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# Long-term metabolic effects of a high birth weight

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### **Abstract**

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The intrauterine environment influences foetal growth as well as future response to risk factors for disease. This occurs partly through epigenetic mechanisms. Thus, birth weight is a possible risk marker of adult disease. Low birth weight is a well-known risk factor for adult disease, particularly when associated with obesity and a U-shaped relationship between birth weight and several metabolic diseases has been suggested.

In this thesis we investigated associations between a high birth weight and risk of adult disease, e.g. obesity, cardiovascular disease, type 2 diabetes and gestational diabetes.

By analyses of national register data on 759 999 subjects up to the age of 37 years, we could demonstrate an increased risk of type 2 diabetes in males, but not in females, with a high birth weight ( $>2$  SDS). The increase was particularly pronounced in males with a birth weight  $>3$  SDS. There was an association between high birth weight and obesity in males and females, but no such relation was seen for hypertension or serum lipid abnormalities.

In a clinical study, 27 cases with a birth weight  $\geq 4$  500 grams were compared with 27 controls with normal birth weight, regarding risk factors for cardiovascular disease and diabetes. The cases had a greater radial artery intima thickness and intima:media ratio compared with the controls indicating early atherosclerotic changes. Body mass index, body composition, insulin sensitivity, lipid profiles, blood pressure, resting energy expenditure and respiratory quotient did not differ between cases and controls, but females with a high birth weight had a more disadvantageous distribution of body fat.

In order to investigate associations between birth weight and pregnancy outcomes, register data on 305 893 females was analysed. The results demonstrated an association between the female's own birth weight and offspring birth weight. A high maternal birth weight was associated with increased risk of obesity. The risk of gestational diabetes was increased in females with a low, but not a high birth weight.

In conclusion, subjects with a moderately high birth weight did not differ substantially from those with a normal birth weight regarding risk factors for cardiovascular disease. However, differences in arterial wall dimensions were demonstrated in a clinical investigation, and there were differences in BMI and risk of type 2 diabetes on a population level. Since risks are most pronounced in subjects with a birth weight  $>3$  SDS, this group is in particular need of follow up and disease preventive measures.

*Keywords:* Body composition, Cardiovascular risk factors, Gestational diabetes, Glucose tolerance, High birth weight, Insulin sensitivity, Large for gestational age, Obesity, Offspring macrosomia, Type 2 diabetes

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*To all my teachers*

Jorden kan du inte göra om. Stilla din häftiga själ.  
Endast en sak kan du göra, en annan människa väl.  
Men detta är redan så mycket, att själva stjärnorna ler.  
En hungrande människa mindre betyder en broder mer.

*Stig Dagerman*



# List of Papers

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

- I     Johnsson I.W., Haglund B., Ahlsson F., Gustafsson J. (2015) A high birth weight is associated with increased risk of type 2 diabetes and obesity. *Pediatr Obes.*, 10(2):77-83
- II    Johnsson I.W., Naessén T., Ahlsson F., Gustafsson J. (2018) High birth weight is associated with increased radial artery intima thickness but not with other investigated cardiovascular risk factors. *Acta Paediatr.*, 107(12):2152-2157
- III   Johnsson I.W., Ahlsson F., Gustafsson J., High birth weight was not associated with altered body composition or impaired glucose tolerance in adulthood. *Submitted*
- IV    Johnsson I.W., Ahlsson F., Gustafsson J., Lundgren M., Females with a high birth weight have increased risk of offspring macrosomia and obesity, but not of gestational diabetes. *Manuscript*

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# Abbreviations

AGA	Appropriate for gestational age
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BP	Blood pressure
CCA	Common carotid artery
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
DOHaD	Developmental origin of health and disease
GDM	Gestational diabetes mellitus
GLM	Generalized linear model
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
HRQoL	Health related quality of life
ICD	International Classification of Disease
IGT	Impaired glucose tolerance
LDL	Low density lipoprotein
LGA	Large for gestational age
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
RA	Radial artery
REE	Resting energy expenditure
RQ	Respiratory quotient
SDS	Standard deviation score
SGA	Small for gestational age
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WHO	World Health Organization



# Introduction

As treatment and prevention of communicable disease are improving, the majority of deaths globally are now caused by non-communicable disorders like cardiovascular disease (CVD), cancer and diabetes [1], conditions which can be related to the world wide epidemic of obesity [2].

Many factors may contribute to the increase of obesity [3], including unbalanced eating habits where energy intake exceeds energy expenditure. Several genes influence the susceptibility to obesity and epigenetics may explain how environmental factors influence gene expression. In addition, viral infections and environmental toxins have been associated with increased obesity [3].

Parallel to the development of the obesity epidemic the prevalence of type 2 diabetes (T2DM) has risen dramatically. WHO estimates that, in 2014, 422 million adults suffered from diabetes, mainly T2DM. The global adult prevalence has almost doubled from 4.7% to 8.5% between 1980 and 2014. The increase continues and is most pronounced in low- and middle income countries [4].

In spite of major improvements in treatment of cardiovascular disease (CVD) it remains the most common cause of death, accountable for almost one third of deaths globally [1]. In Europe CVD accounts for 45% of all deaths and 29% of the mortality in individuals below 65 years of age [5].

To change these trends the underlying mechanisms in the development of non-communicable disease must be understood. This thesis brings a small piece to the big puzzle as it investigates the role of a high birth weight in the development of metabolic and cardiovascular disease.

## Developmental origin of health and disease

According to the concept of developmental origin of health and disease (DO-HaD) the foetal environment influences conditions during adult life [6]. From an evolutionary perspective this may be advantageous since the newborn infant is thus prepared for the postnatal environment. In our society this may lead to maladaptation as seen for infants who experienced scarcity of nutrients during foetal life and later exposure to abundance of nutritional resources [7]. Possible mechanisms behind this include epigenetic changes which may be passed on from one generation to another [8, 9].

Animal and human studies demonstrate that the foetal environment affects endocrine systems and anatomical structures, e. g. the nutritional environment may influence the number of beta-cells in the pancreas, the structure and function of hypothalamic regions involved in the control of hunger and satiety as well as type and distribution of fat cells [10-12].

Changes in disease patterns which occur more rapidly than what can be explained by changes in the genome must be induced by the environment. Such changes can be seen for major current health issues like obesity and CVD [1, 4, 9, 13]. During recent years much information on mechanisms by which the environment influences expression and effects of genes has become available by the development of molecular biology [8].

## Born small or large for gestational age

Genotype is a strong determinant of body size and body composition in different ethnic groups, e.g. in Scandinavia the population is both taller and heavier than most Asian populations. In addition, maternal size has a strong influence on offspring birth weight. The effect, often referred to as maternal constraint, is evolutionary beneficial since it reduces perinatal complications due to relative offspring macrosomia [14]. Maternal constraint is more pronounced in adolescent and primiparous females as well as in multiple pregnancies [14, 15].

Foetal growth is largely dependent on access to nutrients, especially glucose, which in turn is dependent on the maternal diet and glucose production as well as on placental function. Insulin resistance and gestational diabetes (GDM) lead to increased foetal exposure to glucose since passage across the placenta occurs by facilitated diffusion [16, 17]. The foetus, in turn, responds with increased insulin secretion resulting in accelerated growth. Maternal fat mass correlates to the degree of insulin resistance and subsequently to increased hepatic glucose production, also in the absence of GDM [18]. This may explain the association between maternal BMI and offspring birth weight [19].

Studies on long-term consequences of being born small for gestational age (SGA), starting with the findings by Barker and colleagues [20], have demonstrated a strong association between a low birth weight and ischemic heart disease. Being born SGA is also associated with an increased risk of obesity, type 2 diabetes [21] and other conditions including depression [22].

As there is also evidence of increased risk of adult disease in subjects born large for gestational age (LGA), a U-shaped association has been reported between birth weight and adult diseases, such as obesity [23] and diabetes [21]. Even if several studies confirm such an association, results from different

studies are incongruent and a recent umbrella review concluded that the evidence of birth weight as an effective public health marker is not convincing [24].

There are many different definitions of being born SGA or LGA. A low birth weight may be defined as a birth weight below -2 SDS or below the 5th or 10<sup>th</sup> percentiles [25-27]. A high birth weight is correspondingly defined as a birth weight above 2 SDS or above the 90th or 95th percentiles [25-27]. Other common definitions of high birth weight include those above 4 000 or 4 500 g [23].

Few studies have separated subjects with a very high birth weight (>3 SDS) from those with a moderately high birth weight (2-3 SDS) while studying the associations between birth weight and adult health [28].

## Obesity

There is an ongoing pandemic of overweight and obesity and in 2013 the global number of overweight or obese people was estimated to 2.1 billion, or 37% of adult men and 38% of adult women [29]. The prevalence of obesity varies between regions. While around 30% of both men and women in the United States were obese in 2013, the prevalence of obesity was only 4 to 5% in India and China [29]. The highest prevalence was found in some parts of Oceania where 50% of men were considered obese. According to the Public Health Institute 50% of the adult population in Sweden was overweight and 15% was obese in 2016 [30].

Obesity is a strong risk factor for a wide range of diseases [13] including CVD, diabetes [31], certain cancers [32] and dyslipidaemia [33]. The cause of obesity is multi-factorial and treatment is challenging [13]. Interestingly, despite the well documented associations between increased BMI and certain diseases, all-cause mortality has been shown to be reduced in overweight individuals while increased in those with obesity [34]. There is also evidence of metabolically healthy subgroups among obese individuals [35].

## Insulin resistance and glucose tolerance

Glucose tolerance can be defined as the ability of cellular uptake and metabolism of glucose. It is depending on insulin sensitivity, i.e. the effect of insulin on glucose transportation, and the beta-cell capacity to produce insulin. Insulin sensitivity may vary in different tissues such as liver, skeletal muscle and adipose tissue. Insulin resistance, i.e. reduced insulin sensitivity, is associated to adiposity, physical inactivity, inflammation and hereditary factors [36]. To maintain glucose tolerance with progressive insulin resistance there is an increased demand on insulin production. In the long run the beta-cell function

will be diminished, and when compensation no longer occurs blood glucose levels rise and type 2 diabetes (T2DM) is manifest.

The diagnosis of impaired glucose tolerance (IGT) can be based on fasting plasma glucose or on a 75 g oral glucose tolerance test (OGTT) [37]. During the OGTT both glucose and insulin levels are measured, usually up to 120 minutes, and an early sign of impaired beta-cell function is loss of the first phase insulin response that normally occurs within 15 to 30 minutes following glucose intake [38].

## Diabetes

Diabetes has increased globally by around 30% during the last decades and even if the levels are stabilizing in some areas the rise in prevalence continues, especially in low-income countries [36].

In Sweden the diabetes prevalence in the adult population was 6.8% in 2013, and even if the incidence has been stable during recent years, the prevalence is on the rise due to reduced mortality [39]. In Sweden, type 2 diabetes is considered to represent 85 to 90% of the cases. The rest includes type 1 diabetes (T1DM) and unspecified diabetes. The proportion of undiagnosed diabetes is estimated to 36.6% of all diabetes cases [39]. Treatment of T2DM starts with life style interventions, which was sufficient in 22% of known cases in 2013 [39]. According to data from the Swedish national diabetes register (NDR) 2017 [40], approximately 55% had exclusive oral medication, 10% had only insulin and the remaining patients were treated with combination therapy. The WHO defines T2DM by a fasting glucose  $\geq 7.0$  mmol/L or a 2-hour OGTT glucose  $\geq 11.1$  mmol/L [37].

Diabetes is an important risk factor both for CVD and chronic kidney disease and these three conditions together were responsible for 33% of global deaths in 2010 [41].

## Gestational diabetes

During pregnancy insulin resistance normally changes from being initially decreased to a gradual increase towards the end of the foetal development. This is physiological as the mother stores energy during early pregnancy. During late pregnancy the energy stores are mobilized to meet the demands of the growing foetus. After delivery insulin sensitivity is normally restored.

In some cases the insulin resistance leads to elevated blood glucose levels with several potential negative outcomes. The definition of gestational diabetes mellitus (GDM) varies throughout the world [42]. During the study period the predominant definition in Sweden was a 2-hour OGTT blood glucose  $\geq 9.0$  mmol/L, corresponding to a plasma glucose  $\geq 10.0$  mmol/L. The diagnostic

criteria have been lowered during 2018, in accordance with the WHO recommendations [43]. These are based on the results from the HAPO study, demonstrating a correlation between maternal glucose and adverse pregnancy outcomes, with no obvious threshold for increased risks [44]. Negative long-term infant outcomes, including increased risk of obesity and T2DM, have also been described [45].

Risk factors for GDM are obesity, heredity for diabetes and high age. The prevalence of GDM varies between countries and different ethnic groups with incidence as high as 18.9% in India and around 2% in Sweden [42, 46].

Treatment consists mainly of life style interventions e.g. healthy eating and regular exercise. If this is insufficient oral anti-diabetic treatment or insulin may be used.

## The metabolic syndrome

The metabolic syndrome constitutes a cluster of cardiovascular risk factors. There are several similar, but slightly different, definitions all including obesity, hypertension, insulin resistance and dyslipidaemia [9, 47]. Parallel to the trend of increasing obesity, an increasing prevalence of the metabolic syndrome has been demonstrated both in paediatric and adult populations [47, 48]. In a Finnish cohort of young adults the prevalence of the metabolic syndrome was between 10 and 15% depending on which set of criteria that was used [47]. Risk factors include maternal gestational diabetes, low birth weight, certain infant growth patterns as well as socioeconomic and genetic factors [48].

# Aims of the studies

The general aim of these studies was to investigate associations between a high birth weight and metabolic and cardiovascular disease in adults.

We also intended to investigate whether the risk profiles differ between subjects born moderately large and those born very large for gestational age.

## Specific aims:

Paper I        to investigate associations between a high birth weight and type 2 diabetes as well as obesity, by use of national register data.

Paper II       to investigate associations between a high birth weight and risk factors for cardiovascular disease in a clinical case-control study.

Paper III      to investigate associations between a high birth weight and anthropometry, body composition and glucose tolerance in a clinical case-control study.

Paper IV      to investigate associations between maternal birth weight and offspring birth weight, obesity in early pregnancy and gestational diabetes, by use of national register data.

# Subjects

## Paper I

The study cohort (n= 759 999) was identified through the Swedish Medical Birth Register from all term single births, with a birth weight of  $\geq -2$  SDS or more, during 1973-1982. The youngest subjects were 15 years old at the start of follow up and the subjects were between 28 and 38 years old by the end of follow up.

## Papers II and III

The case group derived from all subjects born term between 1975 and 1979, at Uppsala University Hospital, Sweden, with a birth weight  $\geq 4500$  g (n=322). A matched control group comprised subjects with a birth weight within  $\pm 1$  SDS (n=322). The cohort was offered to fill in a questionnaire regarding health related quality of life and the 203 responders who lived in Uppsala County in November 2013 were invited to a clinical examination.

The final cohort consisted of the 54 subjects, 27 cases (14 males) and 27 controls (19 males) who agreed to participate and who did not meet any exclusion criteria (pregnancy, breast feeding, gastric by-pass surgery or ongoing infection, a previous diagnosis of diabetes, hypertension or dyslipidaemia). The subjects were examined at the age of 34-40 years.

## Paper IV

The cohort was based on all females born term in Sweden 1973-1995, studied at the time of their first pregnancy 1991-2013. After exclusion of multiple births as well as subjects with malformations, non-Nordic origin, heredity for diabetes, and those who delivered their first child before the age of 18 years, 305 893 subjects remained. Data on the cohort, their mothers and their offspring was collected from the Swedish Medical Birth Register.

# Methods

## Study design

This thesis investigated associations between a high birth weight and several cardiovascular and metabolic outcomes. We used epidemiological methods in two cohort studies, based on register data covering the population of Sweden. We also performed detailed investigation of a smaller number of subjects in a clinical case-control study. The population based analyses enabled us to study very large cohorts and rare outcomes in small subgroups, while the clinical study provided detailed information on different parameters.

## Data sources

The Swedish Medical Birth Register contains data on birth weight and birth length, gestational age according to last menstrual period (or ultrasound around gestational week 18), maternal demographic factors, health and reproductive history, as well as complications during pregnancy, delivery, and the neonatal period. Information is collected prospectively during pregnancy, from the first antenatal visit. The register, started in 1973, covers more than 99% of Swedish births. Data on maternal weight in early pregnancy and smoking are registered from 1982. Diagnoses are coded by ICD 8 during 1973 to 1986, ICD 9 during 1987 to 1996 and ICD 10 from 1997 [49].

The Causes of Death Register comprises data on time and causes of death for all deceased citizens in Sweden from 1961 with a coverage of 99% [50].

The Inpatient Care Register contains dates of admission and discharge as well as discharge diagnosis, covering private and public hospitalizations from 1987. Outpatient data is available from 2001 (from 1997 for surgical units), but visits to primary health care are not recorded [51].

The Prescribed Drug Register contains information on all prescribed drugs dispatched in Swedish pharmacies from July 1, 2005, with only 0.3% loss of data [52].

Data from the different registers was linked using the unique personal identification number given to every Swedish citizen.

## **Definition of outcomes**

In the register studies we have primarily used ICD codes to identify the different outcomes.

The classification of diabetes proved to be difficult to interpret. In ICD 8 and 9 diabetes type 1 and 2 do not have separate codes and diabetes during pregnancy includes all types of diabetes occurring during pregnancy. After 1997 when ICD 10 was introduced in Sweden, separate codes for the different types of diabetes are at hand but are often inconsistently used. In paper I we defined T2DM by treatment with exclusively oral antidiabetic medication, identified by Anatomical Therapeutic Chemical (ATC) code A10B. With this strategy we would include some subjects with GDM but no subjects with T1DM. Subjects with T2DM and adjuvant insulin treatment as well as subjects on life style interventions only, and the large group with undiagnosed diabetes were misclassified, as non-diabetics.

In the case of GDM in paper IV, the ICD codes were considered reliable and were used to define diabetes in pregnancy and GDM.

## **Blood analyses**

The following venous blood samples were analysed at the certified laboratory at Uppsala University Hospital.

Glucose, insulin, C-peptide, haemoglobin A1c, high sensitive C reactive protein, lipid profile, thyroid hormones, creatinine, cystatin C and liver enzymes.

## **Ultrasound examination of carotid and radial arteries**

The arterial wall consists of three layers: lamina intima, media and externa. The dimensions of the arterial walls can be visualized by use of ultra sound technique. Increased intima-media thickness has been associated to the atherosclerotic process [53, 54]. As the initial step in this process involves inflammatory infiltration of the intima, and may result in atrophy of the media, measuring the intima:media ratio has been demonstrated to increase the specificity and sensitivity of the method [55]. The condition of the carotid artery reflects elastic arteries throughout the body and the radial artery exemplifies the conditions of the muscular arteries. As the coronary circulation consists of muscular arteries this is of special interest with regard to risk of ischemic heart disease [56].

In this study ultra-high frequency ultrasound was used to measure the intima and the media separately, in the right carotid artery (22 MHz) and the left radial artery (50 MHz) [55].

## Body composition and anthropometry

The body composition constitutes the proportion of the different types of tissue. The most commonly used compartments are fat mass, fat free mass and bone mineral [57]. This is relevant since those compartments have very different metabolic features and thus the body composition is related to metabolic outcomes [58, 59].

The proportions of the different compartments may be calculated from whole body density and the estimated standard density of the different compartments [57]. As density is largely dependent on the water content of the tissue, the level of hydration will affect the results. To compensate for this the amount of total body water may be included in the calculations.

Whole body density may be calculated from the subject's weight and volume measured by air displacement plethysmography (BodPod) [57].

By multi-frequency bioimpedance the electric conductivity is measured. As the conductivity is different in water compared with other components of the body, the measurements generate the estimated percentage of total body water. As lean body mass has a higher content of water compared with fat the proportion of lean body mass may be calculated [57].

There are more precise methods e. g. magnetic resonance imaging (MRI) [57], but these are, to this date, not readily available. Instead combinations of the different methods may be used and several multi-compartment methods have been developed for that purpose. In this study, a three compartment model based on BodPod and bio-impedance measurements has been used [60].

Not only the amount, but also the distribution of body fat is associated to metabolic disease, as visceral adiposity is more strongly related to insulin resistance and risk of cardiovascular disease compared with subcutaneous and peripheral fat [31].

In this study several anthropometric methods were used to visualize the fat distribution. Increased sagittal abdominal diameter, waist circumference or waist-hip ratio as well as a decreased thigh circumference are indicating an unfavourable fat distribution with increased amount of visceral fat.

To estimate the amount of subcutaneous fat, as well as total body fat, skin-fold caliper measurements were performed on four locations; subscapular, iliac, biceps and triceps [61].

## Energy expenditure

Total energy expenditure is the sum of the basal energy expenditure and the expenditure related to activity and digestion. Energy expenditure may be measured by the technically very demanding direct calorimetry, meas-

uring heat production, or by indirect calorimetry, measuring oxygen consumption and carbon dioxide production [62]. We used indirect calorimetry with an open-circuit ventilated technique in the clinical study. After a 10-hour overnight fast and 30 minutes of supine rest exhaled air was collected by use of a canopy, and inhaled and exhaled volumes of oxygen and carbon dioxide were measured during  $\geq 15$  minutes [63]. Resting energy expenditure (REE, kcal/min) was calculated from the oxygen consumption and carbon dioxide production. As energy expenditure is dependent on body size and different tissues have different metabolic activity we calculated REE total/day as well as REE/kg/day and REE/kg lean body mass/day to be able to compare metabolic activity between groups of subjects. To estimate energy expenditure related to physical activity the subjects carried an accelerometer on one ankle during four consecutive days [64, 65].

The respiratory quotient between exhaled volumes of carbon dioxide and consumed oxygen ( $RQ = \text{produced CO}_2 / \text{consumed O}_2$ ) corresponds to the proportion of substrate used. An RQ of 1.0 is equivalent to exclusive carbohydrate oxidation and a quotient of 0.7 is equivalent to pure lipid oxidation [66]. Respiratory quotient is influenced by dietary intake, stress and physical activity. A stable RQ was used as an indicator to when a subject was in a resting state and measurements of REE could be recorded.

## Insulin resistance and glucose tolerance

Golden standard for measuring insulin resistance is the hyperinsulinaemic euglycaemic clamp technique. The technique is relatively complicated and does not reflect glucose uptake from the gut.

In this study we chose to perform a 75g oral glucose tolerance test (OGTT), which can be considered more physiological. The test was preceded by a 10-hour overnight fast. Venous blood samples were drawn before and after the intake of 75g of glucose, at -5, 5, 10, 15, 30, 60, 90 and 120 min, for analyses of plasma glucose and insulin.

Increased levels of fasting glucose and insulin were interpreted as impaired fasting glucose, indicating insulin resistance. To analyse the results further, we used the modified homeostasis model assessment, HOMA2, based on fasting measurements, calculated with the HOMA Calculator v.2.2.3 (downloaded from <https://www.dtu.ox.ac.uk/homacalculator/download.php>) {Levy, 1998 #354}. We also used the Matsuda index including analysis of post-load glucose-insulin interaction [67], as well as areas under the curves (AUC) for glucose and insulin from time zero up until 30 minutes and 120 minutes, respectively, calculated using the linear trapezoidal rule on the arithmetic means at each follow up time. The early insulin response during the OGTT was considered to reflect the hepatic

insulin sensitivity [68]. The accuracy of these methods is reduced in subjects with treatment of diabetes or severely impaired beta-cell function [68]. This was not the case in any subject in our cohort.

Impaired glucose tolerance (IGT) was defined according to the WHO criteria as fasting plasma glucose between 6.1 and 6.9 mmol/L or a 2 h glucose during OGTT of 7.8 to 11.0 mmol/L. Fasting glucose above 7.0 mmol/L or 2h glucose of 11.1 mmol/L or more was classified as T2DM [37].

## Calculations and statistical analyses

In paper I the statistical analyses were performed using SAS for Windows, version 9.3, SAS Institute Inc., Cary, NC, USA. Hazard Ratio was calculated with 95% confidence interval (CI) through Cox regression. Risk time was defined as person time from start of follow up until event date, death or end of follow up. Incidence was calculated per 100 000 person years.

Follow up time starts on January 1, 1998 (July 1, 2004 for T2DM), when ICD-10 was used in all of Sweden and follow up time ends on July 31, 2010. Subjects who died before July 1, 2005 (when the Prescribed Drug Register started) were not included. Event date was defined as date of drug prescription (oral antidiabetic medication), date of admission to hospital or date for outpatient visit to hospital.

In papers II and III the statistical analyses were performed with IBM SPSS Statistics 22, IBM Corp., Armonk, NY, USA, SAS 9.3 and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Differences between the case and the control groups were assessed non-parametrically by Mann-Whitney U-test.

By use of the generalized linear model, GLM analysis, group differences were assessed, controlled for gender and smoking, as well as controlled for gender, smoking BMI, systolic and diastolic blood pressure, CRP and apolipoprotein B:A1 ratio.

In paper IV the statistical analyses were performed in IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) and SAS 9.3 (SAS Institute Inc., Cary, NC, USA). The associations between birth weight and GDM and between maternal and offspring birth weight were evaluated by multiple logistic regression and risk estimates were expressed as Odds ratios (OR) with 95% confidence interval (CI).

Two tailed p values of  $<0.05$  were considered significant in all papers.

The studies were approved by the Regional Ethical Review Board in Uppsala (paper I-III: 2009/321; paper IV: 2011/141).

# Results

## Paper I

In this register based cohort study the association between a high birth weight and later metabolic disease was investigated. Main outcomes were T2DM (defined as receiving oral antidiabetic medication), diagnosis of obesity, hypertension, dyslipidaemia or CVD. The cohort was divided into three groups based on birth weight: appropriate for gestational age (AGA), moderately large for gestational age (birth weight 2-3 SDS) and very large for gestational age (>3 SDS). Notable differences were seen between males and females and between subjects with a very high birth weight and those with a moderately high birth weight.

The studied males born with a birth weight between 2 and 3 SDS had a doubled risk of T2DM, whereas the corresponding risk for those with a very high birth weight (>3 SDS) was more than five-fold increased, compared with those with an average birth weight (Table 1). In females the general risk of T2DM was higher than that in males, but a very high birth weight did not increase this risk further. In females, a moderately high birth weight was associated with a lower risk and HR for those with a very high birth weight did not differ from that in controls (Table 1). The risk of obesity increased with increasing birth weight in both genders with almost doubled HR for females and more than doubled HR for males with very high birth weights (Table 1).

Subjects with a moderately high birth weight had a somewhat reduced risk of dyslipidaemia. The incidence of dyslipidaemia was 50% higher in males than in females even if the incidence of obesity was four times higher in females. The incidence of hypertension was three times higher in females and the risk was not associated with birth weight.

**Table 1** Incidence per 100 000 person years and hazard ratio (HR), 95% confidence interval (CI 95%) for T2DM, obesity, hypertension and dyslipidaemia for subjects with moderately high (LGA1) and very high birth weight (LGA2) compared with subjects born appropriate to gestational age (AGA).

<b>Females</b>	<b>N</b>	<b>Incidence</b>	<b>HR (CI 95%)</b>	<b>Adj HR (CI 95%)</b>
<b>T2DM</b>				
AGA	1 583	72.8	1.00*	1.00*
LGA1	23	43.8	0.60 (0.40-0.91)	0.60 (0.40-0.91)
LGA2	8	133.0	1.83 (0.91-3.66)	1.71 (0.85-3.43)
<b>T2DM (PCOS excluded)</b>				
AGA	1 013	46.6	1.00*	1.00*
LGA1	15	28.6	0.61 (0.37-1.02)	0.61 (0.36-1.01)
LGA2	5	83.1	1.79 (0.74-4.30)	1.60 (0.66-3.87)
<b>Obesity</b>				
AGA	11 886	265.2	1.00*	1.00*
LGA1	372	345.0	1.30 (1.18-1.45)	1.32 (1.19-1.46)
LGA2	62	501.7	1.91 (1.49-2.45)	1.85 (1.44-2.37)
<b>Hypertension</b>				
AGA	30 353	690.6	1.00*	1.00*
LGA1	715	673.4	0.97 (0.90-1.05)	0.97 (0.90-1.04)
LGA2	79	646.5	0.94 (0.75-1.17)	0.91 (0.73-1.14)
<b>Dyslipidemia</b>				
AGA	2 076	46.0	1.00*	1.00*
LGA1	34	31.2	0.68 (0.48-0.95)	0.67 (0.48-0.94)
LGA2	9	71.8	1.56 (0.81-3.01)	1.51 (0.78-2.90)
<b>Males</b>				
<b>T2DM</b>				
AGA	447	19.6	1.00*	1.00*
LGA1	23	37.2	1.90 (1.25-2.89)	1.91 (1.25-2.90)
LGA2	8	113.9	5.82 (2.89-11.71)	5.44 (2.70-10.96)
<b>Obesity</b>				
AGA	2 936	62.0	1.00*	1.00*
LGA1	116	90.4	1.46 (1.21-1.76)	1.47 (1.22-1.77)
LGA2	23	157.6	2.56 (1.70-3.85)	2.46 (1.63-3.71)
<b>Hypertension</b>				
AGA	11 514	244.5	1.00*	1.00*
LGA1	302	236.3	0.97 (0.86-1.08)	0.96 (0.86-1.08)
LGA2	46	316.5	1.30 (0.97-1.74)	1.25 (0.94-1.67)
<b>Dyslipidemia</b>				
AGA	3 294	69.6	1.00*	1.00*
LGA1	68	52.9	0.76 (0.60-0.97)	0.75 (0.59-0.96)
LGA2	16	109.2	1.57 (0.96-2.57)	1.47 (0.90-2.40)

## Paper II

**Table 2.** Distribution of risk factors for CVD in cases and controls, illustrated by median, range and group discrimination by Mann-Whitney U-test. n.s.= non-significant.

CVD risk factors	Cases	Controls	P
	Median (range)	Median (range)	
BMI (kg/m <sup>2</sup> )	23.5 (19.6-38.3)	23.6 (18.6-33.1)	n.s.
Systolic BP (mm Hg)	113 (96-127)	115 (100-136)	n.s.
Diastolic BP (mm Hg)	73 (61-86)	76 (62-100)	n.s.
HbA1c (mmol/mol)	33.0 (25-41)	34.0 (29-41)	n.s.
CRP (mg/L)	0.72 (0.00-8.00)	0.62 (0.00-5.70)	n.s.
Triglycerides (mmol/L)	0.73 (0.29-1.74)	0.81 (0.34-3.20)	n.s.
Cholesterol (mmol/L)	4.30 (3.20-5.80)	4.40 (3.40-6.70)	n.s.
HDL (mmol/L)	1.30 (0.90-1.80)	1.20 (0.61-2.10)	n.s.
LDL (mmol/L)	2.60 (1.50-4.40)	2.50 (1.50-5.30)	n.s.
Apo A1 (g/L)	1.40 (0.96-1.80)	1.40 (0.96-1.90)	n.s.
Apo B (g/L)	0.78 (0.49-1.20)	0.76 (0.47-1.50)	n.s.
Apo B/A1	0.60 (0.30-1.00)	0.60 (0.30-1.30)	n.s.
CCA-IMT (mm)	0.60 (0.38-1.08)	0.64 (0.36-1.07)	n.s.
CCA - IT (mm)	0.07 (0.06-0.09)	0.07 (0.06-0.09)	n.s.
CCA - I:M ratio	0.15 (0.08-0.27)	0.13 (0.08-0.22)	n.s.
RA- IT (mm)	0.028 (0.016-0.047)	0.021 (0.013-0.029)	<0.005
RA - I:M ratio	0.21 (0.12-0.43)	0.17 (0.10-0.22)	<0.005

In this clinical study we investigated the occurrence of risk factors for cardiovascular disease in Swedish adults, aged 34 to 40 years, with a birth weight  $\geq 4\ 500$  g in comparison to those of a control group with a birth weight within  $\pm 1$  SDS.

The mean birth weight was  $4\ 737 \pm 273$  g in the cases and  $3\ 475 \pm 267$  g in the controls. The groups did not differ regarding age, smoking or heredity for diabetes. There was a somewhat larger proportion of females in the case group but the difference was not statistically significant.

Most investigated risk factors did not differ between the groups (Table 2). The intima-media thickness of the radial artery was equal in both groups, but the intima thickness was 37% higher and the intima:media ratio was 44% higher in the cases. The prevalence of obesity was 3% in both groups, whereas 8% of the cases and 6% of the controls were overweight, i.e. not representing a significant difference between cases and controls.

## Paper III

**Table 3** Parameters related to glucose homeostasis in cases and controls.  
n.s.= non-significant.

Glucose homeostasis	Cases N=27	Controls N=27	Sig.
	Median (range)	Median (range)	
HbA1c, mmol/mol	33.0 (25.0-41.0)	34.0 (29.0-41.0)	n.s.
Fasting glucose, mmol/L	5.60 (4.7-6.2)	5.45 (4.7-6.4)	n.s.
Fasting insulin, mU/L	4.80 (1.63-21.00)	4.05 (0.83-23.00)	n.s.
Fasting c-peptide, nmol/L	0.50 (0.38-1.10)	0.50 (0.26-1.32)	n.s.
OGTT, glucose 120 min, mmol/L	7.30 (4.9–9.6)	7.00 (4.6–11.7)	n.s.
HOMA2-IR	0.65 (0.38-2.76)	0.55 (0.37-3.06)	n.s.
HOMA2-beta cell function, %	57.7 (34.1-141.5)	53.7 (40.7-133.0)	n.s.
HOMA2-insulin sensitivity, %	154.3 (36.2-263.0)	183.1 (32.7-267.3)	n.s.
Matzuda index	7.66 (2.31-14.27)	8.08 (1.35-26.57)	n.s.

We investigated to what extent anthropometric characteristics, body composition and glucose tolerance differed between 27 subjects with a birth weight of 4 500 g or more and a control group of 27 subjects with a birth weight  $\pm 1$ SDS, at the age of 34 to 40 years.

Both male and female cases were taller than the controls, and female cases had a higher median weight and a greater sagittal abdominal diameter as well as abdominal circumference (Table 4).

Most studied parameters i.e. BMI, body fat proportion, energy expenditure, respiratory quotient, physical activity level, insulin sensitivity and beta cell function (calculated by the HOMA2 method and the Matsuda index as well as areas under the curves for glucose and insulin during the OGTT) did not differ between cases and controls.

Five cases (1 male) and nine controls (7 males) had impaired glucose tolerance according to the WHO criteria and one male control fulfilled criteria for type 2 diabetes.

**Table 4** Anthropometric data and body fat mass in case and control groups separated by gender. n.s. = non-significant

	Females			Males		
	Cases N=13	Controls N=8	Sig.	Cases N=14	Controls N=19	Sig.
<b>Anthropometrics</b>	Median (range)	Median (range)		Median (range)	Median (range)	
Weight, kg	68.5 (58.0-117.6)	60.3 (51.6-77.7)	0.045	87.7 (71.0-135.7)	82.4 (67.2-100.4)	n.s.
Height, cm	172.5 (168.7-181.8)	168.8 (160.7-171.0)	0.000	187.6 (174.4-199.7)	181.4 (170.0-191.8)	0.006
BMI, kg/m <sup>2</sup>	22.9 (19.6-35.6)	21.0 (18.6-27.4)	n.s.	25.8 (20.4-38.3)	24.3 (21.6-33.1)	n.s.
Sagittal abdominal diameter, cm	18.5 (16.4-26.5)	17.4 (15.0-21.9)	0.030	20.8 (17.7-30.0)	19.7 (17.0-26.6)	n.s.
Abdominal circumference, cm	80.5 (72.6-110.5)	72.9 (69.5-91.7)	0.016	89.3 (76.0-121.1)	85.5 (74.0-103.0)	n.s.
Waist-hip ratio	0.88 (0.78-0.97)	0.84 (0.78-0.98)	n.s.	0.91 (0.80-1.06)	0.89 (0.84-1.10)	n.s.
Skinfold caliper sum, mm	61.1 (36.4-155.9)	47.3 (34.0-75.5)	n.s.	52.7 (24.9-145.1)	40.7 (24.7-115.6)	n.s.
Thigh circumference, cm	55.0 (50.5-69.0)	53.4 (48.6-58.0)	n.s.	56.9 (51.0-64.3)	55.0 (51.0-64.7)	n.s.
<b>Body composition, % fat mass</b>						
BodPod, %	29.6 (18.5-49.2)	27.2 (20.3-41.9)	n.s.	21.8 (8.4-40.9)	22.0 (13.2-42.7)	n.s.
Bioimpedance, %	23.5 (15.0-41.0)	21.5 (12.1-31.6)	n.s.	14.6 (8.7-35.0)	15.0 (7.1-35.1)	n.s.
Three compartment model, %	26.3 (17.5-44.5)	23.9 (16.8-36.3)	n.s.	17.9 (9.1-37.8)	18.2 (10.4-38.4)	n.s.

## Paper IV

Offspring birth weight was related to maternal birth weight also when the analyses were controlled for maternal BMI, age and smoking.

Females with a moderately high birth weight (2 to 3 SDS) had more than three-fold risk of moderate or severe offspring macrosomia compared with subjects with an average birth weight (Table 5). The corresponding risks for subjects with a very high birth weight were five-fold and seven-fold increased (Table 5). Offspring birth weight was also closely related to maternal BMI with seven times higher risk of severe offspring macrosomia in obese subjects compared with lean subjects (Table 5).

The birth weight of the female was associated with BMI in pregnancy and those with a very high birth weight (>3 SDS) had 50% increased risk of overweight and doubled risk of obesity compared with normal weight subjects.

High maternal birth weight was not associated with increased risk of GDM, but in subjects with a low birth weight this risk was more than doubled (Table 6). The prevalence of GDM was 0.5% in the whole cohort. Overweight and obesity was associated with increased risk of GDM, with a more than six-fold increase in obese subjects (Table 6).

**Table 5 (following page)** Risk of offspring birth weight (BW) between 2-3 SDS or above 3 SDS, in relation to maternal birth weight SDS, BMI in early pregnancy (kg/m<sup>2</sup>), age (years) and smoking. ORs are adjusted for BMI, age and smoking



**Table 6** Prevalence and risk of gestational diabetes (GDM) in relation to maternal birth weight, BMI, age and smoking.

Maternal characteristics	Prevalence of GDM N (%)	Risk of GDM OR (95%CI)	
		Unadjusted	Adjusted
<b>Birth weight (SDS)</b>			
<-2	87 (1.3)	2.42 (1.95-3.01)	2.49 (2.00-3.12)
-2 to 2	1506 (0.5)	1.00*	1.00*
2 to 3	32 (0.4)	0.86 (0.61-1.22)	0.77 (0.54-1.10)
>3	5 (0.6)	1.23 (0.51-2.98)	1.02 (0.42-2.47)
<b>BMI, kg/m<sup>2</sup></b>			
<18.5	27 (0.4)	1.11 (0.76-1.64)	1.15 (0.78-1.71)
18.5-24.9	514 (0.3)	1.00*	1.00*
25-29.9	396 (0.7)	2.08 (1.84-2.36)	2.13 (1.87-2.42)
>=30	548 (2.0)	6.47 (5.77-7.25)	6.71 (5.97-7.54)
<b>Age, years</b>			
18-24	449 (0.4)	0.81 (0.72-0.91)	0.74 (0.65-0.84)
25-29	669 (0.5)	1.00*	1.00*
30-34	422 (0.6)	1.17 (1.04-1.32)	1.24 (1.10-1.41)
>=35	90 (0.9)	1.71 (1.37-2.14)	1.49 (1.18-1.88)
<b>Smoking</b>			
No	1382 (0.5)	1.00*	1.00*
Yes	181 (0.6)	1.20 (1.02-1.40)	1.22 (1.04-1.43)
* ref.			

# Discussion

Non-communicable diseases such as cardiovascular disease, obesity and diabetes are increasing dramatically and there is an urgent need so understand the underlying mechanisms [1]. Early environmental influences may affect both birth weight and risk of adult disease and primarily low, but also high birth weights have been associated to adverse health outcomes later in life [23, 69].

This thesis comprises two epidemiological register based studies and one clinical case-control study investigating the associations between a high birth weight and risk of adverse adult metabolic outcomes. The results from the epidemiological studies demonstrate an association between a high birth weight and increased risk of obesity. Further, males with a high birth weight, particularly very high, had increased risk of T2DM. Females with a high birth weight had increased risk of having LGA offspring, but there was no association to gestational diabetes. The clinical study demonstrated a difference between cases and controls regarding intima thickness and intima:media ratio in the radial artery, but apart from that there were modest differences between the groups.

In most clinical and research settings infant macrosomia, or LGA is defined as either being born with a birth weight above the 90<sup>th</sup> percentile, above 2 SDS, above 4 000 or 4 500 g. According to the normal distribution of birth weights, the majority of LGA infants have birth weight just above the limit.

Our results point out subjects with very high birth weights i.e. >3 SDS as a group with more pronounced risks of metabolic disease, and preventive efforts should be focused on this group.

## **Strengths and limitations**

The Swedish national health registers with high coverage enabled us to study a large amount of data in a nationwide cohort, and to study subgroups e.g. subjects with birth weight >3 SDS. The individual identity number of all Swedish citizens makes it possible to study intergenerational effects by linking data from different registers. Recall bias is minimized by the forwarding of data to the registers at the time of event. The Swedish population is relatively homogenous regarding ethnicity and socio-economic factors and all citizens have access to public health care including preventive antenatal care. As ethnicity influences our research outcomes we have selected a homogenous cohort for the epidemiological studies, reflecting the situation in a Nordic population.

Even if the clinical cohort was limited in size the cases and controls were well matched and they were thoroughly investigated with several sensitive methods. Data on anthropometrics and body composition was collected in a standardized manner using the same equipment in all cases. Investigator dependent methods, such as the skin fold caliper measurements, were performed by the same experienced research assistant in all subjects. The method of ultra-high frequency ultrasound investigation of the radial artery is more sensitive than the methods commonly used and may provide new knowledge on the development of atherosclerosis.

The limitations of the studies include the general problem of underreporting to registers, even if the coverage in the registers is very high. In the studied age groups metabolic disease is often still asymptomatic, and thus undiagnosed. This is elucidated in a large Finnish study demonstrating a surprisingly high prevalence of metabolic and cardiovascular abnormalities already at the age of 24 to 39 years [47, 70]. As underreporting should not be associated to birth weight, this is a concern when analysing prevalence but not in analyses regarding risk related to birth weight. Some background data on the mothers of the subjects regarding parameters such as diabetes, BMI and smoking were incomplete in the registers, and could not be controlled for in the analyses.

In the recruitment for the clinical study the cohort size became limited due to practical reasons as many of the invited subjects lacked possibility or motivation to spend a full day at the hospital for detailed investigations. The risk of attracting both those who worry about their health and those with a particular interest in a healthy life style, may affect the external validity. Even if the difference in gender distribution was not statistically significant, it may still represent a limitation, as there are differences between the genders regarding risk for CVD [71]. To address this issue gender was entered as a confounding factor in the analyses.

Two different definitions of birth weight were used in this thesis. In the register studies LGA was defined by a birth weight  $>2$  SDS, and the LGA group was further separated into birth weights between 2 and 3 SDS, and birth weights  $>3$  SDS. The clinical case cohort was identified from a previous study, defining high birth weight as a birth weight  $\geq 4500$  g. This definition is well comparable to international studies but does not relate birth weight to gestational age. When translated into SDS, the clinical case group mainly covered birth weights between 2 and 3 SDS. The lack of subjects with a birth weight  $>3$  SDS represents a study limitation since our epidemiological data demonstrated increased risk of metabolic disease particularly in this group [72]. The size of our clinical cohort as well as the narrow range of high birth weight may explain some of the inconsistency in the clinical results compared with the epidemiological studies regarding risk of obesity and diabetes.

## Obesity and lipid profile

In addition to storage of energy adipose tissue also exerts metabolic and inflammatory activity, mediated by secretion of adipokines. The metabolic features largely depend on the location of the adipose tissue and the degree of obesity. Visceral fat is more strongly associated to metabolic disease compared with subcutaneous fat [73]. Adipose tissue in obese individuals primarily release adipokines that are pro-inflammatory and induce insulin resistance, while the corresponding tissue in lean individuals, secrete anti-inflammatory agents that are involved in the normal glucose homeostasis [73]. Adipokines also affect lipolysis and lipid metabolism. In an obese individual lipolysis is stimulated and increased levels of fatty acids are released into the circulation resulting in insulin resistance and increased inflammation [31, 73].

In both register based studies we demonstrated an association between high birth weight and risk of adult obesity. This is in accordance with meta-analyses demonstrating increased risk of obesity in subjects with a birth weight above 4 000 g [74, 75]. The association may partly be explained by the fact that macrosomic infants are more likely to have obese mothers [18, 76]. Consequently, these infants have both a genetic and an environmental risk of obesity [9] as well as possible effects of foetal programming related to maternal overweight [7].

On the other hand, a recent review covering 135 studies from different continents, reported no clear trend regarding associations between high birth weight and obesity [77]. In the clinical study, we did not demonstrate any difference in BMI between the subjects with birth weights  $\geq 4\ 500\text{g}$  and those with a birth weight within  $\pm 1$  SDS. There were, though, a trend where several parameters e. g. BMI, sagittal abdominal diameter and abdominal circumference were higher in the cases. In a larger cohort with a greater range of high birth weights these results may have represented a significant difference.

The prevalence of obesity was lower in the clinical cohort, aged 34 to 40 years, compared with that of the entire adult Swedish population [78], which is to be expected as BMI tends to increase with age [79].

In the investigation of body composition we used a three compartment model based on bioimpedance and air displacement plethysmography data [60], to compensate for limitations in the individual investigative models [57]. The proportion and distribution of body fat is related both to risk of diabetes [31] and CVD [23]. In our clinical cohort there was no difference regarding body composition between cases and controls but the anthropometric data demonstrated a less favourable fat distribution in female cases, with more abdominal fat compared with controls [80].

Energy expenditure and RQ, measured by indirect calorimetry [63], are related to body composition but there are diverging results regarding an association with metabolic disease. Thus, both high and low RQs have been associated to increased risk of metabolic disease [31, 35, 42, 81]. However, we found

no differences in RQ or REE between case and control subjects in the present study.

Abnormal plasma lipid profiles are related to atherosclerosis [82]. In the epidemiological study on parameters of the metabolic syndrome in males and females born 1973 to 1982 [72], the incidence of dyslipidaemia was lower in females than in males. Further, the risk was decreased both in males and females with moderately high birth weight, despite increased obesity in both groups. In accordance with earlier work on both children and adults [70, 83], the clinical study data showed no association between birth weight and dyslipidaemia.

## **Type 2 diabetes**

In the epidemiological study covering both genders, we concluded that the risk patterns differed between males and females [72]. Males with a high birth weight had increased risk of T2DM compared with those with a normal birth weight. In those with a birth weight above 3 SDS the risk was pronounced with a more than five-fold increase. This risk was only to a small extent explained by the association between obesity and T2DM [84]. On the other hand females with a birth weight between 2 and 3 SDS, had a slightly reduced risk of T2DM. Previous studies have demonstrated an inverse association between birth weight and risk of T2DM in the low birth weight spectrum. As far as high birth weight is concerned both increased and reduced risks have been reported [21, 23, 85, 86]. In our cohort the prevalence of T2DM was almost doubled in females compared with males which contrasts with data on the whole Swedish adult population [39], but is in line with data on adolescents in Sweden and elsewhere [87, 88]. The female predominance may to some extent be explained by treatment of insulin resistance due to polycystic ovary syndrome [88], but the estimates of risk related to birth weight did not change substantially when such individuals were excluded.

A major challenge in this study was to validate diabetes diagnoses in the registers. The ICD-codes were of limited value in the separation of different types of diabetes. As the T2DM analyses instead were based on exclusive oral antidiabetic medication, subjects with T2DM treated with insulin or diet and life style adjustments as well as those with undiagnosed disease were misclassified as non-T2DM. This approach should not have overestimated the risk of T2DM. The occurrence of undiagnosed or unreported conditions was relevant to all diagnoses, including obesity, but the error was not related to exposure and was therefore considered non-differential.

In the clinical study we analysed OGTT data according to the HOMA2 and the Matsuda models [67] to assess insulin resistance and glucose tolerance in subjects with a birth weight  $\geq 4500$  compared with a control group with birth weights within  $\pm 1$  SDS. We also compared the AUC for glucose and insulin during the first 30 minutes of the OGTT separately to describe possible differences in the first phase insulin response, as an indicator of prediabetes [38].

There were no differences related to glucose homeostasis between the compared groups. These results are in some contrast to our results in study I [72], in which increased risk of T2DM was demonstrated in males, but in line with other reports on insulin sensitivity in relation to birth weight [23, 86]. In previous studies there is little information on risk of diabetes in subjects with a very high birth weight.

### **Gestational diabetes and offspring macrosomia**

Gestational diabetes is related to T2DM by several common risk factors and individuals who once had GDM also have increased risk of manifest T2DM later in life [89]. Increased risk of GDM has been described both in subjects born SGA and LGA [27, 90]. To explore this association in a Swedish national cohort and to analyse whether risks differ between those with a moderately high, compared with those with a very high birth weight, we performed a register based cross-sectional cohort study on females born 1973 to 1995.

Our results confirmed an increased risk of GDM in individuals with a low birth weight, but no increased risk was found in subjects with a high birth weight, not even in the subgroup with very high birth weights  $>3$  SDS.

The overall incidence of GDM was 0.5%, which was lower than expected as there is evidence of a GDM incidence around 2% in the Swedish population [46]. There are several possible explanations including the fact that our cohort did not include non-Nordic origin, older and multiparous women, i.e. women with increased risk of GDM [91]. Another important factor is that the screening system does not identify all cases with GDM [91]. From 2018 the incidence of GDM will rise as Sweden adheres to the diagnostic criteria of WHO [43] defining GDM by a fasting glucose  $\geq 5.1$  mmol/L or a 2 h glucose  $\geq 8.5$  mmol/L during OGTT.

Apart from long-term metabolic effects in the offspring, high birth weight is associated to several perinatal complications for the infant, such as asphyxia, shoulder dystocia and hypoglycaemia, as well as increased risk of birth injuries for the mother [19]. Our results confirm an intergenerational chain of increasing maternal BMI, leading to increasing birth weight [75, 91-93], in turn resulting in further increase in BMI in next generation of mothers [94]. Even though the level of overweight and obesity was lower in this cohort (22.1% and 10.0%, respectively) compared with many populations [13, 95], our results confirm a trend of increasing obesity between generations [94] that constitutes a possible area of intervention.

### **Cardiovascular risk factors**

In study II we focused on differences regarding risk factors for CVD between subjects with a high birth weight and those in the control group. Our data, both from registers and the clinical study, confirmed earlier findings that a high birth weight does not increase the risk of adult hypertension [34, 96-99].

The risk of CVD is associated to BMI [100] and increased visceral adiposity. These risk factors are also related to an inflammatory process, involved in the development of atherosclerosis, which is reflected by the level of CRP [53, 101]. In our cohort there were no differences in CRP when related to birth weight.

An increase of intima thickness of arterial walls follows early in the atherosclerotic process as a consequence of inflammatory infiltration and storage of lipids, proteins and calcium [53]. This may be accompanied by a decreased media thickness [102]. High frequency ultrasound measurement of carotid intima-media thickness represents a widely used method to assess incipient atherosclerosis and cardiovascular risk [54, 55, 103, 104]. In this study we also examined the radial artery, since this is a muscular artery with characteristics similar to those of the coronary arteries [56]. The intima and media were also measured separately and their ratio was calculated in order to increase the sensitivity of the method [55, 105, 106]. We found no associations between birth weight and the carotid wall dimensions, but the intima thickness and intima:media ratio of the radial artery was increased in the subjects with a high birth weight. This finding may imply that atherosclerosis begins earlier in muscular than in elastic arteries, possibly indicating an increased risk of atherosclerosis in relation to birth weight [56]. In a Finnish cohort of similar age increased carotid intima-media thickness was demonstrated in subjects with a high birth weight, but no measurements were made on the radial artery [70].

Even if this thesis investigates high birth weight mainly from a risk perspective, there are also reports on possible advantages of having a moderately high birth weight. Decreased all-cause mortality have been demonstrated in subjects with a birth weight above the 90<sup>th</sup> percentile [69], and for those with a birth weight between 3.7 to 4.2 kg [107].

# Conclusions

Subjects born with a very high birth weight (LGA >3 SDS) differ from those born with a moderately high birth weight (LGA 2-3 SDS) regarding metabolic outcome.

Males with a birth weight above 3 SDS have a five-fold increased risk of early development of T2DM.

Being born with a birth weight between 2 and 3 SDS is associated with a decreased risk of early development of T2DM in females.

Subjects born with a birth weight above 2 SDS have an increased risk of obesity, and the risk is particularly high in those with a birth weight above 3 SDS.

Subjects born with a birth weight  $\geq 4500$  g display no major differences from those with birth weight within  $\pm 1$  SDS, regarding hypertension, lipid profile or body composition.

Subjects born with a birth weight  $\geq 4500$  g have increased radial intima thickness and intima:media ratio.

Females with a high birth weight (>2 SDS), particularly those with a very high birth weight (>3 SDS), have increased risk of obesity in pregnancy and increased risk of offspring macrosomia.

A low, but not a high, maternal birth weight is associated to increased risk of gestational diabetes.

## Future perspectives

The importance of the foetal environment on risk of adult disease is a vast and active field of research. This thesis has identified individuals with a very high birth weight ( $>3$  SDS) as a group of particular interest for further studies.

Since the subjects in the studies were relatively young and, as metabolic and cardiovascular diseases develop with age, longer follow up regarding body composition, glucose tolerance and other cardiovascular risk factors is needed.

The differences in radial artery wall dimensions demonstrated in subjects with a high birth weight should be evaluated in larger cohorts and followed up prospectively regarding cardiovascular disease. Such investigations should include subjects with very high birth weight.

Epidemiological analyses on causal factors behind very high birth weights should be performed, as the Medical Birth Register now includes detailed maternal data. During recent years the registration of maternal diagnoses, socio-economic factors and metabolic characteristics has been extended. Further, the differences between subjects with a very high birth weight and those with a moderately high birth weight, as well as intergenerational effects of weight should be investigated.

In order to investigate associations between a high birth weight and health related quality of life, data from a self-reported questionnaire will be analysed, comparing individuals with a birth weight of  $\geq 4500$  g with those with average birth weight.

# Summary in Swedish

## Långsiktiga metabola följer av hög födelsevikt

Miljön under fostertiden har inverkan både på fostertillväxt och epigenetiska förändringar i arvsmassan. Dessa förändringar påverkar i sin tur hur vi senare i livet interagerar med vår miljö och vår möjlighet att hantera riskfaktorer för sjukdom. Fostrets näringstillgång styr till exempel, förutom födelsevikten, aktiviteten hos gener kopplade till kontroll av näringsintag och förbränning i vuxen ålder.

I takt med den globala ökningen av övervikt och fetma ökar även sjukdomar som diabetes och hjärt-kärlsjukdom. Dessa sjukdomsprocesser pågår ofta under lång tid innan symtom uppkommer. För att möjliggöra tidig prevention och behandling är det viktigt att identifiera riskgrupper. Låg födelsevikt har visats vara en prognostisk faktor för senare sjukdomsutveckling. Mycket talar för att även hög födelsevikt är kopplad till ökad sjukdomsrisk bland annat via övervikt och fetma senare i livet. Fördelar med en hög födelsevikt finns också beskrivna. Man vet dock inte säkert vid vilken födelsevikt som nackdelarna överväger. I denna avhandling undersöktes samband mellan hög födelsevikt och risk för metabol och kardiovaskulär sjukdom i vuxen ålder.

Det första delarbetet baseras på en nationell registerstudie där samband mellan hög födelsevikt och förekomst av övervikt, fetma, högt blodtryck, blodfetsrubbnings och typ 2 diabetes analyserades. Den studerade gruppen bestod av vuxna i åldrarna 27 till 37 år (n=759 999). I studien jämfördes individer med hög (2-3 SDS) respektive mycket hög födelsevikt (>3 SDS) med en kontrollgrupp med normal födelsevikt ( $\pm 2$  SDS). Resultaten visade ett samband mellan hög födelsevikt och fetma både hos kvinnor och män. Sambandet var accentuerat vid mycket hög födelsevikt. Män med måttligt hög födelsevikt hade dubblerad risk för typ 2 diabetes, medan de med mycket hög födelsevikt hade fem gånger ökad risk. Hos kvinnor sågs ingen motsvarande ökning. Risken för högt blodtryck och blodfetsrubbnings var inte beroende av födelsevikt.

I delarbete II och III presenteras resultat från en klinisk studie där riskfaktorer för hjärtkärlsjukdom, kroppssammansättning, viloförbränning och insulin känslighet undersöktes hos individer mellan 34 och 40 års ålder. Tjugosju individer med hög födelsevikt (>4 500 g) jämfördes med en matchad kontrollgrupp med normal födelsevikt ( $\pm 1$  SDS). Merparten av de undersökta riskfak-

torerna - blodtryck, blodlipider, inflammationsmarkörer och vägg tjocklek i arteria carotis - skiljde sig inte mellan fall och kontroller. Hos individer med hög födelsevikt fanns dock förändringar i radialartären, som kan utgöra tidiga tecken på arterioskleros. Radialartären är av samma typ som hjärtats kranskärl och förändringar i denna skulle kunna avspegla begynnande hjärtsjukdom.

Individerna i gruppen med hög födelsevikt var längre, och kvinnorna något tyngre, men BMI skiljde sig inte mellan fall och kontroller. Mängden kroppsfett skiljde sig inte heller, men midjeomfång och bukhöjd indikerade ökad mängd inre bukfett hos kvinnor med hög födelsevikt. Detta är en känd riskfaktor både för diabetes och kärlsjukdom.

Insulinkänsligheten undersöktes genom oralt glukostoleranstest och energiomsättningen studerades med indirekt kalorimetri. Med hjälp av accelerometern registrerades graden av fysisk aktivitet under fyra dygn. Ingen av dessa parametrar skilde sig mellan grupperna.

Det sista delarbetet är en nationell registerstudie av samband mellan födelsevikt och risk att föda barn med hög födelsevikt. Risken för fetma och diabetes under graviditet undersöktes också. Studien bygger på data från kvinnor födda 1973–1995, vilka fick sitt första barn mellan 1991 och 2013 (n=305 893). Nyföddhetsdata angående kvinnorna och deras barn, liksom mödravårdsdata för kvinnorna och deras mödrar, hämtades från Medicinska födelseregistret.

Studien visade att det finns ett starkt samband mellan kvinnans och barnets födelsevikt. Resultaten visade även ett samband mellan kvinnans födelsevikt och BMI under graviditet, liksom mellan hennes BMI och barnets födelsevikt.

Låg födelsevikt (<2 SDS) var associerad till ökad risk för graviditetsdiabetes, oberoende av BMI. Motsvarande riskökning sågs inte hos kvinnor med hög födelsevikt. I denna grupp förklarades risken för graviditetsdiabetes framför allt av BMI.

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