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## Early life influences on adult organ function, health and disease, including data from Swedish population-based cohorts

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Early life influences on adult organ function,  
health and disease, including data from  
Swedish population-based cohorts

Reproductive Epidemiology

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DEPARTMENT OF CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY





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including data from Swedish population-based cohorts



# Early life influences on adult organ function, health and disease, including data from Swedish population-based cohorts

Reproductive Epidemiology

Shantanu Sharma



**LUND**  
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DOCTORAL DISSERTATION

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**Abstract:**

Prenatal insults or adverse events during the *in-utero* period may lead to suboptimal function of adult organs because of the impairment of critical organ development and growth, as linked to lower birth weight. This may ultimately predispose the individual to the later onset of some diseases in adulthood, a process known as Developmental Origins of Health and Disease (DOHaD). There is ample evidence of the link between early life factors and disease onset; however, the evidence of their associations with organ function and physiological traits is limited. The overall aim of the thesis was to elucidate the influence of early life factors, such as birth weight and gestational age, on adult organ traits and disease risk, based on a systematic review and meta-analysis, and data from three population-based cohorts, including Malmö Offspring Study (MOS) cohort, LifeGene Study cohort, and Malmö Birth Data cohort. We selected 11 peer-reviewed studies for qualitative synthesis in Paper I and had a sample size of 1995 individuals in Paper II, 2012 individuals in Paper III, and 10093 individuals in Paper IV.

We found an increased risk of cancer (any) mortality and prostate cancer mortality with increased birth weight (**Paper I**). However, the association of birth weight with breast cancer mortality was statistically insignificant. In the MOS cohort (**Paper II**), we found that adults born with low birth weight (LBW) but who attained a higher body mass index (BMI) at age 20 (*mismatch*) had significantly higher systolic and diastolic blood pressure (BP) compared to those born with LBW but continued to have low BMI at age 20. Birth weight z-score showed an inverse association with peripheral augmentation index and positive with pulse wave velocity, markers of aortic stiffness. Likewise, in the MOS cohort (**Paper III**), an average 0.054 arbitrary unit decrease in skin autofluorescence advanced glycation end products (sfAGE) value and 0.016 unit decrease in mean ankle-brachial index (ABI) value per 1 kg increase in birth weight (adjusted for gestational age and sex) were noted. In the LifeGene study cohort (**Paper IV**), we found a positive association between birth weight and apolipoproteins A1 (apoA1) but an inverse association with apolipoproteins B (apoB) ( $\beta$ -coefficient [95% Confidence Interval]: -0.023 [-0.034, -0.012];  $p < 0.001$ ). An inverse association was also found between birth weight and the apoB/apoA1 ratio, a marker of cardiovascular risk.

LBW, a surrogate marker of adverse *intrauterine* conditions, is associated with adult cardiometabolic risk traits (markers) such as hypertension, impaired glucose metabolism, and lipid disturbances, increasing the risk of developing cardiovascular diseases and type 2 diabetes. On the contrary, higher birth weight was associated positively with increased cancer mortality risk (i.e., cancer *prognosis*). Our findings highlight the key role of periconception care among young couples as well as the optimization of maternal health care for the prevention of adult cardiometabolic disease.

**Key words:** Advanced glycation end products, birth weight, carotid femoral pulse wave velocity, fetal development, gestational age, lipoprotein, neoplasms, pulse wave analysis, prenatal care, preconception care

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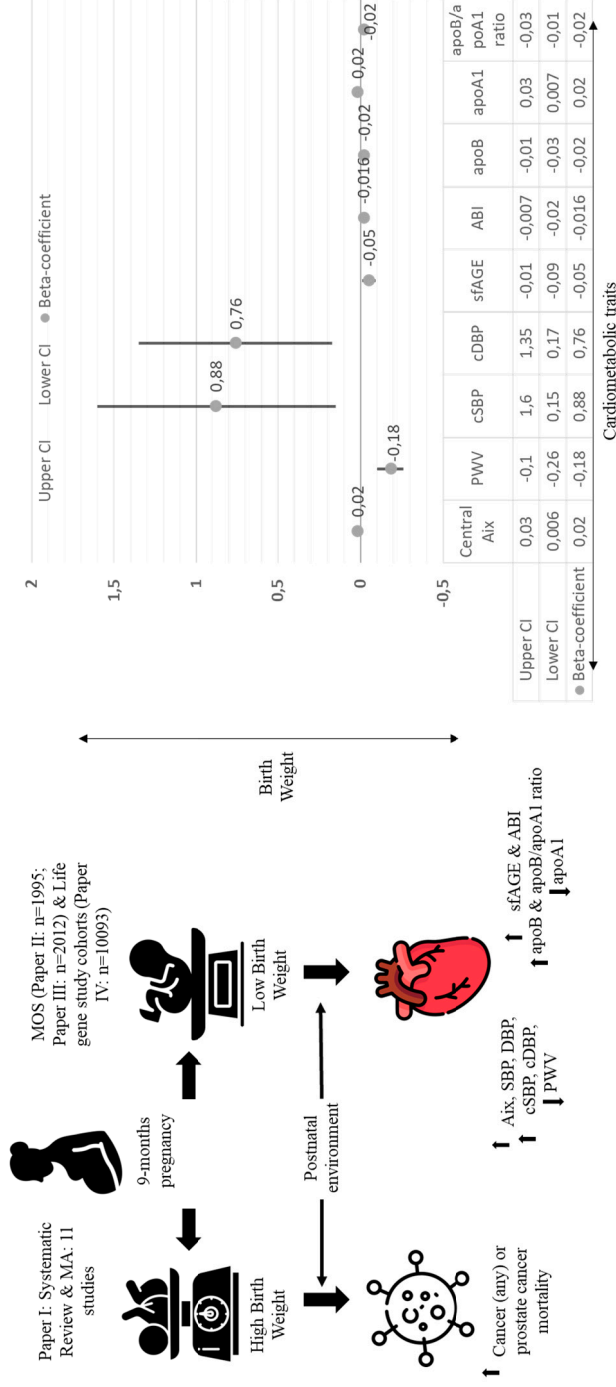
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# Graphical Abstract

## Early life influences on adult organ function, health and disease, including data from Swedish population-based cohorts



**Conclusions:** LBW, a surrogate marker of *intrauterine* insult, is associated inversely with adult cardiometabolic traits like Aix, cSBP, cDBP, sfAGE, ABI, and apolipoproteins, and positively with PWV. These traits are risk markers of later onset of adult risk factors, such as hypertension or diseases like CVD, type 2 diabetes, etc.

**Abbreviations:** Aix: Augmentation Index; apoA1: apolipoproteins A1; apoB: apolipoproteins B; ABI: Ankle-Brachial Index; apoB/apoA1: apolipoproteins B/apolipoproteins A1 ratio; LBW: Low Birth Weight; MA: Meta-analysis; MOS: Malmö Offspring Study; CVD: Cardiovascular Diseases; cSBP: central Systolic Blood Pressure; CI: Confidence Interval; cDBP: central Diastolic Blood Pressure; DBP: Diastolic Blood Pressure; PWV: Pulse Wave Velocity; sfAGE: Skin Autofluorescence Advanced Glycation End Products; SBP: Systolic Blood Pressure

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## Popular summary in English

The overall aim of the thesis was to elucidate the influence of early life factors, such as birth weight and gestational age, on adult organ function, traits, and disease, based on data from three population-based cohorts, including Malmö Offspring Study (MOS) cohort, LifeGene Study cohort, and Malmö Birth Data cohort. The data on adult cardiometabolic traits like Augmentation Index (Aix), carotid-femoral Pulse Wave Velocity (cf-PWV), skin autofluorescence Advanced Glycation End Products (sfAGE), Ankle-Brachial Index (ABI), and apolipoproteins were linked with the Swedish Medical Birth Register data using 10-digit personal identification number.

In **Paper I**, we aimed to conduct a systematic review and meta-analysis of studies that have reported associations between birth weight and length and cancer mortality. We could identify 11 studies published until April 2019. There was a 6% increased risk of cancer (any) mortality with a 1 kg increase in birth weight (Relative Risk, RR 1.06, 95% Confidence interval, CI: 1.01, 1.11). Similarly, there was a 21% increased risk of mortality due to prostate cancer with a 1 kg increase in birth weight (RR 1.21, 95% CI: 1.02, 1.44). However, the effect of birth weight on breast cancer mortality was inconclusive. There was a 16% increased risk of mortality due to breast cancer with a 1 kg increase in birth weight, but it was statistically insignificant with a high statistical heterogeneity ( $I^2=68\%$ ).

In **Paper II**, we aimed to examine the *mismatch* between pre- and post-natal factors influencing adult body weight for the prediction of central and peripheral hemodynamics in a population-based cohort of young adults. Out of 1995 participants, 920 were men and 1075 women. We calculated birth weight z-scores (BWz) with adjustments for gestational age and sex. To perform a *mismatch* analysis, we created four subgroups based on low ( $\leq 0$ ) or high ( $> 0$ ) BWz-scores and low ( $\leq$  median) or high ( $>$  median) Body Mass Index (BMI) at 20 years of age (BMI20). All participants underwent cf-PWV and blood pressure (BP) measurements and pulse wave analysis with Sphygmocor. Adults born with low birth weight (LBW) but attained a higher body mass index (BMI) at age 20 (*mismatch*) had significantly higher systolic and diastolic BP compared to those born with LBW but continued to have low BMI20. On the contrary, adults with higher birth weight but low BMI20 had lower Aix values (both central and peripheral) and central systolic and diastolic BP, compared to adults with LBW and low BMI20. BWz-score showed an inverse association with central Aix and positive with PWV. We noted a 1.29 mmHg increase in central systolic BP and a 1.16 mmHg increase in central diastolic BP among individuals born with low BWz-score compared to their counterparts.

In **Paper III**, we aimed to study associations between LBW and adult sfAGE, a marker of glucose metabolism, and ABI, a marker of peripheral vascular function (e.g., atherosclerosis) in a population-based cohort. MOS is a younger cohort, with the mean (Standard Deviation) age of men at 29.3 (7.3) and of women at 28.6 (7.3) years. We could link 2012 participants (958 men, 1054 women) born between 1973 and 2000 with data on both birth weight and cardiometabolic traits, i.e., sfAGE and ABI. An average 0.054 arbitrary unit decrease in sfAGE value, and 0.016 unit decrease in mean ABI value per 1 kg increase in birth weight (adjusted for gestational age and sex) were noted.

In **Paper IV**, the objective of the study was to assess the associations between birth variables and adult apolipoproteins (apoA1 and apoB) in a population-based cohort (LifeGene). Out of 10093 study participants, 4292 were men and 5801 women. We found a positive association between birth weight (1 kg increase) and apoA1 ( $\beta$ -coefficient [95%CI]: 0.022 [0.007, 0.036];  $p=0.005$ ) but an inverse association with apoB ( $\beta$ -coefficient [95%CI]: -0.023 [-0.034, -0.012];  $p<0.001$ ). An inverse association was also found between birth weight and apoB/apoA1 ratio. No independent association was found with total cholesterol but with triglyceride levels.

# Populärvetenskaplig sammanfattning

Det övergripande syftet med avhandlingen var att belysa inverkan av faktorer tidigt i livet, såsom födelsevikt och graviditetslängd, på vuxnas organfunktion, egenskaper och sjukdom, baserat på data från tre populationsbaserade kohorter, inklusive Malmö Offspring Study-kohort, LifeGene kohorten, och Malmö Birth Data-kohorten. Data för kardiometaboliska variabler (egenskaper) hos vuxna som Augmentation Index (Aix), carotis-femoral Pulse Wave Velocity (cf-PWV), hudautofluorescens Advanced Glycation End Products (sfAGE), Ankel Brachial Index (ABI) och lipidmönster (apolipoproteiner) kopplades till det nationella svenska Medicinska födelseregistret variabler med 10-siffrigt personnummer.

I **Delarbete I** syftade vi till att genomföra en systematisk översikt och metaanalys av studier som har rapporterat samband mellan födelsevikt och längd och cancerdödlighet. Vi kunde identifiera 11 studier publicerade fram till april 2019. Det fanns en 6% ökad risk för cancerdödlighet (oavsett cancerform) associerat med en 1 kg ökning i födelsevikt (Relativ Risk, RR 1,06, 95% konfidensintervall, KI: 1,01, 1,11). Likaså fanns det en 21 % ökad risk för dödlighet på grund av prostatacancer associerad med en 1 kg ökning i födelsevikt (RR 1,21, 95 % KI: 1,02, 1,44). Effekten av födelsevikt på bröstcancerdödligheten var dock inte signifikant. Det fanns en 16% ökad risk för dödlighet på grund av bröstcancer med en 1 kg ökning i födelsevikt, men den var statistiskt icke-signifikant och med en hög statistisk heterogenitet ( $I^2=68\%$ ).

I **Delarbete II** syftade vi till att undersöka obalansen mellan pre- och postnatale faktorer som påverkar vuxnas kroppsvikt för förutsägelse av central och perifer kärl- och blodtrycksreglering (hemodynamik) i en populationsbaserad kohort av unga vuxna. Av 1995 deltagare var 920 män och 1075 kvinnor. Vi beräknade z-poäng för födelsevikt (BWz) med justeringar för graviditetslängd och kön. För att utföra en s.k. *mismatch* analys skapade vi fyra undergrupper baserade på lågt ( $\leq 0$ ) eller högt ( $> 0$ ) BWz och lågt ( $\leq$  median) eller högt ( $>$  median) Body Mass Index (BMI) vid 20 års ålder (BMI<sub>20</sub>). Alla deltagare genomgick cf-PWV och blodtrycksmätningar (BP) samt pulsvågsanalys med Sphygmocor. Vuxna som är födda med låg (lägre än medianen) födelsevikt (LBW) men uppnår ett högre kroppsmassaindex (BMI) vid 20 års ålder (mis-match fenomen) tenderar att ha signifikant högre systoliskt och diastoliskt BP jämfört med de som är födda med LBW men fortsätter att ha lägre (än medianen) BMI vid 20 års ålder. Däremot så hade vuxna individer med högre födelsevikt men lågt BMI vid 20 års ålder, ett lägre s.k. Aix-värden (både centralt och perifert uppmätt, speglande hemodynamik) samt centralt systoliskt och diastoliskt BP, jämfört med vuxna med LBW och lågt BMI vid 20 års ålder. BWz-poäng visade en omvänd association med central Aix, men positiv

med PWV. Vi noterade en 1,29 mmHg ökning av centralt systoliskt BP och en 1,16 mmHg ökning av centralt diastoliskt BP bland individer födda med låg BWz-poäng.

I **Delarbete III** syftade vi till att studera samband mellan låg födelsevikt och hud autofluorescens AGE (sfAGE), en markör för bl.a. glukosmetabolism, och ankel-brachial index (ABI), en markör för perifer kärlfunktion (bl.a. ateroskleros) i en populationsbaserad kohort. MOS är en yngre kohort, med en medelålder (standardavvikelse) för män på 29,3 (7,3) och för kvinnor 28,6 (7,3) år. Vi kunde länka 2012 deltagare (958 män, 1054 kvinnor) födda mellan 1973 och 2000 med data om både födelsevikt och metabola samt vaskulära egenskaper i vuxenlivet, d.v.s. sfAGE och ABI. Resultatet angav en genomsnittlig minskning av 0,054 AU i sfAGE-värde och 0,016 enheters minskning i genomsnittligt ABI-värde per 1 kg ökning av födelsevikt (justerat för graviditetslängd).

I **Delarbete IV** var syftet med studien att bedöma sambanden mellan födelsevariabler och vuxnas blodfettsmönster (s.k. apolipoproteiner; apoA1 och apoB) i en populationsbaserad kohort (LifeGene). Av 10 093 deltagare i studien var 4 292 män och 5 801 kvinnor. Vi fann ett positivt samband mellan födelsevikt (1 kg ökning) och apoA1 ( $\beta$ -koefficient (95%CI): 0,022 [0,007, 0,036];  $p=0,005$ ) och ett omvänt samband med apoB ( $\beta$ -koefficient (95%CI) : -0,023 [-0,034, -0,012];  $p<0,001$ ). Ett omvänt samband hittades mellan födelsevikt och apoB/apoA1-kvoten. Inget oberoende samband sågs med totalt kolesterol men med triglyceridnivåer.



# List of Papers

## *Paper I*

Sharma S, Kohli C, Johnson L, Bennet L, Brusselaers N, Nilsson PM. Birth size and cancer prognosis: a systematic review and meta-analysis. *J Dev Orig Health Dis* [Internet]. 2020; 11(4):309–16.

## *Paper II*

Sperling J, Sharma S, Nilsson PM. Birth weight in relation to post-natal growth patterns as predictor of arterial stiffness and central hemodynamics in young adults from a population-based study. *Artery Res* [Internet]. 2021; 27(3):112.

## *Paper III*

Sharma S, Sperling J, Jujic A, Bennet L, Christensson A, Nilsson PM. Associations between birth parameters and skin autofluorescence advanced glycation end products and ankle–brachial index in young adulthood: the Malmö Offspring Study. *J Hypertens* [Internet]. 2023; 41(7):1184–90.

## *Paper IV*

Sharma S, Bennet L, Laucyte-Cibulskiene A, Christensson A, Nilsson PM. Associations between birth variables and adult apolipoproteins: The LifeGene Cohort. Submitted manuscript to PlosOne June 2023 (under revision after peer-review).

# Abbreviations

ApoA1: Apolipoproteins A1

ApoB: Apolipoproteins B

ABI: Ankle-Brachial Index

AGE: Advanced Glycation End products

Aix: Augmentation Index

BMI: Body Mass Index

CVD: Cardiovascular Diseases

CI: Confidence Interval

DBP: Diastolic Blood Pressure

DOHaD: Developmental Origins of Health and Disease

FOAD: Fetal Origins of Adult Disease

FEV1: Forced Expiratory Volume1

FVC: Forced Vital Capacity

GWAS: Genome-Wide Association Studies

GFR: Glomerular Filtration Rate

HDL: High-Density Lipoproteins

IGF-I: Insulin-Like Growth Factor-I

LBW: Low Birth Weight

LDL: Low-Density Lipoproteins

LGA: Large-for-Gestational-Age

MBR: Medical Birth Register

NCDs: Non-Communicable Diseases

OR: Odds Ratio

PWV: Pulse Wave Velocity

PWA: Pulse Wave Analysis

RR: Relative Risk

sfAGE: Skin Autofluorescence Advanced Glycation End Products

SBP: Systolic Blood Pressure

SGA: Small-for-Gestational-Age

VLDL: Very Low-Density Lipoproteins

WHO: World Health Organization

# Introduction

## Life course epidemiology

Life course epidemiology is a conceptual model of epidemiology that links biological, behavioral, and psychological processes appearing during the periconceptual period to the occurrence of non-communicable diseases (NCDs) later in adulthood (**Figure 1**) (Ben-Shlomo et al., 2014; Jia, 2019). It is a broad field that studies exposures during different phases of life, including pregnancy, childhood, adolescence, and adulthood. However, recently, scientists have suggested the concept of ‘spatial life course epidemiology.’ This considers the time-varying contextual factors, geographical information system-enabled temporal location, and social patterns of disease distribution. Besides, it has the advantage of studying gene-environment interaction with repeated measurements over time and processes operating across generations (Jia, 2019). Reproductive epidemiology is a specialized area of epidemiology focusing on the distribution, determinants, and consequences of reproductive events (Louis & Platt, 2011).

## Evolution of organ development

Life starts with a cell called a zygote, which undergoes multiple cleavages to evolve into a mulberry-shaped morula. Multiple processes like compaction and cavitation occur that transform a morula into a blastocyst. Then, through the gradual changes at the molecular, genetic, and developmental levels, the *embryo* gets implanted in the uterus and starts growing as a *fetus* (Rowan-Hull, 2013; Carlson & Kantaputra, 2019). The rudiments of the major organs are developed except for the limbs and urogenital organs by the fourth week of pregnancy (Carlson & Kantaputra, 2019).

The nine months of pregnancy are marked by three critical phases of embryonic development, namely gastrulation, placentation, and post-gastrulation organogenesis, that establish the blueprint of development (Rossant & Tam, 2022). One of the first systems to develop in the embryo is the cardiovascular system (Rowan-Hull, 2013).



**Figure 1.** An illustration to showcase the different phases in the life course of a woman (*Shantanu Sharma*).

The development of the vascular system starts in the third week of gestation. The development of the blood and vascular system evolves from the need to supply oxygen to different tissues of the embryo. Several genes, transcriptional factors, signaling molecules, and structural molecules are critical in the formation of the cardiovascular system. It is crucial to understand the role of these genes and molecules as exposure to stressors in fetal life may alter their expression, leading to endothelium dysfunction, altered cardiomyocyte numbers, enhanced or reduced cardiac myocardial mass, etc. (Gluckman et al., 2008).

Similarly, other organ systems, such as the kidney, liver, and gastrointestinal systems, develop simultaneously. For example, in the early stages of the development of the urinary system, three structures, including nephrotomes, mesonephros, and metanephros, differentiate to develop into kidneys and ureters (Carlson & Kantaputra,

2019). Eventually, the differentiation of mesenchymal cells leads to the formation of nephrons, renal tubules, and podocytes. The formation of nephrons continues throughout life (Carlson & Kantaputra, 2019). Intrauterine growth restriction and/or prematurity may impair kidney development, leading to reduced nephron endowment (Sutherland & Black, 2023).

The original gut tube of the *fetus* gives rise to the digestive system, liver, pancreas, respiratory system, and other digestive glands. The major function of the fetal liver is hematopoiesis, i.e., the formation of blood cells. Though the liver largely controls lipid synthesis in adults, it mainly happens in adipose tissues in the *fetus* or via transfer from maternal circulation because of the immaturity of the liver. In addition, High-Density Lipoproteins (HDL) is the major lipoprotein in newborns with low concentrations of Low-Density Lipoproteins (LDL) and Very Low-Density Lipoproteins (VLDL) (Desoye & Herrera, 2021).

## Evolution of the Developmental Origins of Health and Disease (DOHaD) concept

There have been decades of research on the risk of diseases passed across generations. The attribution of genetics to the occurrence of disease across generations is limited, though it has been extensively researched by genome-wide association studies (GWAS) (The Wellcome Trust, 2007; Hirschhorn, 2009). Other plausible mechanisms proposed for this ‘missing heritability’ included copy number variations, gene-gene interactions (epistasis), and interaction between genes and environment (Matthews & Turkheimer, 2022). This interaction between genes and environment, known as epigenetics, formed the basis of the emergence of what is known today as the ‘Developmental Origins of Health and Disease’ (DOHaD) (Allis et al., 2007; Gluckman et al., 2010) hypothesis.

Over the years, many researchers have proposed theories to explain the associations between *intrauterine* exposures and the later onset of diseases in the offspring. Notably, Günter Dörner and his team from the German Democratic Republic introduced the term ‘*programming*’ and proposed associations of before and after birth conditions with later onset of arteriosclerosis and obesity in the 1970s (Dörner et al., 2008). Furthermore, Norbert Fienkel proposed ‘fuel mediated teratogenesis,’ Anders Forsdahl, Norway, pointed out the associations with cardiovascular risk in adult life, and Michael Wadsworth reported associations between birth weight and blood pressure (Forsdahl, 1977; Fienkel, 1980; Wadsworth et al., 1985).

The thrifty genotype concept of James Neel suggested that the genetically limited capacity to adapt contributed to disease risk in humans (Neel, 1962). However, it was heavily criticized, following which David Barker and Nicholas Hales proposed a thrifty phenotype hypothesis conceptualized on developmental tradeoffs (Hales & Barker, 1992). Barker's thrifty phenotype was also criticized for the assumptions of the requirement of severe insult *in-utero* and signals of deprivation for the developmental change to occur. Nettle and Bateson proposed developmental programming as the phenomenon when organisms with the same genotype develop different phenotypes based on the different environmental exposures in early life (Nettle & Bateson, 2015). Counting on these limitations, Bateson, Gluckman, and their colleagues put forward developmental plasticity as the phenomenon or process manifesting into DOHaD. They defined developmental plasticity as the mechanism to capacitate a developing organism to respond to the changes in the immediate environment, which may occur over a single or across many generations (Gluckman et al., 2011)

Historically, in Sweden, Gennser *et al.* explored associations between birth weight and raised blood pressure. They found that young adult men coming for conscript testing who were growth retarded at birth had increased diastolic blood pressure (DBP) compared to adults born with a normal birth weight (Odds Ratio, OR (95%Confidence Interval, CI): 3.63 (1.14, 12.57)) (Gennser et al., 1988).

The major difference between Barker's Fetal Origins of Adult disease (FOAD) hypothesis and today's widely accepted DOHaD hypothesis is that the FOAD solely gave importance to prenatal events being the harbinger of chronic diseases, while DOHaD recognized both pre- and post-natal environmental factors and the match/*mismatch* between them as vitally important (Gluckman & Hanson, 2006). In addition, the term DOHaD encompasses the aspects of prevention and health promotion, including wider public health education (Hanson, 2015).

## Early life factors

Early life factors refer to a wide range of influences and experiences that occur during a person's infancy, childhood, and adolescence and can have a significant impact on their development, health, and well-being throughout their lifespan. These factors play a crucial role in shaping an individual's physical, emotional, cognitive, and social development. Primarily, these include birth weight, gestational age, birth length, head circumference, etc. (Haapanen et al., 2022).

Birth weight has been the most extensively studied marker of the *intrauterine* environment in epidemiological research for its prediction and association with adult-

onset diseases. Both low (<2500 grams) and high (>4000 grams) birth weights have emerged as potential risk factors for adverse health outcomes occurring later in life (Belbasis et al., 2016). Low birth weight (LBW) has been suggested as the surrogate marker of the insults a *fetus* is exposed to during the prenatal period and its coping response to the *intrauterine* environment (Gluckman & Hanson, 2006). A high birth weight (macrosomia) could be a marker of maternal factors, such as obesity and gestational diabetes (Gluckman & Hanson, 2006).

Birth weight is largely affected by maternal physiological (placental function) and behavioral characteristics like maternal nutrition, maternal smoking, and socioeconomic factors (Stein & Lumey, 2000). Studies use birth weight based on recall or from records. Recorded birth weight is preferred over recalled birth weight, though the agreement between the two is high (Shenkin et al., 2017). Estimation of fetal weight is a promising marker to correctly predict *intrauterine* growth retardation in pregnancy and prevent adverse birth outcomes. Lu *et al.* proposed a model based on machine learning algorithms to predict fetal weight at a given gestational age. The proposed model has an accuracy of 64% and obviates the need for ultrasonography-based estimation methods (Lu et al., 2020).

Gestational age is an important mediator or an independent risk factor in the pathway of the DOHaD hypothesis. Hence, adults with normal birth weight but born preterm may still be at an elevated risk of diseases. Intrauterine growth retardation can be diagnosed by antepartum ultrasonography, as introduced in the late 1970's, which is difficult to reproduce in the historical cohorts. Hence, birth weight adjusted for gestational age can be a proxy indicator to explore the long-term health consequences of children born small-for-gestational-age (SGA) (Johansson et al., 2020).

The interplay between various maternal, nutritional, placental, fetal, and genetic factors during pregnancy leads to altered *intrauterine* growth, which manifests as a child born SGA or large-for-gestational-age (LGA) (Schupper et al., 2021). SGA children have birth weight <10<sup>th</sup> percentile for the gestational age, and LGA children have birth weight >90<sup>th</sup> percentile for the gestational age (Xu et al., 2010).

Furthermore, the World Health Organization (WHO) has classified preterm birth as babies born before 37 completed weeks of pregnancy. Preterm birth has been further sub-categorized into extremely preterm (born before 28 weeks of pregnancy), very preterm (born between 28-32 weeks of pregnancy), and moderate to late-preterm (born between 32 to 37 weeks of pregnancy) (WHO Preterm Births, 2023). SGA and preterm birth increase the risk of cardiovascular diseases (CVD) in early adulthood, along with the interplay of genetic and hereditary risk factors (Lu et al., 2023).

Other measurements of body size at birth, such as birth length, head circumference, abdominal circumference, chest circumference, and ponderal index ( $\text{birthweight} \times 100 / \text{length}^3$ ), have been studied for their associations with the later onset of adult diseases. In addition, placental weight and the ratio of placental weight to birth weight have been linked to adult coronary heart diseases (Godfrey, 2006). Birth length associations with childhood outcomes like body mass index (BMI) have also been studied, suggesting an inverse association between the two (Baran et al., 2019). The neonatal ponderal index has been described as symmetric when the relationship between birth weight and length is appropriate and asymmetric when either birth length or weight is inappropriate in comparison to the other (Mohajan, 2023).

Besides growth during the pregnancy, the growth and development during the early post-natal phase may have long-term consequences on the health of the adults. Overnutrition and accelerated growth during the early post-natal period and first few years of life have been suggested to be determinantal. Rapid catch-up growth in infants born SGA increases the risks of major components of metabolic syndrome in adulthood, such as glucose intolerance, dyslipidemia, raised blood pressure, and obesity, and hence, the increased risk of CVD and mortality (Lucas et al., 2010). This developmental *mismatch* is a risk marker for obesity in children who undergo a rapid nutritional transition (Kuzawa et al., 2008). This is further supported by a study from Helsinki suggesting a five times increased risk of dying from coronary heart disease among men with lower ponderal index at birth and high BMI at age 12 (Eriksson et al., 2001).

Further to this evidence, many studies have highlighted that LBW associated with subsequent adverse health behaviors like high BMI, smoking, and unhealthy eating are the worst risk factors for CVD in adulthood. So, favorable healthy behaviors during adulthood may alter or decrease the risk of CVD in adults born SGA or with LBW (Liang et al., 2014; Mo et al., 2023).

### **Parental socioeconomic status**

Studies have demonstrated the effect of social environment during early life on the later onset of CVD and mortality. Social environment, such as parental education, social class, occupation, and family income, affects CVD risk in the offspring via two plausible mechanisms. One of the mechanisms includes childhood social (family) environment affecting the exposures occurring later in life, such as education, employment, and development of behavioral risk factors like smoking and drinking in the offspring. The other mechanism includes the childhood social environment causing irreversible effects on future health without altering factors like education, employment, and behavior



(Hossin et al., 2021; Xu & Yilmazer, 2021). Though there is conflicting evidence on such hypotheses, this highlights the need for providing social security, food security, schooling, unemployment wages, and welfare schemes to people living in poor social environments (Hossin et al., 2021; Xu & Yilmazer, 2021; Prætorius et al., 2023).

## **Periconception period**

The periconception period is the period months or a few weeks before conception until the implantation of the embryo in the uterus. It is the critical period as exposure to risk factors like obesity, unhealthy lifestyle, chemicals, drugs, infections, nutritional deficiencies, and other environmental hazards during this period may impact fertility and cause epigenetic changes in the gametes of the parents (Hieronimus & Ensenauer, 2021; Nilsson McDonald lecture, 2023).

Ethnicity plays an important role in determining birth outcomes due to differences in lifestyles, health, and dietary practices. In Sweden, non-European women have a higher likelihood of having a healthy lifestyle, such as decreased smoking and alcohol, coffee, and tobacco consumption; however, they are prone to depressive symptoms and less physical activity compared to European women before and during pregnancy (Hultstrand et al., 2020). Periconception period is critical from the lens of preventive interventions. Hence, educating obstetricians and midwives about DOHaD concepts and exploring opportunities to intervene through routine antenatal care becomes paramount (Jacob, 2022).

## **Adult health outcomes**

### **Phenotypes (Traits)**

Traits are physiological characteristics and risk factors related to health and organ function. Unlike diseases, traits are not inherently problematic or indicative of health issues. They are neutral characteristics that make individuals unique, such as glucose levels, BMI, blood pressure, cholesterol levels, etc. The traits are important indicators of an individual's risk for various diseases, such as cardiometabolic diseases. Cardiometabolic traits are often considered together because they tend to co-occur and share common underlying mechanisms. Traits can be qualitative (eye color) or quantitative (blood pressure) or they can be classified as physical (BMI) or behavioral (smoking) (NHGRI, 2023).

### *Arterial stiffness*

Arterial stiffness is defined as the reduced distensibility of an artery for any given pressure change and starts in the arterial media. It has been found to be a predictor of CVD and cardiovascular mortality in patients suffering from diabetes, hypertension, end-stage renal disease, as well as in middle-aged and elderly patients (Ben-Shlomo et al., 2014). Arterial stiffness leads to increased pulse wave velocity (PWV), which is calculated by measuring the time taken for a pressure pulse to travel between two points (Cecelja & Chowienczyk, 2012). So, PWV is a direct measure of arterial stiffness. Most commonly, carotid-femoral PWV (cf-PWV) is measured to assess central arterial stiffness or aortic stiffness (Boutouyrie et al., 2008).

Decreased development or depletion of the elastin content of the tunica media of large elastic arteries causes or influences arterial stiffness later in life as part of the so-called Early Vascular Ageing syndrome (Nilsson McDonald Lecture, 2023). However, there is mixed evidence on the effect of early life factors on PWV. Some studies suggested the negative influence of LBW or SGA on PWV, while other studies did not find any significant difference in children or young adults (Stock et al., 2018; Hurst et al., 2020; Olander et al., 2022).

### *Augmentation index*

Another marker of arterial stiffness measurement is the augmentation index (Aix). It represents the difference between the second and first systolic peaks derived from the central (aortic) pressure waveform (Climie et al., 2013). Aix has also been found to be associated with increased CVD risk (Nürnberg et al., 2002). Aix reflects aortic stiffness and the influence of peripheral vascular resistance and other determinants like the reflex wave, blood pressure levels, and heart rate. Contrary to PWV, Aix has been shown to have a more consistent association with early life factors (Wilkinson et al., 1998; Sperling & Nilsson, 2020; Nilsson McDonald Lecture, 2023).

### *Advanced Glycation End products*

Advanced Glycation End (AGE) products are complex compounds formed exogenously or endogenously by different chemical reactions. Chronic accumulation of AGE products promotes oxidative stress and inflammation, which eventually leads to the development of chronic diseases, including CVD and diabetes (Twarda-Clapa et al., 2022). AGE products have been implicated in many clinical conditions, such as diabetic microvascular diseases, rheumatoid arthritis, Alzheimer's disease, and end-stage renal disease (Singh et al., 2001).

Non-enzymatic reactions between glucose, proteins, lipids, and nucleic acids producing Schiff bases and Amadori products are called Maillard reactions. Glycation occurring

early during Maillard reactions leads to the formation of AGE products (Singh et al., 2001). AGE products accumulate inside the tissues and structurally and functionally modify them. AGE products that accumulate in the dermal layers of the skin exhibit fluorescent properties and can be measured by skin autofluorescence using an AGE Reader (Cidila et al., 2017). A previous study has shown an inverse association between birth weight and receptors of AGE (Chiavaroli et al., 2012). Skin autofluorescence AGE (sfAGE) measurement is a cost-effective, rapid, and accessible test that can be used for large populations. Raised sfAGE levels have also been implicated in aortic stiffness and are associated with higher cf-PWV measurements, especially in type 2 diabetes patients (van Eupen et al., 2016).

### *Ankle-Brachial Index*

Ankle-brachial index (ABI) is a non-invasive technique to measure the risk for CVD (Woo, 2023). It is a cost-effective screening method to identify asymptomatic peripheral arterial diseases. ABI is categorized into low ( $<0.9$ ), high ( $\geq 1.3$ ), and normal ( $0.9 \leq \text{ABI} < 1.3$ ) (Alves-Cabratosa et al., 2019). The index is calculated by measuring the ratio of ankle vs. brachial systolic blood pressure (SBP). A low ABI value ( $<0.9$ ) is suggestive of peripheral arterial diseases. In addition, low ABI is associated with an increased risk of all-cause, cardiovascular, and non-cardiovascular mortality (Qu et al., 2015). Low ABI values are commonly found in the elderly, chronic smokers, and patients with atherosclerosis caused by diabetes, hypertension, and hyperlipidemia (Qu et al., 2015). However, high ABI values have also been found to carry a risk of CVD and mortality due to the stiffness of arteries in, for example, patients with diabetes (Gu et al., 2019; Yang et al., 2020; Golledge et al., 2020).

ABI has been widely used for screening peripheral arterial diseases in populations (Casey et al., 2019). Abnormal ABI has been linked with an increased risk of overall mortality, cancer mortality, and CVD mortality (Gu et al., 2019; Visonà et al., 2020). Studies suggest a U-shaped association of ABI with diseases where both high and low ABI values appear to be risk markers for mortality due to CVD events (Gu et al., 2019; Alves-Cabratosa et al., 2019). Martyn *et al.* suggested that elderly adults with a history of lower birth weight tend to have low ABI (Martyn et al., 1998).

### *Apolipoproteins*

Plasma apolipoproteins have a crucial role in lipid transport, and hence, they are important for atherogenesis (Patsch & Gotto, 1996). ApoA1 is a protein containing HDL cholesterol that promotes efflux from tissues to the liver for excretion (Chuang et al., 2013). Similarly, apoB helps in binding LDL cholesterol to its receptor, thereby internalizing it and absorbing cholesterol. ApoB primarily exists in two forms: apoB-

48 (synthesized in the intestine) and apoB-100 (synthesized in the liver) (Walldius & Jungner, 2004). Compared to birth weight, abdominal circumference at birth has been found to be a better surrogate marker of the developmental influences on liver function and metabolism (Gluckman & Hanson, 2006).

ApoB, apoA1, and the ratio apoB/apoA1 are risk markers for major adverse cardiovascular events like stroke, myocardial infarction, and cardiovascular mortality, also in the Swedish population (Walldius et al., 2021). Though apoA1, which reflects HDL cholesterol, was found to be inversely associated with CVD risk and mortality, recent studies demonstrated a U-shaped association between apoA1 and CVD risk and mortality. This association of apoA1 with CVD risk is accelerated by covariates/confounders like blood pressure, smoking, and alcohol consumption (Faaborg-Andersen et al., 2023). Furthermore, the apoB/apoA1 ratio has been suggested as a better predictor of CVD risk compared to apoB in patients with pre-diabetes or metabolic syndrome (Walldius et al., 2021). There is accruing evidence of the apoB/apoA1 ratio as a predictor of cancer mortality independent of cardiometabolic risk factors (Mazidi et al., 2020).

#### *Kidney function and kidney injury/damage*

The glomerular filtration rate (GFR) is a measure of kidney function and ranges between 120-130 ml/min per 1.73 m<sup>2</sup> in young women and men, respectively. However, it is related to age, sex, and body size (Stevens et al., 2006). Other potential markers of renal insufficiency include plasma creatinine and cystatin C levels, albuminuria, and albumin-to-creatinine ratio, but some of these measures are not sensitive enough (Schwartz & Furth, 2007; Levey et al., 2022). Studies highlighted that cystatin C estimates GFR better than creatinine (Laucyte et al., 2022). Besides, Cystatin C-based GFR calculations have multiple advantages, including the calculations do not need to know sex and do not depend on muscle mass, the values can be used for adults, children, elderly, and they are better in predicting end-stage renal disease, CVD, hospitalization, and death (Grubb, 2017). Hence, using both Cystatin C and serum creatinine together will provide the best estimates (Stevens et al., 2008). There is accruing evidence of the effect of early life factors (birth variables) on adult chronic kidney disease risk (Yu et al., 2020).

#### *Lung function*

Lung forced expiratory volume (FEV1) and FEV1/Forced Vital Capacity (FVC) ratio are commonly used to measure lung function in adults. There is growing evidence that impaired lung function increases the risk of CVD in late adulthood. A meta-analysis by Xu *et al.* of 406,426 participants showed that asthmatics are at an increased risk of

CVD and its mortality is independent of the effect of smoking (tobacco) (Xu et al., 2017). The plausible mechanism linking asthma and CVD is the state of chronic inflammation, and the evidence on the role of anti-asthmatic therapies in lowering the risk of CVD is evolving (Guo et al., 2022). Hence, lung function testing in early adulthood can help predict the cardiovascular health of late adulthood. FEV1 has been found to be associated with CVD events independent of BMI, age, biochemical parameters like cholesterol, smoking status, sex, diabetic status, etc. (Cuttica et al., 2018).

Furthermore, studies suggest early life exposures alter the growth and development of the lung, which, in turn, enhances the risk of CVD (Edwards et al., 2003; Lawlor et al., 2005; Sakic et al., 2022). Preterm births or those born SGA show an increased risk of chronic respiratory morbidity (Been et al., 2014; Thunqvist et al., 2018). Studies suggested that LBW is associated with adult chronic obstructive pulmonary diseases, impaired lung function, and asthma (Barker, 1992; Lawlor et al., 2005; Canoy et al., 2007; Hancox et al., 2009; Broström et al., 2013; Sakic et al., 2022).

## Diseases

### *Cardiovascular diseases*

CVD are estimated to cause 17.8 million deaths worldwide (Townsend et al., 2022). Among CVD, ischemic heart diseases and stroke account for more than three-fourths of all deaths. Similarly, CVD accounts for a significant number of deaths in Europe, i.e., approx. 4 million (Townsend et al., 2022). According to the global burden of disease estimates, kidney dysfunction accounts for 1.87 million and 3.47 million CVD and overall deaths, respectively (Vaduganathan et al., 2022). The global burden of diseases provided estimates for the multiple environmental, behavioral, and metabolic risk factors for CVD (**Figure 2**).

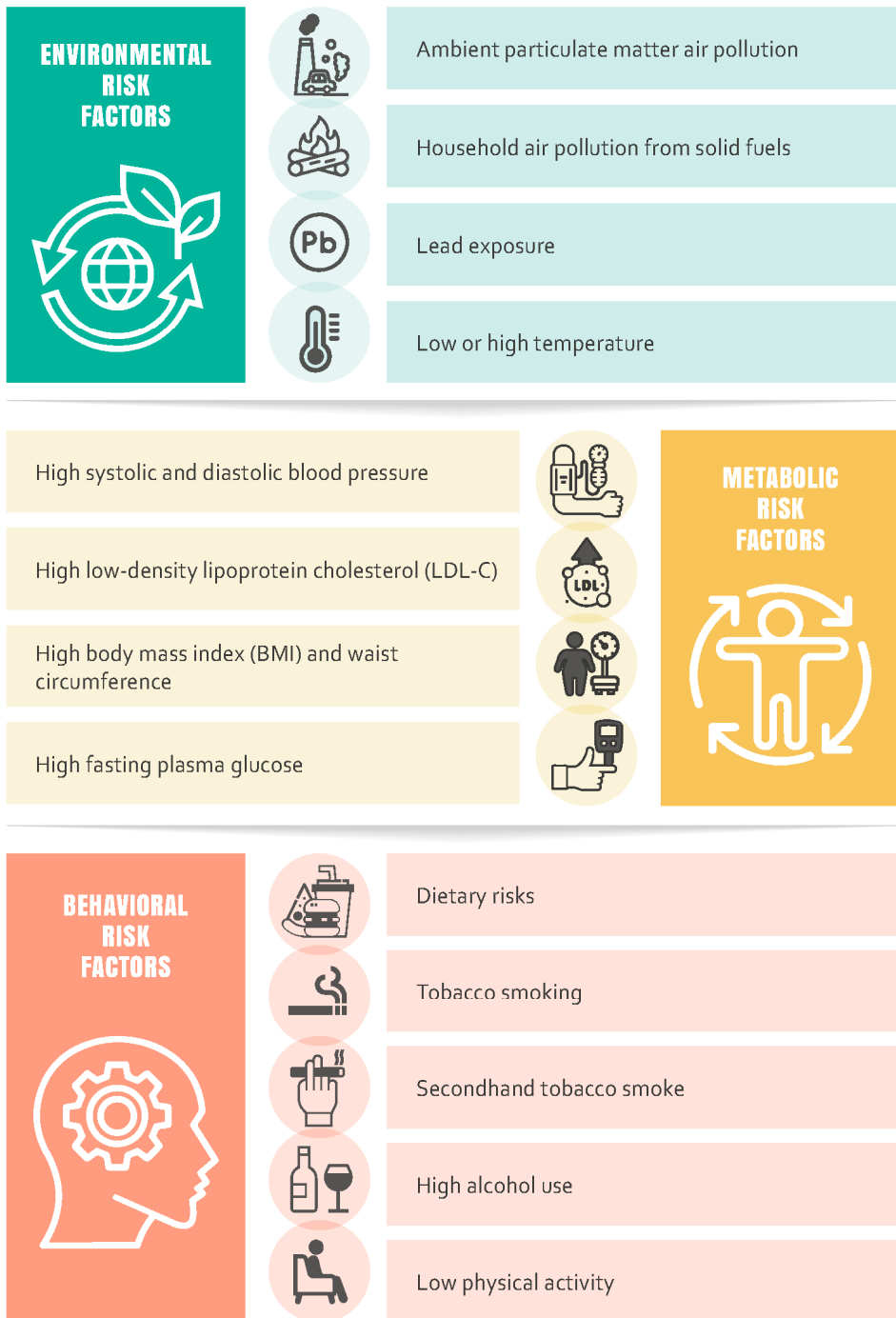
Among important cardiovascular risk factors, high systolic blood pressure (SBP), dietary risks, and high LDL levels contribute to the greatest number of deaths due to CVD (Vaduganathan et al., 2022; Global Cardiovascular Risk Consortium, 2023). Risk prediction tools exist to estimate the individual's risk of CVD. Though most of the risk factors are common, there are differences in the risk factors for CVD among men and women. Female-specific risk factors include hormonal changes, pregnancy conditions, structural heart diseases, etc. (Täufer, 2023). The growing burden of CVD and their associated risk factors highlight the need for prompt public health actions at the community level. Barker *et al.*, in the late 1980s and early 1990s, suggested

associations between early life factors and CVD like ischemic heart disease and raised BP (Barker & Osmond, 1986; Barker et al., 1989; Law & Barker, 1994).

### *Hypertension*

Hypertension, a leading risk factor for CVD, had an age-standardized prevalence of 32% in women and 34% in men worldwide in 2019 (Zhou et al., 2021). Hypertension is defined as a mean SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg (Mills et al., 2020). Age, unhealthy diets, high salt intake, lack of physical activity, alcohol consumption, and obesity are the major risk factors for hypertension (Zhou et al., 2017) against a background of genetic susceptibility. Both LBW and preterm birth have been demonstrated to be risk markers for hypertension and chronic kidney diseases (CKD), which, in turn, are risk factors for CVD (Kanda et al., 2020).

Knop *et al.*, in their meta-analysis of 7,646,267 participants from 135 studies, found an inverse association between birth weight and hypertension. They showed that there was a reduction of 1.36 mmHg in SBP and 0.33 mmHg in DBP with every 1kg increase in birth weight (Knop et al., 2018). The inverse association between birth weight and hypertension is established in many systematic reviews (Mu et al., 2012; Knop et al., 2018; de Mendonça et al., 2020). Low nephron numbers, reduced density of arterioles/capillaries, and the narrowing of arterioles lead to increased peripheral vascular resistance, endothelial dysfunction, reduced elastin production, hypomethylation of the angiotensin-converting enzyme gene promoter, and the Angiotensin II receptor, and sympathetic nerve activation, are some of the proposed mechanisms for increased risk of hypertension among adults born LBW (Kanda et al., 2020).



**Figure 2.** Different types of risk factors for CVD (Shantanu Sharma).

## *Diabetes*

Type 2 diabetes represents a global pandemic, with an estimated 382 million patients in 2013, and projected to increase to more than 590 million by 2035 globally (Reed et al., 2021). According to the Diabetes Atlas (2021) by the International Diabetes Federation, 10.5% of the adult population between 20-79 years are suffering from diabetes, and almost half of them are unaware of their condition (IDF, 2023). Diabetes has been defined as a metabolic disorder of multifactorial etiology with chronic hyperglycemia arising due to defects in insulin secretion, insulin action, or both (Reed et al., 2021). More than 90% of patients with diabetes belong to type 2, characterized by defective insulin production, secretion, and resistance. Besides behavioral risk factors, genes and hormones, such as insulin, glucagon, Glucagon Like Peptide-1, and gastric inhibitory polypeptide, are involved in the etiology of type 2 diabetes (Kahn et al., 2014).

Both LBW and high birth weight have been found to be associated with type 2 diabetes risk. Furthermore, LBW increases the risk of micro- and macrovascular complications in type 2 diabetes, like dyslipidemia, hypertension, CVD, and neurocognitive dysfunction (Hansen et al., 2023). Though a U-shaped association has been established between birth weight and type 2 diabetes, the pathophysiological mechanisms associated with low or high birth weight seem different. The association between LBW and type 2 diabetes is independent of BMI and genetic influences compared to that of high birth weight and diabetes (Wibaek et al., 2023).

## *Obesity*

There is a growing public health problem with obesity and obesity-related diseases across the world (Skinner et al., 2018; World Obesity Federation, 2023). Obesity is an established risk factor for dyslipidemia, type 2 diabetes, hypertension, sleep apnea, some cancers, etc. (Powell-Wiley et al., 2021). Around 2 billion adults are estimated to be overweight ( $BMI \geq 25 \text{ kg/m}^2$ ), out of which 671 million are obese ( $BMI \geq 30 \text{ kg/m}^2$ ) worldwide. It is estimated that the number of adults with obesity will increase to 1 billion globally, which is equivalent to 20% of the world's population, if the current trends continue to rise (Loos & Yeo, 2022).

According to the WHO European Region Report, more than 1.2 million deaths are caused by obesity in the European region alone, and it is among the four top causes of death. The early life approach acknowledges the importance of evidence-based interventions to prevent obesity at key life stages, from preconception to early life, childhood, adolescence, and working age (WHO, 2022). Adults born LGA are found to have a higher risk of obesity compared to those born appropriate for gestational age (Derraik et al., 2020), reflecting maternal and hereditary factors. On the contrary, adults born with LBW are suggested to have, in general, lower BMI with a smaller



number of adipocytes and impaired adipocyte tissue expandability (Xia et al., 2019; Nakano, 2020).

### *Metabolic syndrome and CVD*

Metabolic syndrome is a cluster of risk factors for CVD and type 2 diabetes occurring together more often than by chance alone. It includes raised BP, dyslipidemia (raised triglyceride and low HDL-cholesterol levels), raised fasting plasma glucose levels, and central obesity (Samson & Garber, 2014). Individuals with metabolic syndrome have an increased risk of developing CVD over the 5-10-year period compared to individuals without the syndrome (Ritchie & Connell, 2007). There is a growing prevalence of metabolic syndrome globally, parallel to the increasing burden of type 2 diabetes and obesity (Fahed et al., 2022).

### *Chronic kidney diseases*

The global prevalence of CKD is estimated to be 13.4%, and between 4.9-7 million are suffering from end-stage renal diseases who require renal replacement therapy worldwide (Lv & Zhang, 2019). The growing prevalence of CKD in Asia is alarming. The overall prevalence of CKD in Asia ranged widely between 7-34.3% and of the advanced stage between 0.1-17%. China and India, together, contribute to nearly 69% of all CKD cases in Asia (Liyanage et al., 2022). CKD is characterized by a reduction in GFR, the presence of hematuria and microalbuminuria, or abnormalities identified on laboratory testing or imaging for  $\geq 3$  months. The prevalence of CKD is growing and is estimated to be among the five leading causes of death by 2040 globally (Kalantar-Zadeh et al., 2021). CKD has been identified as a potential risk factor for CVD, with increased morbidity and mortality due to it. Both CKD and CVD share common risk factors, such as diabetes, hypertension, dyslipidemia, etc., and therapies like anti-diabetics, anti-hypertensives, and hypolipidemic therapies are effective treatments for both (Vallianou et al., 2018).

### *Cardio-renal syndrome*

The cardio-renal syndrome is a specific acute or chronic clinical condition wherein the heart and kidney are not functioning properly and affecting each other secondarily (Ricci et al., 2021). Dysfunction of one of the organs may precede the other and induce dysfunction or injury in the other organ. However, in one of the types of the syndrome, injury can occur simultaneously in both the kidney and heart, secondary to any systemic condition (Xhakollari, 2021).

Furthermore, the presence of the metabolic syndrome, along with microalbuminuria and/or reduced renal function, may collectively be called cardio-renal metabolic

syndrome. There is growing evidence of epigenetics and prenatal programming playing a crucial role in the genesis of the cardio-renal syndrome (Nistala et al., 2011). Consequences of the syndrome include an interruption in active nephrogenesis and vasculogenesis, characterized by low nephron number, hyperfiltration, proteinuria, aortic stiffness, decreased ventricular function, chronic inflammation, etc. (DeFreitas et al., 2016).

### *Cancers*

Breast cancer is the leading cause of cancer mortality globally (Arbyn et al., 2020). The incidence of other common cancers like colorectal cancer, lung cancer, and cervical cancer is also increasing (Lima et al., 2021). In the last decade, the incidence of new cancer cases increased by 26.3%, the number of deaths due to cancers increased by 20.9%, and disability-adjusted life years (DALYs) increased by 16% globally. This alarming increase in cancer cases and deaths warrants prompt action, including cancer prevention and control, besides targeting the risk factors at an early stage (Kocarnik et al., 2022).

Studies have shown a positive association between increasing birth weight and many cancers, including breast cancer, total or lethal/aggressive prostate cancer, colon cancer, and adenomas. However, inverse associations have also been demonstrated between birth weight and other cancer forms like testicular and colorectal cancers (Clarke & Joshu, 2017).

Larger birth size is a risk factor for breast cancer in adulthood, the possible mechanism of which includes increased *in-utero* exposure to estrogen and growth hormone in the growing *fetus* (Lahmann et al., 2004; Sovio et al., 2013). A similar study in a Swedish cohort conducted by Lahman *et al.* suggested higher birth weight as a risk factor for breast cancer (OR: 1.06, CI: 1.00–1.12, per 100 g) among post-menopausal women, independent of selected early-life and adult factors (Lahmann et al., 2004). However, several other studies did not find any significant association between birth weight and breast cancer risk (Sandvei et al., 2015; Tastula et al., 2021).

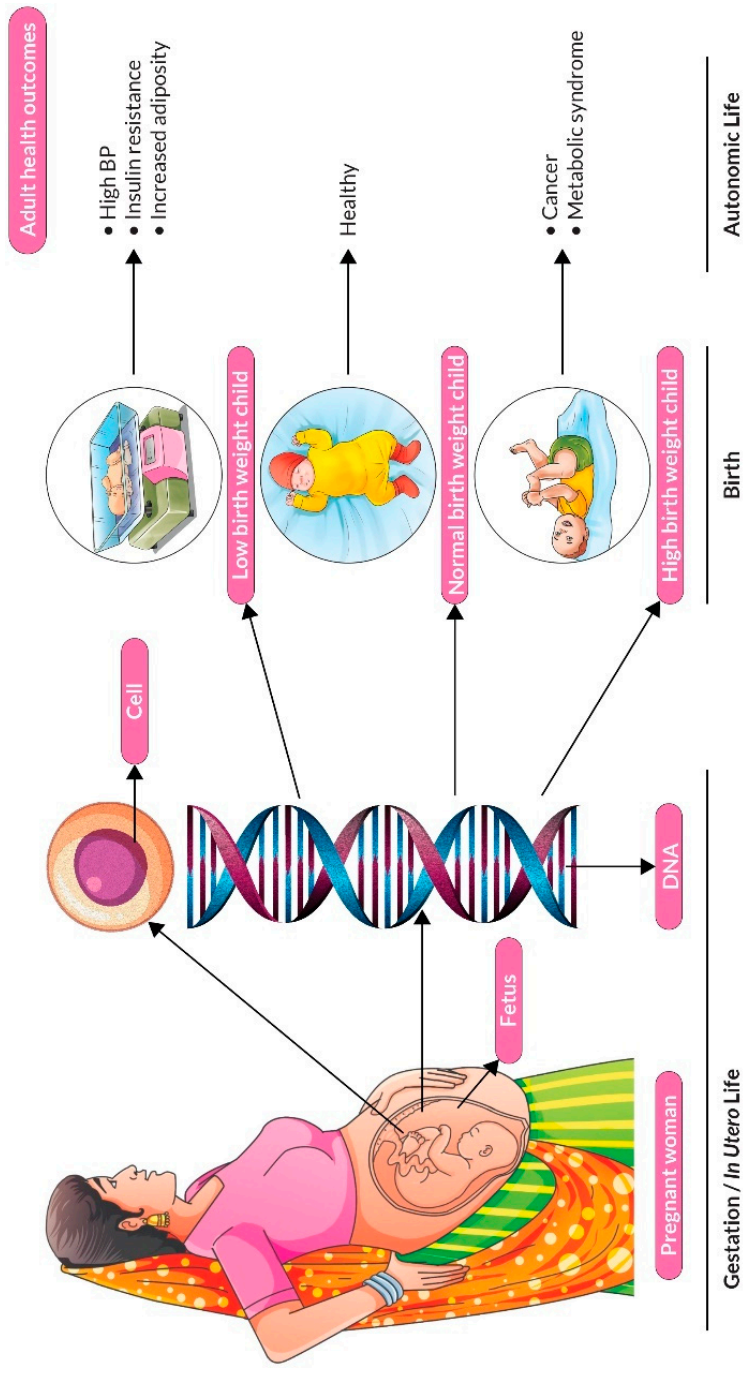
Higher birth weight (>4250 grams) has been found to be associated with prostate cancer incidence and mortality. Prostate cancer, the most common cause of death in malignant diseases among men in Sweden, is also hormone-dependent, like breast cancer. It is suggested that increased hormone exposure during the *intrauterine* period and increased levels of insulin-like growth factor-1 at birth increase the risk of prostate cancer in adulthood (Eriksson et al., 2007). There has been extensive research on DOHaD's effect on cancer incidence; however, the evidence of its effect on cancer *prognosis* is still evolving (Sharma et al., 2020).

# Causal mechanisms

## Early life factors, CVD, & their risk factors

Early life effects on the development of hypertension in adulthood are mediated via impaired renal development as well as other mechanisms, i.e., vascular development and perturbations of neuroendocrine regulation. The decreased supply of nutrients from the mother to the *fetus* compared to the requirement results in the shunting of blood and nutrients from the trunk and limbs to the brain. As a result, there is a decreased supply of blood to the fetal kidney, which activates the renin-angiotensin system. Other than this, Brenner suggested an alternative mechanism of reduced number of nephrons, increased pressure in glomerular capillaries, and glomerular sclerosis to be responsible for raised BP in adults born SGA. Besides, adults with small birth sizes have been found to have altered sympathoadrenal and hypothalamic-pituitary-adrenal responses to stress, resulting in increased sympathetic nervous activity and raised BP in adulthood (Gluckman & Hanson, 2006). In addition to these explanations, studies found that adults born with LBW have a relative deficiency of elastin synthesis and, thereby, have stiffer arteries and raised BP (Martyn & Greenwald, 1997; Sperling & Nilsson, 2020). Furthermore, small size at birth was found to be associated with endothelial dysfunction, hence, reduced ability of the arteries to dilate in response to the increased blood flow (Leeson et al., 1997).

According to the CVD risk continuum, CVD risk factors have been classified into three broad categories, depending upon their time of occurrence. This includes prenatal, childhood, and adulthood risk factors/markers. Epigenetic regulation, including DNA methylation, histone modification, and mRNA expression serve as mechanisms influencing prenatal risk traits and markers. Such epigenetic modifications may cause metabolic programming during the *intrauterine* and/or early post-natal period. Maternal metabolic disorders like diabetes and hypertension have been hypothesized to dysregulate certain mRNA expressions responsible for healthy heart development (Tian & Niu, 2017; Faienza et al., 2022) (**Figure 3**).



**Figure 3.** An illustration depicting the causal mechanism of the effect of *in-utero* exposures on the genes of the *fetus* and birth outcomes (Shantanu Sharma).

Prematurity alone, along with rapid weight gain in childhood, are potential risk markers for CVD and its risk factors in adulthood, such as raised SBP and DBP, impaired glucose tolerance, dyslipidemia, etc. (Eriksson et al., 2001; Bavineni et al., 2019). Bavineni *et al.*, in their review, highlighted potential mechanisms of linking prematurity with CVD risk. Oxidative stress leading to the formation of reactive oxygen species (ROS) results in endothelial dysfunction with reduced nitrous oxide levels, increased PWV, and increased intima-media thickness of the carotid artery. Such increased oxidative stress could be triggered by excess generation of inflammatory cytokines and reduced anti-inflammatory cytokine release in premature infants. The heightened inflammatory response, in turn, is linked to enhanced atherosclerosis, thrombosis, cardiac remodeling, raised cholesterol levels, obesity, and altered gut microbiome (Bavineni et al., 2019). The nature vs. nurture hypothesis of early life influences has highlighted that interaction between environmental influences on genes and resulting epigenetic mechanisms could program organ development and function (Nilsson, 2023).

### Early life determinants and cancers

Two life course epidemiological frameworks have been proposed as explanatory models for the association between early life factors, such as birth variables and cancer risks, including a) the critical period model, and b) the accumulation of risk models. The early life factors acting during critical periods, i.e., *in utero* or during puberty, have a long-lasting effect on the cancer risks in the presence or absence of modifiers (critical period model). On the contrary, the early life factors may have a cumulative effect by increasing the duration of the lifetime exposure or may lead to other exposures. This could increase the cancer risk cumulatively or may trigger the risk indirectly by increasing the probability of a causal exposure later in life (accumulation of risk model) (Clarke & Joshi, 2017).

Gluckman *et al.* have suggested three different causal pathways for the effect of early life factors on adult disease onset. These primarily include disruptive, homeorhetic, and predictive adaptive processes. When the *fetus* is exposed to extreme environmental stress during development, then the developmental change may not have an adaptive advantage but instead have disruptive consequences. Transient environmental stimuli may evoke homeostatic responses that do not alter the developmental trajectory of the growing *fetus*. However, the repeated environmental stimuli may induce so-called homeorhesis (i.e., the orchestrated or coordinated control of metabolism of body tissues necessary to support a physiological process, thereby altering the developmental trajectory) (Garcia-Contreras et al., 2017). This change in development trajectory may have an immediate adaptive advantage with long-term consequences. The predictive

adaptive responses are consequential to a permanent change in the physiology of the individual and give rise to diseases more than predictive reproductive limits (Gluckman & Hanson, 2006).

### **Pregnancy complications and risk of maternal CVD**

Though not falling within the domain of DOHaD, there is ample evidence of pregnancy complications' association with maternal CVD risk. Both maternal and fetal complications are risk markers for mortality and increased hospitalization due to atherosclerotic CVD in the mother herself (Täufer et al., 2022; Täufer, 2023). Besides other mechanisms, one potential pathophysiological mechanism includes activation of inflammation and coagulation due to fibrinogen activation (Täufer et al., 2022). Sharma *et al.*, in their population-based study, showed that women with preeclampsia and SBP >95<sup>th</sup> percentile in early pregnancy are at increased risk of CVD later in life (Sharma et al., 2021).

### **Knowledge gaps**

Given that low- and middle-income countries (LMIC) account for 80% of all the deaths caused by NCDs globally, most of the evidence of the published DOHaD-oriented research comes from Western countries (WHO Non-Communicable Diseases, 2023). Consequently, contextual evidence for public health interventions in the countries with the highest burden of NCDs is limited. The importance of heterogeneity of the environment, different lifestyles, and nutrition in the LMIC are not visible or acknowledged in the Europe-based studies. Collaborations among researchers from multiple LMIC settings are warranted to encourage DOHaD research and build their capacities. Furthermore, DOHaD research focus on vulnerable populations of different ethnicities within the countries is required (Tu'akoi et al., 2020).

Finally, there is a lack of knowledge about DOHaD, its mechanisms, and its impact on health outcomes among various healthcare professionals. As a result, the DOHaD research applications to preventive medicine, bedside medicine, and precision medicine are limited. Animal model-based research constitutes a significant proportion of DOHaD evidence generation related to mechanistic understanding, and corresponding evidence in humans is limited (Molinaro et al., 2021). Placental function and its determinants should probably be studied more in the DOHaD perspective, as the phenotypes at birth are shaped by placental properties and function (Barker & Thornburg, 2013).

# Aims

## Overall Aim

To elucidate the influence of factors acting early in life, such as birth weight and birth length, on adult organ function, health, and disease based on data from population-based cohorts.

## Specific aims

**Paper I:** To determine whether birth size is associated with the *prognosis* of cancer in adults.

**Paper II:** To examine the *mismatch* between pre-and post-natal factors influencing adult body weight for the prediction of central and peripheral hemodynamics in a population-based cohort of young adults.

**Paper III:** To assess the associations of two early life variables, birth weight and gestational age, with levels of sfAGE and ABI obtained at a health examination in a Swedish population-based cohort of young-aged to middle-aged individuals.

**Paper IV:** To assess the associations between birth variables (birth weight, and following adjustments for gestational age and other confounders) and adult apolipoproteins (apoA1, apoB, and their ratio) as well as conventional lipid variables in the LifeGene cohort.

# Methods and Materials

Our first paper is a systematic review and meta-analysis of the articles that are based on cohorts or case-control studies from Sweden, Denmark, Norway, Finland, England, and the USA (Table 1). We worked on three birth cohorts, namely the Malmö Offspring Study (MOS) Cohort (Paper II & III), the LifeGene Study Cohort (Paper IV), and the Malmö Birth Data Cohort (MBDC) (Additional analysis on breast cancer risk and mortality).

## Study Design

**Table 1.** Overview of the four papers and additional analysis on breast cancer risk and mortality.

	Paper I	Paper II	Paper III	Paper IV	Additional analysis on breast cancer risk and mortality
<b>Design</b>	Systematic review and meta-analysis	Observational cohort study	Observational cohort study	Observational cohort study	Nested Case-Control study
<b>Cohort</b>	--	Malmö Offspring Study	Malmö Offspring Study	LifeGene Study	MBDC
<b>Sample</b>	Eleven studies	920 men and 1075 women	958 men and 1054 women	4292 men and 5801 women	154 cases and 322 controls
<b>Primary outcome</b>	<i>Prognosis of adult-onset cancers (any, prostate, and breast)</i>	bSBP, cSBP, bDBP, cDBP, 24-h night-time SBP, Pulse wave velocity, Augmentation Index	Skin auto-fluorescence (sf)AGE and mean ABI	apoA1, apoB, and their ratio, total cholesterol, serum triglycerides	Breast cancer risk and mortality
<b>Statistical analyses</b>	Random effects meta-analytic model	ANOVA, General linear regression	General linear regression	General linear regression	Cox proportional-hazards regression

**Abbreviations:** ANOVA: Analysis of Variance; AGE: Advanced Glycation End products; ABI: Ankle-Brachial Index; apoA1: Apolipoproteins A1; apoB: Apolipoproteins B; cSBP: Central Systolic Blood Pressure; cDBP: Central Diastolic Blood Pressure; bDBP: Brachial Diastolic Blood Pressure; MBDC: Malmö Birth Data Cohort; bSBP: Brachial Systolic Blood Pressure



**Swedish Medical Birth Register (MBR)**, which started in 1973, is the source of information for all early life factors in our original studies. The MBR data is based on the 10-digit personal identity numbers for mothers and their live-born infants. With data on more than 200 variables, the MBR records information from the mother's first visit to the antenatal care until the discharge of both mother and infant post-delivery. The MBR's quality and completeness of data is reported to be as high as 99% since 2015. The data on maternal factors, such as age, parity, smoking habits, weight, height, ethnicity, and common maternal diagnoses like (pre)gestational diabetes, (pre)gestational hypertension, (pre)eclampsia, and placental abruption, are good to excellent. Similarly, the data on birth and neonatal factors, such as date of birth, type of delivery, gestational age, birth weight, sex, Apgar scores, and infant diagnoses, are very good to excellent (Cnattingius et al., 2023).

## Systematic Review and Meta-analysis (Paper I)

**Search strategy:** Three databases, including PubMed, EMBASE, and Web of Sciences, were searched from inception until the end of April 2019. We looked for observational studies that have shown the effect of birth weight, birth length, and head circumference on the *prognosis* of any adult-onset cancer, using overall or cancer-specific mortality. In addition to searching databases, we looked for reference lists and citation indices in the included studies. The key terms used for the search strategy included: ('Birth weight' OR 'Birth size' OR 'Birth parameters' OR 'Birth length' OR 'Gestational age' OR 'Head Circumference') AND (cancer OR neoplasm OR carcinoma OR 'Neoplasms' OR tumor OR tumour) AND ('prognosis' OR survival OR mortality). An additional search was made for the papers published between April 2019 and 31<sup>st</sup> August 2023, using the same search strategy and criteria.

**Inclusion criteria:** All the observational studies that have reported on cancer mortality in adults aged 20 years or more in relation to the birth data.

**Exclusion criteria:** Conference abstracts, anecdotal reports, or non-peer-reviewed articles or articles published in any language other than English.

In case there was more than one published article based on the same set of population, the most recent publication was selected.

**Quality Assessment:** Since mainly two types of studies, i.e., case-control and cohort studies, were identified, the Newcastle-Ottawa scale (Peterson et al., 2011) was used to assess the quality of the papers.

# Study populations

## Malmö Offspring Study Cohort (Papers II & III)

The Malmö Offspring Study (MOS) was conducted between 2013 and 2021. The study aimed to understand the family patterns of major diseases based on gene-environment interactions. It was a population-based cohort study where adult (>18 years old) children and grandchildren of participants of the Malmö Diet and Cancer Cardiovascular Cohort (MDC-CC; generation 1, G1) living in the region Skåne were recruited.

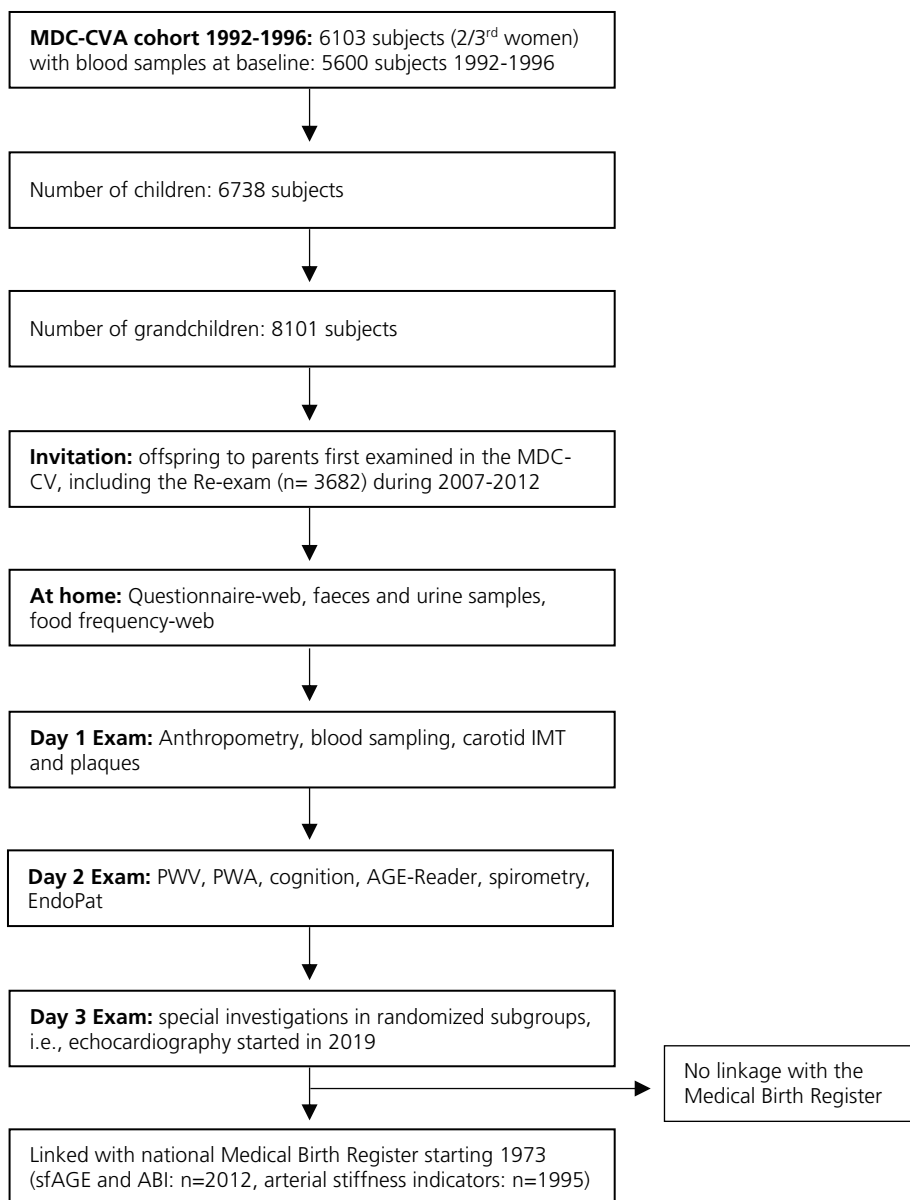
In MOS, apart from questionnaire-based data collection, physical examination, blood sampling, technical examinations, diet intake, and urine and faeces sampling were performed. In the technical examinations, investigators performed carotid ultrasound, arterial stiffness measurement, 24-hour peripheral and central blood pressure measurement, peripheral circulation assessment, ankle-arm index measurement, and spirometry. Furthermore, cognitive tests, glucose metabolic control assessments, and AGE product measurement through skin autofluorescence were done.

Invitations were sent by mail with a follow-up over phone calls to the adult children (generation 2; G2) and grandchildren (generation 3; G3) of index individuals G1. The study had data from approximately 5260 individuals. Subjects with deviant samples or technical examination results were informed and referred for further treatment and follow-up. The blood samples were drawn during the first visit of the MOS participant to a Clinical Research Unit after an overnight fast. The analyses of blood samples were performed at the Department of Clinical Chemistry, Skåne University Hospital, Malmö.

The details about MOS can be accessed through its webpage (<https://www.malmo-kohorter.lu.se/malmo-offspring-study-mos>) and the publication describing the study's design and methodology (Table 2) (Brunkwall et al., 2021). The flow of the study participants is shown in Figure 4.

**Table 2.** Brief description of a subsample of the Malmö Offspring Study (MOS) Cohort used for this thesis, with participants born in 1973 or later, and with birth data.

<b>Start year</b>	2013
<b>Birth cohort years</b>	1973 or later
<b>Source of birth data</b>	Medical Birth Register
<b>Source of data on traits</b>	Study data
<b>Attendance rate of participants</b>	47%
<b>End of Examination</b>	31 <sup>st</sup> December 2021
<b>Type of study design</b>	Cohort



**Figure 4.** Flow chart of the study participants in the Malmö Offspring Study (MOS).

**Abbreviations:** AGE: Advanced Glycation End Products; IMT: Intima Media Thickness; MDC-CVA: Malmö Diet Cancer Study-Cardiovascular Arm; PWV: Pulse Wave Velocity, PWA: Pulse Wave Analysis; sfAGE: Skin Autofluorescence Advanced Glycation End Products; ABI: Ankle-Brachial Index

## LifeGene Study Cohort (Paper IV)

This is a population-based prospective cohort that consists of individuals between 7-50 years of age. The participants were randomly sampled from the general population, mostly in the Stockholm area, besides those who registered voluntarily for participation. The participants provided data through a web-based questionnaire that had questions on sociodemographic characteristics and nine other domains, including lifestyle, self-care, women's health, living habits, health history, asthma and allergies, injuries, and mental health.

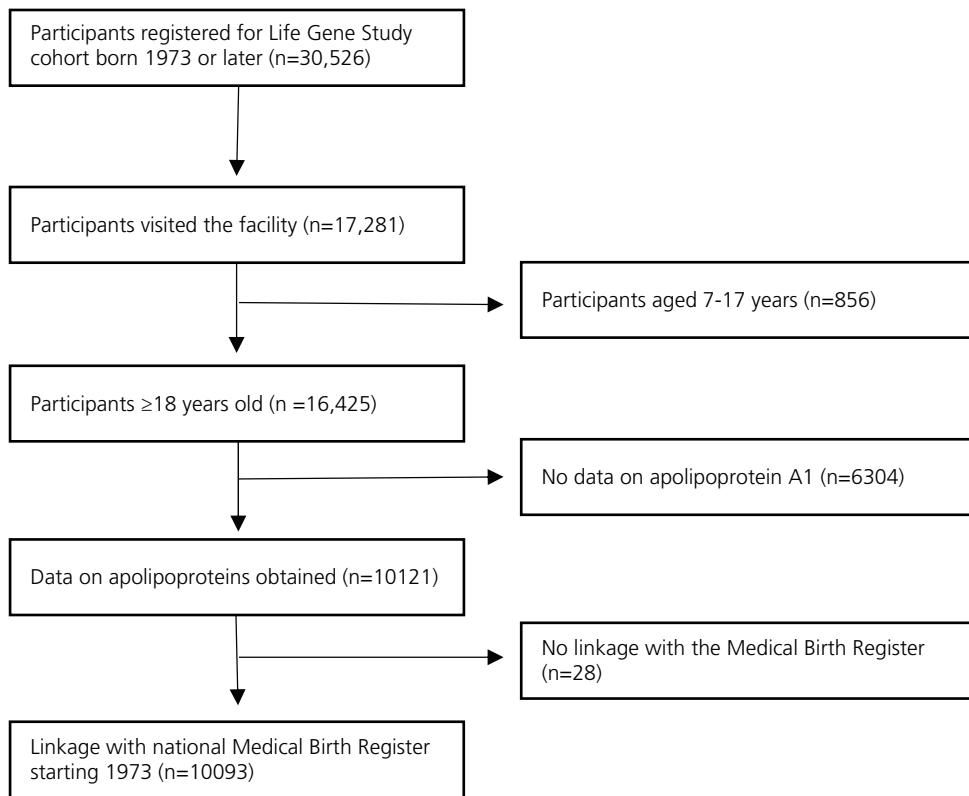
In addition, physical parameters and blood samples were collected at the testing centers, and the samples were analyzed at Unilabs, St. Göran Hospital, Stockholm, between 2009 and March 2010, and at Dept. Clinical Chemistry, Karolinska University Hospital, between 2010 and 2016. Body weight (kg), height (m), waist, hip, and chest circumference (cm), heart rate (beats/min), and BP (mmHg) were measured using standard methods (Table 3). The blood samples were collected in a non-fasting state. The details about the procedures of the LifeGene examination are available at:

<https://lifegene.se/wp-content/uploads/1LifeGeneresource20170203version24.pdf>

The flow of study participants is shown in Figure 5.

**Table 3.** Brief description of the LifeGene Study Cohort, the subjects used in our analysis.

<b>Start year</b>	2010
<b>Birth cohort years</b>	1973 or later
<b>Source of birth data</b>	Medical Birth Register
<b>Source of data on traits</b>	Study data
<b>Attendance rate of participants</b>	<10%
<b>End of screening</b>	22 <sup>nd</sup> December 2016
<b>Type of study design</b>	Cohort



**Figure 5.** Flow chart of the study participants in the LifeGene Study Cohort.

### **Malmö Birth Data Cohort (MBDC) (Additional analysis)**

The MBDC is derived from two nested case-cohort studies, including the Malmö Preventive Project (MPP) and the Malmö Diet and Cancer study (MDCS) from the city of Malmö, Sweden. The strengths of the MBDC include birth weights that were derived from birth records documented by midwives (i.e., the possibility of modelling of a continuous variable) and stored in archives, but also an extensive mid-life screening. This has been complemented by a registry-based follow-up of many diagnoses based on national and regional health registries. Men in the MBDC were derived from a nested case-control study composed of prostate cancer cases and cancer-free controls born within one year of the cases from both MDCS and the MPP (Gerdtsson et al., 2015).

In total, 1355 cases were ascertained and matched to 5271 controls. Some cases were matched as controls during the time before prostate cancer diagnosis, resulting in a total number of cases and controls of 5726. Birth weights were identified from hospital

records as well as regional state archives under the hospital name and year and were located using the study participants' date of birth as well as the name and year of birth of the mother, which had been obtained from the Swedish Tax Agency after linkage with the study participants, personal identity number. Individuals born in the region of Skåne or the other major Swedish cities of Gothenburg and Stockholm were included. The detailed data collection procedures have been explained in the original publication (Gerdtsen et al., 2015). There were some data overlaps with a previous study on prostate cancer by Lahmann *et al.* (Lahmann et al., 2012). Birth weight was available for 3671 men.

Women in the MBDC were derived from a case-control study of breast cancer nested in the MDCS cohort, including 131 incident breast cancer cases during the years 1991-2001 and 345 age-matched controls. However, the number of cases went up to 154, and we were left with 322 controls during the follow-ups until 2020. The detailed data collection procedures have been explained in the original publication (Lahmann et al., 2004). The present study was nested within the MDCS cohort.

The MDCS was started in 1991, and people were recruited between 1991 and 1996 (Table 4). This population was born between 1923-1945. The birth details of this population were retrieved from hospital archives. The attendance rate of the participants in MDCS was just 41%. The data on the incidence and prevalence of breast cancer was obtained from the National Cancer Registry.

**Table 4.** Brief description of the Malmö Birth Data Cohort (MBDC), including subjects used for early life studies on the risk of cancer.

Characteristics	Malmö Birth Data Cohort (MBDC)	
	Malmö Preventive Project (MPP)-subsample	Malmö Diet Cancer Study (MDCS)-subsample
<b>Start year (Baseline)</b>	1974 (1974-1994)	1991 (1991-1996)
<b>Birth cohort years</b>	1921-1949	1923-1945
<b>Source of birth data</b>	Hospital archives	Hospital archives
<b>Source of death data for cancers</b>	National Cancer Registry and Cause of Death Registry	National Cancer Registry and Cause of Death Registry
<b>Source of data on vascular traits</b>	Baseline survey	Baseline survey and re-examination
<b>Attendance rate of participants</b>	74%	41%
<b>Follow-up for cancers</b>	31 <sup>st</sup> December 2020	31 <sup>st</sup> December 2020
<b>Type of study design</b>	Nested case-control	Nested case-control

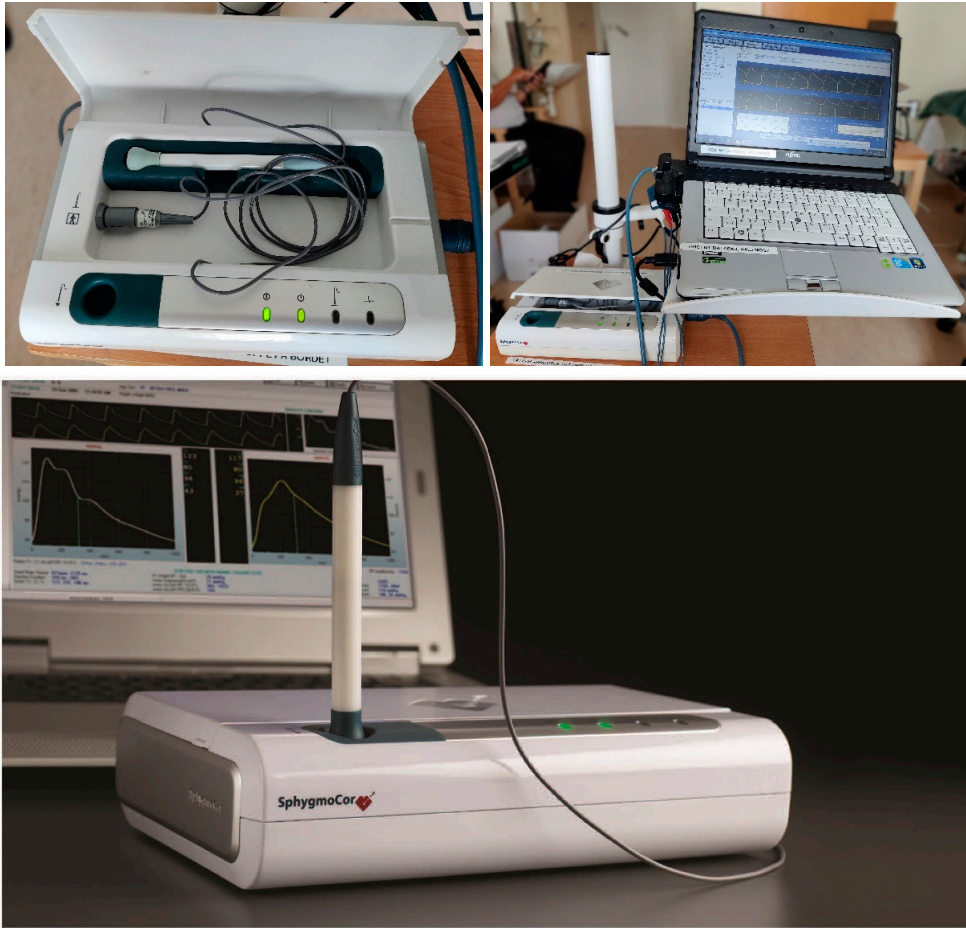
# Variables

## Outcomes

- a) **Cancer prognosis:** In the systematic review paper (**Paper I**), the outcome was the *prognosis* of any adult-onset cancer (overall), breast cancer, and prostate cancer.
- b) **Pulse Wave Velocity (PWV) and Pulse Wave Analysis (PWA):** These variables were used in **Paper II**. On the second day, participants underwent measurements of central aortic pressure, central SBP (cSBP), central diastolic blood pressure (cDBP), cf-PWV, and analysis by use of SphygmoCor Cardiovascular Management System (CVMS) (Atcor, Australia), using applanation tonometry with a high-fidelity sensor (**Figure 6**). The investigator recorded participants' height (cm), weight (kg), and the distance between carotid and femoral arteries using a scale and recorded their brachial SBP and DBP. Anthropometric measurements were done in light indoor clothes. OMRON M5-1 (IntelliSense, Brighton, United Kingdom) was used to measure SBP and DBP after 5 minutes of rest in the supine position, and a mean was calculated from two repeated measurements.

The participants were asked to come after 12 hours of abstinence from alcohol and 4 hours of abstinence from caffeine and food on the day of examination. The pulse wave was recorded using standard methods, and cf-PWV was calculated by the manufacturer's software. Similarly, a pulse wave was recorded at the site of radial artery pulsation with a high-fidelity sensor using applanation tonometry. Thereafter, a central pressure waveform was estimated with a transfer function (PWA), also calculating the cSBP and cDBP.

A scale was used to measure the carotid-femoral distance by measuring the length from the point of feeling the carotid pulse until the point of feeling the femoral pulse. This measurement was multiplied by 0.8 (correction factor) and entered manually into the program (Van Bortel et al., 2012). The accuracy of the measurements was assessed by obtaining two measurements, and if the investigator found a difference of  $>0.5$  m/s between the two measurements, a third measurement was obtained. The mean value of the measurements was used. SphygmoCor transducer captured the pulse curve of the radial artery to perform the PWA. In addition, 24h Ambulatory Blood pressure Monitoring (ABPM) was conducted on a subgroup of study participants using 24h Arteriograph. Mean day-time and night-time values of SBP, DBP, and pulse pressure were calculated.



**Figure 6.** The complete set used for performing pulse wave analysis (up and right) and the SphygmoCor® CVMS device with tonometer used in MOS (up and left and bottom) (*Shantanu Sharma*).

- c) **Augmentation Index:** Aix was defined as the ratio of the difference between the early and late systolic peak and early systolic peak, or the difference between early and late systolic peak divided by pulse pressure. Abstinence from alcohol for 12h and nicotine or heavy meals for at least 4h was followed before measuring Aix based on PWA. All the measurements were obtained using standard methods at regulated temperature and dimmed light, with the participant in a supine position resting for five minutes before start. We had two types of Aix: peripheral and central Aix. Since both peripheral and central Aix were skewedly distributed, log transformation was done while using them in the generalized linear regression analysis. However, for comparing medians



of Aix among birth weight and BMI groups, analysis of Variance (ANOVA) or Kruskal-Wallis's test (non-parametric test) was performed.

- d) **Skin Autofluorescence AGE (sfAGE):** In MOS, sfAGE has been measured through AGE Reader <sup>®</sup> (DiagnOptics, The Netherlands) and used as a continuous variable in the analysis (**Paper III**). The UV Lamp in the AGE reader emits light at 360-370 nm peak wavelength, and the in-built spectrometer in the AGE Reader measures the light reflected and emitted from the skin at the wavelength between 300-360 nm (**Figure 7**). These measurements were obtained on the volar side of the forearm. The readings have been obtained on normal skin with minimal sunlight exposure.



**Figure 7.** The AGE Reader used to obtain sfAGE recordings from the MOS participants (*Shantanu Sharma*).

- e) **Ankle-Brachial Index (ABI):** This was used as a continuous variable in the analysis (**Paper III**). ABI was calculated by measuring SBP from both brachial arteries and from art. tibialis posterior and art. dorsalis pedis in the foot. The participants were asked to rest supine for 10 minutes before obtaining these measurements. The right ABI was calculated by dividing the higher pressure of the two arteries in the right foot by the highest pressure in the two arms. Similarly, the left ABI was calculated by dividing the higher pressure of the two arteries in the left foot with the highest pressure in the two arms. We used the mean ABI value, which was calculated as an average of right and left side readings. The sphygmomanometer and Doppler (Hadeco Bidop ES100V3) were used to measure the blood pressure variables on the right and left sides (arm and ankle) (**Figure 8**).



**Figure 8.** Four pressure cuffs for 2 arms and foot ankles with the sensor used in MOS (*Shantanu Sharma*).

- f) **Apolipoproteins apoA1 and apoB:** The blood sample for assessing apolipoproteins, total cholesterol, and triglycerides was obtained in the non-fasting state in the LifeGene Study, and analyses were performed in two laboratories using standardized methods (immunochemistry, turbidimetry). The data were used for **Paper IV**.

### **Exposures, confounders, and covariates**

- a) **Birth weight:** The details of the birth weight were obtained from the national Medical Birth Register (MBR). It was expressed in grams or kgs. It was normally distributed in both cohorts (MOS and LifeGene). Birth weight was used as a continuous variable in all the analyses; however, we also performed additional analysis using categories of birth weight. Birth weight z-scores adjusted for gestational age and sex were calculated (personal communication, Karin Källén, 2019; Bonnevier et al., 2022).
- b) **Gestational age:** This was calculated from the last day of the menstrual period to the day of delivery. It was expressed in weeks. Gestational age was also obtained from the MBR.
- c) **Sex:** We used only two biological sexes in our analysis: men and women. We had a roughly equal distribution of men and women in the MOS; however, there were more women relative to men in the LifeGene Study.

- d) **Adult age:** Participants' age at the time of the screening or data/sample collection was used in the analysis.
- e) **Adult BMI:** This was calculated using the formula:

$$BMI = \frac{Weight(kg)}{(Height * Height (m^2))}$$

The adult height and weight were collected at the time of the study screening or sample collection. In addition, BMI at age 20 was calculated in Paper II by using recalled weight at age 20 and height at the time of screening. The participants were asked to stand with their legs held together, looking straight ahead, in indoor clothing without shoes or hats. A calibrated balance beam or digital scale was used to record body weight (kg) in MOS.

- f) **Systolic blood pressure:** It was measured in the resting state using the OMRON apparatus, and a mean of two readings (mmHg) in the supine position after 10 min rest was recorded in the MOS.
- g) **Fasting plasma glucose:** Blood samples for calculation of fasting plasma glucose (mmol/L) were collected on Day 1 of MOS using standardized methods.
- h) **Serum Triglyceride:** Blood samples of serum triglycerides (mmol/L) were collected in the fasting state on Day 1 of MOS using standardized methods.
- i) **Blood cholesterol levels:** Blood samples of blood cholesterol were collected in the fasting state on Day 1 of MOS using standardized methods. No LDL- or HDL cholesterol tests were performed in the LifeGene Study due to non-fasting conditions.
- j) **Smoking history:** In MOS, there was a question on smoking: “*Do you smoke?*” with three options: “never”, “yes”, or “used to do earlier and stopped now”. In the LifeGene Study, since there were many questions on smoking history and it was a branched variable with stepwise added more specific questions, we selected only one question for our analysis: “*Have you smoked more than 100 cigarettes in your entire life?*”.

# Statistical analysis

## Paper I

For the meta-analysis, the most fully adjusted reported risk estimates, with 95% confidence intervals of the associations, were included. The risk estimates for the highest versus lowest categories were used for the categorical exposure variables, and a 0.5 -1 kg increase in birth weight and per cm increase in birth length was used for the continuous exposure variables. The random effects meta-analytic model was used to calculate pooled and weighted relative risks (RR). In addition, we performed sub-group analysis for cancer sub-types or continuous or categorical birth exposures or different sexes. The symmetry of the funnel plot was assessed to measure the publication bias. The statistical analysis was performed using STATA version 14 (Stata Corp., College Station, TX, USA).

## Paper II

The continuous variables were presented as mean (Standard Deviation; SD) or median (Interquartile Range). Z-scores were calculated for birth weight (adjusted for gestational age and sex). To test the *mismatch* hypothesis, we subdivided all the study participants into four groups: a) low birth weight z-score ( $\leq 0$ ) and low BMI at age 20 ( $\leq$  median); b) low birth weight z-score ( $\leq 0$ ) and high BMI at age 20 ( $>$ median); c) high birth weight z-score ( $> 0$ ) and low BMI at age 20 ( $\leq$  median); and d) high birth weight z-score ( $> 0$ ) and high BMI at age 20 ( $>$ median). We performed an Analysis of Variance (ANOVA) to compare the difference in means of all the normally distributed independent variables among the four groups, as discussed above. The Bonferroni *post hoc* correction was used while performing ANOVA. However, the Kruskal-Wallis's test was performed to compare the difference in medians of skewed variables among the four groups. The LBW and low BMI at age 20 group was used as the reference group (category a).

We drew DAGitty software to show a causal association between the exposures and outcomes (Available online: <https://www.dagitty.net/>). Furthermore, general linear regression analysis was done to find associations between exposures (birth weight and BMI at age 20 sub-groups) and different outcomes, including cf-PWV, PWA, and hemodynamic parameters (before and after adjustment for sex). Full factorial models were run in the general linear regression analysis. The strength and direction of the association were expressed as  $\beta$  coefficients with a 95% Confidence Interval (95% CI). In addition, stepwise general linear regression analysis was done to explore associations

between birth weight z-score categories (Low or High) and cf-PWV, peripheral and central Aix, and cSBP and cDBP.

**Model I:** Birth weight z-score categories

**Model II:** Model I + adjustment for sex, age, BMI

**Model III:** Model II + adjustment for smoking history, brachial SBP, Heart Rate

*(Note: SBP was not adjusted for in the regression analysis with cSBP and cDBP)*

### **Paper III**

We showed categorical variables as frequencies and percentages and continuous variables as mean (median if data were skewed). Log transformation was performed for fasting plasma glucose levels, triglyceride levels, and cholesterol levels, as their distribution was skewed. We performed general linear regression to assess the association between birth variables (birth weight, gestational age) and sfAGE and mean ABI levels, respectively, before and after adjustments for confounders and covariates. Full factorial models were run in the general linear regression analysis. The strength and direction of the association were expressed as  $\beta$  coefficients with a 95% Confidence Interval (95% CI) on the box and whisker chart (sfAGE) and violin chart (ABI) using displayr software (ref: <https://app.displayr.com>).

Stepwise regression models for **sfAGE** as the dependent variable and birth weight as the prime exposure:

**Model I:** Birth weight adjusted for gestational age

**Model II:** Model I + additional adjustment for sex

**Model III:** Model II + additional adjustment for smoking history, fasting plasma glucose, SBP, triglyceride, and cholesterol levels

Stepwise regression models for **ABI** as the dependent variable and birth weight as the prime exposure:

**Model I:** Birth weight adjusted for gestational age

**Model II:** Model I + additional adjustment for sex

**Model III:** Model II + additional adjustment for BMI, SBP, triglyceride and cholesterol levels, and smoking history.

## Paper IV

We showed categorical variables as frequencies and percentages and continuous variables as mean (median if data were skewed). Since all the variables were normally distributed, no log-transformation was needed. We performed general linear regression to assess the association between birth variables (birth weight, gestational age) and apoA1, apoB, and their ratio, before and after adjustments for confounders and covariates. Full factorial models were run in the general linear regression analysis. The strength and direction of the association were expressed as  $\beta$ -coefficients with a 95% Confidence Interval (95% CI).

Stepwise regression models for **apoA1** and **apoB** as the dependent variables and birth weight as the prime exposure:

**Model I:** Adjusted for gestational age and sex

**Model II:** Model I + additional adjustment for BMI and adult age

**Model III:** Model II + additional adjustment for smoking history

All analyses of **Papers II, III, and IV** were done using IBM SPSS Statistics 27.0 for Windows (IBM Corporation, Armonk, NY, USA). Two-sided p-values < 0.05 were statistically significant.

### Additional analysis on breast cancer risk and mortality

The cases were defined as women with breast cancer and controls as women free of breast cancer, all from the MDCS. We included five birth parameters in the analysis (birth weight, birth length, head circumference, gestational age, and ponderal index). The birth parameters were normally distributed. All the continuous variables were expressed as mean (SD). The Cox proportional-hazard regression analysis was done to find associations between birth weight (with and without adjustment for gestational age), birth length, head circumference, ponderal index (with and without adjustment for gestational age), gestational age, and breast cancer risk and mortality in adulthood. The end date for the follow-up time was the date of the diagnosis of cancer or the date of the death or migration out of the country, or 31<sup>st</sup> December 2020, whichever occurred earlier. Risk estimates were expressed as Hazard ratio (HR) and the confidence interval (CI). Statistical analysis was performed using IBM SPSS statistics for Windows version 27.0 (IBM Corp., Armonk, N.Y., USA). A p-value <0.05 was taken to indicate statistical significance. The ponderal index was calculated from the formula:

$$\text{Ponderal Index} = \frac{\text{Weight (grams)} * 100}{\text{Height}^3(\text{cm})}$$

## Ethical approval

### *Malmö Offspring Study (MOS) Cohort*

Ethical approval has been obtained for MOS from the regional Ethics Committee in Lund (Dnr. 2012/594 and Dnr 2013/761, respectively).

### *LifeGene Study Cohort*

This study was approved by the Ethics Review Authority (“Etikprövningsmyndigheten”), Sweden (Dnr: 2019-02408), based on an earlier approval of the Life-Gene study from the Ethics Review Board at Karolinska Institute (Dnr: 2009/615-31/1), and in addition the Life-Gene legal permission by Swedish law (Lag 2013:794).

### *Malmö Diet and Cancer Study (MDCS)*

The original MDCS study was approved by the Lund University Ethical Committee, Sweden (LU 51-90).

### *Malmö Preventive Project (MPP)*

The epidemiological follow-up studies in the MPP were approved by the Lund University Ethical Committee, Sweden (85/2004).

# Results

## Paper I

We could identify 11 eligible published peer-reviewed articles based on our criteria for the qualitative synthesis. Out of 11, 8 studies demonstrated associations between birth weight and cancer mortality, and 3 studies demonstrated associations of both birth weight and birth length with cancer mortality. However, none of the identified studies showed an association between head circumference at birth and cancer mortality. Table 5 showcases the details of the 11 included studies. On the Newcastle–Ottawa Scale, all the studies scored six stars or more, and hence, their quality was good enough to be eligible for inclusion in the review. In these eligible studies, 7 were cohort studies, and 4 were case-control studies. There was a difference in the use of birth data among studies. All studies except one used data on birth weight from hospital archives, medical records, or registers. Most of the included studies were from the Nordic countries except for two, which were from England and the USA. In the meta-analysis, we included nine studies due to a lack of reported risk estimates in the other two.



**Table 5.** Characteristics of included studies on birth weight or birth length in relation to cancer mortality (n = 11).

First author	Study country	Study design	Cancer type	Case number (deaths)	Control number	Published association for BW/BL with 95% CI	Adjustment for covariates
Ekborn et al., 1996	Sweden (Uppsala)	Nested case-control	Prostate cancer	80	196	OR per 500g BW increase: 1.22(0.87-1.70) OR per 20mm BL increase: 0.91(0.68-1.21)	Matched by birth year and age at diagnosis. *
Leon et al., 1998	Sweden (Uppsala)	Cohort	All neoplasms	M:599 W:480	NA	RR per 1 kg BW increase: M: 1.13(0.96-1.33) W: 1.04(0.87-1.24)	Adjusted for period of birth as a three-level categorical variable (1915-9, 1920-4, 1925-9).
Syddall et al., 2005	England (Hertfordshire)	Cohort	All neoplasms	M:1867 W:1049	NA	HR per 1SD score of BW increase: M:1.06(1.02-1.11) W:1.01(0.95-1.07)	Adjusted for year of birth
*Kajantie et al., 2005	Finland (Helsinki)	Cohort	All cancers	M:361 (BW); 357(BL) W:269 (BW); 267 (BL)	NA	HR per 1 Kg BW decrease: M:0.76(0.61-0.95) W:1.09(0.82-1.43) HR per 1 cm decrease in BL: M:0.97(0.91-1.03) W:1.06(0.99-1.14)	Adjusted for birth years and gestational age
Sanderson et al., 2006	USA	Case-control	Breast cancer	W:279	739 alive out of 1024 cases	HR of BW >4000g over ref BW<2500g 1.80(1.0-3.10)	Adjusted for age at diagnosis, diagnosis year, stage of diagnosis and birth order
Eriksson et al., 2007	Sweden (Gothenburg)	Cohort	Prostate cancer	M:68	NA	CR per 1 Kg BW increase 1.41(0.93-2.12)	Adjusted for the birth year and age
Baker et al., 2008	Denmark (Copenhagen)	Cohort	All cancers	M: 2110 W: 2335	NA	HR of BW 4251-5000g over ref BW 2000-2150g: 1.12(0.99-1.28)	Adjusted for the birth year

Maehle <i>et al.</i> , 2010	Norway	Case control	Breast cancer	W: 87	244 alive out of 331 cases	HR of BW >3850g over ref BW ≤ 3050g: 1.16(0.59-2.29) HR of BL >52 cm over ref BL <48 cm: 1.83 (1.03-3.25)	Adjustment for place of birth and year of diagnosis
Sovio <i>et al.</i> , 2013	Sweden (Uppsala)	Cohort	Breast cancer	W:171 women died due to breast cancer out of 311 deaths	NA	HR for 1 SD (BW for GA) increase: 1.27(1.09-1.47)	Adjusted for gestational age and other factors <sup>§</sup>
Wennerström <i>et al.</i> , 2015	Denmark	Cohort	All cancers	1813	NA	-----	Adjusted for gestational age
Gerdtsen <i>et al.</i> , 2015	Sweden (Malmö)	Nested case-control	Prostate cancer	159	636	-----	Matched by birth year and age at diagnosis

**Abbreviations:** BW: Birth weight; BL: Birth length; CI: Confidence interval; CR: Crude rate; G: Grams; GA: Gestational age; HR: Hazard ratio; kg: Kilogram; LGA: Large-for-Gestational-Age; M: Men; MPP: Malmö Preventive Project; MDCCS: Malmö Diet Cancer Study; NA: Not Available; OR: Odds ratio; RR: Rate ratio; ref: Reference; SGA: Small-for-Gestational-Age; SD: Standard Deviation; W: Women

\*Also adjusted for maternal age, socioeconomic status, parity, pre-eclampsia, eclampsia, prematurity, age at menarche and neonatal jaundice.

<sup>†</sup>Other factors included birth length, age at first child, number of children, adult occupational social class in 1960, educational level in 1970, and personal income in 1970.

<sup>§</sup>Additionally, for cancer-specific estimates: Prostate cancer (n=125 deaths); HR (95%CI) per 1 SD score of BW increase: 1.12 (0.95, 1.32) and Breast cancer (n=284 deaths); HR (95%CI) per 1 SD score of BW increase: 0.95 (0.85-1.07).

<sup>‡</sup>Additionally, for cancer-specific estimates: Prostate cancer (n=22 deaths); HR (95%CI) per 1 Kg BW decrease: 0.42 (0.17, 1.01) and Breast cancer (n=70 deaths); HR (95%CI) per 1 Kg BW decrease: 0.93 (0.54-1.59).

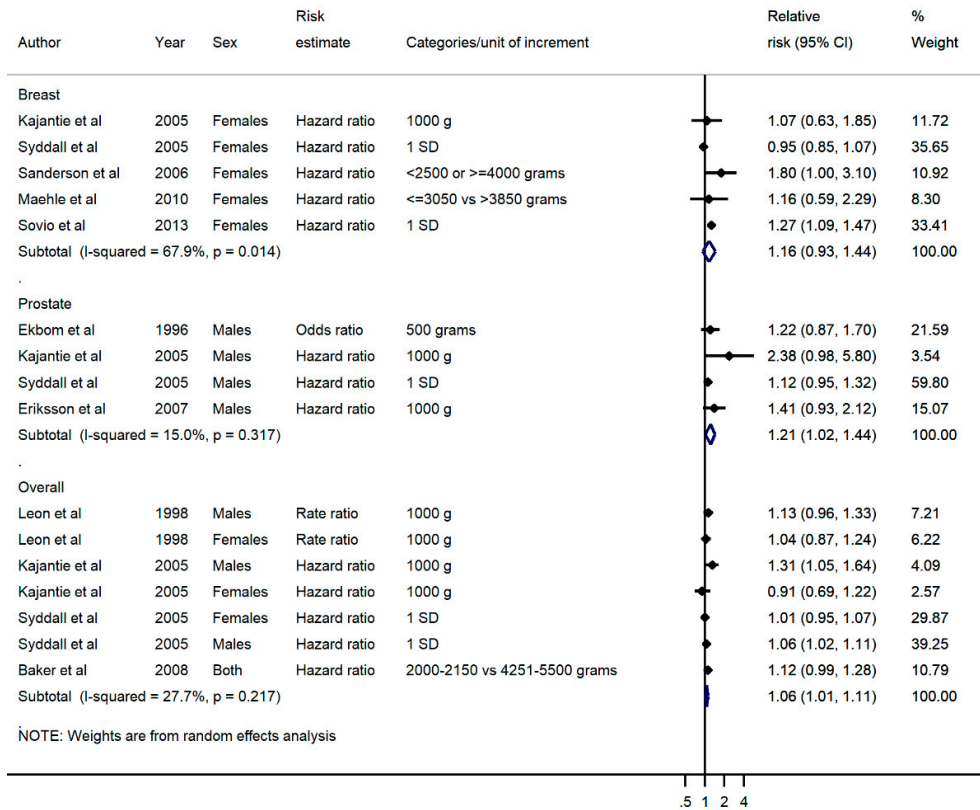
**Table 6.** Characteristics of the new studies published online after 2019.

First author	Study country	Study design	Cancer type	Case number (deaths)	Control number	Published association for BW/BL/GA with 95% CI	Adjustment for covariates
Crump et al., 2019	Sweden	National cohort	Overall cancer	814+999	-	HR(95%CI); p-value for GA (one additional week): Adults aged 20-29 years: Both sexes combined: 0.96 (0.92, 0.99); 0.02 Men: 0.96 (0.92, 1.01); 0.11 Women: 0.95 (0.90, 1.00); 0.07 Adults aged 30-45 years: Both sexes combined: 0.99 (0.95, 1.02); 0.43 Men: 1.01 (0.96, 1.06); 0.81 Women: 0.97 (0.93, 1.01); 0.19	Adjusted for birth year, sex, birth order, maternal age, maternal education, and maternal smoking
Wang et al., 2022	US	Cohort	Overall cancer	10379	-	Men: Adjusted HR for BW>4.5 kg, 1.22 (95%CI, 1.07 to 1.40) Women: Adjusted HR for BW>4.5 kg, 1.15 (95%CI, 1.0 to 1.31)	Adjusted for Ethnicity, tiers of birth, maternal history of diabetes, maternal history of hypertension, parental history of CVD before age 60 years, parental history of smoking during childhood, and time-varying adult smoking status, alcohol consumption, physical activity, diet quality score, and BMI

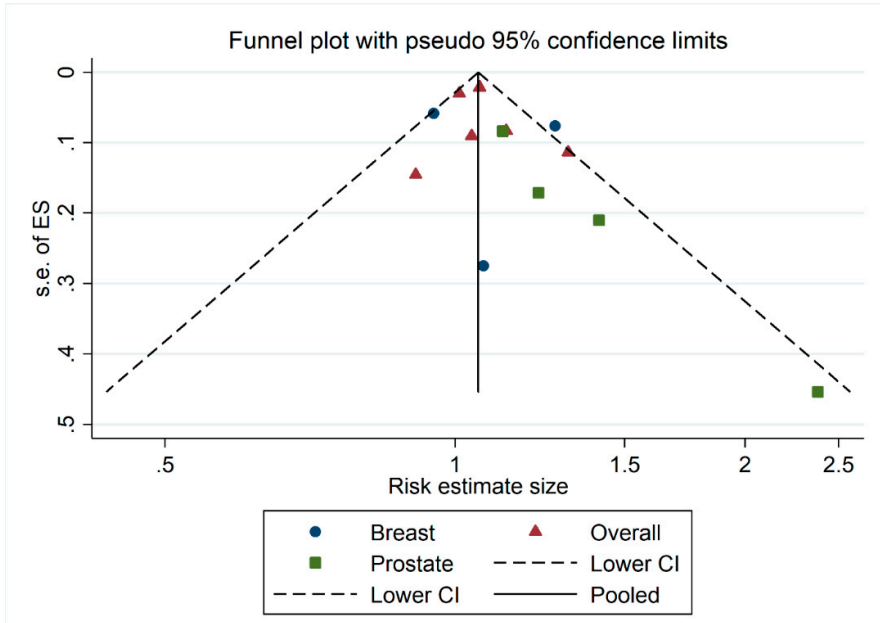
**Abbreviations:** BMI: Body Mass Index; BW: Birth Weight; BL: Birth Length; CI: Confidence Interval; CVD: Cardiovascular Disease; GA: Gestational Age; HR: Hazard Ratio

After doing an additional search on PubMed (post-publication of Paper I), we could identify 906 studies. Out of 906 studies, only four studies were found eligible and were screened. Out of 4 studies, 2 were removed after reading the abstract, as 1 had reported on mortality due to childhood cancers (Kessous et al., 2020), and another reported only on breast cancer risk and not mortality (Bothou et al., 2021). The 2 included studies are shown in **Table 6**. There is a 22% increased mortality risk due to cancers among men born with birth weight >4.5 kg and a 15% increased mortality risk due to cancers among women born with birth weight >4.5 kg (Wang et al., 2022). Lower gestational age was found to be associated with an increased risk of mortality from any cancer ( $p=0.02$ ) (Crump et al., 2019).

There was a positive association between birth weight and breast cancer poor *prognosis* in all the studies except one (Syddall et al., 2005) (**Figure 9**). However, only the study by Sovio *et al.* reported a statistically significant association (Sovio et al., 2013). Out of 5 studies, only Sanderson *et al.* and Maehle *et al.* used birth weight adjusted for gestational age in the analyses (Sanderson et al., 2006; Maehle et al., 2010). Similarly, all the studies reported an increased risk of prostate cancer mortality with increasing birth weight; however, all such associations were statistically insignificant. Two of the studies reported a statistically significant positive effect of birth weight on overall (any) cancer mortality (Kajantie et al., 2005; Syddall et al., 2005). We used a random effect model to assess the pooled risk estimates from 9 studies. The pooled RR estimate for the association between birth weight and overall (any) cancer mortality was RR 1.06 (95% CI, 1.01-1.11). There was a 21% increased risk of prostate cancer mortality among adults having higher birth weight (RR, 95%CI, 1.21, 1.02-1.44). Though there was a 16% increased risk of mortality due to breast cancer among women born with higher birth weight, the association was statistically insignificant (**Figure 9**). There was no publication bias (**Figure 10**).

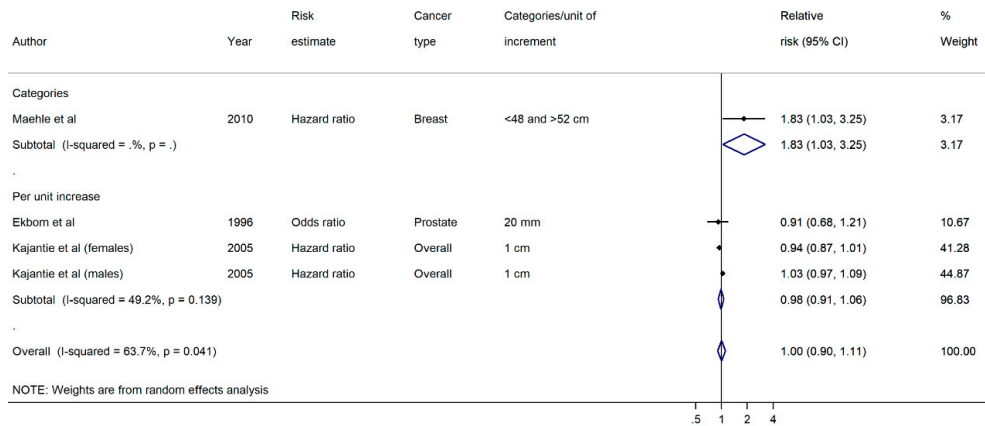


**Figure 9.** Birthweight (per kg) in relation to risk of cancer mortality; overall (n=4), prostate (n=4), and breast (n=5) by using a random-effects model.



**Figure 10.** Funnel plot showing publication bias for meta-analysis of birth weight and birth length in relation to risk of cancer mortality.

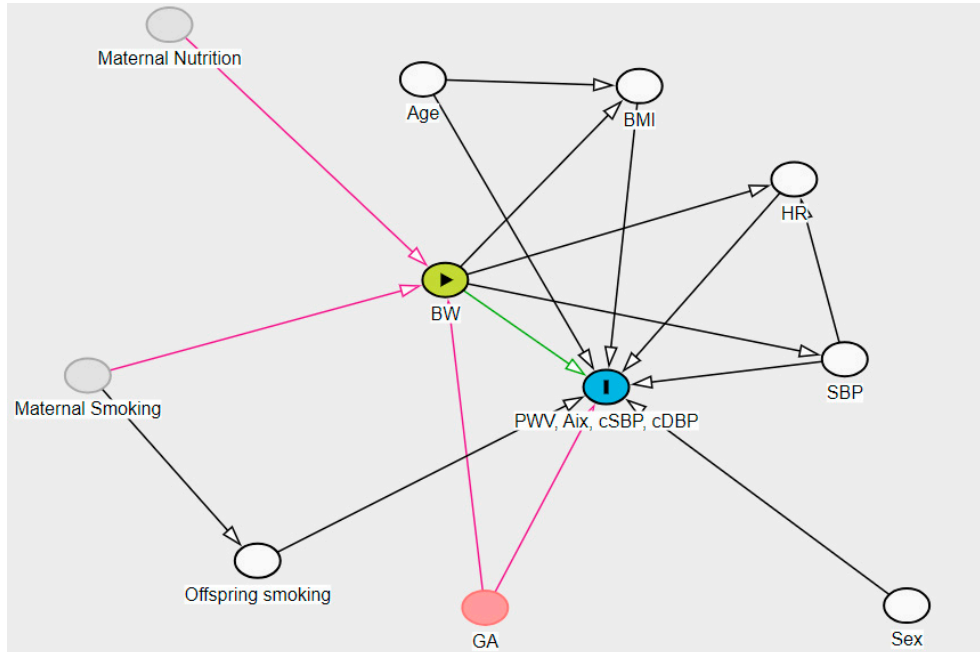
Except for the study by Maehle *et al.*, none of the other studies reported a statistically significant association between birth length and cancer mortality (Maehle *et al.*, 2010) (Figure 11). The pooled risk estimate was RR (95%CI), 1.0 (0.90-1.11). The statistical heterogeneity was high ( $I^2$ : 63.7%).



**Figure 11.** Birth length (per cm) in relation to risk of cancer mortality, overall ( $n=1$ ), prostate ( $n=1$ ), and breast ( $n=1$ ), by using a random-effects model.

## Paper II

We analyzed birth weight, self-reported weight at age 20 years, cf-PWV, and PWA data of a total of 1995 adults. A proposed causal diagram showing the causal pathway of the linkage between birth weight and PWA is presented in **Figure 12** using DAGitty software. The causal mechanism is quite applicable to other outcomes of this thesis, including sfAGE and ABI (**Paper III**), apoA1 and apoB (**Paper IV**).



**Figure 12.** Directed Acyclical Graph (DAG) of the assumed causal relations between study variables in Paper II.

**Abbreviations:** Aix: Augmentation Index; BW: Birth Weight; BMI: Body Mass Index; GA: Gestational Age; HR: Heart Rate; PWV: Pulse Wave Velocity; cSBP: Central Systolic Blood Pressure; cDBP: Central Diastolic Blood Pressure; SBP: Brachial Systolic Blood Pressure

**Table 7** shows the general characteristics, birth characteristics, and hemodynamic parameters of the study participants. The median (Interquartile Range) age of men was 29.7 (24.0-35.9), and of women was 28.9 (23.4-35.0) years. The median birth weight of men (3580 grams) was higher than that of women (3460 grams) by 120 grams. The median (Interquartile Range) cf-PWV among men was 6.7 (6.1-7.5) m/sec. In men, the median (Interquartile Range) central Aix was 103 (94-110), and in women, it was 108 (99-119).

**Table 7.** Characteristics of the study population stratified for sex (n=1995) in Paper II.

Variables	Men (n=920), median (IQR)	Women (n=1075), median (IQR)
<b>General characteristics at screening</b>		
Age (years)	29.7 (24.0-35.9)	28.9 (23.4-35.0)
Height (cm)	182 (177-187)	168 (164-172)
Weight (Kg)	83 (75-94)	67 (60-77)
BMI (kg/m <sup>2</sup> )	25.1 (22.9-28.0)	23.6 (21.3-27.1)
BMI (kg/m <sup>2</sup> ) at age 20 years	23.0 (21.2-24.9)	21.7 (20.0-24.0)
<b>Birth characteristics</b>		
Birth weight (grams)	3580 (3231.2-3950.0)	3460 (3140-3800)
Gestational age (weeks)	40 (39-41)	40 (39-40)
Missing	0	1
<b>Hemodynamic parameters</b>		
Brachial SBP (mmHg)	115 (110-122)	103 (98-109)
Missing	15	16
Brachial DBP (mmHg)	67 (63-73)	66 (62-71)
Missing	15	16
cf-Pulse wave velocity, cf-PWV (m/sec)	6.7 (6.1-7.5)	6.3 (5.8-6.9)
Missing	71	80
<b>Pulse wave analysis</b>		
Central Augmentation Index	103 (94-110)	108 (99-119)
Peripheral Augmentation Index	46 (36-57)	53 (43-66)
Central SBP (mmHg)	97 (91-103)	89 (85-96)
Central DBP (mmHg)	67 (62-72)	66 (62-72)
<b>Ambulatory blood pressure monitoring</b>		
SBP during day (mmHg)	124 (120-132)	115 (109-124)
Missing	825	948
DBP during day (mmHg)	73 (67-80)	67 (62-72)
Missing	825	948
PP during day (mmHg)	52 (48-56)	49 (46-53)
Missing	825	948
SBP during night (mmHg)	110 (104-116)	103 (94-109)
Missing	825	948
DBP during night (mmHg)	60 (55-66)	54 (49-60)
Missing	825	948
PP during night (mmHg)	49 (46-52)	47 (43-51)
Missing	825	948

**Abbreviations:** BMI: Body Mass Index; DBP: Diastolic Blood Pressure; IQR: Interquartile Range; PP: Pulse Pressure; SBP: Systolic Blood Pressure

Data presented as median (Interquartile Range)

Compared to the category with LBW and low BMI at age 20, the *mismatch* group (adults born with LBW who gained high BMI at age 20) had a higher adult weight and BMI at age 20 ( $p < 0.001$ ), as shown in **Table 8**. A similar association exists for the effect on SBP and DBP (central and brachial). However, this *mismatch* group did not have a significantly different association with cf-PWV or Aix. On the contrary, the other *mismatch* group (adults born with high birth weight but reported low BMI at age 20)



had lower brachial DBP, cSBP, cDBP, and Aix compared to the group with LBW and low BMI at age 20. The high BW/high BMI at age 20 group had significantly higher SBP compared to the LBW/Low BMI at age 20 group ( $p < 0.05$ ).

**Table 8.** Distribution of mean and SD of general characteristics, pulse wave measurements, and ABPM measurements among study participants categorized into four subgroups.

Variables	Low BW/Low BMI (reference) (n=540)	Low BW/High BMI (n=500)	High BW/Low BMI (n=434)	High BW/High BMI (n=520)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
<b>General characteristics</b>				
Age at MOS screening (years)	31.1 (7.6)	30.2 (7.3)	<b>29.3 (7.1)*</b>	<b>29.3 (7.3)*</b>
Adult Height (cm)	172.9 (9.4)	172.7 (9.2)	<b>176.7 (9.4)*</b>	<b>175.6 (9.4)*</b>
Adult Weight (kg)	68.2 (12.6)	<b>82.8 (16.1)*</b>	<b>70.9 (13.0)<sup>†</sup></b>	<b>85.6 (17.1)*</b>
Weight at age 20 (kg)	61.1 (9.3)	<b>76.1 (13.5)*</b>	<b>64.1 (9.1)*</b>	<b>78.9 (13.7)*</b>
BMI at age 20 (kg/m <sup>2</sup> )	20.3 (1.5)	<b>25.4 (3.3)*</b>	20.4 (1.4)	<b>25.5 (3.4)*</b>
<b>Birth characteristics</b>				
Birth weight (grams)	3156.9 (451.8)	3161.3 (436.1)	<b>3835.6 (452.3)*</b>	<b>3906.2 (424.5)*</b>
<b>Hemodynamic characteristics</b>				
Brachial SBP (mmHg)	108.4 (11.5)	<b>111.7 (11.8)*</b>	107.5 (10.6)	<b>110.3 (11.5)<sup>†</sup></b>
Brachial DBP (mmHg)	67.2 (7.8)	<b>68.9 (7.6)<sup>#</sup></b>	<b>65.8 (6.7)<sup>†</sup></b>	68.0 (8.0)
Pulse wave velocity (m/sec)	6.6 (0.9)	6.5 (1.0)	6.7 (0.9)	6.6 (1.0)
<b>Pulse wave analysis</b>				
Central Augmentation Index <sup>§</sup>	107 (98-119)	105 (96-115.75)	<b>103 (94-113)*</b>	106 (96-114)
Peripheral Augmentation Index <sup>§</sup>	52 (42-65)	50 (40-62)	<b>47 (37.5-60)*</b>	49 (38-62)
Central SBP (mmHg)	93.3 (9.6)	<b>95.6 (9.8)*</b>	<b>91.6 (8.5)<sup>†</sup></b>	94.4 (9.8)
Central DBP (mmHg)	67.4 (7.6)	<b>69.0 (7.6)<sup>#</sup></b>	<b>65.9 (6.9)<sup>†</sup></b>	67.9 (7.9)
<b>Ambulatory Blood Pressure Monitoring</b>				
SBP during day (mmHg)	119.3 (10.7)	123.1 (12.2)	117.2 (8.3)	123 (10.4)
DBP during day (mmHg)	69.4 (9.9)	71 (10.4)	68.9 (6.8)	71.3 (7.6)
PP during day (mmHg)	49.9 (5.4)	52.1 (4.7)	48.2 (4.4)	51.6 (5.9)
SBP during night (mmHg)	102.9 (10.8)	109.5 (10.9)	103.1 (7.7)	107.9 (11.7)
DBP during night (mmHg)	56.1 (9.2)	59.5 (9.5)	56.5 (6.2)	58.5 (8.7)
PP during night (mmHg)	46.8 (5.5)	<b>49.9 (5.4)<sup>†</sup></b>	46.6 (4.1)	49.4 (6.4)

\* $p$ -value $<0.001$ ; # $p$ -value:  $<0.01$ ; <sup>†</sup> $p$ -value:  $<0.05$

<sup>§</sup>We performed Kruskal-Wallis's test as the distribution was skewed.

**Abbreviations:** ABPM: Ambulatory Blood Pressure Monitoring; BW: Birth Weight; BMI20: BMI at 20 years of age; BMI: Body Mass Index; SBP: Systolic Blood Pressure; SD: Standard Deviation; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; n: number of subjects.

Data presented as mean (SD) or median [Interquartile Range] for all participants divided into four groups: Low BWz-score/Low BMI20 (reference group): Birth weight z-score  $\leq 0$  and BMI20  $\leq$  median. Low BWz-score/High BMI20: Birth weight z-score  $\leq 0$  and BMI  $>$  median. High BWz-score/Low BMI20: Birth weight z-score  $> 0$  and BMI  $\leq$  median. High BWz-score/High BMI20: Birth weight z-score  $> 0$  and BMI  $>$  median.  $P < 0.05$  was considered statistically significant. All statistically significant associations have been highlighted in bold.

Compared to the participants with low BWz-score/low BMI20, participants with low BWz-score/high BMI20 had a 3.26 mmHg increase in brachial SBP, 1.72 mmHg increase in brachial DBP, 2.24 mmHg increase in cSBP, and 1.65 mmHg increase in cDBP (Table 9). On the contrary, individuals with high BWz-score/low BMI20 had a 1.40 mmHg decrease in brachial DBP, 1.70 mmHg decrease in cSBP, and 1.47 mmHg decrease in cDBP compared to individuals with low BWz-score/low BMI20. In addition, individuals with high BWz-score/high BMI20 had a 1.86mmHg increase in brachial SBP compared to low BWz-score/low BMI20 individuals. All the associations remained statistically significant even after adjustment for sex. Men had a positive association with all the blood pressures (brachial SBP, brachial DBP, cSBP, cDBP), and cf-PWV but an inverse association with peripheral and central Aix.

**Table 9.** General linear regression to assess the effect of birth weight and BMI groups on bSBP, bDBP, cSBP, cDBP, Aix, and cf-PWV with and without adjustment for sex.

Variable	bSBP, $\beta$ coefficient (95% CI)	bDBP, $\beta$ coefficient (95% CI)	cSBP, $\beta$ coefficient (95% CI)	cDBP, $\beta$ coefficient (95% CI)	P_Aix, $\beta$ coefficient (95% CI)	C_Aix, $\beta$ coefficient (95% CI)	PWV, $\beta$ coefficient (95% CI)
<b>BW z-score and BMI20 categories</b>							
High BWz-score/High BMI20	<b>1.86</b> ( <b>0.48, 3.25</b> ) <sup>#</sup>	0.79 (-0.13, 1.71)	1.02 (-0.15, 2.20)	0.53 (-0.40, 1.48)	-0.01 (-0.08, 0.06)	<b>-0.025</b> ( <b>-0.046, -0.004</b> )	-0.02 (-0.14, 0.10)
Low BWz-score/High BMI20	<b>3.26</b> ( <b>1.86, 4.67</b> ) <sup>*</sup>	<b>1.72</b> ( <b>0.78, 2.66</b> ) <sup>*</sup>	<b>2.24</b> ( <b>1.05, 3.44</b> ) <sup>*</sup>	<b>1.65</b> ( <b>0.69, 2.60</b> ) <sup>*</sup>	-0.05 (-0.12, 0.03)	-0.007 (-0.029, 0.014)	-0.09 (-0.21, 0.039)
High BWz-score/Low BMI20	-0.92 (-0.23, 0.52)	<b>-1.40</b> ( <b>-2.37, -0.42</b> ) <sup>#</sup>	<b>-1.70</b> ( <b>-2.94, -0.46</b> ) <sup>#</sup>	<b>-1.47</b> ( <b>-2.46, -0.48</b> ) <sup>#</sup>	-0.05 (-0.13, 0.02)	<b>-0.041</b> ( <b>-0.063, -0.019</b> )	0.06 (-0.06, 0.19)
Low BWz-score/Low BMI20	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<b>BW z-score and BMI20 categories</b>							
High BWz-score/High BMI20	<b>1.99</b> ( <b>0.83, 3.15</b> ) <sup>*</sup>	0.80 (-0.12, 1.72)	1.07 (-0.02, 2.17)	0.54 (-0.39, 1.48)	-0.01 (-0.08, 0.06)	<b>-0.02</b> ( <b>-0.04, -0.005</b> )	-0.02 (-0.15, 0.09)
Low BWz-score/High BMI20	<b>3.38</b> ( <b>2.20, 4.56</b> ) <sup>*</sup>	<b>1.73</b> ( <b>0.80, 2.67</b> ) <sup>*</sup>	<b>2.28</b> ( <b>1.17, 3.39</b> ) <sup>*</sup>	<b>1.65</b> ( <b>0.70, 2.60</b> ) <sup>*</sup>	-0.05 (-0.12, 0.02)	-0.008 (-0.03, 0.01)	-0.09 (-0.21, 0.03)
High BWz-score/Low BMI20	-0.91 (-2.13, 0.31)	<b>-1.39</b> ( <b>-2.36, -0.42</b> ) <sup>#</sup>	<b>-1.70</b> ( <b>-2.85, -0.55</b> ) <sup>#</sup>	<b>-1.47</b> ( <b>-2.46, -0.48</b> ) <sup>#</sup>	-0.05 (-0.13, 0.02)	<b>-0.04</b> ( <b>-0.06, -0.02</b> )	0.06 (-0.06, 0.19)
Low BWz-score/Low BMI20	Reference	Reference	Reference	Reference	Reference	Reference	Reference
<b>Sex</b>							
Men	<b>12.43</b> ( <b>11.57, 13.28</b> ) <sup>*</sup>	<b>1.23</b> ( <b>0.55, 1.90</b> ) <sup>*</sup>	<b>7.06</b> ( <b>6.26, 7.87</b> ) <sup>*</sup>	<b>0.76</b> ( <b>0.07, 1.45</b> ) <sup>†</sup>	<b>-0.16</b> ( <b>-0.22, -0.11</b> ) <sup>*</sup>	<b>-0.06</b> ( <b>-0.07, -0.04</b> )	<b>0.42</b> ( <b>0.33, 0.51</b> ) <sup>*</sup>
Women	Reference	Reference	Reference	Reference	Reference	Reference	Reference

**Abbreviations:** bSBP: Brachial Systolic Blood Pressure; bDBP: Brachial Diastolic Blood Pressure; CI: Confidence Interval; cSBP: Central Systolic Blood Pressure; cDBP: Central Diastolic Blood Pressure; C\_Aix: Central Augmentation Index; P\_Aix: Peripheral Augmentation Index; PWV: Pulse Wave Velocity

\*p-value <0.001; <sup>#</sup>p-value<0.01; <sup>†</sup>p-value<0.05

Low BWz-score/Low BMI20 (reference group): Birth weight z-score ≤ 0 and BMI20 ≤ median. Low BWz-score/High BMI20: Birth weight z-score ≤ 0 and BMI20 > median. High BWz-score/Low BMI20: Birth weight z-score > 0 and BMI20 ≤ median. High BWz-score/High BMI20: Birth weight z-score >0 and BMI20 > median. All statistically significant associations have been highlighted in bold.

Though the BWz-score showed an inverse association with peripheral Aix, it was statistically non-significant (Table 10). With a one-year increase in age, there was a 0.02 unit increase in peripheral Aix, and with one beat/min increase in heart rate, there was a 0.007 unit decrease in peripheral Aix (Model III). The adjusted R<sup>2</sup> in Model III was 8.9%.

**Table 10.** General linear regression to assess associations between birth weight z-score categories and peripheral Aix, crude and adjusted models.

	<b>Model I <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model II <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model III <math>\beta</math> coefficient (95% CI); p-value</b>
<b>BWz-score*</b>			
Low	0.008 (-0.04, 0.06);	-0.01 (-0.07, 0.03); 0.52	-0.01 (-0.06, 0.04); 0.60
High	0.77 <i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Sex</b>			
Men	-	<b>-0.18 (-0.23, -0.12); &lt;0.001</b>	<b>-0.21 (-0.27, -0.14); &lt;0.001</b>
Women		<i>Reference</i>	<i>Reference</i>
<b>Age (years)</b>	-	<b>0.02 (0.01, 0.02); &lt;0.001</b>	<b>0.02 (0.01, 0.02); &lt;0.001</b>
<b>BMI (kg/m<sup>2</sup>)</b>	-	0.004 (-0.002, 0.01); 0.20	0.006 (-0.001, 0.01); 0.07
<b>SBP (mmHg)</b>	-	-	0.001 (-0.002, 0.004); 0.61
<b>Heart rate (beats/min)</b>	-	-	<b>-0.007 (-0.009, -0.004); &lt;0.001</b>
<b>Smoking history</b>	-	-	
Yes, smoking currently			0.05 (-0.01, 0.12); 0.12
Smoking in the Past			0.04 (-0.03, 0.11); 0.25
Never smoked			<i>Reference</i>

**Abbreviations:** Aix: Augmentation Index; BMI: Body Mass Index; BW: Birth Weight; CI: Confidence Interval; SBP: Systolic Blood Pressure

\*Low BWz-score: Birth weight z-score  $\leq$  0; High BWz-score: Birth weight z-score  $>$  0

Adjusted R<sup>2</sup> in Model III: 8.9%

p-value  $<$  0.05 was considered statistically a significant association.

All statistically significant associations have been highlighted in bold.

There was a 0.02 unit increase in central Aix among adults born with LBW compared to the counterpart (Table 11). There was a 0.003 and 0.008 unit increase in central Aix with a 1 kg/m<sup>2</sup> increase in BMI and 1 year increase in age. Smokers were found to have a 0.025 unit increase in central Aix compared to the non-smokers (p=0.008).

**Table 11.** General linear regression to assess associations between birth weight z-score categories and central Aix, crude and adjusted models.

	<b>Model I <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model II <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model III <math>\beta</math> coefficient (95% CI); p-value</b>
<b>BWz-score*</b>			
Low	<b>0.03 (0.01, 0.04);</b>	<b>(0.004, 0.03); 0.01</b>	<b>0.02 (0.006, 0.03); 0.005</b>
High	<b>&lt;0.001</b> <i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Sex</b>			
Men	-	<b>-0.06 (-0.08, -0.05); &lt;0.001</b>	<b>-0.08 (-0.09, -0.06); &lt;0.001</b>
Women		<i>Reference</i>	<i>Reference</i>
<b>Age (years)</b>	-	<b>0.008 (0.007, 0.009); &lt;0.001</b>	<b>0.008 (0.007, 0.009); &lt;0.001</b>
<b>BMI (kg/m<sup>2</sup>)</b>	-	<b>0.003 (0.001, 0.004); 0.002</b>	<b>0.003 (0.002, 0.005); &lt;0.001</b>
<b>SBP (mmHg)</b>	-	-	0.0 (0.0, 0.001); 0.29
<b>Heart rate (beats/min)</b>	-	-	<b>-0.003 (-0.003, -0.002); &lt;0.001</b>
<b>Smoking history</b>	-	-	<b>0.025 (0.006, 0.043); 0.008</b>
Yes, smoking currently			0.017 (-0.001, 0.036); 0.07
Smoking in the Past			<i>Reference</i>
Never smoked			

**Abbreviations:** Aix: Augmentation Index; BMI: Body Mass Index; BW: Birth Weight; CI: Confidence Interval; SBP: Systolic Blood Pressure

\*Low BWz-score: Birth weight z-score  $\leq$  0; High BWz-score: Birth weight z-score  $>$  0

Adjusted R<sup>2</sup> in Model III: 21%

p-value  $<$  0.05 was considered statistically a significant association

All statistically significant associations have been highlighted in bold.

There was a 0.18 m/sec decrease in cf-PWV among adults with low BWz-score compared to those with high BWz-score (Table 12). Similarly, with one kg/m<sup>2</sup> increase in BMI, there was a 0.02 m/sec decrease in cf-PWV.

**Table 12.** General linear regression to assess associations between birth weight z-score categories and cf-PWV, crude and adjusted models.

	<b>Model I <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model II <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model III <math>\beta</math> coefficient (95% CI); p-value</b>
<b>BWz-score*</b>			
Low	-0.06 (-0.15, 0.03); 0.19	<b>-0.15 (-0.23, -0.07); &lt;0.001</b>	<b>-0.18 (-0.26, -0.10); &lt;0.001</b>
High	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Sex</b>			
Men	-	<b>0.39 (0.31, 0.47); &lt;0.001</b>	<b>0.15 (0.06, 0.25); &lt;0.001</b>
Women	-	<i>Reference</i>	<i>Reference</i>
<b>Age (years)</b>	-	<b>0.06 (0.05, 0.06); &lt;0.001</b>	<b>0.06 (0.05, 0.06); &lt;0.001</b>
<b>BMI (kg/m<sup>2</sup>)</b>	-	0.001 (-0.009, 0.010); 0.866	<b>-0.02 (-0.03, -0.01); 0.001</b>
<b>SBP (mmHg)</b>	-	-	<b>0.02 (0.02, 0.03); &lt;0.001</b>
<b>Heart rate (beats/min)</b>	-	-	<b>0.02 (0.01, 0.02); &lt;0.001</b>
<b>Smoking history</b>			
Yes, smoking currently	-	-	(-0.07, 0.13); 0.60
Smoking in the Past	-	-	-0.007 (-0.10, 0.09); 0.89
Never smoked	-	-	<i>Reference</i>

**Abbreviations:** BMI: Body Mass Index; BW: Birth Weight; CI: Confidence Interval; cf-PWV: Carotid-Femoral Pulse Wave Velocity; SBP: Systolic Blood Pressure

\*Low BWz-score: Birth weight z-score  $\leq$  0; High BWz-score: Birth weight z-score  $>$  0

Adjusted R<sup>2</sup> in Model III: 34.5%

p-value  $<$  0.05 was considered statistically a significant association.

All statistically significant associations have been highlighted in bold.

There was a 1.29 mmHg increase in cSBP among individuals with low BWz-score compared to individuals with high BWz-score (Table 13). The association remained statistically significant even after adjustment for sex, age, BMI, heart rate, and smoking history.

**Table 13.** General linear regression to assess associations between birth weight z-score categories and cSBP, crude and adjusted models.

	<b>Model I <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model II <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model III <math>\beta</math> coefficient (95% CI); p-value</b>
<b>BWz-score*</b>			
Low	<b>1.29 (0.42, 2.16); 0.004</b>	<b>0.94 (0.21, 1.67); 0.01</b>	<b>0.88 (0.15, 1.60); 0.01</b>
High	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Sex</b>	-		
Men		<b>6.36 (5.62, 7.09); &lt;0.001</b>	<b>6.72 (5.98, 7.46); &lt;0.001</b>
Women		<i>Reference</i>	<i>Reference</i>
<b>Age (years)</b>	-	<b>0.36 (0.31, 0.41); &lt;0.001</b>	<b>0.38 (0.33, 0.44); &lt;0.001</b>
<b>BMI (kg/m<sup>2</sup>)</b>	-	<b>0.50 (0.42, 0.59); &lt;0.001</b>	<b>0.47 (0.38, 0.55); &lt;0.001</b>
<b>Heart rate (beat/min)</b>	-	-	<b>0.09 (0.06, 0.13); &lt;0.001</b>
<b>Smoking history</b>	-	-	
Yes, smoking currently			0.44 (-0.53, 1.41); 0.37
Smoking in the Past			0.08 (-0.89, 1.05); 0.87
Never smoked			<i>Reference</i>

**Abbreviations:** BMI: Body Mass Index; BW: Birth Weight; CI: Confidence Interval; cSBP: Central Systolic Blood Pressure

\*Low BWz-score: Birth weight z-score  $\leq 0$ ; High BWz-score: Birth weight z-score  $> 0$

Adjusted R<sup>2</sup> in Model III: 31.2%

p-value < 0.05 was considered statistically a significant association

All statistically significant associations have been highlighted in bold.

Likewise, there was a 1.16 mmHg increase in cDBP among individuals born with low BWz-score compared to their counterparts (Table 14). Though the association was weak, it remained statistically significant even after adjustment for covariates like BMI, smoking, heart rate, sex, and age.

**Table 14.** General linear regression to assess associations between birth weight z-score categories and cDBP, crude and adjusted models.

	<b>Model I <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model II <math>\beta</math> coefficient (95% CI); p-value</b>	<b>Model III <math>\beta</math> coefficient (95% CI); p-value</b>
<b>BWz-score*</b>			
Low	<b>1.16 (0.47, 1.85);</b>	<b>0.90 (0.28, 1.52); 0.04</b>	<b>0.76 (0.17, 1.35); 0.01</b>
High	<b>&lt;0.001</b> <i>Reference</i>	<i>Reference</i>	<i>Reference</i>
<b>Sex</b>			
Men	-	0.11 (-0.50, 0.74); 0.71	<b>0.86 (0.26, 1.47); 0.005</b>
Women	-	<i>Reference</i>	<i>Reference</i>
<b>Age (years)</b>	-	<b>0.30 (0.26, 0.34); &lt;0.001</b>	<b>0.34 (0.30, 0.38); &lt;0.001</b>
<b>BMI (kg/m<sup>2</sup>)</b>	-	<b>0.48 (0.41, 0.55); &lt;0.001</b>	<b>0.40 (0.33, 0.47); &lt;0.001</b>
<b>Heart rate (beat/min)</b>	-	-	<b>0.20 (0.17, 0.23); &lt;0.001</b>
<b>Smoking history</b>	-	-	
Yes, smoking currently			0.61 (-0.18, 1.41); 0.13
Smoking in the Past			0.18 (-0.60, 0.98); 0.64
Never smoked			<i>Reference</i>

**Abbreviations:** BMI: Body Mass Index; BW: Birth Weight; CI: Confidence Interval; cDBP: Central Diastolic Blood Pressure

\*Low BWz-score: Birth weight z-score  $\leq 0$ ; High BWz-score: Birth weight z-score  $> 0$

Adjusted R<sup>2</sup> in Model III: 28.0%

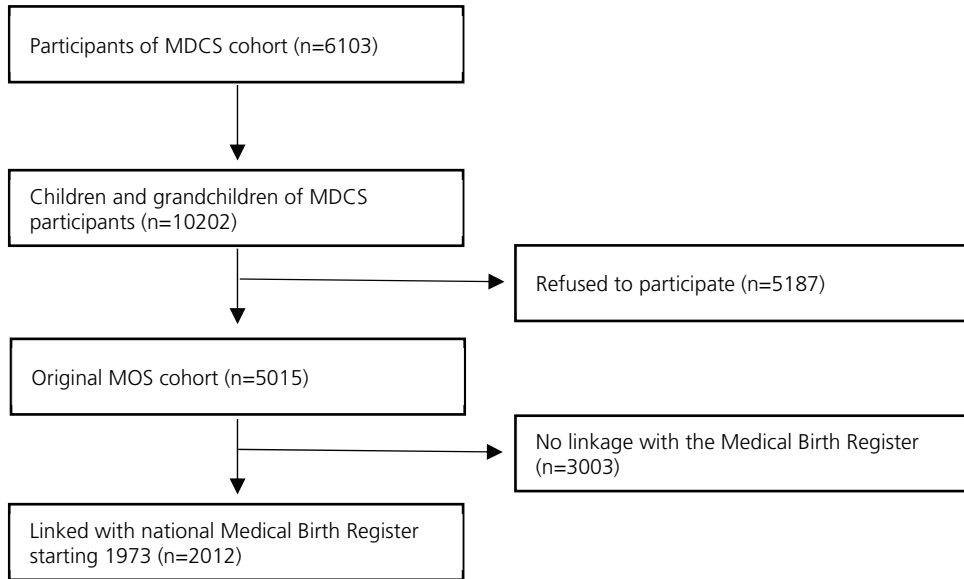
p-value < 0.05 was considered statistically significant association.

All statistically significant associations have been highlighted in bold.



## Paper III

A flow chart of the study participants is shown in **Figure 13**. In the end, we could link 2012 participants of MOS with their own birth data from the MBR. Out of 2012 subjects, 958 men and 1054 women were included in the study. Descriptive data of variables are presented for factors in early life and in adult life in **Table 15**.



**Figure 13.** Flow chart of the study participants of the MOS cohort.

**Abbreviations:** MDCS: Malmö Diet and Cancer Study; MOS: Malmö Offspring Study

The mean (SD) age of men was 29.3 (7.3) years, and for women 28.6 (7.3) years. The mean birth weight of men was 3.55 kg and for women 3.45 kg (**Table 15**). The median (Interquartile Range) sfAGE levels were same in both men and women, i.e., 1.5 (1.3-1.7) arbitrary units (AU).

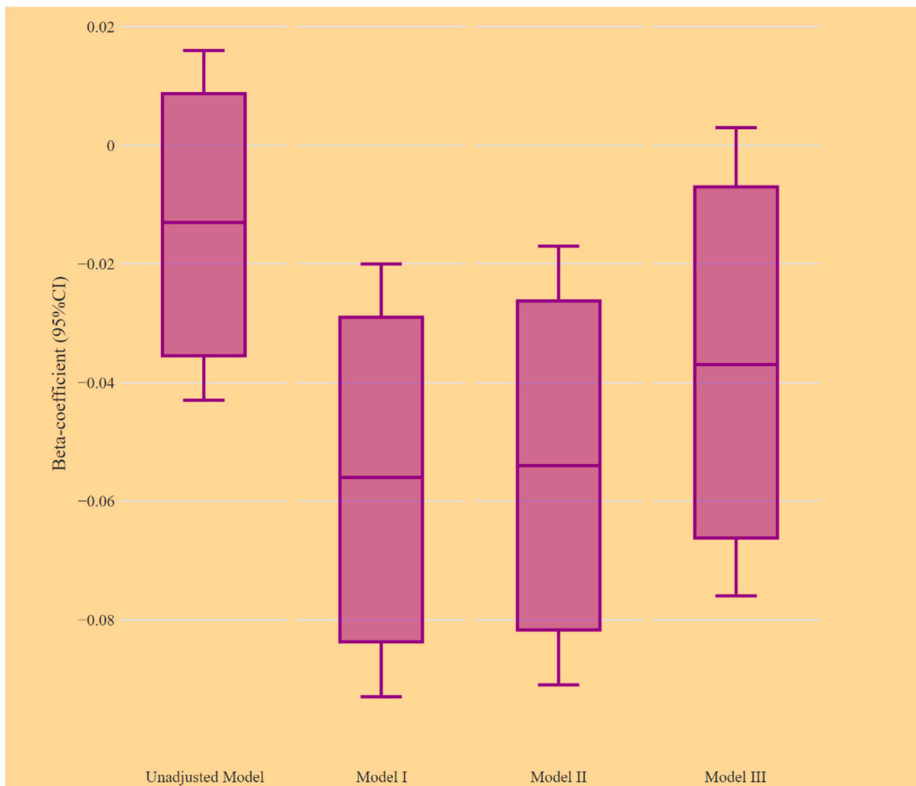
**Table 15.** Distribution of birth variables and clinical data among men and women participating in the Malmö Offspring Study (MOS) cohort.

	Men (n=958)	Women (n=1054)
<b>Age at health examination (years)</b> Mean (SD)	29.3 (7.3)	28.6 (7.3)
Missing	0	2
<b>Birth parameters</b>		
<b>Birth weight (kg)</b> Mean (SD)	3.55 (0.61)	3.45 (0.53)
Median (IQR)	3.57 (3.22-3.93)	3.48 (3.15-3.79)
<b>Gestational age (weeks)</b> Mean (SD)	39.5 (2.0)	39.4 (1.6)
Median (IQR)	40 (39-41)	40 (39-40)
Missing	20	17
<b>Adult traits</b>		
<b>sfAGE (Arbitrary Unit; AU)</b>		
Mean (SD)	1.5 (0.3)	1.5 (0.4)
Median (IQR)	1.5 (1.3-1.7)	1.5 (1.3-1.7)
Missing	118	118
<b>Mean ABI</b>		
Mean (SD)	1.20 (0.09)	1.21 (0.09)
Median (IQR)	1.19 (1.14-1.26)	1.21 (1.15-1.26)
Missing	66	67
<b>Fasting plasma glucose levels (mmol/L)</b>		
Mean (SD)	3.2 (0.6)	5.2 (0.8)
Median (IQR)	5.2 (4.8-5.6)	5.2 (4.8-5.5)
Missing	3	2
<b>Serum Triglycerides (mmol/L)</b>		
Mean (SD)	1.1 (0.6)	0.9 (0.5)
Median (IQR)	0.9 (0.7-1.3)	0.8 (0.6-1.1)
Missing	9	13
<b>Total cholesterol (mmol/L)</b>		
Mean (SD)	4.5 (1.0)	4.4 (0.8)
Median (IQR)	4.5 (3.8-5.2)	4.4 (3.9-4.9)
Missing	3	9
<b>SBP (mmHg)</b>		
Mean (SD)	117.2 (10.1)	103.8 (9.4)
Median (IQR)	116.0 (111.0 - 123.0)	103.0 (97.0 - 109.0)
Missing	65	67
<b>BMI (kg/m<sup>2</sup>)</b>		
Mean (SD)	25.7 (4.4)	24.5 (4.7)
Median (IQR)	24.9 (22.8 – 27.7)	23.4 (21.2 – 26.8)
Missing	0	2
<b>Smoking n(%)</b>		
- Yes	157 (19.1)	205 (21.6)
- Former	131 (16.0)	157 (16.5)
- Never	532 (64.9)	588 (61.9)
Missing	138	104

**Abbreviations:** ABI: Ankle-Brachial Index; BMI: Body Mass Index; IQR: Interquartile Range; MOS: Malmö Offspring Study; SD: Standard Deviation; sfAGE: Skin Autofluorescence Advanced Glycation End products; SBP: Systolic Blood Pressure

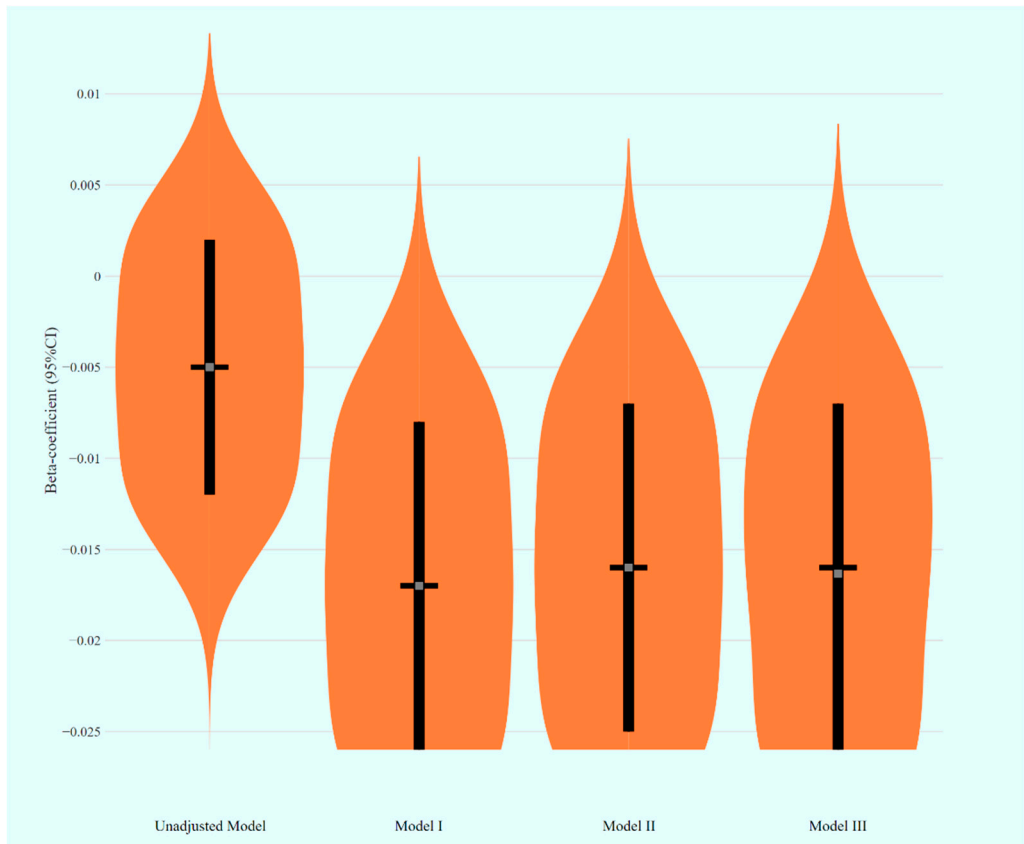
As shown in **Figure 14**, birth weight adjusted for gestational age was inversely (negatively) associated with sfAGE. There was an average 0.056 (unit) decrease in sfAGE value per 1 kg increase in birth weight (adjusted for gestational age) (*Model I*). After adjustment for sex, fasting plasma glucose, triglyceride, SBP, and cholesterol levels, as well as smoking history, a 1 kg increase in birth weight was associated with a 0.037 decrease in sfAGE (95%CI: -0.076, 0.003; p=0.06) (*Model III*). Smokers (current or former) had a 0.07 and 0.16 unit increase in sfAGE levels compared to non-smokers.

As shown in **Figure 15**, there was an average 0.017 (unit) decrease in mean ABI per 1 kg increase in birth weight (adjusted for gestational age) (*Model I*). This association remained significant even after adjustment for sex, BMI, SBP, triglyceride, and cholesterol levels, as well as smoking status (*Model III*). There was an average 0.016 (unit) decrease in mean ABI per 1 kg increase in birth weight (*Model III*). Adult BMI was positively associated with ABI ( $\beta$ -coefficient, 95%CI: 0.003, 0.002-0.004).



**Figure 14.** Box and Whisker plot to demonstrate the association between birth weight and sfAGE. Adjusted R<sup>2</sup> in unadjusted model: 0%; Adjusted R<sup>2</sup> in Model I: 0.7%; Adjusted R<sup>2</sup> in Model II: 0.7%; Adjusted R<sup>2</sup> in Model III: 5.3%

**Model I:** birth weight + gestational age; **Model II:** Model I + sex; **Model III:** Model II + fasting plasma glucose + triglyceride levels + total cholesterol levels + smoking + systolic blood pressure



**Figure 15.** Violin chart to demonstrate associations between birth weight and ankle-brachial index (ABI). Adjusted  $R^2$  in unadjusted model: 0%; Adjusted  $R^2$  in Model I: 1.1%; Adjusted  $R^2$  in Model II: 1.6%; Adjusted  $R^2$  in Model III: 4.5%

**Model I:** birth weight + gestational age; **Model II:** Model I + sex; **Model III:** Model II + BMI + triglyceride levels + total cholesterol levels + smoking + systolic blood pressure.

## Paper IV

The general characteristics and biochemical parameters of men and women are shown in **Table 16**. The mean (SD) age of men was 30.2 (5.7) and for women was 28.9 (5.8) years. The mean (SD) apoB levels among men was 0.86 (0.22) and among women 0.78 (0.18) g/L. More than one-third (36%) of both men and women had smoked more than 100 cigarettes in their lifetime. However, 38-39% of the data on smoking was missing for both men and women, due to methodological reasons (i.e., a branched questionnaire, *see Methods*).

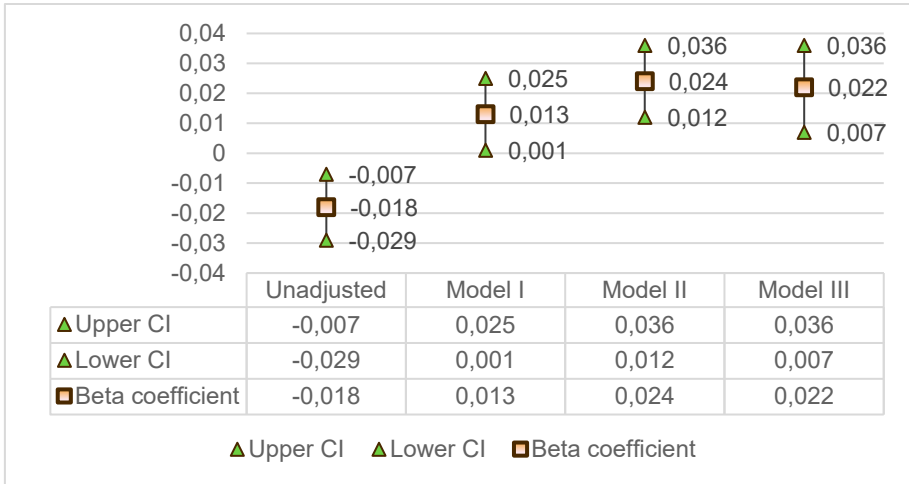
**Table 16.** Distribution of age, birth variables, and adult clinical parameters among men and women participants of the LifeGene Cohort.

Variables	Men (n=4292), mean (SD)	Women (n=5801), mean (SD)
<b>Age (years)</b>	30.25 (5.73)	28.95 (5.84)
Missing	6	129
<b>Birth weight (kg)</b>	3.59 (0.53)	3.45 (0.50)
Missing	0	0
<b>Gestational age (weeks)</b>	39.56 (1.80)	39.58 (1.71)
Missing	19	20
<b>Adult BMI (kg/m<sup>2</sup>)</b>	24.45 (2.98)	22.73 (3.21)
Missing	6	129
<b>apoA1 (g/L)</b>	1.46 (0.22)	1.68 (0.29)
Missing	0	0
<b>apoB (g/L)</b>	0.86 (0.22)	0.78 (0.18)
Missing	12	23
<b>apoB/apoA1 ratio</b>	0.61 (0.19)	0.48 (0.13)
Missing	12	23
<b>Have you smoked more than 100 cigarettes in your entire life?<sup>5</sup></b>		
- Yes n(%)	1554 (36.20)	2122 (36.58)
- No n(%)	1082 (25.21)	1333 (22.97)
- Do not know/refuse n(%)	23 (0.53)	46 (0.79)
- Missing n(%)	1633 (38.04)	2300 (39.64)

**Abbreviations:** apoA1: Apolipoprotein A1; apoB: Apolipoprotein B; BMI: Body Mass Index; SD: Standard Deviation

Continuous normally distributed variables presented as Mean (Standard Deviation)

There was a positive association between birth weight (adjusted for gestational age) and apoA1 levels (**Figure 16**), but an inverse association with apoB levels and apoB/apoA1 ratio (**Figure 17** and **Figure 18**) was noted.

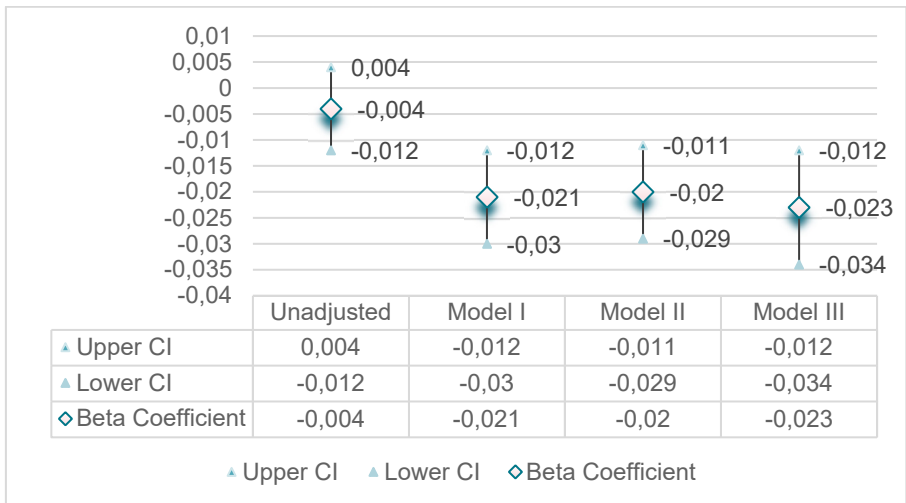


**Figure 16.** Associations between birth weight and apoA1 levels with and without adjustments for covariates and confounders.

**Abbreviations:** CI: Confidence Interval

In **Model I**, birth weight was adjusted for gestational age and sex. In **Model II**, apart from gestational age and sex, BMI and adult age was adjusted for. Similarly, in **Model III**, apart from variables adjusted for in Models I and II, a history of smoking was adjusted.

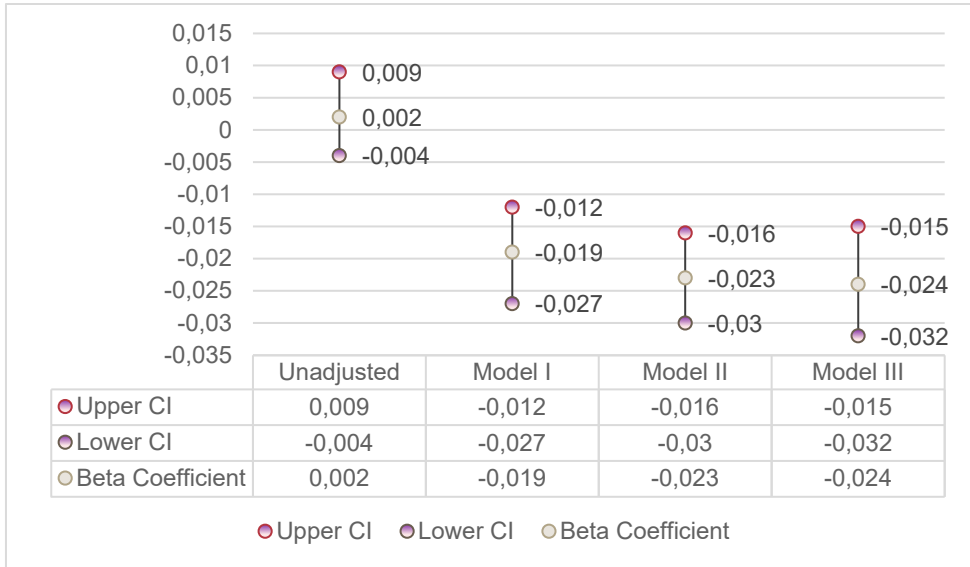
Adjusted  $R^2=17.2\%$  in Model III



**Figure 17.** Associations between birth weight and apoB levels with and without adjustments for covariates and confounders.

**Abbreviations:** CI: Confidence Interval

In **Model I**, birth weight was adjusted for gestational age and sex. In **Model II**, apart from gestational age and sex, BMI and adult age was adjusted for. Similarly, in **Model III**, apart from variables adjusted in Models I and II, a history of smoking was adjusted. Adjusted  $R^2=13.2\%$  in Model III



**Figure 18.** Associations between birth weight and the apoB/apoA1 ratio with and without adjustments for covariates and confounders.

**Abbreviations:** CI: Confidence Interval

In **Model I**, birth weight was adjusted for gestational age and sex. In **Model II**, apart from gestational age and sex, BMI and adult age was adjusted. Similarly, in **Model III**, apart from variables adjusted in Models I and II, the history of smoking was adjusted.

Adjusted R<sup>2</sup>=22.7% in Model III

### Additional analysis on breast cancer risk and mortality

We selected a subset of women with breast cancer and additional measurement of estrogen receptors (Jonas Manjer, personal communication, 2021) but also added additional cases during long-term follow-ups. Of 476 women in the cohort, 154 (32.3%) developed breast cancer. **Table 17** shows the birth characteristics of the study participants. The mean (SD) age of onset of breast cancer was 60.7 (8.1) years. The controls lived a life longer than the cases ( $p=0.03$ ). None of the associations of birth variables with breast cancer risk or mortality were statistically significant, as shown in **Table 18**. We also performed a sub-analysis among women with onset of breast cancer at post-menopausal age ( $\geq 55$  years) (results not shown). However, none of the associations were statistically significant.

**Table 17.** Baseline characteristics of women from the MDCS cohort (n=476).

Characteristics	Breast cancer cases (n=154) mean (SD)	Controls (n=322) mean (SD)	p-value
Birth weight (grams)	3490.8 (546.7)	3425.3 (547.9)	0.22
Birth length (cm)	51.5 (2.7)	51.2 (2.4)	0.31
Gestation age (weeks)	39.4 (1.8)	39.3 (1.7)	0.53
Missing	7	10	
Head circumference (cm)	34.8 (1.7)	34.7 (1.6)	0.40
Missing	0	2	
Ponderal index (grams/cm <sup>3</sup> )	2.5 (0.2)	2.5 (0.2)	0.59
Age at endpoint (years)	<b>60.7 (8.1)</b>	<b>79.1 (7.3)</b>	<b>&lt;0.001</b>
Age in years (lived)	<b>77.5 (8.9)</b>	<b>79.1 (7.3)</b>	<b>0.03</b>

**Abbreviations:** SD: Standard Deviation

**Table 18.** Unadjusted and adjusted association between birth parameters and risk of breast cancer, hazard ratio (HR) with 95% confidence interval (95% CI).

Independent variables	Sample size	Breast cancer risk	Sample size	Mortality
	n	HR (95% CI); p-value	n	HR (95% CI); p-value
Birth weight (grams)	154	1.0 (1.0-1.0); 0.21	60	1.0 (0.9-1.0); 0.76
Birth length (cm)	154	1.02 (0.96-1.09); 0.46	60	0.96 (0.87-1.07); 0.50
Gestational age (weeks)	147	1.03 (0.94 -1.14); 0.50	56	0.91 (0.79-1.04); 0.19
Ponderal index (grams/cm <sup>3</sup> )	154	1.33 (0.74-2.39); 0.34	60	1.09 (0.42-2.79); 0.85
Head circumference (cm)	154	1.03 (0.93-1.14); 0.48	60	1.01 (0.85-1.20); 0.87
Birth weight adjusted for gestational age (grams)	147	1.0 (1.0-1.0); 0.30	56	1.0 (1.0-1.0); 0.82
Ponderal index adjusted for gestational age (grams/cm <sup>3</sup> )	151	1.27 (0.69-2.34); 0.44	56	0.94 (0.35-2.49); 0.90

**Abbreviations:** CI: Confidence Interval; HR: Hazard Ratio

p-value <0.05 was considered statistically significant.



# Discussion

## Main findings

1. Children born with a higher birth weight have higher overall cancer mortality (poor *prognosis*) (**Paper I**)
2. Children born with LBW (adjusted for gestational age and sex) have increased Aix values, brachial SBP and DBP, but lower cf-PWV after adjusting for confounders in adulthood (**Paper II**)
3. Children born with LBW but attain higher BMI at a young age (20 years) have higher blood pressure levels compared to children with LBW and low BMI at age 20 (*mismatch* hypothesis) (**Paper II**)
4. Children born with LBW (adjusted for gestational age) have an increased risk of elevated sfAGE levels and higher ABI in young adulthood (**Paper III**)
5. Children born with LBW (adjusted for gestational age) have an increased risk of higher apoB and apoB/apoA1 ratio adjusted for multiple confounders, but lower apoA1 levels in adulthood, adjusted for age, sex, adult BMI, and smoking (**Paper IV**)

## Interpretations and comparisons with the existing literature

The focus of the thesis was to link early life factors with cardiometabolic risk traits as precursors of CVD, as well as cancer risk and mortality in adulthood, as these disease entities constituted the highest burden of deaths, years of life lost, and disability-adjusted life years (DALYs) globally in 2019 (Kocarnik et al., 2022).

## Paper I

We found a positive association between birth weight and (any) cancer mortality (*prognosis*) as well as mortality due to prostate cancer. Our findings concord with the results from a previously published meta-analysis in 2011 but discord with the findings from an umbrella review that suggested LBW as a risk marker for all-cause mortality (Risnes et al., 2011; Belbasis et al., 2016). Unlike the prostate or breast cancer incidence risk, the association of birth variables with their *prognosis* was weak (Zhou et al., 2016; Xue & Michels, 2007). Similarly, US women and men born with a high birth weight of >4.5 kg had a higher risk of (any) cancer mortality (Wang et al., 2022). Furthermore, it has been explored that a child born to mother suffering from hypertensive disorder of pregnancy had a higher risk of (any) cancer mortality (adjusted Hazard Ratio;95%CI: aHR, 1.37; 1.04–1.81, p=0.026) (Hammad et al., 2020).

There is accruing evidence of the effect of birth weight on breast cancer risk among pre- and post-menopausal women; however, the evidence on cancer *prognosis* is limited. The degree of risk of breast cancer among women born with a high birth weight varied in different reviews. The risk varied from 2% to 9% per 500-gram increase in birth weight among women of all ages and pre-menopausal women, respectively, in one review (Zhou et al., 2020) and varied from 24% to 15% among women born with birth weight >4kg and >3.5 kg, respectively (Park et al., 2008). On the contrary, Wang *et al.* review of 21 cohort studies did not show any significant association between birth weight and breast cancer risk among pre-or post-menopausal women. The study showed that there was a 19% increased risk of invasive breast cancer among pre-menopausal women born with birth weight >2850 grams and a 14% increased risk of invasive breast cancer among post-menopausal women born with birth weight >3750 grams (Wang et al., 2021).

Testicular, prostate, and breast cancers are the most studied cancers for their association with birth variables. Common factors linked to all three is exposure to exogenous hormones during *intrauterine* life, such as placental hormones, estrogens, other hormones, or their metabolites. Placental hormones act as growth factors that may stimulate cell proliferation, leading to genetic errors and malignant transformation later in life. Estrogens and their metabolites may have genotoxic effects (Ekbom, 2006).

## Paper II

We found that adults born with LBW but who attained a higher BMI at age 20 (*mismatch*) had significantly higher SBP, DBP, cSBP, and cDBP compared to those born with LBW but continued to have low BMI at age 20. On the contrary, adults

with higher birth weight but low BMI at age 20 had lower Aix values (both central and peripheral), cSBP, and cDBP, compared to adults with LBW and low BMI at age 20. The *mismatch* between pre- and post-natal environment leads to inappropriate predictive adaptive responses induced during a poor *intrauterine* environment. Inappropriate predictive adaptive responses eventually increase the risk of CVD in adulthood.

Our results are congruent with other studies that highlight the role of the post-natal environment in influencing later health (Gluckman et al., 2008; Savoy & Van Lieshout, 2022). Li *et al.* evaluated outcomes in children, suggesting a positive association between rapid growth in early childhood and risk factor levels for CVD and metabolic diseases in preschool children (Li et al., 2020). Weight gain during childhood (rapid catch-up) may independently be associated with higher BP later in life (Ben-Shlomo et al., 2008; Leunissen et al., 2012). In addition, the *mismatch* group (children born SGA but had a rapid catch-up growth) has been found to have a higher intima-media thickness in young adulthood than the comparison group (Leunissen et al., 2012). Different weight gain periods (catch-up) have been studied from infancy to adulthood for their effect on outcomes later in life. For example, we studied recalled weight gain at age 20, while Law *et al.* studied registered weight gain during infancy up to 1-5 years of age. The study reported that children born with LBW but had weight gain during 1-5 years of age tend to have higher SBP (Law et al., 2002).

Notably, in our study, the *mismatch* group born with higher birth weight but attaining low BMI in adulthood tended to have better health outcomes, such as lower Aix, cSBP, and cDBP. This finding concords with the findings from other studies suggesting the protective role of lower BMI for the risk of developing hypertension (Tang et al., 2022). There is an established linkage (inverse association) between birth weight and BP in adulthood. Our study results are in congruence with the results from other studies suggesting such an inverse association between birth weight and adult SBP (Kaakinen et al., 2014).

Furthermore, we found that adults with low BWz-score had lower cf-PWV measurements compared to those with high BWz-score, reflecting a positive relation between the two. However, adults with low BWz-score were found to have higher Aix values compared to those with high BWz-score, reflecting an inverse relation between the two. These observations are in line with the results of other studies, suggesting LBW as a potential risk factor for markers of arterial stiffness (Sperling & Nilsson, 2020). Researchers have also explored the effect of early life determinants on PWV in children and adolescents. However, the evidence is not strong enough to conclude that children born SGA have increased PWV (Varley et al., 2022).

Studies have found narrower retinal arterioles, narrower retinal arteriolar bifurcation angles, longer retinal arterioles, and fewer vascular branching points in adults with a history of LBW or born SGA. This is critical as a narrower arteriole is a structural vascular marker of hypertension and CVD. This supports the hypothesis that *intrauterine* exposures may cause structural changes in the cardiovascular system (Liew et al., 2008; Mitchell et al., 2008).

### Paper III

There is emerging evidence of sfAGE as an important predictor of type 2 diabetes and CVD. It has also been implicated in predicting complications and mortality due to type 2 diabetes, such as renal insufficiency, retinopathy, etc. (Bentata et al., 2017; Boersma et al., 2021; Smit et al., 2022). There is an established inverse association between birth weight and type 2 diabetes, as evidenced in various studies (Mi et al., 2017; Birth Gene Study Working Group et al., 2019). Furthermore, Wibaek *et al.* demonstrated an association between LBW and risk of type 2 diabetes independent of BMI and genetic susceptibility (Wibaek et al., 2023). The inverse association between birth weight and sfAGE could reflect an increased risk of type 2 diabetes and CVD. However, the evidence of the direct effect of birth weight on the trait (sfAGE) that is associated with diabetes is practically non-existent.

The adjustment for smoking is crucial in the analysis as it is a potential covariate linked directly with the traits and risk of CVD (van Waateringe et al., 2017). There is ample evidence from the literature that demonstrates an increased risk of CVD associated with smoking, and current or recent smokers are at greater risk than those who smoked in the past. Besides, it is the duration of use and intensity of smoking, i.e., the number of cigarettes smoked per day or period (pack-years), that also increases the CVD risk (Banks et al., 2019). Increasing age, BMI, and SBP exhibit positive associations with sfAGE (Paolillo et al., 2019), and hence, the plausible mechanism of the effect of birth weight on sfAGE can be through one of the intermediates like BMI or SBP or as a direct effect on sfAGE.

### Paper IV

Our study found an increase of 0.022 g/L in apoA1 levels per 1 kg increase in birth weight ( $p=0.005$ ) and a decrease of 0.023 g/L in apoB levels per 1 kg increase in birth weight ( $p<0.001$ ) after adjusting for covariates. Furthermore, birth weight was inversely associated with the apoB/apoA1 ratio. The hypothesis of the effect of early life factors on adult apoB and LDL-cholesterol levels was proposed way back in 1993 by Barker *et*

*al.* (Barker et al., 1993). Barker *et al.* showed that a 1 SD (2.54 cm) increase in abdominal circumference was associated with a decrease in apoB concentrations by 0.04 g/l (0.02, 0.07) (Barker et al., 1993).

On the contrary, Starnberg *et al.* did not demonstrate any significant difference in the blood lipid levels between LBW and normal birth weight children measured at age 7 years (Starnberg et al., 2019). The plausible mechanism for this association could be the impaired growth of the liver that may cause permanent changes in the LDL-cholesterol metabolism (Barker et al., 1993). The apolipoproteins are linked to CVD risk and cardiovascular events in adulthood (Walldius et al., 2021). Studies have suggested apoB as a better CVD risk marker than LDL-cholesterol (Behbodikhah et al., 2021). Dyslipidemia is a risk factor for metabolic syndrome, and the evidence linking LBW and metabolic syndrome is growing (Byrne & Phillips, 2006).

### **Additional analysis on breast cancer risk and mortality**

All birth variables were found not to be associated with the onset of breast cancer in women in MDCS during long-term follow-up. These findings differ from other recent studies claiming a positive relationship between birth length and birth weight with the onset of breast cancer in adulthood (Zhou et al., 2020; Aarestrup et al., 2020). The results are also contrary to another study published on the Swedish population by Lahman *et al.* (Lahmann et al., 2004) from the same cohort. One reason for this could be that associations occurred in cohorts of women with shorter follow-ups (lower mean age) than longer follow-ups (higher mean age), or in relation to menopausal status, as in Lahmann *et al.* 2004.

Ponderal index was also not found to be associated with the risk of breast cancer in women in our study. Likewise, a study by McCormack *et al.* based on Uppsala Birth Cohort, Sweden, reported a statistically insignificant association between the ponderal index and breast cancer in pre-menopausal women, HR (95%CI):1.06 (0.79–1.42) (McCormack et al., 2005). Ponderal index at birth has been explored in various studies as a risk marker for many diseases in adult women, such as infertility (Dupont et al., 2020), and perimenopausal disorders (Gao et al., 2019). A plausible explanation can be drawn from the findings of a previous study stating a positive association between the ponderal index at birth and high estradiol levels during the menstrual cycles in adults (Jasienska et al., 2006).

LBW can be considered as a heterogenous group of infants who are born premature or growth retarded or both. Studies, including ours, have suggested that children born with LBW are at a high risk of morbidity and mortality perinatally and thereafter

(Morton, 2006). Wilcox suggested the ‘LBW paradox’ wherein the risk of mortality among LBW children is affected by the prevalence of LBW in the population, i.e., LBW born in a population with a high prevalence of LBW tend to have lower mortality compared to the LBW with the same absolute birth weight born in a population with a lower prevalence of LBW (Wilcox, 2001).

There is empirical evidence on the effect of poor maternal nutritional status and diet during pregnancy on fetal growth restriction; however, the extent of the effect depends on the timing of the nutritional limitation. Early maternal nutritional limitation in pregnancy leads to symmetrical growth restriction (i.e., children proportionately small in all anthropometric measurements), but nutritional limitation occurring late in pregnancy leads to asymmetrical growth restriction (i.e., children born long and thin for their birthweight) (Barker, 1995).

## Strengths and limitations

We have data on birth variables recorded in the Swedish MBR with >99% accuracy, which is more exact and, therefore, better than recall data prone to bias, as used in many other studies. The use of birth weight z-scores after adjustment for sex and gestational age is a better predictor of future events than birth weight alone. Our studies are based on large sample sizes and derived from population-based cohorts. Furthermore, we had access to information on a plethora of clinical, biochemical, and anthropometric parameters, making cohorts rich in data. For example, the availability of data on potential covariates or confounders in our cohorts, like age, sex, adult BMI, history of smoking, and SBP, helped us to adjust for them in the regression models to reflect true associations between exposures and outcomes. This strengthened the analysis and interpretations.

The major limitation in **Paper I** was the presence of moderate heterogeneity due to different study designs and outcomes of the included studies. In addition, our meta-analysis was based on aggregated estimates instead of individual participant data. The individual participant data is known to allow powerful and uniformly consistent analyses (Tudur et al., 2016). The results of our cohort-study papers (**Paper II, III, IV**) should be interpreted in view of the following limitations. Firstly, we used only a single reading of adult BMI to reflect post-natal growth in **Paper II**. The lack of childhood growth data or weight trajectories during childhood and adolescence limits the wider acceptability of the findings. Secondly, we did not adjust for maternal factors before or during pregnancy in any of our papers because of a lack of data in the MBR before 1983, the year when maternal BMI and smoking were introduced to the register. Lastly,

the attendance rate in the MOS (~47%) was modest and in the LifeGene study cohort (~10%) low, and participants were mostly white North Europeans, making extrapolation of the results to non-Swedish populations and from different ethnicities more difficult.

## Methodological considerations

- a) **Selection bias and generalizability:** Papers II, III, and IV are based on population-based cohorts with voluntary participation ranging between <10% attendance in the LifeGene study cohort and 47% in MOS. Most of the participants in both cohorts were Swedish-born, with little variation in their ethnic background. Hence, the generalizability of the findings beyond Nordic countries will be difficult.
- b) **Confounding/covariates:** The common confounders/covariates associated with both birth variables and adult traits, such as age, sex, BMI, SBP, fasting plasma glucose levels, smoking history, and gestational age, were adjusted for in the model. Though studies have adjusted for many other adult variables, such as physical activity scores, socioeconomic scores, etc., we did not use them to avoid overadjustment in the models.
- c) **Measurement errors:** All the clinical, anthropometric, and biochemical measurements were obtained at clinical research units or by analyses in certified laboratories under standardized conditions. Multiple readings of the parameters were obtained, and the mean of the readings was used to minimize measurement error.

# Conclusions

LBW, a surrogate marker of *intrauterine* insult, is associated with an increase in adult cardiometabolic risk traits like Aix, cSBP, cDBP, sfAGE, ABI, and apolipoprotein apoB and apoB/apoA1 ratio, but a decrease in cf-PWV and apoA1. These traits are risk markers of later onset of adult risk factors such as hypertension or diseases like CVD and type 2 diabetes. High birth weight was associated positively with increased cancer mortality risk. Our study strengthens the DOHaD hypothesis and generates new evidence on the effect of early life factors on adult risk traits. The present study's findings highlight the key role of periconception care and the need to engage with pregnant women and young couples through educational means in their early adulthood to improve their lifestyles, nutrition, and health – for better health for themselves as well as for their offspring.



# Implications for public health interventions

The findings from the Ph.D. work provide an impetus for developing and implementing preventive measures to improve maternal and child health and, thereby, reducing the risk of CVD and diabetes in the offspring later in life.

Researchers and scientists work on cohorts in many LMICs, such as India, Brazil, and Guatemala. The **New Delhi Birth Cohort**, which was started in the year 1969 with a cohort of 7119 infants, has assessed various measurements, including weight, height, and length/weight from birth every six months until the age of 21 years. Between the age of 26-32 years, 1526 adults were studied for anthropometry, cardiovascular traits like BP and electrocardiogram (ECG), and biochemical parameters like oral glucose tolerance test, fasting insulin, lipids, pro-inflammatory markers, and homocysteine. Additional cardiovascular parameters, such as intima-media thickness, DEXA (body composition), and endothelial function, were studied on 1149 adults between 32-37 years. Currently, apart from the above-mentioned anthropometric, biochemical, and cardiovascular parameters, a sub-cohort of 841 adults is being studied for left ventricular dimensions, function, and mass (Huffman et al., 2015; Vasan et al., 2018).

The **New Delhi Birth Cohort** suggested many interesting findings congruent with our results. LBW with rapid weight gain in early childhood is associated with an increased risk of adult type 2 diabetes, higher adult blood pressure, plasma lipids, and pro-inflammatory factors, poorer endothelial function, and greater carotid intima-media thickness (Vasan et al., 2018). Similarly, two cohorts (rural and urban) are currently running in Vellore, Chennai, South India. Started with 1302 (urban) and 2790 (rural) live births in 1969, the Vellore cohort is undergoing an IndEcho study of similar cardiovascular, biochemical, and anthropometric measurements with 1,500 participants (combined rural and urban). The Vellore cohorts suggested that adults who have a faster gain in BMI during childhood and adolescence exhibit higher cardiometabolic risk markers (Antonisamy et al., 2017; Vasan et al., 2018).

On similar lines, the **South Asian Birth Cohort Study (START)** was started to study the environmental and genetic basis of adiposity among 750 South Asian offspring.

The study aimed to recruit people from rural and urban India, but also urban Canada (Anand et al., 2013). Another cohort in west India, the **Pune Maternal Nutritional Study Cohort (PMNS)**, was started, including 797 undernourished pregnant women (G0: Generation 0) in 1994 in six villages near Pune city of Maharashtra, India. Starting with anthropometric and dietary data of pregnant women, the cohort collected data on *intrauterine* fetal growth (G1: Generation 1) using ultrasonography, on birth parameters, followed by measurements of body composition, cardiometabolic risk factors, and cognitive function at age 6, 12, 18 and 24 years (n=700). The PMNS cohort highlighted that adults born with LBW tend to have elevated plasma glucose levels at a young age (Kumaran et al., 2017).

The **Mysore Birth Record Cohort** comprised over 1000 men and women born in the Holdsworth Memorial Hospital (HMH), Mysore, between 1934 and 1966. Falling in the age bracket of 50-85 years as of 2019, the cohort had undergone multiple measurements of CVD risk markers (e.g., BP, symptoms assessment, ECG signs of coronary heart disease, plasma lipid concentrations), type 2 diabetes, left ventricular mass (using echocardiography) and PWV. The participants were assessed for cognitive function, dementia, depression, and lung function as well (Krishna et al., 2015).

# Scope for future research and actions

Lifestyle interventions aimed to deliver customized counselling on diet and exercise to the populations in the community will be of great importance. The findings of DOHaD research are useful in making future parents conscious of their health and nutrition, and governments are formulating public health policies for promoting healthier lifestyles and nutrition. DOHaD also highlights the importance of the ‘First 1000 days’ as the period of crucial growth and development for fetuses, neonates, and infants. Nutritional shortfalls and adverse exposures during the first 1000 days of life may have long-term adverse effects on offspring health (Epure et al., 2020; Taveras et al., 2021). There is growing evidence of the effectiveness of multiple interventions, including nutritional, health, Water and Sanitation Hygiene (WASH), and iron supplementation, during the first 1000 days on birth outcomes and infant growth, but also on maternal health (Taneja et al., 2022; Soofi et al., 2022).

Prospective studies form the main evidence base for future research in the DOHaD domain (Suzuki, 2018). Large birth cohort studies are described, investigated, or underway in Europe, North America, and Australia. These include the **Generation R** study in Rotterdam, the Netherlands, the **National Children’s Study** in the United States, the **Women’s Health of Australia** study, the **Hokkaido Study on Environment and Children’s Health** in Japan, and the Nutritional intervention Preconception and during Pregnancy to maintain healthy glucosE levels and offspRing health (**NiPPeR trial**) in the United Kingdom (Southampton), Singapore, and New Zealand (Landrigan et al., 2006; Kooijman et al., 2016; Tavener et al., 2016; Godfrey et al., 2017; Kishi et al., 2021). In addition, other interventional and observational follow-up studies are contributing to the DOHaD research area, including the Docosahexaenoic acid (DHA) to Optimize Mother Infant Outcome (**DOMInO**) trial, the **Southampton Women’s Survey**, the **Danish National Birth Cohort**, and **Project VIVA** (Ernst et al., 2020; Simpson et al., 2022; Soria-Contreras et al., 2022).

Sweden has many birth cohorts from different cities, including the first one, the **Uppsala Birth Cohort**; later on, the Malmö Offspring Study (MOS) Cohort, **Helsingborg Study Cohort**, LifeGene Study Cohort, **BAMSE project**, The **Gothenburg H70 Birth cohort** study 2014–16, **EXPRESS cohort** study, Malmö Diet

and Cancer Study Cohort, and **MONICA Cohort** in Gothenburg and Northern Sweden, (Juárez et al., 2016; Sterner et al., 2019; Almquist et al., 2020; Maelstrom, 2021; Sakic et al., 2022; Morgan et al., 2022; Kilanowski et al., 2023). In addition, register-based studies from Sweden have been published on national birth data linked to national registers on mortality and morbidity (Crump et al., 2019; Hellsten, 2022).

## List of non-Ph.D. publications with co-authors from Lund University

Laucyte-Cibulskiene A, **Sharma S**, Christensson A, Nilsson PM. Early life factors in relation to albuminuria and estimated glomerular filtration rate based on cystatin C and creatinine in adults from a Swedish population-based cohort study. *J Nephrol.* 2022;35(3):889–900.

Sakic A, Ekström M, **Sharma S**, Nilsson PM. Can birth weight predict offspring's lung function in adult age? Evidence from two Swedish birth cohorts. *Respir Res.* 2022;23(1):348.

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Wennerberg J, **Sharma S**, Nilsson PM, Ohlsson B. A possible association between early life factors and burden of functional bowel symptoms in adulthood. *Scand J Prim Health Care.* 2021; 39(4):506–14.

Saidi K, **Sharma S**, Ohlsson B. A systematic review and meta-analysis of the associations between endometriosis and irritable bowel syndrome. *Eur J Obstet Gynecol Reprod Biol.* 2020; 246:99–105.

## List of non-Ph.D. publications with co-authors from outside Lund University

Kurian K, Lakiang T, Sinha RK, Kathuria N, Krishnan P, Mehra D, *et al.* Scoping review of intervention strategies for improving coverage and uptake of maternal nutrition services in southeast Asia. *Int J Environ Res Public Health*. 2021;18(24):13292.

**Sharma S**, Akhtar F, Kumar Singh R, Mehra S. Dietary patterns and determinants of pregnant and lactating women from marginalized communities in India: A community-based cross-sectional study. *Front Nutr*. 2020;7:595170.

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**Sharma S**, Mehra D, Brusselaers N, Mehra S. Menstrual hygiene preparedness among schools in India: A systematic review and meta-analysis of system-and policy-level actions. *Int J Environ Res Public Health*. 2020;17(2):647.

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