity (in this study sample it varied by both parental income and education). However, after adjustment for nativity, SEP had no independent association with the odds of being overweight/obese. The relationship between ethnicity and SEP is complex. Socioeconomic gradients in OW/OB probably evolve over time with dynamic interactions between acculturation and socioeconomic advancement, which also depend on other factors including gender, age, religious and traditional beliefs, and country of origin, and it is still possible that parental SEP in ethnic minorities becomes more important at a later stage when the children are older (4). It is also likely that we lack statistical power to detect any possible mediating role of parental SEP within ethnic minority groups.

The finding that children of Finnish mothers had a decreased risk for OW/OB is partly explained by nonrandom missingness in maternal BMI; in contrast to the children of Swedish maternal nativity, the risk of being overweight/obese for children of Finnish maternal nativity with maternal BMI available was lower than the risk for those with missing maternal BMI, such that in the CCs, children of Finnish maternal nativity had lower risk of OW/OB.

**Conclusion**

Obesity in childhood may have significant long-term physical and psychosocial consequences. Although there is no immediate risk for any major illness, studies have documented early development of insulin resistance and type 2 diabetes in overweight/obese children. Ethnic differences in the proportions of overweight/obese children are contextual. The same ethnic groups in different countries may not necessarily have the same risk of being overweight/obese. From our results, it is apparent that further studies are needed using larger nationally representative study populations. How ethnic differences in OW/OB change across the life-course as children develop into adults needs to be studied. Such investigations could help in understanding mechanisms underlying OW/OB and framing health interventions that may target modifiable risk factors such as lifestyle (unhealthy diet or lack of physical activity), ensuring equitable health care access including screening of risk factors, and early intervention can save children from becoming overweight/obese.

**METHODS**

The study sample was drawn from a population of children born during the period 2000–2004, registered as residents in Uppsala county, Sweden (n = 20,520) when they were aged 4–5 y (Figure 1) (35). Of these, 19,123 were born in Sweden and had data on birth weight. The study sample was first restricted to singletons (n = 18,555) and then to children who attended annual routine examinations at child health care centers when anthropometric measurem ents (height and weight—used to compute BMI) were recorded and whose valid BMI at the age of 4 or 5 y was available. For children who had not yet completed the examination at the age of 5, measurements from the examination at the age of 4 y were included. Therefore, the BMI of 10,509 children aged 5 y (born during the years 2000–2003) and 4,331 children aged 4 y (born 2000–2004 and with BMI at age 5 missing) were included. Children were classified as being overweight or obese using age- and sex-specific cutoffs proposed by the International Obesity Task Force (30). Of the 14,840 children with valid BMI data, 10,628 had complete data on parental socioeconomic variables, maternal BMI, smoking during pregnancy, and breastfeeding.

Data on the child’s birth weight, date of birth, sex, mother’s BMI before pregnancy, multiple births, and mother’s smoking habits were accessed through linkage (using personal identity numbers) with the Medical Birth Registry. Mothers were classified as overweight (25–29.99 kg/m2) or obese (≥30 kg/m2) using World Health Organization criteria. Smoking at time of registration at maternal health clinics (generally reflecting smoking habits during the first trimester of pregnancy) was used in the analysis. Mothers were grouped into non-smokers and smokers.

Information on breastfeeding was collected retrospectively by questioning mothers on feeding habits when the child was aged 6 mo and was available from the database of the Child Health Care Unit, Uppsala County, consisting of child health records reported by nurses in Child Health Centres. In our analyses, breastfeeding was treated as...
Ethnicity and overweight/obesity

Four models with additional covariates were fitted—model 2: model 1 covariates + adjustment for socioeconomic factors such as income and education of both parents and father’s family status; model 3: model 2 covariates + adjustment for breastfeeding, maternal smoking, and birth weight; model 4: model 3 covariates + adjustment for maternal BMI; and in a separate analysis (model 5), model 4 was run with the addition of father’s nativity (categorized in the same way as mother’s nativity variable). We ran the same logistic regression models stratified by sex of the child. Differences in the nativity—OW/OB associations between males and females were formally tested using interactions. Robust standard errors allowing for clustering of children within families were used for all logistic regression models.

Supplementary Material

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

STATEMENT OF FINANCIAL SUPPORT

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REFERENCES


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Figure 1. Flowchart explaining how the study sample for this investigation was conceived. SEP, socioeconomic position.

Missing Data

Mother’s BMI, her smoking status, and breastfeeding habits were missing for 17, 3, and 9% of children, respectively, who had complete data on valid BMI, parental nativity, and SEP (n = 14,296, Figure 1). This left 10,628 children available for CC analyses.

CC analysis gives valid results if the probability of being a CC is independent of the outcome (OW/OB), given the model covariates (36). Missingness occurred primarily in child OW/OB, maternal breastfeeding, and maternal BMI (Figure 1). It is plausible that missingness in each of these variables is independent of the child’s overweight/obese status, given the logistic regression covariates, implying validity of the CC analysis, although this assumption cannot be verified from the observed data. Because we fitted a series of logistic regression models with increasing levels of adjustment for potential confounders, the assumption of conditional independence is more plausible for the more complex models (i.e., model 4). Multiple imputation was not implemented due to the clustered nature of the data, which cannot be accommodated by standard imputation routines. Our results are, thus, based on the 10,628 CCs.

All statistical analyses were performed using STATA 11 software (Stata Corp, College Station, TX).

The study sample was drawn from the register of statistics of the Child Health Care Unit in Uppsala County. The data were collected with parental consent and linked to national registers (Statistics Sweden and the National Board of Health and Welfare) using personal identity numbers of the child. Permission to conduct the study was granted by the regional ethics committee in Uppsala, Sweden.

Total population available

Children born during the period 2000–2004 and registered as residents in Uppsala, Sweden at ages 4–5 y, n = 30,530

Study sample

Children with data on all covariates, n = 10,628

Excluded

1,301 children born abroad, 580 non-natives, 3,720 children lacking valid BMI, 430 children with unknown parental country of birth and SEP, n = 14,296

Children with complete data (a minimum of 80) were excluded from the above regional analyses.

Ethnicity and overweight/obesity

Total population available

Children born during the period 2000–2004 and registered as residents in Uppsala, Sweden at ages 4–5 y, n = 30,530

Study sample

Children with data on all covariates, n = 10,628

Excluded

1,301 lacking breast feeding, 100 lacking maternal smoking, and 2,030 lacking maternal BMI
IV
Preterm and postterm birth in immigrant- and Swedish-born parents: a national population register-based study

Amal R. KHANOLKAR, MSc1,2, Sara WEDRÉN, MD PhD2, Birgitta ESSÉN, PhD3, Pär SPARÉN, PhD4, and Ilona KOUPIL, MD DSc1

1. Centre for Health Equity Studies (CHESS), Stockholm University/Karolinska Institutet, Sweden
2. Institute of Environmental Medicine, Karolinska Institutet, Sweden 3. Department of Women’s and Children’s Health, International Maternal and Child Health, Uppsala University, Sweden and 4. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden.

Corresponding author: Amal R. Khanolkar,
Centre for Health Equity Studies (CHESS),
Stockholm University/Karolinska Institutet,
10691 Stockholm, Sweden
Telephone: +46(0)8 162584
Fax: +46 (0)8 162600
amal.khanolkar@ki.se

Running title: Ethnic background and preterm and postterm birth
Abstract

**Objective** Investigate differences in risk of preterm and postterm birth between Swedish-born and immigrant parents.

**Design** Register-based population study.

**Setting** Sweden.

**Population** 1,028,303 mothers that gave birth to 1,766,026 singleton infants (1982-2002).

**Methods** Immigrant parents were identified by country of birth. Multinomial logistic regression was used and analyses were adjusted for birth year, sex, maternal age, parity, education, cohabitation, smoking, and gestational hypertension.

**Main outcome measures** Early preterm, late preterm and postterm birth.

**Results** Polish, Yugoslavian, Iranian, South Asian, East Asian, Sub-Saharan-African, Swedish mothers and non-Swedish fathers and parents from different immigrant groups had higher risk of early preterm birth (adjusted relative risk, (RR) (95% CI) 1.76, (1.24-2.50), 1.57, (1.31-1.87), 1.67, (1.30-2.14), 1.52, (1.07-2.16), 1.51, (1.08-2.10), 2.03, (1.32-3.12), 1.56 (1.45-1.67), 1.55 (1.35-1.77) respectively). South Asian, Sub-Saharan-African, East Asian immigrants had a higher risk of late preterm birth. North African and Middle Eastern, Somali, and Ethiopian/Eritrean groups had increased risk of postterm birth (adjusted RR 1.31, (1.16-1.47), 2.57 (2.31-2.86), 1.85 (1.67-2.04) respectively). Adjustment for covariates did not substantially change the associations. Immigrant mothers resident <3 years had higher risk for early preterm and postterm birth compared to residents >10 years (adjusted RR 1.46 (1.24-1.71) and 1.16 (1.11-1.23) respectively).

**Conclusions** In addition to higher risk for preterm birth (Polish, Yugoslavian, Iranian, South Asian, East Asian and Sub-Saharan-African), some immigrant groups are also at higher risk for postterm birth (North African and Middle Eastern, Somali, Ethiopian/Eritrean). Recent immigrants are at higher risk of non-term deliveries.

**Keywords** Immigrant, ethnicity, preterm birth, postterm birth, Sweden
Introduction

Preterm and postterm birth, ie births before 37 completed gestational weeks or after 41 completed gestational weeks respectively, are associated with both short and long term health risks to the infant\textsuperscript{1-3}. Preterm birth is one of the leading causes of neonatal mortality globally\textsuperscript{4} and is unequally distributed between ethnic and socioeconomic groups\textsuperscript{5-16}. Less is known on ethnic variation in risk for postterm birth. While there has been significant progress in care for premature infants, reducing its prevalence is more challenging and rates have even increased in some regions\textsuperscript{3, 8, 17}.

A previous study among immigrants and residents in Sweden found only slight differences in preterm birth rates between immigrants and Swedes\textsuperscript{18}. Since the time of this study, Sweden has become more diverse and multicultural with larger numbers of non-European immigrants. 23% of the population are either foreign-born or have both parents born abroad\textsuperscript{19}. Thus, there is greater potential for differences in non-term births between Swedish and immigrant mothers today but the extent of these differences is not known. This is especially so, as maternal health and birth outcomes tend to vary by both socioeconomic status and ethnic group in high income countries\textsuperscript{20-23}.

Using data from the Swedish Medical Birth Register, which includes all births in the country, we studied the risk for early preterm, late preterm, and postterm birth among immigrant parents compared to Swedish-born parents. We considered a number of covariates such as socioeconomic characteristics or duration of residence in order to investigate possible mechanisms. Differences if any, in preterm and postterm births between Swedish and immigrant parents that appear to be mediated by modifiable factors will provide opportunities for targeted interventions for those groups that experience higher rates of adverse perinatal outcomes. The overall aim is to help reduce ethnic-related disparities and inequities in maternal and child health.
Methods

Study population

We undertook a register-based population study of 1,130,427 mothers who gave birth to 2,044,208 live singleton births during 1982-2002, all resident in Sweden at time of birth and included in the Medical Birth Register (MBR). We chose 1982 onwards as information on cohabitation status and maternal smoking was collected from this year (considered as potential confounders) and it coincided with the introduction of ultrasound in gestational age estimation. The register holds detailed information on 98% of all births in the country and on maternal characteristics (pre- and post-pregnancy anthropometrics, previous births, parity, diagnoses of illness, smoking habits and gestational duration), mode of delivery, birth circumstances, and anthropometrics of the infant. We selected 1,028,303 mothers (with 1,766,026 infants), who constitute 86% of the eligible population with complete information on all covariates for the analysis. Using the unique personal identity number assigned to all residents in Sweden, we linked data from the Education and Total Population Registers.

Immigrants (i.e. those not born in Sweden) were identified by their country of birth (nativity) obtained from the Total Population Register. Only births to parents of the same nativity were considered to belong to a particular immigrant group. Births to parents born in different countries were classified into one of three following groups: i. Swedish born mothers and non-Swedish born fathers, ii. Swedish born fathers and non-Swedish born mothers and iii. Non-Swedish born mothers and non-Swedish born fathers of differing nativity. Given that Sweden has attracted a larger number of immigrants from certain specific countries, we first identified infants with both parents from countries with the largest immigrant populations, defined as having a minimum of N=3000. These included: Finland, Poland, Turkey, Iran, Iraq, Lebanon, Syria, Ethiopia and Eritrea, Somalia, and Chile. Based on geographical origin, the remaining infants not classified in any of the preceding ten countries were grouped into: Sweden, Western Europe and North America, Eastern Europe, Former Yugoslavia, Latin America, North Africa and Middle East (Arab league nations), South Asia, East Asia and Sub-Saharan-Africa. In total there were 21 categories of immigrant groups which included ten individual countries, nine regional groupings and three categories where parents originated from different countries. These were compared to the group with both parents born in Sweden (reference). This system of categorization of immigrant groups was used in all analyses.

Maternal education and cohabitation status (socioeconomic indicators), were accessed from the Education Register and MBR respectively. Maternal education (highest level achieved) was grouped as: primary education (<9 years), secondary education (12 years), post-secondary education of less than three years and post-secondary education of three years or longer. Mother’s cohabitation status was categorised as married/cohabiting and single. Duration of residence in
Sweden was calculated by subtracting the birth date of the infant from the date of first immigration of the mother (obtained from the Immigration Register) and was categorised as: <3 years, 3-10 years, ≥11 years.

Information on maternal age, weight and height, parity, gestational duration, smoking habits and hypertension in pregnancy were obtained from the MBR. Maternal age at delivery was categorised into <25, 25-29, 30-34, 35-39 and ≥40 years. Parity was classified as one, two and three or more deliveries. Weight and height used to calculate pre-pregnancy BMI (weight in kg divided by height in m²) were recorded at first antenatal check-up. Mothers were classified as underweight (<18.5kg/m²), normal (18.5-24.9kg/m²), overweight (25-29.9kg/m²), obese class I (30-34.9kg/m²) and obese classes II & III (≥35kg/m² - combined due to relatively small numbers) as per the WHO criteria. Gestational age at delivery was estimated by ultrasound (around 17th week of pregnancy). If ultrasound was not available, gestational age was defined as the time from last menstrual period (LMP) to birth. Ultrasound was chosen over LMP if there was a discrepancy between the two. Mothers were grouped into early preterm (<32 completed weeks of gestation), late preterm (32-36 weeks), term (37-41 weeks) and postterm (≥42 weeks) births25. Smoking habits were recorded at the time of registration at antenatal clinics and generally reflect smoking habits during the first trimester. Mothers were grouped into: 1. Non-smokers, 2. Smokers (<10 cigarettes/day) and 3. Smokers (≥10 cigarettes/day).

Mothers with hypertensive disorders that correspond to any of the following ICD codes as entered in the MBR were considered to have hypertension during pregnancy: ICD-8:401, 637, ICD-9:642 and ICD-10:O10-11, O13-16.

Patterns of missing data differed substantially between immigrant groups. While 12% of Swedish mothers had missing data on at least one variable, corresponding proportions of missing data were higher in Finnish (38%), Somali (36%), Latin American (28%) and highest in Western European (54%) mothers.

The study was approved by the Regional Ethics review board in Stockholm.

**Statistical analyses**

Associations between immigrant group and maternal characteristics were analyzed using univariable linear regression or Chi-square tests for differences of proportions for continuous and categorical variables respectively.

We assessed if prevalence of early and late preterm and postterm birth differed between the first and second half of the study-period, ie between 1982-1991 and 1992-2002 in three study samples: 1. Immigrants only, 2. Swedish-born parents only and 3. The entire study population.

We calculated relative risk (RR) of early and late preterm and postterm birth with term birth as baseline comparing infants of various immigrant groups to infants of Swedish-born parents using multivariable multinomial logistic
regression. The multinomial logistic regression model calculates the relative risk ratio, which is the ratio of two relative risks and is interpreted for a unit change in the predictor variable. It can be interpreted as the relative risk (RR). Five models were constructed as follows: Model one – minimally adjusted for infant’s sex & birth year, Model two – additionally adjusted for maternal age and parity, Model three – additionally adjusted for maternal education and cohabitation status, Model four – additionally adjusted for smoking and Model five – additionally adjusted for hypertension in pregnancy. We also ran a model additionally adjusted for maternal height in a smaller sample of 945,035 mothers (1,500,168 infants) adjusted for confounders as Model 5 above.

Lastly, we tested the effect of duration of residence in Sweden on the risk for early and late preterm birth and postterm birth in the sample of 221,245 immigrant parents adjusted for confounders as in Model 5 above.

Robust standard errors allowing for clustering of infants within families were used for all logistic regression models.

We conducted all statistical analyses using STATA 12 (College Station, Texas, USA).
Results

There were differences in prevalence of risk factors for preterm and postterm birth between Swedish and immigrant groups (Table 1). Swedish mothers were the tallest and along with Western European and North American, Eastern European, Polish, and East Asian mothers, had the highest proportions of normal BMI. The highest proportions of overweight and obesity were found in North African and Middle Eastern, Iraqi, Somali, and Sub-Saharan-African mothers (overweight ≥30% and obesity ≥8%). North African and Middle Eastern, Lebanese, Somali, Syrian, and East Asians had the highest proportions of lowest educated mothers while Western European and North American, Eastern European, Polish, and Iranian groups had the largest proportions of highly educated mothers (≥20%). Finnish mothers had highest proportion of smokers (19%) whereas North African and Middle Eastern, Iraqi, Somali, South Asian, East Asian, Ethiopian, and Sub-Saharan-African mothers had the lowest (≤3%).

Mean gestational age for the study sample was 278.8 days (39.4 weeks). While gestational age distributions appeared shifted to the left by 2-3 days in offspring of South Asian, East Asian and Sub-Saharan-African parents, it was shifted to the right by 2-3 days in Somali and Ethiopian groups in comparison to offspring of Swedish parents (Table 1 and Figure 2).

There were no differences in prevalence of early preterm and term birth in the entire study population, but proportion of postterm birth increased from 6.96% to 7.40% between 1982-1991 and 1992-2002. While overall risk of early and late preterm birth in immigrants reduced (from 0.81% to 0.70% and 4.89% to 4.18% respectively) between 1982-1991 and 1992-2002, we found an increase in postterm birth prevalence (6.67% to 7.00%). There were no differences in prevalence of early preterm birth in Swedish-born parents but risk for late preterm birth reduced from 4.54% to 4.11% and postterm birth increased from 7.02% to 7.50% between those two periods.

Immigrant differences in risk for early preterm, late preterm and postterm birth

Higher prevalence of early and late preterm birth combined was found in South Asians (7.1%), Sub-Saharan-Africans (6.2%), Polish (6%) and East Asians (5.8%). We found the highest prevalence of postterm birth in the Somali (16.3%), Ethiopian and Eritrean (13%), and North African and Middle Eastern (9.3%) groups (Table 1).

In model 1 (adjusted for sex and birth year), Polish, Yugoslavian, Iranian, and Sub-Saharan-Africans had higher risk of early preterm birth compared to Swedish-born parents (RR 1.76, (95% CI 1.25-2.50), 1.48, (1.24-1.76), 1.46, (1.14-1.87) and 1.81, (1.18-2.78), respectively) (Table 2). Couples of mixed nativity, i.e. Swedish-born mothers and non-Swedish-born fathers or parents from two different immigrant groups were at higher risk for early preterm birth (unadjusted RR 1.67 (95% CI 1.56-1.80) and 1.51 (1.32-1.73) respectively). Only the Chilean group had decreased risk
of early preterm birth (RR 0.55 (0.31-0.94). Adjustment for covariates only marginally changed RRs of early preterm birth in the above groups compared to Swedish-born mothers (Table 2).

South Asian-, Sub-Saharan-African-, and East Asian-born parents (latter not significant after adjustment for maternal socioeconomic indicators) had a higher risk of late preterm birth compared to Swedish-born parents (unadjusted RR 1.52 (1.33-1.73), 1.26 (1.03-1.53) and 1.16 (1.03-1.31)) (Table 2). Yugoslavian, Somali, and Syrian parents had decreased risk of late preterm birth.

North African and Middle Eastern, Somali and Ethiopian/Eritrean parents had increased RRs of postterm birth (unadjusted RR 1.27, (1.13-1.43), 2.34 (2.11-2.60), 1.83 (1.66-2.03)) compared to infants of Swedish-born parents (Table 2). Decreased RRs of postterm birth were found in Eastern European, Polish, Iraqi, Syrian, Iranian and Latin Americans. Lowest RR of postterm birth were observed in South Asian, East Asian, and Chilean (Table 2) parents. Adjustment for covariates did not appreciably change these associations. Figure 1 summarizes RR of preterm and postterm birth across different immigrant groups.

In the sensitivity analysis restricted to mothers with information on height, adjustment for height did not substantially change the previously observed RR for preterm and postterm birth by ethnicity (data not shown).

Immigrant mothers resident in Sweden for <3 years had increased risk of early preterm birth (adjusted RR 1.46 (1.24-1.71) compared to mothers resident for >10 years. Those resident <3 years and 3-10 years had increased risk of postterm birth as well (adjusted RR 1.16 (1.11-1.23) and 1.12 (1.07-1.17) respectively (Table S1).
Discussion

Main findings

In Sweden, larger immigrant groups are at higher risk of preterm, and/or postterm birth which is not explained by confounders controlled for. Some of this disadvantage in immigrants decreases with longer residence in Sweden. Mixed ethnicity – Swedish-born mothers and non-Swedish fathers, and parents from two differing foreign countries had increased risks of early preterm birth.

Overall risk for preterm birth was 5%, comparable with other high-income countries. Substantial research on ethnic differences in perinatal outcomes is from the USA, largely focusing on Black, Hispanic and white women. Previous studies showed Black women are at higher risk of preterm birth compared to non-Hispanic whites, even among college educated. We found lower risk of preterm birth among North African and Middle Eastern groups as in previous studies. Instead these mothers had an increased risk of postterm birth not previously reported. Contrary to a previous Swedish study, ours clearly shows excess risk of non-term birth in immigrant groups exist today. Few studies have specifically analyzed risk of adverse perinatal outcomes in mixed ethnicity couples and these studies are mostly restricted to comparison of white-Black mixed couples. Confirming previous findings, we found mixed ethnicity couples had higher risk of preterm birth.

Strengths and limitations

Our study was based on data of a well maintained high-quality nationwide population-based perinatal register which includes all births. Population-wide coverage offers a design with minimal selection bias. Mothers with missing data (N= 278,034) were on average 0.67 cm shorter, had 0.32 units lower BMI, and slightly higher proportions of both lowest and highest educated mothers and higher proportion of single mothers compared to mothers included in the analyses (N=1,766,026). Nonetheless data on infant sex, birth year, maternal age, gestational age and nativity had >98% coverage. Moreover, for each ethnic group, the proportions of preterm and postterm birth were very similar in the total eligible sample when compared with the study sample. Thus there was no underestimation or overestimation in preterm/postterm birth in ethnic groups in the study sample. Misclassification of exposure is minimised as data is collected routinely for official statistical purposes.

Differences in risk of preterm and postterm birth between Swedish-born and immigrant parents could be due to differences in lifestyle, genetics and/or other components of ethnicity not measured here. While self-identified ethnicity is considered to be the gold standard, country of birth is regarded as a good proxy when the former is unavailable. Unlike similar studies that often analyze differences in the largest ethnic/immigrant groups; we included all immigrant
groups, either as individual countries of origin if sufficient in size or by regional groups. To our knowledge this is one of the largest studies to analyze immigrant differences in perinatal outcomes by not only the size of the study population but also the large number of immigrant groups. Similar studies often only consider maternal ethnicity which makes interpretation difficult due to potentially different mechanisms that are thought to take place in mixed ethnicity couples (such as intermixing of different cultures and genetic effects). We avoided this by considering paternal origin which enables us to have more clearly defined immigrant/ethnic groups. Analyzing mixed ethnicity couples separately is another strength. These had, however, to be combined into larger groups due to their small numbers.

While inaccuracies in estimation of expected date of delivery and calculation of gestational age are inherently associated when calculated by LMP alone, it can be substantially reduced when supplemented with ultrasound information as in the Swedish MBR. For the period 1982-2002, ultrasound was used to estimate gestational age in 60% of all pregnancies. We cannot, however, exclude a possibility of differential misclassification of gestational duration, with higher degree of misclassification in immigrant groups. This might lead to overestimation of non-term births in those groups.

Evidence suggests gestational age varies by ethnicity, for e.g. Patel et al found the entire gestational age distribution is shifted to the left by one week in South Asians and Blacks and that fetuses of these groups probably matured faster as well\textsuperscript{30,31}. We observed similar shifts in gestational age distributions in East and South Asians, Somali and Ethiopian/Eritrean mothers, but these shifts were smaller (between 2 to 3 days). Evidence for such shifts in gestational age distribution is limited to few ethnicities, and it is possible we may have overestimated preterm births and underestimated postterm births in some ethnic groups. This will be problematic until the development of ethnic-specific guidelines for gestational age and what constitutes a ‘term infant’ in various ethnic groups.

Maternal height and body structure could potentially affect the risk of preterm and postterm birth as shorter or smaller-built mothers are likely to have constitutionally smaller fetuses\textsuperscript{32,33}. These maternal variables also vary by ethnicity – non-European mothers were shorter and in some groups showed higher mean BMI. We were unable to control for BMI as it was missing for a large proportion of mothers, but adjustment for height did not change the observed RR for preterm or postterm birth.

Interestingly, maternal education did not mediate the differences in risk of non-term birth in this study, although educational levels differed considerably across ethnic groups. Maternal education is considered a strong predictor for preterm birth (and the strongest predictor of various socioeconomic indicators)\textsuperscript{35,34}. Education was inversely associated with risk for preterm birth in univariate analysis comprising the entire study sample and in analyses stratified by ethnic group. The associations of education with preterm birth were however not statistically significant for most ethnic
groups. This might explain why adjusting for education in the main model (Table 2) did not change the ethnicity – preterm and postterm associations.

Interpretations

Studies mostly focus on two possible explanations for ethnic differences in preterm birth: socioeconomic and biological\(^{12}\). However later studies propose more complex explanations. Kramer in his review on 32 studies on Black/white differences in preterm birth suggests three possible intermediaries between ethnic disparities and preterm birth: stress (acute and chronic), preconceptional health and genetic/epigenetic differences (hypothesized to induce vascular dysfunction, inflammation and/or hypothalamic-pituitary-adrenal-axis (HPAX) dysfunction which lead to preterm birth)\(^{12}\).

Maternal stress has received attention especially in regard to the HPAX, important in both response to psychosocial stress and in regulation and timing of birth\(^{35}\). Differential levels in corticotropin-releasing hormone and cortisol biomarkers were reported in ethnic minorities with increased risk for preterm birth\(^{36, 37}\). Studies showed a direct association between stress (like racial discrimination, exposures to adverse life events, anxiety) and increased risk for preterm birth\(^{38, 39}\). Stress may occur before, or during pregnancy or could be a result of accumulation over the life time. Immigrant mothers may experience higher levels of stress due to segregation, institutionalized racism, lower income levels or in overcoming cultural and language barriers which contribute to increased risk for preterm birth. We found shorter duration of residence to be associated with increased risk of postterm birth in immigrant mothers.

Preconceptual health including prevalence of genital tract infections, hypertension and diabetes vary between ethnic groups and are linked to increased risk of preterm birth. Despite the differences in prevalence of hypertension between ethnic groups, controlling for the same did not change the observed RR. Access to and quality of health care services may influence risk for non-term birth. We were unable to control for the same but a previous Swedish study showed Somali and Ethiopian/Eritrean mothers were at higher risk for perinatal mortality due to higher prevalence of suboptimal factors related to health care (like miscommunication with health care providers, insufficient surveillance for suspected IUGR)\(^{40}\).

Genetic differences (within and between ethnic groups) could contribute to differences in risk of preterm birth. Studies have found genetic differences between ethnic groups in the underlying biological pathways that lead to preterm birth and genetic differences in maternal and fetal contributions to preterm birth\(^{41, 42}\).

Etiology of postterm birth is less clear. Risk factors include genetic predisposition, maternal obesity, higher maternal age, male fetal sex, fetal anencephaly, and previous postterm pregnancies\(^{43}\). Higher rates of obesity in Somali and
Northern African/Middle Eastern women could contribute towards their increased risk for postterm birth. Several risk factors for postterm birth like higher BMI, stress, and socio-cultural differences could interact together in increasing prolonged pregnancy in these groups. While the genetic differences in preterm birth are largely thought to be driven by the maternal genotype, evidence now shows that some differences in the risk for postterm birth might be explained by the paternal genotype. In general the findings between ethnicity and preterm birth were opposite to those between ethnicity and postterm birth. Ethnic groups may have developed evolutionarily different mechanisms in gestational duration and initiation of labour along with differences in fetal growth and maturation as they have been exposed to very different environments.

Somali mothers had the highest RR (2.58) for postterm birth. Earlier Swedish studies have shown an increased risk for adverse maternal outcomes including perinatal and pregnancy related mortality related to sub-optimal care in immigrants and particularly Somali mothers. Another study found that immigrant Somali women practiced different ‘survival’ childbirth strategies that involved reduced food intake, to diminish fetal growth thereby reducing the risk for a cesarean section and mortality. Such behavioral strategies were based on past experiences in Somalia where maternal mortality is high.

Conclusion

We show immigrant differences in early and late preterm and postterm birth. Immigrants resident in Sweden for <3 years need specific interventions that will help reduce their risk of early preterm and postterm birth. Whether the reasons for this are related to attendance to antenatal care or other ways amenable to intervention should be further studied to reduce perinatal risks and inequities.

Our study highlights the importance of studying unique immigrant groups as opposed to broader regional and ethnic groupings. We identified the most vulnerable immigrant groups, like the Sub-Saharan-African and South Asian groups at increased RR for both early and late preterm birth and parents of mixed ethnic origin who are at increased risk for early preterm birth.

As postterm birth is linked to both short-term and long-term consequences in the infant, it could be beneficial to specifically study reasons behind this outcome in Somali, Ethiopian/Eritrean and North African and Middle Eastern mothers not previously reported in Sweden. These immigrant groups should be made aware of potential adverse outcomes linked to postterm birth so they can make more informed choices when presented alternatives for delivery.
Disclosure of Interests

The authors report they have no disclosures of interest.

Acknowledgments

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Contribution to authorship

AK and IK conceived the original idea of the study and designed it together with SW. AK conducted the statistical analysis. AK, IK, SW, BE and PS participated in developing the strategy of analysis and interpretation of the results. AK drafted the manuscript and wrote the final version with input from IK, SW, BE and PS. AK, IK, SW, BE and PS approved the final version.

Details of ethics approval

This study was approved by the regional ethics committee of Karolinska Institutet, Stockholm, Sweden (Dnr 03-466).

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References

Table 1. Descriptive characteristics of 1,766,026 singleton offspring delivered in Sweden 1982 – 2002; by parents’ ethnic group.

<table>
<thead>
<tr>
<th>Immigrant group</th>
<th>Sweden</th>
<th>Western Europe and North America</th>
<th>Finland</th>
<th>Eastern Europe</th>
<th>Poland</th>
<th>Yugoslavia</th>
<th>North Africa and Middle East</th>
<th>Iraq</th>
<th>Lebanon</th>
<th>Somalia</th>
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<th>Turkey</th>
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<tbody>
<tr>
<td>Number of subjects</td>
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<td>4798</td>
<td>1224</td>
<td>3510</td>
<td>16966</td>
<td>3985</td>
<td>9285</td>
<td>6960</td>
<td>3593</td>
<td>3963</td>
<td>11462</td>
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<tr>
<td>Mother's age (years)</td>
<td>28.5</td>
<td>29.4</td>
<td>28.5</td>
<td>29.6</td>
<td>27.7</td>
<td>28.9</td>
<td>28.6</td>
<td>26.5</td>
<td>28.0</td>
<td>27.4</td>
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<tr>
<td>Mother's height (cm)</td>
<td>166.7</td>
<td>165.0</td>
<td>168.9</td>
<td>164.3</td>
<td>164.7</td>
<td>161.6</td>
<td>160.1</td>
<td>161.5</td>
<td>164.1</td>
<td>161.0</td>
<td>160.0</td>
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</tr>
<tr>
<td>Mother's pre-pregnancy BMI (kg/m²)</td>
<td>23.2</td>
<td>23.0</td>
<td>23.2</td>
<td>22.9</td>
<td>22.2</td>
<td>23.9</td>
<td>24.9</td>
<td>25.0</td>
<td>24.6</td>
<td>25.7</td>
<td>24.0</td>
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<tr>
<td>Underweight (%)</td>
<td>4.6</td>
<td>6.8</td>
<td>6.2</td>
<td>5.4</td>
<td>6.7</td>
<td>4.0</td>
<td>3.2</td>
<td>2.6</td>
<td>3.0</td>
<td>5.2</td>
<td>2.5</td>
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<td>Normal %</td>
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<td>70.0</td>
<td>67.8</td>
<td>72.3</td>
<td>77.5</td>
<td>64.2</td>
<td>53.0</td>
<td>52.7</td>
<td>57.6</td>
<td>41.3</td>
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<td>10.9</td>
<td>19.3</td>
<td>17.4</td>
<td>24.4</td>
<td>24.2</td>
<td>31.2</td>
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<td>38.0</td>
<td>32.9</td>
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<tr>
<td>Obese class I &amp; II %</td>
<td>4.6</td>
<td>4.7</td>
<td>5.3</td>
<td>4.2</td>
<td>2.0</td>
<td>6.2</td>
<td>9.6</td>
<td>8.6</td>
<td>8.6</td>
<td>14.1</td>
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<td>Obese class III %</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
<td>0.8</td>
<td>0.4</td>
<td>1.5</td>
<td>2.0</td>
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<td>2.7</td>
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<td>33.0</td>
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<td>44.1</td>
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<td>35.7</td>
<td>35.8</td>
<td>27.4</td>
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<td>31.2</td>
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<td>31.0</td>
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<td>11.4</td>
<td>30.8</td>
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<td>51.0</td>
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<td>50.3</td>
<td>52.8</td>
<td>35.4</td>
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<td>32.7</td>
<td>42.1</td>
<td>37.5</td>
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<tr>
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<td>17.0</td>
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<td>12.0</td>
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<td>31.4</td>
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<td>27.5</td>
<td>31.3</td>
<td>7.6</td>
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<td>Ethiopia &amp; Eritrea</td>
<td>East Asia</td>
<td>Latin America</td>
<td>Chile</td>
<td>Sub-Saharan Africa</td>
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<td>727 (17)</td>
<td>826 (19)</td>
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<td>359 (17)</td>
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<td>3959 (4.7)</td>
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<td>210 (4.9)</td>
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*Data available for only 1,262,302 mothers. ** Not applicable to Swedish-born mothers.
Table 2: Risk ratios (RR) for early preterm (<32 weeks), late preterm (32-36 weeks) and postterm (≥42 weeks) births in 1766026 singleton offspring of immigrant parents compared to Swedish-born parents. Sweden and term birth (37-41 weeks) are reference categories.

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<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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</table>

Model 1: adjusted for infant sex and birth year, Model 2: adjusted for model 1 + maternal age and parity, Model 3: adjusted for model 2 + maternal education and cohabitation status, Model 4: adjusted for model 3 + maternal smoking in pregnancy, Model 5: adjusted for model 4 + hypertension in pregnancy.
Figure 1. Risk ratios with corresponding 95% confidence intervals for early preterm, late preterm and postterm birth by ethnic groups in Sweden. Estimates are adjusted for infant sex, birth year, maternal age, parity, education, cohabitation status, smoking, and gestational hypertension. Term birth is a reference category.
Figure 2. Comparison of gestational age distribution (in days) for mothers of selected immigrant groups.

Legend for Figure 2:
- Sweden
- East Asia
- South Asia
- Sub-Saharan-Africa
- North Africa/Middle East
- Ethiopia/Eritrea
- Somalia
Table S1. Effect of duration of residence in Sweden on risk for early preterm birth (<32 weeks), late preterm (32-36 weeks) and postterm (≥42 weeks) births in 221,245 immigrant mothers who gave birth 1982-2002. Term birth (37-41 weeks) is the reference category.

<table>
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<th>Late preterm N=9,727</th>
<th>Postterm N=15,069</th>
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<td>Model 1</td>
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<td>&lt;3 years</td>
<td>1.23 (1.07-1.40)</td>
<td>1.46 (1.24-1.71)</td>
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<td>3-10 years</td>
<td>0.91 (0.80-1.03)</td>
<td>1.06 (0.93-1.22)</td>
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<td>&gt;10 years</td>
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<td>1</td>
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<td>Test for trend</td>
<td>P&lt;0.05</td>
<td>P&lt;0.001</td>
<td>P=0.53</td>
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Model 1: Adjusted for infant sex and birth year. Model 2: additionally adjusted for maternal age, parity, education, cohabitation status, smoking, hypertension in pregnancy, and ethnicity.
Ethnic differences in the associations of foetal growth rate with BMI and systolic blood pressure in young adulthood

Amal R. KHANOLKAR, MSc¹,², Sara WEDRÉN, MD PhD², George B. PLOUBIDIS, PhD³, Pär SPARÉN, PhD³, and Ilona KOUPIL, MD DSc¹

1. Centre for Health Equity Studies (CHESS), Stockholm University/Karolinska Institutet, Sweden
2. Institute of Environmental Medicine, Karolinska Institutet, Sweden, 3. Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, United Kingdom and 4. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden.

Short title: Ethnicity, foetal growth rate and blood pressure

Corresponding author: Amal R. Khanolkar,
Centre for Health Equity Studies (CHESS),
Stockholm University/Karolinska Institutet, Sweden
Ph: +46 (0)8 162584
amal.khanolkar@ki.se
Abstract

We analyzed ethnic differences in the association of i. foetal growth rate and ii. gestational age with systolic blood pressure.

Foetal growth rate was measured by birth weight standardized to gestational age (z-scores) and subjects were grouped into preterm, term and postterm births. Systolic blood pressure and body mass index measurements of 406,833 (born 1973-1990, mean age 18.2 years) were measured at military conscription examinations. Associations were analyzed using linear regression. Structural equation modeling was used to assess direct and indirect effects between foetal growth rate and systolic blood pressure stratified by ethnic-origin.

Non-Europeans had lower mean systolic blood pressure compared to ethnic Swedes (adjusted -3.75mmHg, 95%CI -4.18,-3.32). Foetal growth rate was inversely associated with systolic blood pressure in Swedish men (-0.13mmHg, 95%CI -0.16,-0.09 per SD increase in foetal growth rate) and was strengthened on adjustment for concurrent body mass index in both Swedes (-0.65,-0.70,-0.62) and Europeans (-0.42mmHg, -0.65,-0.20). Swedish and European men born postterm had decreased systolic blood pressure. Foetal growth rate and gestational age were not associated with systolic blood pressure in non-Europeans. The total effect of foetal growth rate on systolic blood pressure (sum of the direct and indirect – via – body mass index effects) was of relatively similar magnitude in Swedish and Europeans (-0.042mmHg, P<0.05 and -0.022mmHg, P<0.05 per SD increase in foetal growth rate respectively) but not observable in non-Europeans (-0.002mmHg, P>0.05).

Foetal growth rate and length of gestation is inversely associated with systolic blood pressure in Europeans but not in non-Europeans, suggesting that ethnicity potentially modifies these associations.

Keywords: Immigrant, Ethnicity, Systolic blood pressure, Foetal growth rate, gestational age.
Introduction

Hypertension is a risk factor for several potentially life threatening conditions (stroke, myocardial infarction, heart failure, peripheral arterial disease, and aneurysms)(1). There is sustained interest in the association of low birth weight with elevated blood pressure in childhood and adulthood as a possible explanation for increased prevalence of hypertension, which can be traced to the foetal origins hypothesis (2-6). Inverse statistical associations were demonstrated mostly between birth weight (but also other measures of foetal development) and subsequent blood pressure (BP), while other studies did not support this claim (7).

Studies have demonstrated strong ethnic differences in BP at different ages in multiethnic populations (8-14). Studies have investigated if the association between birth weight and later childhood and adulthood BP could be modified by ethnicity (14-20). Most of these studies, often based on smaller study samples, focus on differences between African-American and white populations where the ethnic differences in hypertension are larger. The aetiology of hypertension is complex, involving genetic components (both within and between population differences), lifestyle factors and intergenerational mechanisms that involve both pre- and post-natal factors affecting growth in-utero and in childhood (7, 21, 22).

Gestational age is also inversely associated with BP in offspring (4, 23-25). These studies are fewer in number and have not analyzed whether the gestational age – BP associations differs across ethnic groups.

There is considerable debate on the relevance and consequences of adjustment for concurrent body size in studying associations between birth weight and subsequent BP (9, 16, 26). A different approach in analyzing the birth weight and subsequent BP associations that does not mutually adjust for concurrent BMI could better help in understanding the importance of this association and if it interacts with ethnic-origin.

The aim of this study was to assess ethnic differences in systolic blood pressure (SBP) and in the associations of 1. foetal growth rate (FGR) and 2. gestational age with SBP. We used a generalized structural equation modeling framework to simultaneously analyze pathways previously shown to be independently linked to elevated BP and address the issue concerning adjustment for concurrent body mass index (BMI).
Methods

We undertook a study of men born 1973-1990 who attended Swedish military conscription medical examinations between 1990 and 2009, N=590,909. Through linkages with routine registers we obtained i) Information on birth weight, and gestational age from the Medical Birth Register, ii) Data on parental nativity from the Total Population Register and iii) Data on maternal education from the Education register.

The Military Conscription register includes information recorded at medical examinations. Conscription was mandatory by law for all Swedish male citizens until the year 2000. Only those with severe disabilities or chronic diseases were exempted. After 2000, the register only includes information on those conscripts accepted for military service and is thus more selective. 14% of men included in our study population attended the examination after 2000. Of 928,341 men born in Sweden 1973-1990, 12,554 died and 44,646 emigrated before the age of 23 years leaving 871,141 men eligible to attend conscript examinations. Of these, 590,909 men (participation rate of 67.8%) had data in the Military Conscription register.

Of the above 871,141 men eligible for conscript examinations, participation rates varied significantly by ethnic-origin, from 67% in Swedes, 57% in Europeans, 35% in non-Europeans to 61% in mixed ethnic-origin (latter group later excluded from analysis).

Height and weight recorded at these examinations were used to calculate BMI. BP was measured in the supine position after 5-10 minutes of rest. We were unable to use diastolic BP measurements due to heaping of values to the nearest 10mmHg. This was not a problem for systolic BP (SBP), which tended to be rounded-off to the nearest 2mmHg. Other variables recorded at the examination and used in analysis include age, and conscription office. Men were expected to attend the examination at the conscription office closest to their registered address. Controlling for conscription office accounts for difference in methods used for measuring SBP and anthropometry. The mean age of men at conscript examinations was 18.2 years with a range from 17 to 25 years.

Gestational age (in completed weeks) was estimated from first day of last menstrual period or by ultrasound where available. Men were grouped into preterm (<37 completed gestational weeks) term (37-41 completed gestational weeks) and postterm (>41 completed gestational weeks) birth. Birth weights (BW) in grams were converted into z scores representing BW standardized to gestational age in completed weeks (BW Z scores), calculated as BW minus mean BW divided by the SD, (using gestational age-specific BW means and SDs from the Swedish MBR in 1973-2002 as a standard). BW z scores were used as a measure of foetal growth rate (FGR).

Ethnic-origin of the conscripts was based on both parents’ nativities. Conscripts of parents not born in Sweden were considered to be of non-Swedish ethnic-origin whereas those of parents born in Sweden were considered to be of Swedish origin. Only conscripts with parents of the same nativity were considered to belong to a particular ethnic-origin group. Conscripts of mixed ethnic-origin, i.e. with parents born in two different countries were excluded from analysis. Conscripts were grouped into Swedish (reference group), European and non-European groups. Countries that comprised the three groupings are listed in Appendix Table 1.

Maternal education was used as an indicator of socioeconomic circumstances around time of birth and during childhood and was based on the highest level achieved and recorded in the register as grouped as follows: primary education (<9years), secondary education (12 years), post-secondary education (>12 years).

Of 590,909 men with conscript data, we excluded 10,138 men who were not born singletons, 108,997 who lacked valid SBP, 2109 who lacked BMI, 2714 who lacked FGR measurement, 11,861 who lacked data on maternal education, and 5154 who lacked valid age at conscription. We further excluded 126 men who lacked valid ethnic-origin and 42,977 men of mixed ethnic-origin which left 406,833 men (69%) to be included in the main analysis.

Statistical analyses
Associations between ethnic origin, birth characteristics and conscript characteristics (SBP, BMI, height) were analyzed using linear regression or Chi-square tests for differences of proportions for continuous and categorical variables respectively.

We used multivariable linear regression models to study the associations between (i) Ethnic-origin and SBP; (ii) FGR – SBP and gestational age – SBP stratified by ethnic-origin groups to assess if the strength of association between BW and SBP differed by ethnic-origin, and tested further with formal tests for interaction. All above regression models were run adjusted for age at conscription, birth year, and conscription office (model 1). The ethnic-origin – SBP models were additionally adjusted in subsequent models for concurrent BMI (model 2), concurrent height (model 3), maternal education (model 4), FGR (model 5) and gestational age (model 6). The FGR-SBP and gestational age-SBP models stratified by ethnicity were adjusted for conscription, birth year, and conscription office (model 1) and additionally for concurrent BMI and height, maternal education, and FGR/gestational age (model 2). All models stratified by ethnicity were tested for possible interactions with the same variable. We tested associations using FGR as a continuous variable and in tertiles in those models where it was the independent predictor. Models with gestational age as exposure of interest were run separately with the variable as continuous (in weeks) and categorical. Robust standard errors allowing for clustering of conscripts within families were used for all regression models.

Analyses were conducted using the statistical software package STATA 11 (College Station, Texas, USA).

We used path analysis to estimate linear associations between (i) FGR and SBP; (ii) FGR and concurrent BMI and (iii) concurrent BMI and SBP (Figure 1) using the statistical software package MPLUS (Muthén and Muthén). Path analysis is an extension of regression analysis, allowing the simultaneous modelling of several related regression relationships. A variable can be a dependent variable in one relationship and an independent variable in another. Path analysis can be considered as a special case of structural equation modelling (SEM), where the structural model but not the measurement model is specified. It is possible to assess both direct and indirect (and thus total) effects of one variable on another (27). Figure 1 shows the relationships between FGR, BMI, SBP and other covariates that formed the conceptual framework for analysis. Age at conscription, birth year, conscription office and maternal education were considered as confounders and controlled for. We stratified by ethnic-origin to assess if associations differed between the Swedish, European and non-European groups, thus three sets of parameter estimates are presented for the three ethnic groups. We undertook formal-model based-estimation of the indirect effect of FGR on SBP via BMI stratified by ethnic-origin group. This allowed us to formally estimate and quantify the indirect effect–via BMI on SBP. This would not be possible using standard multiple regression models because the latter estimates only the reciprocally adjusted effects of FGR and BMI therefore neglecting the indirect perspective. All reported model parameters are standardized to enable comparison. Models were fit using a full information maximum likelihood estimation which allows all subjects who have data for at least one of the variables in the path model to contribute to the analysis under the assumption of data being missing at random (MAR). Thus, the study sample included in path analysis was larger (N=466,583).

Ethical permission for the study was granted by the regional ethical committee in Stockholm, Sweden.
Results

Ethnic Swedish conscripts were the tallest (180.10cm) and non-Europeans the shortest (175.71cm), Table 1. Mean BMI was highest in non-Europeans (23.15kg/m²) and lowest in Swedes (22.37kg/m²). Non-Europeans also had the lowest mean birth weight. There was little variation in age at conscription by ethnic-origin. (Table 1).

Ethnic-origin differences in SBP

Conscripts of non-European origin had significantly lower mean SBP compared to conscripts of Swedish-origin (-3.75mmHg 95% CI (-4.18, -3.32)). Adjustment for covariates explained only a small part of the observed differences in mean SBP, with adjustment for concurrent height leading to greatest changes in the strength of those associations. Adjustment for maternal education did not affect the coefficients (Table 2). Differences in mean SBP between European and Swedish men were small (-0.27mmHg, (-0.49, -0.05) and statistically significant only after adjustment for concurrent BMI.

Ethnic-origin differences in the association between FGR and SBP

FGR was inversely and similarly associated with SBP in Swedish and European conscripts (-0.65 mmHg, -0.70 to -0.62 and -0.42 mmHg, -0.65 to -0.20 respectively after adjustment for all covariates). However, the association was not statistically significant in the non-European group (-0.31 mmHg, -0.78 to 0.16 after adjustment for all covariates). Test for interaction to assess if ethnic-origin modified the FGR-SBP association between Swedish, European and non-European men was statistically significant in both unadjusted (P<0.001) and adjusted models (P<0.05), Table 3.

Ethnic-origin differences in the association between gestational age and SBP

Gestational age was inversely associated with SBP in all three ethnic groups but the association was not statistically significant in non-Europeans. Adjustment for confounders slightly strengthened these associations (Table 3). In analysis stratified by ethnic group, we observed increased SBP in only Swedish conscripts born preterm (1.55mmHg, 1.38 to 1.72, after adjustment). There was no similar association in European and non-European conscripts born preterm (Table 3). Decreased SBP was observed in Swedish (-0.84mmHg, -0.94 to -0.72, after adjustment) and European conscripts (-0.93mmHg, -1.64 to -0.22 after adjustment) born postterm but not in non-Europeans (Table 3). Tests for interaction with ethnic-origin was statistically significant in both unadjusted and adjusted models (P<0.001 for both).

Structural equation modeling

FGR was inversely associated with SBP in all three ethnic groups (‘direct effect’ - Path C in Figure 1), but the association was statistically insignificant in non-Europeans. FGR was positively and similarly associated with concurrent BMI (Path A in Figure 1) in all three groups, (Swedish 0.09kg/m², (0.088-0.093), European 0.11kg/m², (0.095-0.125), and non-European 0.09kg/m², (0.060-0.124)). The association between concurrent BMI and SBP (Path B in Figure 1) was also similar in all three groups, but marginally stronger in non-Europeans (0.20mmHg vs. 0.16mmHg per SD change in BMI in non-European and Europeans respectively – Table 4).

Maternal education was inversely and weakly associated with conscript BMI in all three ethnic groups, with conscripts of mothers with highest education (post-secondary) having the lowest mean BMI. The association between maternal education and FGR was positive in the Swedish group with foetal growth rate increasing with higher levels of maternal education. We did not observe a similar effect in the European and non-European groups (Table 4).

Total indirect and direct effects

The total indirect effect of FGR on SBP via BMI (i.e. the product of the estimates of the two linear regressions of FGR on BMI and BMI on SBP – Path A*Path B in Figure 1) was similar and statistically significant in all three ethnic groups. For one SD increase in FGR, the effect of FGR on SBP that was mediated by BMI was equivalent to an increase of 0.015mmHg, 0.018mmHg and 0.018mmHg in the Swedish, European and non-European groups. However, the total
effect from FGR to SBP (Path A*Path B + Path C) while negative in the Swedish and Europeans, it was zero in Non-
Europeans (Table 4) 5).
Discussion

Our study shows that compared to ethnic Swedish men, non-European origin men born and living in Sweden had lower mean SBP at age 18. We also confirm previous results that FGR is inversely associated with adulthood SBP but this association is weak and strengthened on adjustment for concurrent BMI. Conscripts born preterm had increased SBP whereas those born postterm had decreased SBP. We found that associations between FGR and adulthood SBP; and gestational age and adulthood SBP while observable in European-origin men, is absent in men of non-European-origin. Lastly, it is evident that differences in SBP in young adult men by ethnic origin are unlikely to be explained by in-utero factors.

Comparison with similar studies

The association between impaired intrauterine growth (using markers such as birth weight, ponderal index, head circumference) and adulthood BP has been shown in several studies from different populations at different ages around the world. Similarly, other studies including a few using the Swedish conscript data used here (but with smaller study samples) also found increased blood pressure in subjects born preterm (11, 12, 16, 17). Our results are in concordance with most other similar studies in both direction and magnitude.

Despite apparent and strong ethnic differences in measures of both foetal growth and BP, relatively few studies have analyzed if the foetal growth – blood pressure association does in fact vary across ethnic groups. Mzayek et al using data (N=2,275) from the famous Bogalusa heart study reported that BW and adulthood BP associations did not differ between the white and African-American subjects, despite strong differences in mean BW, and proportions of low BP and premature subjects between the two ethnic groups (16). Hemachandra et al reported contradictory results and concluded that BW was positively associated with SBP in Black but not white children (N=29,710) (7).

Huxley et al in their meta-analysis of more than 50 studies concluded that the inverse association between BW and subsequent BW was largely a result of ‘random error’ and inappropriate adjustment for current body size, but they do not comment on potential differences across ethnic groups and the vast majority of the studies reviewed were conducted in high-income countries with largely Caucasian study populations (8). In a study including more than 5000 participants, Järvelin et al found little change in the coefficients for associations between BW and SBP at age 31 after adjustment for concurrent BMI. These coefficients were also three times as large as those found in studies of similar size. Authors concluded that their robust findings were due to careful design and appropriate adjustment for several prenatal and adult confounders (25).

There has been substantial discussion on the adjustment for current body size (usually measured by BMI) when analyzing BW and subsequent BW associations (8, 18, 26, 28, 29). As seen in our study, the FGR – SBP associations were seen in univariable analyses but became considerably strengthened after adjustment for concurrent BMI. This suggests that concurrent BMI is a negative confounder indicating that adjustment for the same would provide more correct estimates of the FGR coefficients. If concurrent BMI is instead a mediating variable in this association as suggested by some, then adjustment for the same would be inappropriate and would inflate the estimates. We choose to present linear regression models both unadjusted and adjusted for concurrent body size. In order to better address this statistical controversy we used path analysis to estimate the direct pathway between FGR and subsequent SBP and the indirect pathway via concurrent BMI. While the specific indirect – via BMI – effect was of similar magnitude in three ethnic groups, the total effect differed suggesting an interaction with ethnic-origin. This is in line with our results from multivariate linear regression models stratified by ethnic-origin, where the association between FGR and SBP though inverse in direction, it did not reach statistical significance in non-Europeans. Similar results were found for associations between gestational age and subsequent SBP.

Adjustment for height explained only a small part of the difference in mean SBP levels between European and non-Europeans (and height is a strong predictor of SBP). One could hypothesize that the difference could be due to factors we were unable to control for including differences in genetics, and lifestyle (primarily diet and physical activity). The interaction between ethnicity and FGR in predicting SBP could also be due to unmeasured confounding (both hereditary and prenatal/postnatal factors such as ethnic differences in catch-up growth). Factors such as maternal
smoking and diet are known to strongly influence foetal growth and differ between ethnic groups. We were unable to investigate long term consequences of these behaviors or control for these characteristics in our analysis. Maternal SEP strongly predicts foetal growth and to a lesser extent offspring BMI and indirectly SBP (most probably via offspring BMI), but controlling for maternal education, a robust socioeconomic indicator did not significantly change the associations studied. We did not control for subjects’ current socioeconomic indicators. Given their young age, it is unlikely that these men would have independent sources of income or as yet attained their highest educational level.

Differences in the FGR – SBP associations between Europeans and non-Europeans could also be due to ethnic differences in the physiology of foetal programming. As the underlying mechanisms are not well understood in humans (most theories rely on nutritional programming and epigenetics as potential causes of impaired foetal growth and later disease), it is difficult to explain the ethnic differences observed in terms of physiological differences (30). Both BW and gestational age are most likely proxies for ‘real’ intrauterine exposures such as maternal undernutrition and metabolic health. Stern et al suggest that random environmental factors (non-familial or the non-genetic environmental component) may contribute to both low BW and impaired foetal growth as well metabolic syndrome in adult life (31). While these theories are quite plausible in explaining the FGR and adult SBP associations, less is known about potential differences in such mechanisms between ethnic groups.

We ascertained both BW and gestational age from the medical birth register, a reliable and accurate source of birth measurements (32). However, we are aware that degree of misclassification e.g. gestational age may be greater among non-Swedish groups and if that is a case, this may contribute to our inability to demonstrate associations in these groups. Other variables were also obtained from routine registers eliminating reporting bias. Ours is one of the largest independent studies to analyze the associations investigated here. We were unable to investigate potential ethnic differences in FGR-SBP associations in women as only very limited and selective conscription data is available for them. We were unable to analyze associations with diastolic BP also shown to be associated with FGR. Nonetheless, SBP is known to be a more clinically significant and reliably measured risk factor for CVD than diastolic BP (33). Measuring SBP in the supine position as it was done here may have resulted in lower mean BP compared to measurement with subjects in a seated position, but this should not affect our results. As conscription is mandatory for Swedish citizens only, we possibly lost those men resident in the country but holding foreign nationalities. We found that participation rates in conscription examinations were substantially lower in non-Swedish ethnic men and are aware that results for this particular group may be biased. Furthermore, we acknowledge that both European and non-European groups are heterogeneous and a more detailed examination of FGR-SBP associations are needed using a more detailed categorization of ethnicity. We were unable to do this due to small numbers in these groups.

Perspectives

Our study, the largest to date to investigate associations of FGR and gestational duration with subsequent SBP in different ethnic groups, adds support to the concept that the foetal environment is a determinant of future SBP patterns. Though the strength of these associations is generally small, the systematic differences between ethnic groups may help to better understand the developmental trajectories of hypertension in adulthood. This is important as studies show an increase in the strength of BW-SBP association with increasing age (34). Whether foetal programming of endocrine and metabolic pathways occurs in humans, as shown in animals models and if such mechanisms differ between ethnic groups will have to be investigated.
Sources of funding

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Conflicts of Interest – “None”
References


29. Tu YK, Gilthorpe MS, Ellison GTH. What is the effect of adjusting for more than one measure of current body size on the relation between birthweight and blood pressure? *J Hum Hypertens* 2006;20(9):646-57.


Table 1. Characteristics of 406,833 Swedish military conscripts by parental nativity (ethnic-origin group). Values are means (SD) or percentages (%).

<table>
<thead>
<tr>
<th>Ethnic-origin</th>
<th>Swedish N=394,050</th>
<th>European N=10,287</th>
<th>Non-European N=2,496</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>18.18 (0.42)</td>
<td>18.53 (0.91)</td>
<td>18.47 (0.93)</td>
</tr>
<tr>
<td>Birth year</td>
<td></td>
<td>1978</td>
<td>1980</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>180.10 (6.47)</td>
<td>178.43 (6.62)</td>
<td>175.71 (6.31)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.37 (3.10)</td>
<td>23.05 (3.44)</td>
<td>23.15 (3.22)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3595.13 (532.68)</td>
<td>3556.17 (536.35)</td>
<td>3458.80 (487.44)</td>
</tr>
<tr>
<td>Birth weight Z scores</td>
<td>-0.03 (0.99)</td>
<td>-0.04 (0.99)</td>
<td>-0.23 (0.97)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.07 (11.06)</td>
<td>129.24 (11.14)</td>
<td>126.62 (11.25)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>17,037 (4)</td>
<td>562 (5)</td>
<td>122 (5)</td>
</tr>
<tr>
<td>Term</td>
<td>331,848 (84)</td>
<td>8,697 (85)</td>
<td>2,177 (87)</td>
</tr>
<tr>
<td>Postterm</td>
<td>45,165 (12)</td>
<td>1,028 (10)</td>
<td>197 (8)</td>
</tr>
<tr>
<td>Maternal Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>68,103 (17)</td>
<td>4,319 (42)</td>
<td>1,229 (49)</td>
</tr>
<tr>
<td>Secondary</td>
<td>194,445 (49)</td>
<td>4,489 (44)</td>
<td>865 (35)</td>
</tr>
<tr>
<td>Post-secondary</td>
<td>131,502 (34)</td>
<td>1,479 (14)</td>
<td>402 (16)</td>
</tr>
</tbody>
</table>
Table 2. Multivariate linear regression analyses of the effect of ethnic-origin on systolic blood pressure in 406,833 Swedish military conscripts.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
<th>Model 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>95% CI</td>
<td>estimate</td>
<td>95% CI</td>
<td>estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Swedish</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>European</td>
<td>0.18</td>
<td>-0.40, 0.04</td>
<td>0.55</td>
<td>-0.77, 0.34</td>
<td>0.33</td>
<td>-0.55, -0.12</td>
</tr>
<tr>
<td>Test for heterogeneity</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3. Multivariate linear regression analyses of the effect of i. foetal growth rate (birth weight z scores standardized to gestational age) on systolic blood pressure in and ii. Gestational age on systolic blood pressure in 406,833 Swedish military conscripts stratified by ethnic group.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Foetal growth rate</th>
<th>Gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td></td>
<td>Estimate (mmHg)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Swedish</td>
<td></td>
<td>Per 1 std dev.</td>
</tr>
<tr>
<td></td>
<td>-0.14</td>
<td>-0.18,0.11</td>
</tr>
<tr>
<td>Tertiles 1st</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2nd</td>
<td>-0.12</td>
<td>-0.20,0.03</td>
</tr>
<tr>
<td>3rd</td>
<td>-0.30</td>
<td>-0.38,0.21</td>
</tr>
<tr>
<td>Test for trend</td>
<td>P&lt;0.001</td>
<td>P=0.001</td>
</tr>
<tr>
<td>European</td>
<td></td>
<td>Per 1 std dev.</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>-0.05,0.38</td>
</tr>
<tr>
<td>Tertiles 1st</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2nd</td>
<td>0.51</td>
<td>-0.01,1.03</td>
</tr>
<tr>
<td>3rd</td>
<td>0.42</td>
<td>-0.09,0.93</td>
</tr>
<tr>
<td>Test for trend</td>
<td>P&gt;0.05</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Non-European</td>
<td></td>
<td>Per 1 std dev.</td>
</tr>
<tr>
<td></td>
<td>0.20</td>
<td>-0.24,0.65</td>
</tr>
<tr>
<td>Tertiles 1st</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2nd</td>
<td>0.07</td>
<td>-0.94,1.10</td>
</tr>
<tr>
<td>3rd</td>
<td>0.32</td>
<td>-0.75,1.40</td>
</tr>
<tr>
<td>Test for trend</td>
<td>P&gt;0.05</td>
<td>P=0.05</td>
</tr>
<tr>
<td></td>
<td>Test for ethnicity interaction</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Model 1: adjusted for adjusted for age, birth year, and conscript office, Model 2: adjusted for model 1 + current BMI, height, maternal education and foetal growth rate/gestational age.
Table 4. Results of path analysis in investigating ethnic differences in the association between foetal growth rate and systolic blood pressure in adulthood (estimates and 95% CI’s for 467225 military conscripts included in the study).

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Reference group</th>
<th>Ethnic group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Swedish</td>
<td>Europeans</td>
<td>Non-Europeans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=450,720</td>
<td>N=12,748</td>
<td>N=3,115</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
<td>95% CI</td>
<td>Estimate</td>
</tr>
<tr>
<td><strong>SBP on</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Continuous, kg/m²</td>
<td>0.164 (0.161, 0.166)</td>
<td>0.164 (0.148, 0.180)</td>
<td>0.207 (0.174, 0.241)</td>
<td></td>
</tr>
<tr>
<td>FGR*</td>
<td>Continuous, std dev.</td>
<td>-0.057 (-0.059, -0.054)</td>
<td>-0.040 (-0.056, -0.024)</td>
<td>-0.018 (-0.054, 0.019)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Continuous, years</td>
<td>0.012 (0.010, 0.014)</td>
<td>0.023 (0.007, 0.039)</td>
<td>-0.010 (-0.043, 0.023)</td>
<td></td>
</tr>
<tr>
<td>Birth year</td>
<td>Continuous, years</td>
<td>0.059 (0.056, 0.061)</td>
<td>0.051 (0.035, 0.066)</td>
<td>0.107 (0.074, 0.140)</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>Continuous, cm</td>
<td>0.096 (0.093, 0.098)</td>
<td>0.113 (0.097, 0.128)</td>
<td>0.078 (0.042, 0.114)</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td>primary education</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td></td>
<td>0.001 (-0.004, 0.003)</td>
<td>0.002 (-0.015, 0.018)</td>
<td>0.028 (-0.006, 0.062)</td>
<td></td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>0.003 (0.00, 0.007)</td>
<td>-0.002 (-0.018, 0.015)</td>
<td>0.011 (-0.026, 0.047)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conscript office</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.117 (-0.120, -0.114)</td>
<td>-0.068 (-0.086, -0.046)</td>
<td>-0.232 (-0.277, -0.178)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.077 (0.074, 0.080)</td>
<td>0.150 (0.129, 0.174)</td>
<td>-0.080 (-0.134, -0.026)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>-0.114 (-0.118, -0.111)</td>
<td>-0.018 (-0.038, 0.001)</td>
<td>-0.172 (-0.217, -0.127)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI on</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGR*</td>
<td>Continuous, std dev.</td>
<td>0.090 (0.088, 0.093)</td>
<td>0.110 (0.095, 0.125)</td>
<td>0.090 (0.060, 0.124)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Continuous, years</td>
<td>0.033 (0.030, 0.035)</td>
<td>0.109 (0.092, 0.126)</td>
<td>0.155 (0.119, 0.191)</td>
<td></td>
</tr>
<tr>
<td>Birth year</td>
<td>Continuous, years</td>
<td>0.074 (0.072, 0.076)</td>
<td>0.052 (0.038, 0.067)</td>
<td>0.090 (0.062, 0.119)</td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td>primary education</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td></td>
<td>-0.028 (-0.032, -0.024)</td>
<td>-0.051 (-0.067, -0.035)</td>
<td>-0.002 (-0.033, 0.028)</td>
<td></td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>-0.083 (-0.087, -0.079)</td>
<td>-0.062 (-0.077, -0.046)</td>
<td>-0.051 (-0.080, -0.021)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conscript office</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-0.003 (-0.006, 0.000)</td>
<td>-0.016 (-0.035, 0.002)</td>
<td>0.007 (-0.039, 0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.020 (-0.023, -0.017)</td>
<td>-0.042 (-0.061, -0.022)</td>
<td>0.009 (-0.042, 0.060)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.028 (0.025, 0.032)</td>
<td>-0.002 (-0.021, 0.017)</td>
<td>0.008 (-0.034, 0.049)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>FGR</em> on</em>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td>primary education</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Secondary education</td>
<td></td>
<td>0.025 (0.021, 0.028)</td>
<td>-0.007 (-0.023, 0.009)</td>
<td>-0.041 (-0.071, -0.011)</td>
<td></td>
</tr>
<tr>
<td>Post-secondary education</td>
<td>0.038 (0.034, 0.041)</td>
<td>-0.029 (-0.044, -0.013)</td>
<td>-0.055 (-0.086, -0.023)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>Continuous, years</td>
<td>0.098 (0.095, 0.100)</td>
<td>0.123 (0.109, 0.138)</td>
<td>0.163 (0.133, 0.193)</td>
<td></td>
</tr>
<tr>
<td><strong>Total effect from FGR to SBP</strong></td>
<td>-0.042 (-0.044, -0.039)</td>
<td>-0.022 (-0.039, -0.006)</td>
<td>0.001 (-0.036, 0.037)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Specific indirect effect from FGR to SBP via BMI

|  | 0.015 (0.014, 0.016) | 0.018 (0.015, 0.021) | 0.018 (0.012, 0.025) |

*Birth weight Z scores standardized to gestational age. Text in bold indicates statistical significance at p<0.05.*
Figure 1. Conceptual path diagram used in the analysis with standardized parameters showing adjustment for potential confounders.

The 3 parameters for each arrow (in bold) presented refer to the 3 groups of the stratifying variable ethnicity in the order: Swedish, European and non-European. Structural paths with systolic blood pressure as dependent variable are adjusted for conscript age, birth year, concurrent height, conscript office and maternal education. Structural paths with BMI as dependent variable are adjusted for conscript age, birth year, conscription office and maternal education. All coefficients represented are from linear structural equation modelling.

*Indicates significance $P < 0.05$ level.

For simplicity the figure does not show estimates for adjusted confounders, instead estimates for all covariates are listed in Table 4.
Appendix 1.  

<table>
<thead>
<tr>
<th>Ethnic groups defined by both parent's country of birth/nativity</th>
<th>Grouping used the analysis</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Sweden</td>
<td>Swedish</td>
<td>394,050</td>
<td>96.86</td>
<td>394,050</td>
<td>96.86</td>
</tr>
<tr>
<td>2 Western Europe &amp; North America</td>
<td></td>
<td>1,170</td>
<td>0.30</td>
<td>1,170</td>
<td>0.30</td>
</tr>
<tr>
<td>3 Finland</td>
<td></td>
<td>5,396</td>
<td>1.30</td>
<td>5,396</td>
<td>1.30</td>
</tr>
<tr>
<td>4 Eastern Europe</td>
<td></td>
<td>574</td>
<td>0.14</td>
<td>574</td>
<td>0.14</td>
</tr>
<tr>
<td>5 Poland</td>
<td></td>
<td>521</td>
<td>0.13</td>
<td>521</td>
<td>0.13</td>
</tr>
<tr>
<td>6 Former Yugoslavia</td>
<td></td>
<td>2,626</td>
<td>0.65</td>
<td>2,626</td>
<td>0.65</td>
</tr>
<tr>
<td>7 Latin America</td>
<td></td>
<td>138</td>
<td>0.03</td>
<td>138</td>
<td>0.03</td>
</tr>
<tr>
<td>8 Chile</td>
<td></td>
<td>214</td>
<td>0.05</td>
<td>214</td>
<td>0.05</td>
</tr>
<tr>
<td>9 Arab League</td>
<td></td>
<td>584</td>
<td>0.14</td>
<td>584</td>
<td>0.14</td>
</tr>
<tr>
<td>10 Turkey</td>
<td></td>
<td>1,060</td>
<td>0.26</td>
<td>1,060</td>
<td>0.26</td>
</tr>
<tr>
<td>11 Iran</td>
<td></td>
<td>113</td>
<td>0.03</td>
<td>113</td>
<td>0.03</td>
</tr>
<tr>
<td>12 South Asia</td>
<td></td>
<td>117</td>
<td>0.04</td>
<td>117</td>
<td>0.04</td>
</tr>
<tr>
<td>13 East Asia</td>
<td></td>
<td>210</td>
<td>0.05</td>
<td>210</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>406,833</td>
<td>100</td>
<td>406,833</td>
<td>100</td>
</tr>
</tbody>
</table>
Abstracts of the five papers in Swedish
I. Sociala bestämningsfaktorer för biomarkörer vid kardiovaskulära sjukdomar: undersökning av en kohort av svenska män i åldrarna 50 samt 70 år.

**Bakgrund:** Social status är associerat med prevalens och incidens av kardiovaskulära sjukdomstillstånd.

**Syfte:** Att undersöka sambandet mellan socioekonomisk position (SEP) och vanliga biomarkörer inklusive adiponektin, vid kardiovaskulära sjukdomar som inte tidigare undersömts i en svensk befolkning, och att avgöra om dessa associationer förändras med ålder.

**Design:** Populationsbaserad longitudinell kohortstudie av män födda 1920-1924 med kliniska mätningar, blodprover, frågeformulärdatal och information från registerdata om SEP och dödsorsak.


**Slutsats:** Associationer mellan SEP och kolesterolnivå samt LDL/HDL-kvot vilka existerar vid 50åå syns inte längre hos samma grupp vid 70åå. Vi fann ingen signifikant association mellan SEP och adiponektinnivåer vid 70åå.
II. Föräldrars inflytande på kardiovaskulära riskfaktorer hos svenska barn i åldrarna 5-14 år.

**Bakgrund:** Faktorer relaterade till kardiovaskulära sjukdomar uppkommer i barndomen. Vi studerade sambanden mellan kardiovaskulära riskfaktorer hos barn och föräldrarnas socioekonomiska position (SEP) samt livsstil, och hur dessa kardiovaskulära riskfaktorer korrelerar inom familjer.

**Metod:** Vi studerade 602 familjer bestående av två helsyskon mellan 5-14 år och deras biologiska föräldrar ("Uppsala Family study"), totalt 2141 individer. Information om föräldrarnas SEP (sysselsättningsgrad och utbildning) och livsstilsvanor (rökning, fysisk aktivitet (FA), alkoholkonsumtion) erhölls från frågeformulär. Associationer mellan kolesterol, ApoB/ApoA1, leptin, adiponektin, blodtryck samt BMI och övervikt/fetma analyserades med linjär/logistisk regression. Resultatet kontrollerades för barnens ålder, kön, pubertalt stadium och familjestruktur.

**Resultat:** Inga konsekventa samband mellan föräldrarnas SEP och barnens kardiovaskulära riskfaktorer har observerats. Föräldrarnas livsstil hade starkare effekt, oberoende av SEP. Barn till fäder som röker hade högre BMI (4%, 95% CI 1-7%) samt leptinnivåer (27%, 95% CI 1.00-61.60%). Barn till mödrar som rapporterar hög FA-nivå hade lägre BMI, kolesterol och minskat odds för övervikt/fetma med eventuell dosberoende effekt. Jämfört med mödrar som inte rapporterar hög FA-nivå, hade mödrar med ≤75 min och 76-150 min/vecka av hög FA-nivå 43% (OR 0.57, 95% CI 0.22-0.89) respektive 72% (OR 0.28, 95% CI 0.14-0.6) lägre risk att ha ett överviktigt barn, efter kontroll för confounders. Oberoende, konsekvent starkare och signifikanta samband kunde hittas mellan alla föräldrars och barns kardiovaskulära riskfaktorer.

**Slutsats:** Föräldrars beteende: rökning, alkoholkonsumtion, låg fysisk aktivitetsnivå är associerade med högre nivåer av kardiovaskulära riskfaktorer (BMI, övervikt/fetma, kolesterol) hos barn. Starka korrelationer av kardiovaskulära riskfaktorer inom familjer, vilka inte är relatade till föräldrarnas SEP/livsstil indikerar att genetiken kan påverka kardiovaskulära riskfaktorer hos barn. Folkhälsopolicy bör riktas mot familjer med ohälsosam livsstil.
III. Socioekonomiska- samt barndomsfaktorer och risk för övervikt/fetma hos barn till svensk- och utrikesfödda föräldrar.

**Bakgrund:** Det finns differentiella hälsoskillnader mellan etniska minoriteter/invandrare och inrikes födda. Övervikts- samt fetmaepidemin hos barn i Sverige håller på att plana ut, men lägre socioekonomiska grupper och invandrare/etniska minoriteter tar eventuellt inte del av denna trend till lika utsträckning. Vi undersökte om icke-etniska svenska barn löper ökad risk för övervikt/fetma och om dessa associationer går via föräldrarnas socioekonomiska position (SEP) och/eller barndomsfaktorer som t.ex. födelsevikt, rökning hos modern, BMI, samt amning.


**Resultat:** Barn av Nordafrikansk, Iransk, Sydamerikansk och Turkisk etnicitet hade ökat odds för övervikt/fetma jämfört med barn av svensk etnicitet (justerad oddskvot: 2.60 (95% konfidensintervall: 1.57-4.27) respektive 1.67 (1.03-2.72), 3.00 (1.86-4.80), samt 2.90 (1.73-4.88)). Finska barn hade minskat odds för övervikt/fetma (justerad oddskvot: 0.53 (0.32-0.90)).

**Slutsats:** Etniska skillnader i barns risk för övervikt/fetma, vilka inte kan förklaras av SEP eller faktorer relaterade till modern eller födseln, existerar i Sverige. Eftersom övervikt/fetma ofta fortsätter in i vuxenlivet behövs effektivare folkhälsopolicyer, som sätts in vid tidig ålder.
IV. Prematura födsla och överburna graviditeter hos invandrade och svenskfödda föräldrar: ennationell registerbaserad populationsstudie.

Syfte Att undersöka skillnader i risken för förlössning utanför normal fullgången tid mellan svenskfödda och invandrade föräldrar.

Studiedesign Registerbaserad-populationsstudie.

Sammanghang Sverige.


Metoder Invandrade föräldrar klassificerades enligt födelseland. Multinomial logistisk regression användes och analyserna justerades för födelseår, kön, moderns ålder, antalet födelselver, utbildning, civilstånd, rökning, och graviditetshypertoni.

Utfall Tidiga prematura, sena prematura och överburna födsla.

Resultat Polska, jugoslaviska, iranska, sydasiatiska, östasiatiska, afrikanska, och föräldrar där modern och fadern kom från olika invandrargrupper eller där endast fadern var invandrad hade högre risk för tidig prematur födsel (justerad relativ risk (RR), (95 % konfidensintervall, (KI)) 1,76, (1,24–2,50), 1,57, (1,31–1,87), 1,67, (1,30 – 2,14), 1,52, (1,07–2,16), 1,51, (1,08–2,10), 2,03, (1,32–3,12), 1,55 (1,35–1,77) och 1,56 (1,45–1,67) för respektive grupp)). Föräldrar från södra Asien, Afrika samt östra Asien hade en högre risk för sen prematur förlössning. Föräldrar från Nordafrika, Mellanöstern, Somalia och Etiopien/Eritrea hade en ökad risk för en överburna graviditet (justerad RR 1,31, (1,16–1,47), 2,57 (2,31–2,86) respektive 1,85 (1,67–2,04)). Justering för möjliga förväxlingsfaktorer påverkade inte associationerna nämnvärt. Invandrade föräldrar bosatta i Sverige < 3 år hade en högre risk för tidig prematur och överburnen graviditet jämfört med invandrarer bosatta > 10 år i Sverige (justerat RR 1,46 (1,24–1,71) respektive 1,16 (1,11–1,23)).

V. Etniska skillnader i associationerna mellan fetal tillväxttakt och BMI samt systoliskt blodtryck i ung vuxen ålder

Vi analyserade etniska skillnader i associationen mellan i. fetal tillväxttakt samt ii. gestationsålder och systoliskt blodtryck.


Icke-europeiska män hade ett lägre genomsnittligt systoliskt blodtryck jämfört med etniska svensk (justerat -3.75mmHg, 95 % CI -4,18, -3,32), medan det inte fanns några skillnader mellan europeiska och svenska män. FGR hade en omvänt association på systoliskt blodtryck hos svenska män (-0.13 mmHg, 95 % CI -0.16, -0.09 per SD ökning FGR) vilket även stärktes efter justerandet för BMI på både svenska (-0.65, -0.70, -0.62) och europeiska män (-0.42mmHG, -0.65, -0.20). Svenska och europeiska män med överburen födsel hade lägre systoliskt blodtryck. Varken FGR eller gestationsålder var associerade med systoliskt blodtryck hos icke-europeer. Den summanlagda effekten av FGR på systoliskt blodtryck (summan av de direkta och indirekta - via – effekten av BMI) hade en relativt likartad påverkan på svenskar och européer (-0.042mmHG, P < 0,05 respektive -0.022mmHg, P < 0,05, per SD ökning i FGR) men observeras inte hos icke-européer (- 0.002mmHg, P > 0,05).

Fetal tillväxttakt och längden på graviditeten har ett omvänt men svagt samband med systoliskt blodtryck hos européer men inte hos icke-européer, vilket tyder på att etnicitet möjligen har en inverkan på dessa associationer.