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**POPULATION-BASED STUDIES OF BODY MASS
INDEX, OVERWEIGHT AND SYSTOLIC BLOOD
PRESSURE AMONG SWEDISH YOUNG MEN**

by

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*Att våga är att förlora förfästet en liten stund.
Att inte våga är att förlora sig själv.*

Sören Kierkegaard

ABSTRACT

Overweight and obesity has increased in Sweden and worldwide in recent decades. Lifestyle and environmental changes, genetic susceptibility and interactions between these factors are believed to be important. A theoretical framework often referred to, as the fetal origins hypothesis has been extensively debated over the last 15 years. According to this controversial hypothesis, overweight and other components of the metabolic syndrome – such as high blood pressure – might be long-term consequences of impaired fetal growth.

The overall objectives of the studies were to investigate the epidemiology of body mass index and overweight among young men in Sweden and to explore relationships between growth in fetal life on the one hand and overweight and systolic blood pressure in young adulthood on the other. Specific aims were to: 1) study time trends and socio-economic differences in body mass index and overweight among young men over the last decades; 2) study the occurrence of overweight among male international adoptees; and, 3) test the fetal origins hypothesis by analyzing relationships between aspects of fetal growth and overweight, and also between fetal growth and systolic blood pressure among singletons and twins in young adulthood.

This thesis is based on nationwide data sets created by record linkages between the Medical Birth Register, the Military Service Conscription Register and several other national registers. The twin studies include additional information collected by a mailed questionnaire.

The prevalence of overweight among 18-year-old men increased two-fold over a 25-year period. The results show large socio-economic differentials in overweight, with higher prevalence among young men from low-educated families. Socio-economic differentials did not change over time. The prevalence of overweight was 2-3 times higher among young men adopted from Latin America in early childhood than among non-adopted individuals of the same ages. By contrast, the risk of overweight was not higher among adoptees from the Indian subcontinent or the Far East than among non-adopted individuals.

The results show a positive relationship between gestational-age-adjusted birthweight and overweight at 18 years of age among singletons. Clearly, this finding does not support the fetal origins hypothesis. However, the hypothesis was further tested in a population-based twin study. A weak positive association was uncovered for the within-pair effects of birthweight on body mass index at the age of 18 among monozygotic twin pairs. The twin brother with the highest birthweight had a slightly higher risk of overweight at age 18 than his co-twin. No between-pairs effect of birthweight on body mass index was observed for monozygotic pairs of twins. And no relationships were observed among dizygotic twin pairs. Neither of these findings supports the fetal origins hypothesis.

When studying fetal growth and systolic blood pressure among singletons, a clear inverse association was found between gestational-age-adjusted birthweight and systolic blood pressure at 18 years of age. That there was an independent inverse association between gestational age per se and systolic blood pressure is a novel finding. For monozygotic twins the results show an inverse between-pairs effect of birthweight on systolic blood pressure at age 18. There was an inverse within-pair effect of birthweight on systolic blood pressure among monozygotic twins, although the effect was not significant. No relationships were found among dizygotic twins. Although the results of the singleton study are in accordance with the fetal origins hypothesis, the twin study does not provide substantial support.

In sum, the results show a strong increase in overweight over the last decades among young men, and also demonstrate large socio-economic differentials in overweight. Large and unexplained differences in overweight among international adoptees compared with non-adopted young men were found. The studies addressing the fetal origins hypothesis showed mixed results with clear support for an inverse association between birthweight and blood pressure in the singleton study, weak support in the twin study, and no clear-cut support in either of the two other studies.

LIST OF PUBLICATIONS

This thesis is based on the following six papers, which will be referred to in the text by their Roman numerals.

- I** Rasmussen F, Johansson M, Hansen H-O. Trends in overweight and obesity among 18-year-old males in Sweden between 1971 and 1995. *Acta Paediatr* 1999;88:431-437.
- II** Johansson-Kark M, Rasmussen F, Hjern A. Overweight among international adoptees in Sweden. A population-based study. *Acta Paediatr* 2002;91:827-832.
- III** Rasmussen F, Johansson M. The relation of weight, length and ponderal index at birth to body mass index and overweight among 18-year-old males in Sweden. *Eur J Epidemiol* 1998;14:373-380.
- IV** Johansson M, Rasmussen F. Birthweight and body mass index in young adulthood. The Swedish young male twins study. *Twin Research* 2001;4:400-405.
- V** 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 epidemiologic study of 165,136 Swedish men aged 18 years. *Am J Epidemiol* 2000;152:597-604.
- VI** Johansson-Kark M, Rasmussen F, De Stavola B, Leon DA. Fetal growth and systolic blood pressure in young adulthood. The Swedish young male twins study. *Paediatr Perinat Epidemiol* 2002;16:200-209.

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TABLE OF CONTENTS

ABSTRACT	5
LIST OF PUBLICATIONS	7
TABLE OF CONTENTS	9
LIST OF ABBREVIATIONS	11
INTRODUCTION	13
GLOBAL INCREASE IN OVERWEIGHT.....	13
OVERWEIGHT AMONG SIBLINGS.....	13
OVERWEIGHT AMONG ADOPTEES.....	13
TRACKING OF OVERWEIGHT FROM CHILDHOOD TO ADULTHOOD.....	14
FETAL PROGRAMMING.....	14
FETAL PROGRAMMING IN ANIMALS.....	15
FETAL GROWTH AND GROWTH FACTORS.....	15
FETAL GROWTH AND OVERWEIGHT IN ADULTHOOD.....	15
BIRTHWEIGHT AND BLOOD PRESSURE IN ADULTHOOD.....	16
TWIN STUDIES.....	16
AIMS OF THE STUDIES	17
MATERIALS AND METHODS	18
INFORMATION FROM RELEVANT REGISTERS.....	18
INFORMATION COLLECTED BY A MAILED QUESTIONNAIRE–ZYGOSITY.....	19
OVERVIEW OF OUTCOMES AND SOME IMPORTANT DEFINITIONS OF VARIABLES.....	20
Overweight and obesity.....	20
Measurement of blood pressure.....	20
Adoptees.....	20
Definition of perinatal groups.....	20
Z-scores.....	21
Potential confounding factors.....	21
INCLUSION CRITERIA.....	21
ELIGIBILITY CRITERIA AND INCLUDED SUBJECTS.....	22
STATISTICAL ANALYSES	24

RESULTS	25
PAPER I.....	25
PAPER II.....	25
PAPER III.....	26
PAPER IV.....	27
PAPER V.....	27
PAPER VI.....	28
GENERAL DISCUSSION	30
METHODOLOGICAL ISSUES.....	30
Missing information on key variables.....	30
Measurement of overweight.....	30
Measurement of systolic blood pressure.....	31
Measurement of fetal growth.....	31
Relationships between birthweight and health-related outcomes– methodological considerations.....	32
Data linkage error among twins.....	33
Zygosity.....	33
Chorionicity.....	33
COMMENTS ON MAIN FINDINGS.....	33
Global increase in overweight.....	33
Overweight among adoptees.....	34
Fetal growth and overweight in adulthood.....	35
Fetal growth and systolic blood pressure in adulthood.....	35
FETAL PROGRAMMING AND GENOMIC IMPRINTING.....	36
SAMMANFATTNING (Summary in Swedish)	37
ACKNOWLEDGEMENTS	39
REFERENCES	40

LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
DZ	Dizygotic
MBR	Medical birth register
MR	Multiple-generation register
MSCR	Military service conscription register
MZ	Monozygotic
OR	Odds ratio
RE	Register of education
RR	Relative risk
PHC	Population and housing census
RTP	Register of the total population
SBP	Systolic blood pressure
XZ	Undetermined zygosity

INTRODUCTION

GLOBAL INCREASE IN OVERWEIGHT

The prevalence of overweight and obesity has increased over the last decades (1-4). Overweight has become a global health problem, and it is known that genetic, environmental, psychosocial and socio-economic factors are all involved (5-7). This rise in overweight may be due to increased or unchanged energy intake in combination with reduced physical activity (1). Overweight is strongly related to high blood pressure and type-2-diabetes, and the consequences of the increasing prevalence of overweight will be enormous in the future.

The relative importance of genetic and environmental factors has been studied through adoption studies, twin studies and other family studies. Groups of individuals with genetic susceptibility to overweight are at increased risk. In a review of familial resemblance, genetic factors were found to explain about two-thirds of the variance in body mass index (BMI) (8).

OVERWEIGHT AMONG SIBLINGS

Full-sibling pairs, father-son pairs and half-sibling pairs were recently analyzed and compared in a large population-based Swedish study of young men (9). That study showed higher correlations within pairs of full-siblings (0.36) than within father-son pairs (0.28). Interestingly, the BMI associations were found to be twice as high for maternal half-brothers (0.21) than for paternal half-brothers (0.11). Both types of half-siblings share 25% of their genes, and these results emphasize the great importance of common environmental factors for resemblance in BMI and overweight. The authors argue that, if the equal-environment assumption does not hold, heritability of BMI and overweight may have been overestimated in many previous studies of twins raised together.

Heritability is the proportion of the total variability in a trait or disease explained by genetic factors. The equal-environment assumption states that monozygotic (MZ) and dizygotic (DZ) twins are equally exposed to common environmental factors in childhood and adolescence. Accordingly, differences between MZ and DZ pairs, as regards associations within pairs, are due to genetic factors (or unique environmental factors).

OVERWEIGHT AMONG ADOPTEES

Since 1945 more than 48,000 children from foreign countries have been adopted into Sweden. Most of these children have come from Latin America, the Indian subcontinent and the Far East. Growth in infancy and childhood, and also the risk of developing chronic diseases in adulthood, may differ between international adoptees from poor countries with large social inequalities and individuals born and brought up in Sweden. International adoptees are exposed to fundamental changes in family life, culture, and physical environment early in life. They adapt to new lifestyles, including new eating habits, and become part of a society where unlimited access to food is the

main problem. Several studies indicate that international adoptees from some continents, such as India, are often stunted compared with children born and raised in countries in the Western world (10-11).

TRACKING OF OVERWEIGHT FROM CHILDHOOD TO ADULTHOOD

Many studies have shown positive relationships between weight in childhood and risk of overweight in adulthood. A review from the United States, which covered the years 1970-1992, showed twice as high a risk of obesity in adulthood among obese children (under the age of 18) than non-obese children after adjustment for age (12). The same review showed that one-third of obese pre-school children and one-half of obese school children became obese as adults. In a Swedish prospective study, Mossberg found that 47% of overweight children were overweight in adulthood (13). A study from the United States showed largely similar results; 36% of overweight children became overweight as adults, compared with 14% of low-weight or normal-weight children (14).

An Israeli cohort study of 30,000 infants, followed from birth to 17 years of age, found a positive correlation between high birthweight and high BMI (15). Sørensen et al. and Phillips and Young have also reported a positive association between birthweight and obesity in adulthood (16-17). Loos et al. studied within-pair differences in birthweight and BMI in adulthood among female twins. The results showed that the twin who was heavier at birth was generally taller and heavier in adulthood than the thinner co-twin at birth (18).

A Finnish twin study showed that BMI in adolescence could be predicted, to some extent, from birthweight and parents' BMI. Subjects with an average birthlength and high birthweight showed the highest risk of overweight in adolescence (19). However, the authors were unable to disentangle the relative importance of genetic and environmental factors for BMI in adolescence. In a study from the United States, Kahn et al. found a stronger positive association between birthweight and BMI in later life among individuals with relatively high increments in lean body mass tissue than among those with increments in fat mass (20). The authors suggest that this increase in muscularity in young men might partly explain decreased cardiovascular disease among persons with high birthweight. Parsons et al. found a positive association between birthweight and BMI, but this association was strongly influenced by maternal size (21). In the authors' view, other measures of fetal growth than birthweight are needed for better understanding of the role of the intrauterine environment in the development of obesity later in life.

FETAL PROGRAMMING

According to the fetal origins hypothesis, insufficient nutrition during a critical period or window of fetal life may permanently affect metabolic pathways or endocrine regulatory systems. Barker et al. reported that babies affected by growth restriction in fetal life were at greater risk of non-insulin dependent diabetes mellitus in adulthood than babies with normal fetal growth (22). The thrifty phenotype hypothesis, which may be considered as a refinement of the fetal origins hypothesis, states that inadequate nutrition in fetal life or infancy that shifts into nutritional excess after birth increases the

risk of chronic diseases related to the metabolic syndrome in adulthood (23-27). The components of the metabolic syndrome are high blood pressure, overweight, insulin resistance and dyslipidemia. It has been suggested, and some studies have also indicated, that catch-up growth in infancy may modify the effect of intrauterine growth retardation on the risks of chronic diseases in later life (25, 28-29).

In 1962 Neel hypothesized that intrauterine growth retardation may have persisting health consequences. He introduced the thrifty genotype hypothesis, stating that a complex set-up of genes that improves the chance of survival of an undernourished fetus may become detrimental to health in later life in a society with unlimited access to food (30).

The fetal insulin resistance hypothesis was introduced quite recently by Hattersley and Tooke (31). In essence, this hypothesis states that thinness at birth in relation to gestational age and insulin resistance syndrome in adulthood are different phenotypic expressions of the same underlying genotypes.

FETAL PROGRAMMING IN ANIMALS

Fetal programming has been described in terms of processes whereby a metabolic stimulus during critical periods of fetal development has a permanent effect on the structure or function of the body. From experimental research on rats, Gluckman and Harding reported intrauterine growth retardation to be related to resistance to Insulin-like Growth Factor 1 (IGF-1) (32). A relationship between fetal growth restriction and the development of a condition similar to the metabolic syndrome has been reported from animal experimental research (33-34). Another animal model, also using rats, has shown that insulin resistance and hypertension may occur following maternal protein restriction in pregnancy (35). Results based on the uterine artery ligation model have shown that impairment to utero-placental circulation, which reduces the placental transport of nutrient to the fetus, may lead to obesity in adulthood (33).

FETAL GROWTH AND GROWTH FACTORS

It is well known that insulin and growth factors are of great importance to development during fetal life. Verhaeghe et al. described low levels of IGF-1 in serum from the umbilical cords of newborn babies who were small-for-gestational-age, and high levels for large-for-gestational-age babies (36). In a further paper, the same research team reported a stronger correlation of IGF-1 cord serum levels among MZ twins than among DZ twins, which would indicate the importance of both genetic and environmental factors (37).

FETAL GROWTH AND OVERWEIGHT IN ADULTHOOD

Ravelli et al. studied the occurrence of obesity among the offspring of women pregnant during the Dutch famine in the Second World War (38). Children whose mothers had been exposed to famine during the first half of pregnancy showed an increased risk of developing severe overweight at 19 years of age. Malnutrition in fetal life may give rise to persistent disturbances to the regulation of insulin, and insulin-like growth factors and growth hormone (22). Irreversible disturbances to these and other hormonal

mechanisms may increase the risk of overweight in adult life. In Leningrad, during 1941 and 1944, individuals experienced a famine similar to that in the Netherlands (39). However, a study based on the data from Leningrad did not reveal any association between intrauterine malnutrition and glucose intolerance, dyslipidemia, hypertension or cardiovascular disease in later life. A Finnish study based on famine from 1866 to 1868 did not show any long-term effect with regard to mortality later in life (40).

BIRTHWEIGHT AND BLOOD PRESSURE IN ADULTHOOD

A large number of studies have shown an inverse association between birthweight and blood pressure later in life (41-45). Also, several recent longitudinal studies have found an inverse association between birthweight and systolic blood pressure (SBP) (46-47). Although the factors that underlie the association remains unclear, it has been suggested that malnutrition during sensitive periods of fetal life plays an important role (23, 48). This could be due to different maternal characteristics, including diet (48-49), weight in pregnancy (50), or even the mother's own circumstances in utero, all of which are known to influence birthweight (51-52). The inverse association between birthweight and later SBP is well established and cannot be explained by confounding with socio-economic factors (42, 53-54). Some results from animal models indicate that changes in the fetal environment can have permanent effects on the physiology of offspring, including blood pressure (55). Different mechanisms have been proposed as underlying this association. Special attention has been paid to the effect of in utero circumstances on the functioning of the hypothalamic-pituitary-adrenal axis, and the long-term consequences of this for health in later life (56).

TWIN STUDIES

Twins studies enable research into the effects of environmental exposures on outcomes such as blood pressure or BMI with partial or complete control for genetic factors (57-58). An inverse association within MZ pairs of twins, e.g. lower blood pressure for the co-twin with the highest birthweight, would support the fetal origins hypothesis, and could not be explained by genetic factors. Comparison of the strength of an association observed for blood pressure and within-pair difference in birthweight and the strength of an association observed for blood pressure and between-pairs difference in birthweight would also be informative. Such information might help to clarify whether variations in fetal growth within a single pregnancy have similar effects on an outcome in later life, e.g. blood pressure, as variations in fetal growth observed between pregnancies (at least in so far as these differences can be adequately measured in terms of birthweight). If genetic factors were the main cause of inverse associations between birthweight and BMI and/or blood pressure later in life, no association (or only a weak association) would be expected within MZ pairs.

Most twins have lower birthweight for gestational age than singletons and are at higher risk of intrauterine growth retardation (23, 59). However, twins catch-up with singletons in childhood with respect to height and weight (60-61). Christensen et al. compared the mortality of twins with that of singletons, and found no differences after 6 years of age (59), thus providing no support for the fetal origins hypothesis.

AIMS OF THE STUDIES

The overall objectives were to study the epidemiology of body mass index and overweight among young men in Sweden and to explore relationships between growth in fetal life, body mass index and blood pressure in adulthood. Specific aims were to:

- 1) study time trends and socio-economic differences in body mass index and overweight among young men over the last decades (Paper I);
- 2) study the occurrence of overweight among international adoptees compared with non-adopted young men (Paper II);
- 3) test the fetal origins hypothesis by analyzing relationships between aspects of fetal growth and body mass index and overweight (papers III-IV), and also between fetal growth and systolic blood pressure (papers V-VI) among singletons and twins in young adulthood.

MATERIALS AND METHODS

INFORMATION FROM RELEVANT REGISTERS

Data from Sweden's *Military Service Conscription Register* (MSCR) have a central role to play in this thesis. This is why similar research questions are not addressed with regard to women. Quite simply, the data are not available. Table 1 shows the registers used in this thesis.

Table 1. The various registers used for the papers (I-VI) covered by the thesis.

	I	II	III	IV	V	VI
Register of the Total Population (RTP)	+	+	+	+	+	+
Population and Housing Censuses (PHCs)	+	+	+	-	+	-
Register of Education (RE)	+	+	+	+	+	+
Multiple-generation Register (MR)	+	+	+	+	+	+
Military Service Conscription Register (MSCR)	+	+	+	+	+	+
Medical Birth Register (MBR)	-	-	+	+	+	+

+Included; -Not included

Statistics Sweden maintains the *Register of the Total Population* (RTP). All permanent and current residents of Sweden are included in this register (or should be included in it). Information obtained from this register concerns place of residence (county, municipality, parish), marital status, country of birth, current citizenship, and year of immigration (where applicable).

Statistics Sweden also maintains the *Multiple-generation Register* (MR), with records of the unique personal ID numbers of the biological mothers and fathers of nearly all individuals born after 1941 and living in Sweden after 1991. The biological parents of the study subjects were identified by record linkage to this register.

Population and Housing Censuses (PHCs) are also administered by Statistics Sweden. Censuses for the years 1970, 1975, 1980, 1985 and 1990 were used for the current studies. By law, all persons living and registered in Sweden are required to participate, with only partial missing data on specific variables being permissible. No PHCs have been conducted since 1990. Information obtained from the censuses for the current studies comprised place of residence, socio-economic status, marital status, country of birth, and educational level.

Statistics Sweden's *Register of Education* (RE) was used to obtain information about mothers' and fathers' level of education.

The *Medical Birth Register* (MBR) covers more than 99% of all children born in Sweden. A quality assessment of the MBR has shown the validity of its variables to be good (62). From the MBR information was obtained about the following variables: date of birth, birth order, birthweight, birthlength, gestational age, mother's parity, mother's age, diagnoses for maternal diseases in pregnancy or at birth according to the

International Classification of Diseases (ICD), and ICD diagnoses for possible diseases in offspring. In the MBR, gestational age is primarily estimated as age in days from the first day of the last menstrual period, which has been shown to be a reasonably good measure in large-scale epidemiologic studies. Further, information on stillbirths and perinatal deaths in the study cohort was obtained jointly from the MBR and the Cause of Death Register. Unfortunately, no reliable information is available about chorionicity in the MBR (63-64).

The nationwide MSCR contains information from conscription examinations performed at 18 years of age. Data employed in the studies from this information source covered height, weight, SBP, diastolic blood pressure (DBP), muscle strength (a weighted mean for arm-flexion, knee-extension and hand-grip), physical work capacity (collected by cycle ergometer test), and ICD diagnoses for possible diseases. The conscription examination is compulsory by law for all young men with Swedish citizenship. Missing data on weight and height may be explained by a chronic disease or severe handicap precluding an individual from participating in the conscription examination (see Paper III). In such cases, which are uncommon, a judgment with written diagnostic information provided by a physician is required.

INFORMATION COLLECTED BY A MAILED QUESTIONNAIRE–ZYGOSITY

A questionnaire was mailed to 3,566 twins (1,783 pairs) in 1998 (papers IV and VI). Among other items, the questionnaire covered zygosity, birthweight, birth order, height, and weight. Twins who had not responded after two reminders were approached and, if possible, interviewed by telephone.

Of the 3,566 twins, 2,806 (79%) responded to the questionnaire. Among all 1,783 twin pairs, complete answers were obtained from 1,327 (74%). Most twins responded to the questionnaire, but in the case of 313 individuals information was collected by telephone interview. There were 55 twins from 40 pairs who decided not to take part in the cohort study, and 57 twins could not be traced. After the questionnaire had been mailed 1 twin died and the co-twin did not reply. No reply was obtained from the remaining 646 twins.

The questions about zygosity have been widely used in twin research (65-66) and were based on: a) self-reports of degree of similarity in childhood, and b) difficulties teachers had had in distinguishing between the twin brothers in school. Those pairs where both twins responded “as like as two peas in a pod” and that teachers “always or nearly always” had problems in distinguishing between them were categorized as MZ. Those pairs where both twins responded “not more like than siblings in general” to the first question and “seldom” or, “never or almost never” to the second question were categorized as DZ. The rest of the twins were categorized as of undetermined zygosity (XZ). Numbers of subjects for the studies reported in papers IV and VI were 888 MZ twins, 1,118 DZ twins and 1,480 XZ twins. Among the XZ twins, 680 did not respond to the questionnaire in 1998. Of the 2,806 twins, 800 (28.5%) were of undetermined zygosity.

OVERVIEW OF OUTCOMES AND SOME IMPORTANT DEFINITIONS OF VARIABLES

Overweight and obesity

BMI is defined as weight in kilograms divided by height in squared meters ($BMI = \text{kg}/\text{m}^2$). Overweight was defined as $BMI \geq 25.00 \text{ kg}/\text{m}^2$, and obesity as $BMI \geq 30.00 \text{ kg}/\text{m}^2$ (67). The normal BMI range is $18.50 \text{ kg}/\text{m}^2$ to $24.99 \text{ kg}/\text{m}^2$. Measurements of height and weight were taken under the supervision of a nurse or physician, both at birth and at military conscription examination.

Measurement of blood pressure

The blood pressure data used in papers V and VI were obtained from the MSCR. According to guidelines, blood pressure was measured after 5 to 10 minutes rest in the supine position with a standard mercury sphygmomanometer. If SBP was 145 mmHg or below and DBP between 50 and 85 mmHg no further measurements were taken. However, if blood pressure was above or below these limits, a second measurement was performed on the next day. In such cases the result of the second measurement was entered into the registry. Our analyses revealed that rounding practices had developed among the nurses and health personnel responsible for blood pressure measurements over the years. This phenomenon was much less apparent for SBP, which was generally rounded to the nearest 2 mmHg. Because of the considerable rounding of DBP only data on SBP were used for the studies reported in papers V and VI. It was apparent that there were systematic differences between centers, with two of the six centers recording mean SBPs 4 to 6 mmHg above the others. This is explained to some extent by differences in rounding practices. The extent of rounding and systematic differences between centers varied across the years of observation. Much attention was given to these issues in the data analyses. As reported in papers V and VI, adjustments were made for year and center of conscription. Another research limitation to the blood pressure measurements consists in a change in equipment implemented during the years 1995 and 1996. The standard mercury sphygmomanometer was replaced by automatic measurements of blood pressure.

Adoptees

Identification of international adoptees was based on the assumption that a child born in a country other than Sweden having both parents born in Sweden is an adopted individual. An additional criterion was that the migration files at Statistics Sweden did not contain information about a possible long-term stay abroad. One hundred and twenty-eight young men born outside Sweden with Swedish parents were excluded from the adopted population (Paper II) because their parents' records showed indications of long-term stay abroad.

Definition of perinatal groups

For the study in Paper III the newborn children were divided into six perinatal groups according to percentiles of birthweight *and* birthlength for each gestational week. The basic idea or principle was to categorize newborn children according to their combined

likelihood of being thin, medium and heavy, and also short, medium and long for gestational age. A detailed description of the combined categories is presented in Paper III.

Z-scores

Birthweight Z-scores and birthlength Z-scores were used in papers V and VI. The birthweight and birthlength distributions were transformed into the normal standard distribution $N(0, 1)$. For Paper V transformations were performed within each individual week of gestation, from 35 to 44 weeks, using the whole study population of singletons as reference. Using Z-scores is a well-established procedure for creating a measure of size at birth that is considered independent of gestational age. The birthweight distributions of all the 27,658 twin boys born in Sweden between 1973 and 1997 were used as reference when creating Z-scores for the twins covered by the analyses in Paper VI. A Z-score was created for each individual week of gestation, from 28 to 44 weeks, as described above for singletons.

Potential confounding factors

For papers I-VI, different statistical analyses were conducted to adjust for variables such as living area, country of birth, muscle strength and physical work capacity. Other variables adjusted for were mother's educational level, parity, marital status and socio-economic group.

Living area (Paper I) was divided into four different categories: large city, medium-sized town, country area, and rural area. Country of birth (Paper II) was categorized according to continent or continental region, such as Latin America, Indian subcontinent, or Far East.

Muscle strength (papers I and II) was used as a crude proxy measure of muscle mass or lean body mass. This variable was composed of three measures – hand-grip, arm-flexion and knee-extension. Physical work capacity (Paper I) was measured through a standardized sub-maximal cycle-ergometer exercise test.

Since the young men had not yet finished their education, mother's (and father's) educational level (papers I-III) was considered the most appropriate measure of social position. Level of education was divided into low (less than 9 years in school), medium (9 years of compulsory school), high/medium (Swedish high/upper-secondary school), and high (university or higher). Mother's parity (Paper III) was used as an indicator of the number of children delivered before the study subject himself. Mother's marital status (papers I and III) was divided into cohabiting or living alone with her child. Mothers and fathers were categorized into socio-economic groups (Paper I), such as blue-collar or white-collar workers, according to the occupational codes available in the PHCs.

INCLUSION CRITERIA

Mainly due to differences in study design, slightly different criteria were used for inclusion of study subjects in papers I-VI. It is important to acknowledge that this thesis

is primary based on very large, regular, nationwide data sets not created specifically for research purposes. The MBR and MSCR both contain a small number of extreme values on a range of variables. Such extreme values may be true values, or represent measurement errors, data-entry errors, etc. Clearly, outliers present a challenge, and there is a risk of misclassification in the case of a low proportion of subjects. For example, due to measurement errors or data-entry errors some normal weight subjects may be registered as overweight and vice-versa. In order to minimize these types of problems, cut-off limits for birthweight, birthlength, weight, height, BMI and SBP were implemented (as shown in Table 2).

As seen from the values in the final column of Table 2, the proportion of subjects excluded for this reason was less than 0.5% in all of the studies. For papers IV to VI it was additionally required (for inclusion) that military conscription examination was performed between 17 and 19 years of age. Further criteria used for papers IV and VI were that both twins in a pair should have participated in conscription examination at the same center and within 6 months of each other. However, it is fair to say that Table 2 does not give a complete picture of non-participation. For example, a cross-over problem appeared in the studies reported in papers IV and VI, which resulted in the exclusion of a considerable number of twin pairs from the analyses. The medical birth record of a twin was in some cases incorrectly associated with the personal identification number of his co-twin.

Table 2. Inclusion criteria applied (papers I-VI).

Paper	Gestational age (week)	Birthweight (gram)	Birthlength (cm)	Weight at 18 years (kg)	Height at 18 years (cm)	BMI at 18 years (kg/m ²)	Proportion of excluded values (%)
I	n.a.	n.a.	n.a.	40-150	150-210	n.a.	0.02
II	n.a.	n.a.	n.a.	n.a.	n.a.	>15.00	0.02
III	37-42	1,850-5,300	43-59	40-150	155-205	n.a.	0.37
IV	28-44	800-4,400	30-60	45-120	155-200	n.a.	0.17
V	35-44	1,500-5,500	39-60	40-150	155-205	n.a.	0.22 ¹
VI	28-44	800-4,400	30-60	45-120	155-200	n.a.	0.26 ²

n.a.=not applicable; ¹Also restricted to SBP 90-180 mmHg; ²Also restricted to SBP 100-180 mmHg

ELIGIBILITY CRITERIA AND INCLUDED SUBJECTS

The data sets used for papers I-VI were created by linkage between the source registers, described in Table 1 and under the heading “Information from relevant registers” (see above). All young men were initially identified in the RTP or the PHCs for all the studies (papers I-VI), and the unique Swedish personal identification numbers were used for all record linkages. For papers IV and VI additional information from a mailed questionnaire was linked to the register data. Table 3 shows the proportion of subjects with missing values for all studies (papers I-VI). For inclusion into the different studies of papers I to IV, values on weight and height were required (within the boundaries shown in Table 2). An additional requirement for papers V and VI was information on SBP (boundaries according to Table 2).

Table 3. Percentage of subjects with missing values in outcome variables in papers I-VI.

Paper	Sources	Birth years	Eligible subjects	Percentage with missing values
I	RTP, PHC	1953,1958,1963, 1968,1973-1977	503,689 men	10.9 ⁴
II	RTP, PHC	1973-1977	2,400 adoptees 263,173 non-adopted	12.7 ⁴ 10.8 ⁴
III	RTP, PHC, MBR	1973-1976	182,312 alive and singleton men ¹	9.1 ⁴
IV	RTP, PHC, MBR	1973-1979	3,474 alive twins ²	9.2 ⁴
V	RTP, PHC, MBR	1973-1976	196,519 alive and singleton men ³	14.5 ⁵
VI	RTP, PHC, MBR	1973-1979	3,474 alive twins ²	12.8 ⁵

¹Gestational weeks 37-42; ²Gestational weeks 28-44; ³Gestational weeks 35-44; ⁴Missing values on weight and/or height; ⁵Missing values on weight and/or height and SBP

STATISTICAL ANALYSES

For Paper I trends in overweight and obesity were estimated using the Mantel-Haenszel method (68). Pooled estimates of relative risks (RRs) of overweight and obesity were calculated using this classical technique. For papers II and III logistic regression analyses were performed using the proc logistic procedure in SAS (69-70). Confidence intervals (CIs) for odds ratios (ORs) were calculated by means of logarithmic transformation (71). For Paper IV mixed linear models were used for analyzing within-pair and between-pairs differences in birthweight in relation to BMI (the outcome) at 18 years of age. The proc mixed procedure in SAS was used for the analyses in Paper IV (69-70). For Paper V multiple linear regression analysis was conducted using the STATA statistical package (72-73). Finally, for paper VI standardized birthweight values (Z-scores) were computed to allow an evaluation of the effect of size at birth independent of gestational age. Random-effect linear models were fitted to the individual SBP values in order to obtain separate estimates of the effect of between-pairs and within-pair differences in birthweight (and Z-scores). Likelihood ratio tests for heterogeneity of the within and the between effects were calculated by comparing the likelihood of the original model with that of a model where these effects were constrained to be identical. STATA software was used extensively for papers V and VI (72-73).

RESULTS

PAPER I

The mean body weight of Swedish military conscripts increased from 67.4 kg in 1971 to 72.1 kg in 1995. Mean height increased slightly from 178.7 cm to 179.2 cm during the same period. The prevalence of overweight increased from 6.9% to 16.3%, and the prevalence of obesity from 0.9% to 3.2%. Overweight was more common among males with low-educated mothers. The social gradient for overweight was quite stable from 1971 to 1995, with a similar proportional increase in the prevalence of overweight among young men from low-educated families as among young men from highly educated homes. Table 4 shows the increased risk of overweight among young men born in the 1970s compared with those born in the early 1950s (following adjustment for living area, etc.).

Table 4. Time trend for overweight (BMI \geq 25.00) among 18-year-old males by year of birth (1953-1977).

Year of birth	Unadjusted RR		Adjusted RR ¹	
	RR for overweight	95% CI of RR for overweight	RR for overweight	95% CI of RR for overweight
1953 ²	1.00	-	1.00	-
1958	1.31	1.25-1.36	1.18	1.15-1.21
1963	1.45	1.39-1.51	1.26	1.23-1.30
1968	1.63	1.56-1.69	1.35	1.32-1.39
1973	1.86	1.78-1.93	1.47	1.43-1.51
1974	1.89	1.82-1.96	1.50	1.46-1.54
1975	2.06	1.98-2.14	1.57	1.53-1.61
1976	2.14	2.06-2.23	1.60	1.56-1.64
1977	2.35	2.26-2.44	1.67	1.63-1.71

¹Adjustments made for living area, mother's marital status and mother's country of birth;

²Reference category

PAPER II

Of 2,094 internationally adopted boys, the 623 from South America had a mean BMI of 23.21 kg/m², and 21.5% were overweight at 18 years of age. Among 266 young males adopted from Chile, mean BMI was 23.93 kg/m², and 28.6% were overweight. Of the 502 young males adopted from the Indian subcontinent, 8.4% were overweight; they had a mean BMI of 20.75 kg/m². For 317 adoptees from India, the corresponding figures were 8.8% and 20.73 kg/m². The 817 young males adopted from the Far East had a mean BMI of 21.80 kg/m², and 12.0% were overweight. Finally, 404 adoptees from South Korea had a mean BMI of 21.80 kg/m², and 10.9% were overweight. The corresponding figures for 234,606 non-adopted young males in Sweden were 22.21 kg/m² and 14.1% respectively. Table 5 clearly shows the increased risk of overweight among Latin Americans compared with non-adopted individuals. Chilean adoptees showed an OR of 2.40 when compared with non-adopted individuals.

Table 5. Results of logistic regression analyses of overweight (BMI \geq 25.00) among international adoptees (selected countries) and non-adopted individuals at 18 years of age born between 1973 and 1977.

Region/country of origin	Unadjusted OR		Adjusted OR ¹	
	OR for overweight	95% CI of OR for overweight	OR for overweight	95% CI of OR for overweight
Non-adopted ²	1.00	-	1.00	-
Adoptees				
Latin America	1.65	1.36-2.00	1.76	1.45-2.14
Chile	2.40	1.84-3.14	2.47	1.88-3.23
Colombia	0.89	0.56-1.40	0.99	0.62-1.56
Ecuador	1.15	0.63-2.08	1.20	0.66-2.18
Peru	2.77	1.31-5.85	3.21	1.51-6.83
Indian subcontinent	0.56	0.41-0.77	0.60	0.43-0.82
India	0.59	0.40-0.87	0.64	0.44-0.95
Sri Lanka	0.53	0.30-0.96	0.55	0.31-1.00
Far East	0.83	0.67-1.03	0.87	0.70-1.08
Indonesia	0.71	0.34-1.47	0.73	0.35-1.53
South Korea	0.74	0.54-1.01	0.77	0.56-1.05
Thailand	1.09	0.79-1.49	1.16	0.84-1.58

¹Adjusted for mother's educational level and subject's birth year; ²Reference category

PAPER III

One of the main findings was that there is a positive relationship between birthweight (after controlling for gestational age) and BMI at 18 years of age. Similarly, a positive association was observed between birthweight and prevalence of overweight in young adulthood. Table 6 shows an increased risk of overweight (OR=1.53) among young men who were heavy and of normal length at birth (Group 4). Similarly, an increased risk of overweight (OR=1.41) was found among the young men who had been heavy and long at birth (Group 5).

Table 6. Results of logistic regression analyses of overweight (BMI \geq 25.00) at 18 years of age among males from different perinatal groups born 1975 or 1976.

Perinatal group	Unadjusted OR		Adjusted OR ¹	
	OR for overweight	95% CI of OR for overweight	OR for overweight	95% CI of OR for overweight
1	0.85	0.78-0.92	0.85	0.76-0.95
2	1.02	0.96-1.08	1.01	0.93-1.10
3	0.85	0.75-0.96	0.73	0.60-0.89
4	1.53	1.43-1.64	1.52	1.38-1.68
5	1.41	1.27-1.56	1.34	1.15-1.56
6 ²	1.00	-	1.00	-

¹Adjustments made for living area, and mother's age, educational level, parity and marital status (only 1975 and 1976 birth cohorts included); ²Reference category

PAPER IV

The birth characteristics of MZ and DZ twins are as follows: mean birthweight for MZ is 2,644±511 g (mean±standard deviation), for DZ 2,733±527; mean gestational age for MZ is 37.2±2.5 weeks, for DZ 37.2±2.3 weeks; and, mean birthlength for MZ is 47.2±2.7 cm, for DZ 47.7±2.7 cm. At age 18 the DZ twins were heavier (70.2±9.1 kg compared with 68.7±9.5 kg) and taller (179.4±6.0 cm compared with 178.7±6.8 cm) than the MZ twins. The results of the mixed linear analyses shown in Table 7 reveal a weak positive within-pair effect of birthweight on BMI at the age of 18 among the MZ pairs of twins. No between-pairs effect of birthweight on BMI was observed for the MZ pairs. No clear-cut relationships were found for the DZ twin pairs. The within-pair effect observed among the MZ pairs persisted after the various adjustments shown in Table 7.

Table 7. Within-pair and between-pairs effects of a 1 kg increase in birthweight on BMI (kg/m²) among 18 years old male twins born between 1973 and 1979.

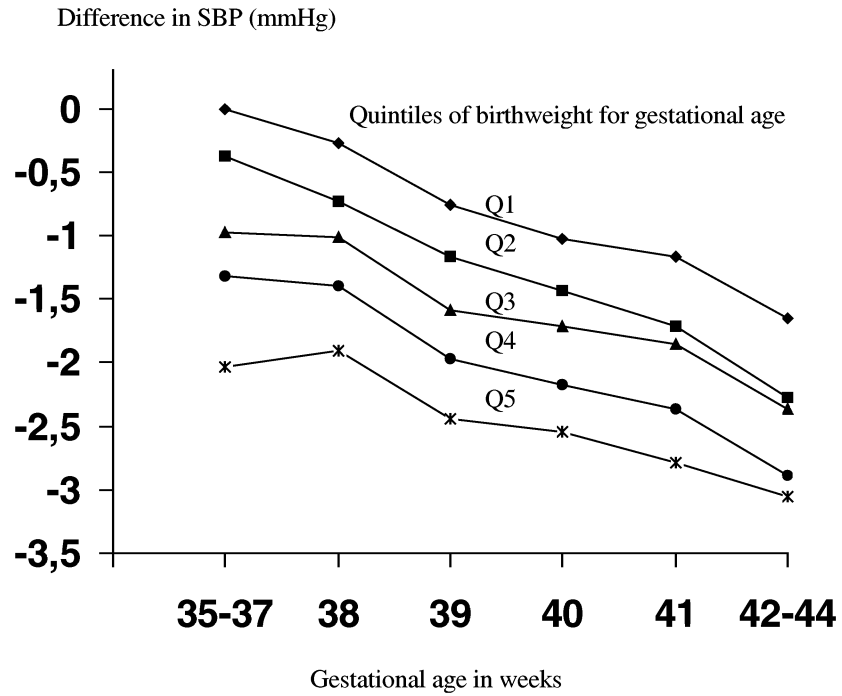
	MZ pairs (n=400)		DZ pairs (n=284)		XZ pairs (n=239)		All pairs (n=923)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Crude								
Within	0.58	0.22,0.94	0.43	-0.28,1.15	0.58	0.04,1.12	0.53	0.22,0.84
Between	0.06	-0.45,0.58	-0.01	-0.55,0.54	0.26	-0.36,0.88	0.12	-0.20,0.44
Adjusted¹								
Within	0.58	0.22,0.95	0.44	-0.29,1.16	0.58	0.04,1.12	0.53	0.22,0.84
Between	0.02	-0.63,0.67	0.35	-0.47,1.17	0.87	0.02,1.72	0.41	-0.02,0.83

¹Regression adjusted for age, year, center for conscription examination, and gestational age

PAPER V

This paper, which was based on a study of 165,136 young men, showed a weak but very clear inverse association between birthweight for gestational age and SBP at age 18. A novel finding was that there is an independent inverse association between age at gestation and SBP in young adulthood after adjustment for birthweight for gestational age (Figure 1). No independent association between age at gestation and SBP later in life was found following adjustment for birthlength for gestational age (data not shown).

Figure 1. Differences in systolic blood pressure at 18 years of age by gestational age and quintile of birthweight for gestational age (relative to Q1, 35-37 weeks) among males born between 1973 and 1976, adjusted for birthlength for gestational age and height, weight, age and center for conscription examination.



PAPER VI

The main finding was that of an inverse between-pairs effect of birthweight on SBP at age 18, which remained after adjustment for potential confounding factors (Table 8). The relationship was observed only for MZ twin pairs. A weak inverse but non-significant effect on SBP of within-pair differences in birthweight was shown among MZ twin pairs. No within-pair effects of birthweight on SBP were observed for DZ twin pairs.

Table 8. Between-pairs and within-pair effects of 1 kg increase in birthweight on SBP (mmHg) among 18 years old male twins born between 1973 and 1979.

	MZ pairs (n=384)		DZ pairs (n=269)		XZ pairs (n=233)		All pairs (n=886)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Adjusted¹								
Between	-2.47	-4.35, -0.59	0.22	-1.87, 2.30	-1.06	-3.27, 1.16	-1.22	-2.41, -0.04
Within	-0.06	-2.87, 2.75	1.49	-2.14, 5.12	1.54	-2.08, 5.15	0.92	-0.98, 2.82
Adjusted²								
Between	-2.68	-4.95, -0.42	0.28	-2.35, 2.91	-2.28	-5.00, 0.45	-1.68	-3.15, -0.22
Within	-1.30	-4.15, 1.54	0.14	-3.49, 3.76	1.33	-2.35, 5.01	-0.21	-2.13, 1.71

¹Regression adjusted for age, year and center for conscription examination; ²Regression adjusted for age, year, center for conscription examination, adult height and weight, and gestational age

GENERAL DISCUSSION

METHODOLOGICAL ISSUES

Missing information on key variables

The proportion of subjects with missing values or extreme values on birthweight, birthlength and gestational age in the MBR was below 0.5% for papers III-VI (Table 2). The proportions of individuals with missing values from the MSCR on the outcome variables (weight, height and SBP) are below 15% for all papers (I-VI). See Table 3. Although these levels of attrition are low from an international perspective, it is important to consider whether individuals with morbid obesity (or high SBP) are over-represented among individuals with missing values on BMI (or SBP) at the age of 18.

It is impossible to exclude the possibility that some of the young men who did not attend military conscription examination suffered from morbid obesity. However, anyone not participating in a conscription examination is required to present a certificate, issued by a physician, containing information on diagnosis. During the study years, the great majority of all young men in Sweden participated in conscription examination, although some of them may have been exempted from later military service due to a severe chronic disease (including morbid obesity or another rare disease associated with high SBP). However, missing data on BMI may be explained by severe chronic disease or handicap precluding an individual from participating in examination. As shown in Paper III, most of the chronic diseases reported to the MSCR seem to be unrelated to BMI. It seems unlikely that any possible slight underestimation of the prevalence of obesity would have changed over time.

Measurement of overweight

Many studies have shown that overweight individuals tend to underestimate their weight relative to their height (74-75). However, all six papers in this thesis are based on measured data on weight and height collected by health-care personnel, or under their supervision, at military-induction examinations or at birth. Overweight and obesity can be determined by BMI, measurements of skin folds, bioelectric impedance, dual energy X-ray absorptiometry (DXA), computed tomography, or magnetic resonance imaging (76-77). BMI is the measure recommended by the WHO International Obesity Task Force (78) for epidemiologic studies of overweight and obesity. Many studies have shown strong associations between BMI and fat mass measured by DXA scanning (79). A limitation, however, especially relevant to Paper II, is that individuals from different ethnic groups fulfilling the WHO's BMI-based definition of overweight can differ substantially with respect to fat mass or percentage body fat (80-81). Wang et al., for example, found that Asians had lower BMI than whites, but a higher percentage of fat mass (82). Groups of individuals belonging to different ethnic groups and with, on average, the same BMI also differ with regard to risk of long-term complications, such as hypertension, non-insulin dependent diabetes and hyperlipidemia.

Kuh et al. found an inverse association between fetal growth and waist-hip ratio in adulthood among women (but not men) after adjustment for current body size (83). The study also showed inverse associations between body size in childhood (age 7 years) and waist-hip ratio and waist circumference in adulthood. It pointed to an independent inverse association between body size in childhood and risk of abdominal obesity at the age of 43, possibly due to mechanisms or pathways other than an inverse association between fetal growth and adult body size.

Measurement of systolic blood pressure

The blood pressure data used for papers V and VI were collected as part of a routine health examination at military conscription. The quality of these data is presumably lower than blood pressure data collected ad hoc as part of a longitudinal study or in a clinical trial. Rounding and a preference for values to end in 0 or 5 were observed in the blood pressure distributions. Such digit preference was more pronounced in the data from some conscription centers than others. In 1994-95 automatic measurement devices replaced the mercury sphygmomanometers in the conscription centers. Possible measurement errors were taken into account by adjusting for calendar year and center of conscription in the statistical analyses (papers V and VI). Additional criteria for inclusion of study subjects were laid down for the study reported in Paper VI. The twin brothers had to have participated in conscription examination at the same center and within six months of each other. This can be presumed to have minimized the effect of bias on measurements of SBP. It should be noted that the variance of SBP reported in papers V and VI was not considerably higher than that observed in other studies for which SBP was measured ad hoc (47, 84). Data on SBP were acquired independently of the information on birthweight, birthlength and gestational age obtained from the MBR. Bias in estimates of the association between birthweight and SBP should therefore be non-differential, leading to an underestimation of the strength of the effect.

Measurement of fetal growth

Midwives, physicians and nurses were responsible for the measurements of birthweight, birthlength and gestational age. The data were noted on the birth record directly after delivery and entered into the MBR centrally at the National Board of Health and Welfare. In such a large-scale routine, data-set errors can be introduced at various steps in the process from measurement at an obstetric department to release of a final version of the register for a certain calendar year. But, for all four papers (III-VI), using preset upper and lower limits for birthweight, birthlength and gestational age eliminated implausible values. Many studies in the literature addressing the fetal origins hypothesis have lacked data on gestational age (15, 22, 85). For papers III-VI, gestational-age-adjusted birthweight was applied as a proxy measure of fetal growth. Clearly, this is a crude measure, and data from successive measurement of fetal growth by ultrasound would have been desirable. Data on maternal weight, height and BMI in early pregnancy would also have been very useful, but such data were not available in the MBR for the early cohorts.

According to Jackson et al., half of the fetal weight gained during the third trimester may be adipose tissue, and as much as 40% of the variation in birthweight at term may be due to fat tissue (86). This interesting observation on birthweight is related to the

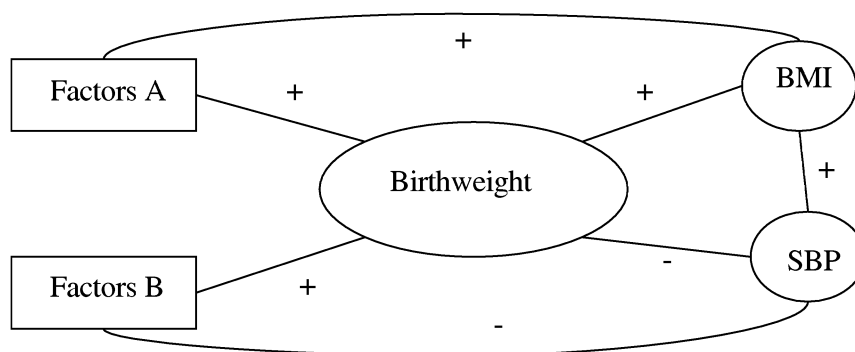
issue of the relative contributions of fat mass and lean body mass to body composition and BMI in young adulthood (see the section “Measurement of overweight”, above). Stettler et al. observed that rapid weight gain during the first four months of life was associated with an increased risk of overweight at seven years of age (87). These and other tentative findings indicate the need for biomarkers of body composition at birth and in later life in future research.

**Relationships between birthweight and health-related outcomes—
methodological considerations**

Gestational-age-adjusted birthweight, as a proxy for fetal growth, is a complex measure influenced by fetal genes and environmental factors in utero, and also by characteristics of pregnancy, such as maternal ethnicity (88), maternal height and weight (21), maternal smoking habits (89), maternal nutrition and physical activity, etc. Gestational-age-adjusted birthweight may be seen as a “snapshot” of the trajectory of fetal growth during gestation.

Social and psychosocial factors that affect fetal growth may also be determinants of postnatal growth or be associated with postnatal exposures (90). Birthweight might possibly be an intermediate variable in causal pathways between social, psychosocial and biological determinants already present in early pregnancy and health outcomes in adulthood (including BMI and SBP). All this relates to the important issue of whether to adjust associations between exposure (birthweight) and outcome (health) for other determinants that have been found to be related to exposure and/or outcome (57, 91). In this thesis, results have generally been presented both with and without such adjustments. Our knowledge is still limited, and birthweight and its determinants may well have both direct and independent influences on health-related outcomes in later life on top of the causal pathways in which birthweight acts as an intermediate variable (see Figure 2).

Figure 2. Factors related to birthweight as a proxy measure of fetal growth and to health-related outcomes in later life (such as BMI and SBP).



BMI=body mass index; SBP=systolic blood pressure.

Data linkage error among twins

In Sweden, when a baby is a few weeks old, the civil registration authorities assign a unique personal identification number to him or her. As reported earlier under the heading “Inclusion criteria”, there is evidence that for some twin pairs this process led to a “cross-over” misclassification problem. The medical birth record of a twin was in some cases incorrectly associated with the personal identification number of the co-twin. Since record linkages between the MBR and the MSCR for papers IV and VI were based on personal identification number, this would lead to an underestimation of the strength of the association between within-pair differences in birthweight and outcomes in young adulthood. For 59 twin pairs there was clear evidence of “cross-over”, with self-reported information from a twin completely matching the MBR information of the co-twin. The records of these 59 pairs were corrected by reassignment of birth registry information of each twin to their co-twin. For 671 twin pairs, however, the likelihood of “cross-over” was classified as indeterminate because of inconsistencies between self-reported information and that from the MBR. Accordingly, their records were excluded from the data set for further analysis. It is extremely important to acknowledge the “cross-over” problem in future research. The current authors have developed a SAS code for how to correct or exclude observations as described. The procedure is described in detail in papers IV and VI.

Zygosity

Twin pairs were classified as MZ, DZ or XZ with respect to zygosity according to their responses to two questionnaire items that have been widely used in previous twin research (65-66). Twenty-nine percent of the twin pairs with complete answers were classified as XZ. The high proportion of XZ pairs was completely unexpected, but the possible availability of DNA samples in future studies may make it possible to reclassify many XZ pairs as MZ or DZ.

Chorionicity

No information is available in the MBR about chorionicity (63-64). Such information would have been of great interest, since monochorionic MZ twins are at much higher risk of fetal growth retardation (and fetal death) than dichorionic MZ twins. It is well known in perinatal medicine that one of the twins in monochorionic MZ pairs may become severely undernourished and growth retarded due to insufficient blood flow from placenta to the fetus. If information about chorionicity had been available, the analyses conducted for papers IV and VI would have been performed separately for monochorionic MZ and dichorionic MZ twin pairs. Larger within-pair differences in birthweight would have been expected for monochorionic MZ pairs than for dichorionic MZ pairs. However, seen in an international perspective, absence of information about chorionicity is the rule rather than the exception in twin research.

COMMENTS ON MAIN FINDINGS

Global increase in overweight

During the last 25 years the prevalence of overweight and obesity has increased gradually among young men in Sweden without a break in trend. Although not

included in this thesis, the time trend has been followed-up to the end of 1998 (92). This increase in overweight seems to be worldwide, although the development is less pronounced in Sweden than in the most severely affected countries, such as the United States (1-4). The prevalence of overweight in Sweden increased 2.4 times during this 25-year period, and the prevalence of obesity 3.5 times. Clear-cut socio-economic differentials, with a higher prevalence of overweight and obesity among conscripts from low-educated homes were evident in the study reported here. The socio-economic gap has remained unchanged from the early 1970s through to the mid-1990s. Prentice and Jebb have suggested that unchanged energy intake combined with a decline in energy consumption due to a decrease in physical activity is the driving force behind the epidemic of overweight and obesity (1). The increasing prevalence of overweight and obesity comprises a severe public-health problem, and effective primary preventive strategies are urgently needed (93). Unfortunately, no primary preventive strategy or intervention has so far been shown to be effective in preventing the development of overweight and obesity (93-94).

Overweight among adoptees

International adoption to Sweden and other Western societies from developing countries is a rather recent phenomenon, which started in the early 1970s. Many aspects of the acculturation process and the long-term health consequences are as yet unknown. When adopted, an individual with a different genetic set-up changes culture as well as family circumstances at early age. International adoption provides a model for studying the consequences of migration and changing family. Ideally, markers of health among adoptees, such as BMI, should be compared with the same markers among biological relatives in the country of origin and among non-biological adoptive family members. However, for Paper II, there were very few adoptive parents with biological offspring, and data on the BMI of biological parents or full-siblings in the country of origin were not available.

The results of Paper II show strikingly large variations in the prevalence of overweight between young men adopted from different countries of origin in early childhood. The prevalence of overweight was two to three times higher among adoptees from Chile than among those from South Korea and India. These differences cannot reasonably be explained by differentials in socio-economic status (as measured here by the adoptive parents' level of education). As discussed above, the limitation of BMI as a measure of adiposity relates to its failure to distinguish between fat and lean body mass; also, individuals from different ethnic groups have been found to vary in percent fat mass when BMI has been taken into account (80-81). For Paper II, muscle strength was used as a proxy measure of muscle mass, which is an important component of lean body mass. However, differences in prevalence of overweight remained unchanged after adjustment for muscle strength.

Several studies in this thesis, including those reported in papers III and IV, have shown that size at birth and growth in infancy may affect the risk of overweight in adulthood (13-19). Earlier Swedish research indicates that female adoptees from India are often severely growth retarded at birth (10). However, for Paper II no information was available about adoptees' size at birth, and it is therefore an unresolved question

whether sub-optimal fetal growth may partly explain differentials in overweight between adoptees from various countries. However, it seems unlikely that adoptees from different developing countries should have considerably different birth outcomes. Alternatively, these substantial differences in occurrence of overweight might be due to diversity in genetic susceptibility to overweight, or a combination of poor fetal growth and genetic susceptibility.

Fetal growth and overweight in adulthood

Paper III showed a positive association between size at birth and BMI at the age of 18. Paper IV showed a positive effect of within-pair differences in birthweight on BMI at age 18 among MZ pairs of twins. No effect of between-pairs differences in birthweight on BMI was observed among the MZ twin pairs. Among the DZ twins, within-pair and between-pairs differences in birthweight had no impact on BMI at the age of 18. While these results do not contradict the notion that growth in utero may have important effects on BMI in adulthood, they do not support the fetal origins hypothesis. To be in accordance with the fetal origins hypothesis, the results would have indicated an effect of the within-pair differences in birthweight on BMI in adulthood in a direction opposite to that seen in the empirical data (summarized above).

Results inconsistent with the fetal origins hypothesis have been reported in previous twin research (19). If the hypothesis is true, one would intuitively expect a higher mortality rate from myocardial infarction among twins than singletons, since twins generally have lower birthweight and are more often growth retarded in utero (95). Forsén et al. have recently reported that newborns with strong catch-up growth in infancy carry with them an increased risk of cardiovascular disease into adulthood (96). Twins typically show a strong increase in weight during the first year of life and have normally caught up with singletons by the age of 1-2 years. Vågerö and Leon, however, did not find higher mortality from myocardial infarction among twins than among singletons (97). As mentioned above, the results of Paper IV are in accordance with those of Paper III in that they show a positive relation between birthweight and BMI in adulthood. For Paper IV the MZ twin pairs were matched with regard to both genetic factors and a variety of environmental factors in fetal life, early childhood and adolescence. This design made it possible to search for the effect of fetal growth on BMI in adulthood.

Fetal growth and systolic blood pressure in adulthood

The results presented in Paper V show an inverse relationship between gestational age and SBP. They also show an inverse relationship between gestational-age-adjusted birthweight and SBP. The finding of a relation between SBP and birthweight among 18-year-old singleton men is in accordance with several other studies of young adults (46, 98-99). Uiterwaal et al. reported a clear-cut inverse association between birthweight and SBP in adolescents 15-19 years of age. An increase in birthweight of 1 kg was associated with a change in SBP of -3.1 mmHg (46). Interestingly, a population-based study of 17-year old Israeli conscripts showed a change in SBP of -0.94 mmHg per kg increase in birthweight (99). As reported in Paper V, SBP changed by -1.47 mmHg per kg increase in birthweight, a finding that lies between the figures in the two studies referred to above. In accordance with the singleton study, Paper VI

showed an inverse but non-significant effect on SBP of within-pair differences in birthweight among MZ twin pairs. An inverse between-pairs effect of birthweight on SBP was observed among the MZ pairs of twins. Clearly within-pair effects are of primary interest in this context, and clear inverse within-pair effects of birthweight on SBP have been reported in two recent twin studies (100-101). If the inverse association between birthweight and blood pressure association was due only to genetic factors, no effect on blood pressure of within-pair differences in birthweight among MZ twins would be expected. The findings of Paper VI neither contradict nor offer strong support for the fetal origins hypothesis.

Law et al. recently reported low birthweight and catch-up growth in early childhood to be associated with increase of SBP in young adulthood (102). There is a growing understanding that not only fetal growth but also growth in early childhood may influence long-term risks of diseases related to the metabolic syndrome. In the current work, no anthropometrical information was available from early childhood, and it was therefore impossible to take early childhood growth into account.

FETAL PROGRAMMING AND GENOMIC IMPRINTING

There is strong support for the concept of fetal programming in the huge animal-experiment literature. It has been demonstrated that metabolic stimuli during critical periods of fetal development may have permanent effects on the structure and function of the body of many species (22-24, 33-35). But the fetal origins hypothesis in epidemiologic research is more like a black box theory. It is much harder to measure specific nutritional or metabolic exposures in critical windows of fetal development in humans. As discussed, birthweight is influenced by many factors, and it may not be the most appropriate measure of nutritional or metabolic exposures in fetal life.

Metabolic imprinting might be a useful concept for future research (103). This concept focuses on adaptive responses to certain nutritional conditions early in life that are characterized by: 1) a susceptibility to a critical window during fetal life, 2) a persistent influence that lasts into adulthood, 3) a certain measurable outcome, 4) a dose response or threshold relationship between a specific exposure and outcome. Another useful concept is genomic imprinting (104). Imprinted genes are only expressed by one parental allele, while the allele received from the other parent remains silent. Insulin-like growth factors play a key role in fetal growth and development, influencing fetal cell division, differentiation and possibly metabolic regulation (105). Experimental research on mice has demonstrated that one copy of the IGF-2 gene is made silent by genomic imprinting. Further studies have demonstrated that mice inheriting a paternal allele made silent by molecular genetic methods tend to have a much lower body weight than mice inheriting a normal allele. By contrast, mice inheriting a maternal silent allele were not found to differ from those receiving a normal maternal allele (106). This clearly shows the importance of the paternal IGF-2 allele in mice. Imprinted genes might also be important for growth of the human fetus and possibly for the risk of chronic disease in later life. Although this is pure speculation, it might be worthwhile considering the concept of genomic imprinting in future epidemiologic research.

SAMMANFATTNING (Summary in Swedish)

Övervikt och fetma har ökat under de senaste årtiondena både i Sverige och i övriga världen. Förändringar i livsstil och miljö samt genetisk känslighet är troligen viktiga faktorer till denna ökning. En hypotesbildning, ofta kallad, den fetala inprogrammeringshypotesen ("the fetal origins hypothesis") har blivit mycket omdebatterad under de senaste 15 åren. Enligt denna kontroversiella hypotes är övervikt och andra komponenter i det metabola syndromet – t.ex. högt blodtryck – långsiktiga konsekvenser av tillväxthämning i fosterlivet.

Det övergripande syftet i denna avhandling var att studera kroppsmasseindex och övervikt bland unga män i Sverige samt att utforska samband mellan tillväxt i fosterlivet och övervikt respektive systoliskt blodtryck senare i livet. Specifika syften har varit att: 1) studera tidstrender och socioekonomiska skillnader i kroppsmasseindex och övervikt bland unga män under de senaste årtiondena; 2) studera förekomst av övervikt bland internationellt adopterade unga män; och 3) testa den fetala inprogrammeringshypotesen genom att titta på tillväxt i fosterlivet och övervikt samt tillväxt i fosterlivet och systoliskt blodtryck bland unga män födda genom enkelbörd respektive som tvillingar.

Denna avhandling baseras på nationella dataset som har skapats genom ett flertal registersamkörningar mellan Medicinska födelseregistret, Pliktverkets inskrivningsregister och flera register innehållande sociodemografiska data. Tvillingstudierna tillför även information från ett frågeformulär.

Andelen övervikt bland 18-åriga män fördubblades över en 25-års period. Resultaten visar även på en betydande socioekonomisk skillnad i övervikt, med en högre andel överviktiga unga män från lågutbildade familjer. De socioekonomiska skillnaderna tycks inte förändras över tid. Andelen övervikt var 2-3 gånger högre bland 18-åriga unga män adopterade från Latinamerika än bland unga män som inte är adopterade. Risken för övervikt var inte högre för de unga män adopterade från Indiska subkontinenten eller Fjärran östern jämfört med unga män som inte är adopterade.

Det förekom ett positivt samband mellan den gestationsåldersspecifika födelsevikten och övervikt vid 18 års ålder bland enkelbörds födda unga män. Detta resultat ger inte stöd för den fetala inprogrammeringshypotesen. Hypotesen testades även i en populationsbaserad tvillingstudie. Ett svagt positivt samband förekom för inom-pars skillnader i födelsevikt och kroppsmasseindex vid 18 års ålder bland enäggstvillingar. Tvillingbrodern med den högsta födelsevikten hade också något högre risk för övervikt vid 18 år än sin tvillingbror. Det fanns ingen mellan-pars skillnad i födelsevikt och kroppsmasseindex bland enäggstvillingar. Det förekom inga samband bland tvåäggstvillingar. Dessa resultat bland tvillingar ger inte heller stöd för den fetala inprogrammeringshypotesen.

Resultaten från studien om tillväxt i fosterlivet och systoliskt blodtryck bland unga män födda genom enkelbörd visade ett omvänt samband mellan den

gestationsåldersspecifika födelsevikten och systoliskt blodtryck vid 18 års ålder. Att det var ett oberoende omvänt samband mellan gestationsålder per se och systoliskt blodtryck är ett nytt intressant fynd. För enäggstvillingar visade resultaten på ett omvänt samband för mellan-pars skillnader i födelsevikt och systoliskt blodtryck vid 18 års ålder. Det förekom även ett omvänt samband för inom-pars skillnader i födelsevikt och systoliskt blodtryck bland enäggstvillingar, dock var inte skillnaden statistiskt säkerställd. Inga samband förekom bland tvåäggstvillingar. Resultaten från studien bland enkelbörds födda män ger stöd för den fetala inprogrammeringshypotesen men kan inte stärkas av resultaten från tvillingstudien.

Som slutsats visar resultaten från denna avhandling en stark ökning i övervikt under de senaste decennierna bland unga män. Det förekommer även betydande socioekonomiska skillnader i övervikt. Stora och oförklarade skillnader i övervikt förekommer bland internationellt adopterade jämfört med unga män som inte är adopterade. Studierna som är inriktade på den fetala inprogrammeringshypotesen visar på blandade resultat med ett klart omvänt samband mellan födelsevikt och systoliskt blodtryck bland enkelbörds födda unga män, svagt stöd i tvillingstudien och inget stöd från de övriga två studierna.

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