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EARLY LIFE PREDICTORS OF CARDIOVASCULAR HEALTH IN AN AUSTRALIAN ABORIGINAL COHORT

The Aboriginal Birth Cohort study

Pauline Sjöholm

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To my family

UNIVERSITY OF TURKU
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PAULINE SJÖHOLM: Early life predictors of cardiovascular health in an Australian Aboriginal cohort
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ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is the leading cause of death worldwide. In Australia, the Aboriginal population is particularly affected. This is manifested as a significantly lower life expectancy compared to the non-Indigenous population with CVD explaining a large part of the mortality gap. In addition to conventional cardiovascular risk factors such as smoking, obesity and high blood pressure, several early life factors such as socioeconomic status (SES), birth weight and childhood obesity are known to affect future cardiovascular health. These associations have been scarcely studied in the Indigenous population of Australia.

PARTICIPANTS: The Aboriginal Birth Cohort (ABC) study is a prospective life course study that has followed 686 Indigenous Australians from birth into adulthood. It was initiated in the 1980s in order to shed light on possible reasons originating in early life for the high burden of disease of the Indigenous population and to identify possibilities for early prevention.

AIMS: In this doctoral thesis, the relationship between early life factors, including birth weight and SES, and later cardiovascular health in the ABC was examined.

RESULTS: It was found that overall, ideal cardiovascular health was rare. Areal socioeconomic disadvantage in childhood was associated with higher rates of ideal physical activity and ideal blood pressure levels. Children from urban environments tended to have less ideal blood pressure than those from remote locations. Household size, maternal body mass index (BMI) and sex were also found to be predictors of future cardiovascular health. Area-level social disadvantage at birth was found to affect the longitudinal development of BMI, systolic blood pressure (SBP) as well as HDL- and LDL-cholesterol levels. Nutritional status indicated by BMI and waist-to-height-ratio (WHtR) was shown to track from childhood into adulthood, and children with both low and high BMI and WHtR had a tendency to express the same nutritional status in adolescence and adulthood. Finally, findings from the ABC were compared with the Finnish STRIP cohort, and it was found that birth weight affected cardiovascular risk factors in both cohorts with the strongest associations found between birth weight and future nutritional status. Babies with smaller birth weight had lower BMI than babies born larger for gestational age.

CONCLUSIONS: Socioeconomic and other family factors in early life as well as birth weight influence later cardiovascular health in the Aboriginal population in Australia.

KEYWORDS: areal disadvantage, birth weight, cardiovascular health, indigenous, longitudinal study, nutritional status, socioeconomic status

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Sisätautioppi
PAULINE SJÖHOLM: Sydän- ja verisuoniterveyden varhaiset ennustetekijät australialaisessa aboriginaalikohortissa
Väitöskirja, 140 s.
Turun kliininen tohtoriohjelma
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TIIVISTELMÄ

TAUSTA: Sydän- ja verisuonitaudit ovat yleisin kuolinsyy maailmassa. Australiassa kuolleisuus sydän- ja verisuonitauteihin on erityisen korkea aboriginaaliväestössä, mikä näkyy huomattavasti matalampana elinajanodotteena ei-alkuperäisväestöön verrattuna. Perinteisten riskitekijöiden, kuten lihavuuden, tupakoinnin ja korkean verenpaineen lisäksi usean elämän varhaisvaiheen tekijän, kuten sosioekonomisen aseman, syntymäpainon sekä lapsuusajan lihavuuden, tiedetään vaikuttavan myöhempään sydänterveyteen. Näiden varhaisten ennustetekijöiden vaikutusta Australian alkuperäisväestössä ei ole juurikaan tutkittu.

AINEISTO: The Aboriginal Birth Cohort (ABC) on seurantatutkimus, joka aloitettiin 1980-luvulla. Sen tarkoituksena on selvittää varhaiselämän tekijöiden merkitystä alkuperäisväestön korkealle sairastavuudelle ja löytää mahdollisuuksia varhaiseen ennaltaehkäisyyn. Kohorttitutkimus on seurannut 686:ta alkuperäisväestöön kuuluvaa australialaista syntymästä aikuisuuteen.

TAVOITTEET: Tässä väitöskirjatyössä selvitettiin varhaisten ennustetekijöiden, kuten sosioekonomisen aseman ja syntymäpainon, vaikutusta aikuisiän sydän- ja verisuoniterveyteen ABC-kohortissa.

TULOKSET: Ihanteellisen sydänterveyden havaittiin olevan harvinaista ABC-kohortissa. Alueellinen huono-osaisuus lapsuudessa liittyi korkeampaan fyysiseen aktiivisuuteen ja optimaalisempiin verenpainearvoihin myöhemmissä seurannoissa. Kaupungeissa kasvaneilla lapsilla oli harvemmin optimaalinen verenpainetaso verrattuna lapsiin, jotka asuivat kaukana kaupungeista. Myös sukupuoli, perhekoko ja äidin painoindeksi ennustivat tulevaa sydänterveyttä. Alueellinen huono-osaisuus syntymähetkellä vaikutti painoindeksin, systolisen verenpaineen, sekä HDL- ja LDL-kolesterolitasojen pitkittäiskehitykseen. Painoindeksi ja vyötärö-pituus-suhde osoittivat pysyvyyttä lapsuudesta aikuisuuteen; lapsilla, joilla oli korkea painoindeksi tai vyötärö-pituus-suhde, oli usein korkeat arvot myös aikuisuudessa. Samanlainen jatkuvuus lapsuudesta aikuisuuteen havaittiin matalalle painoindeksille ja vyötärö-pituus-suhteelle. Kun ABC-kohortin löydöksiä verrattiin suomalaiseen STRIP-kohorttiin, havaittiin, että syntymäpaino on yhteydessä myöhempään sydänterveyteen molemmissa kohorteissa ja vahvin yhteys löytyi syntymäpainon ja myöhemmän ravitsemustilan välillä. Molemmissa kohorteissa pienipainoisilla vauvoilla oli seurannassa matalampi ja suurempipainoisilla vauvoilla korkeampi painoindeksi.

YHTEENVETO: Sosioekonomiset ja muut perheeseen liittyvät tekijät varhaiselämässä sekä syntymäpaino ovat yhteydessä myöhempään sydänterveyteen australialaisessa aboriginaaliväestössä.

AVAINSANAT: alueellinen huono-osaisuus, syntymäpaino, sydän- ja verisuoniterveys, alkuperäiskansa, pitkittäistutkimus, sosioekonominen asema

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Abbreviations

ABC	Aboriginal Birth Cohort
AGA	appropriate for gestational age
AHA	American Heart Association
ARIA	Accessibility Remoteness Index of Australia
BMI	body mass index
CHD	coronary heart disease
CI	confidence interval
cIMT	carotid intima media thickness
CVD	cardiovascular disease
DALY	disability adjusted life years
DBP	diastolic blood pressure
DOHaD	developmental origins of health and disease
ECG	electrocardiogram
HbA1c	haemoglobin A1c (glycated haemoglobin)
HDL	high-density lipoprotein
hsCRP	high-sensitivity C-reactive protein
IRSEO	Indigenous Relative Socioecomic Outcomes Index
LDL	low-density lipoprotein
LGA	large for gestational age
NT	Northern Territory
OR	odds ratio
RDH	Royal Darwin Hospital
SBP	systolic blood pressure
SD	standard deviation
SES	socioeconomic status
SGA	small for gestational age
SNP	single nucleotide polymorphism
STRIP	Special Turku Coronary Risk Factor Intervention Project
TE	Top End
WHO	World Health Organization
WHtR	waist-to-height ratio

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Sjöholm P, Pahkala K, Davison B, Juonala M, Singh GR. Early life determinants of cardiovascular health in adulthood: the Australian Aboriginal Birth Cohort study. *International Journal of Cardiology*, 2018; 269: 304-309.

II Juonala M, Sjöholm P, Pahkala K, Ellul S, Kartiosuo N, Davison B, Singh GR. The Australian Aboriginal Birth Cohort study: socio-economic status at birth and cardiovascular risk factors to 25 years of age. *Medical Journal of Australia*, 2019; 211(6): 265-270.

III Sjöholm P, Pahkala K, Davison B, Juonala M, Singh GR. Socioeconomic status, remoteness and tracking of nutritional status from childhood to adulthood in an Australian Aboriginal Birth Cohort: the ABC study. *BMJ Open*, 2020; 10: 1-9.

IV Sjöholm P, Pahkala K, Davison B, Niinikorpi H, Raitakari O, Juonala M, Singh GR. Birth weight for gestational age and later cardiovascular health: a comparison between longitudinal Finnish and Indigenous Australian cohorts. *Annals of Medicine,* 2021; 53(1):2060-2071.

1 Introduction

Cardiovascular diseases (CVDs), including diseases of the heart, the vasculature of the brain, and the systemic vasculature, are the leading cause of death and the leading cause of disease burden worldwide. (Roth et al., 2020) A large proportion of CVD related deaths are preventable and occur before the age of 60 years. The proportion of premature deaths from CVD has been estimated to 4% in high-income countries and 42% in low-income countries, representing an immense inequality in cardiovascular mortality between populations. (Mendis et al., 2011) The Australian Aboriginal population represents a disadvantaged population in a developed country. In Australia, the Indigenous population is particularly affected by CVD, with 1.5 times higher mortality rates compared to the non-Indigenous population (Australian Institute of Health and Welfare, 2015a).

The most common condition that leads to coronary, carotid and peripheral artery disease is atherosclerosis, which is an immunoinflammatory systemic disease of the arteries. Atherosclerosis causes lipid plaque formation in the arterial walls, impeding free circulation and possibly leading to thrombotic events in case of plaque rupture. (Falk, 2006) The pathophysiologic processes leading to CVD begin early in life, even before birth. Carotid intimal thickening, a condition preceding plaque formation, has been found in autopsies of infants under one year of age who had died of noncardiac causes, suggesting that atherosclerotic processes may begin already *in utero*. (Milei et al., 2010; Pesonen et al., 1975)

The risk factors for CVD are manifold and include both modifiable factors such as sedentary lifestyle, smoking, unhealthy dietary habits, excessive body fat, dyslipidaemia and hypertension as well as environmental, psychosocial and even genetic factors (Piepoli et al., 2020). The Aboriginal Birth Cohort (ABC) was initiated in the 1980's to shed light on the factors that lie behind the high incidence of CVD's and the large burden of disease in the Australian Aboriginal population. It is one of the largest and longest-running indigenous birth cohorts in Australasia. This doctoral thesis focuses on the data on longitudinal cardiovascular risk factor accumulation acquired in the study with the aim of better understanding the early-life origins of CVD in this unique cohort. Results from the ABC regarding the relationship between birth weight and later cardiovascular health were compared with findings from the Finnish STRIP cohort study.

2 Review of the Literature

2.1 Cardiovascular disease: a global health threat

While death rates due to communicable, maternal, neonatal and nutrient-related conditions are declining globally, mortality rates for non-communicable diseases keep rising. CVD is the leading cause of death worldwide, accounting for about one third of global mortality. (Roth et al., 2018) During the last three decades, the age-standardized CVD mortality rates have declined steadily in high-income countries. However, in low- and middle-income countries, the age-standardized CVD mortality rates have remained the same and the absolute numbers of CVD-related deaths are increasing, leading to widening global disparities in cardiovascular death. (Jagannathan et al., 2019) Ischaemic heart disease and stroke together account for 84.9% of global CVD mortality. Most of these deaths occur in low- and middle-income countries. (Roth et al., 2018)

CVDs are a major economic burden for national economies, especially in low- and middle-income countries. Some of the reasons why low- and middle-income countries are most affected by CVDs include limited access to health services for early detection and treatment of risk factors as well as delayed diagnosis. Improvements in these aspects would therefore benefit the wellbeing of individuals, households, communities and national economies worldwide. (World Health Organization, 2017)

2.2 Cardiovascular disease in Indigenous Australia

Indigenous Australians, a term used respectfully to include both Aboriginal and Torres Strait Islander peoples, constitute 3.3% of the total Australian population. The age structure is younger in the Indigenous population, with a median age of 20.3 years versus 37.8 years in the non-Indigenous population. (Australian Bureau of Statistics, 2018). Life expectancy in 2015-2017 was 8.6 years lower for Indigenous males and 7.8 years lower for Indigenous females compared to their non-Indigenous counterparts. The disease burden for Indigenous Australians is over two times higher than that of non-Indigenous Australians. These differences are largely explained by higher rates of chronic, non-communicable diseases, such as CVD, respiratory

diseases, cancer, diabetes, and kidney disease as well as higher rates of mental health conditions and substance abuse. The reasons behind these inequities in health are complex, but longstanding disparities in income, employment and education are thought to play an important part. The access to health services is also often inadequate. (Australian Institute of Health and Welfare, 2015a, 2020a)

CVD mortality in Australia has declined substantially over the last three decades. Even though the decline has been even greater in the Indigenous population compared to the non-Indigenous population, the age-standardised prevalence rate of coronary heart disease (CHD) remains over twice as high in the Indigenous population. (Australian Institute of Health and Welfare, 2017c)

Many CVD risk factor rates are high in the Indigenous population, including smoking, hypertension, and diabetes. An estimated 9.8% of the adult Indigenous population were at high risk of a primary CVD event, with the proportion increasing with age. Among 65-74-year-old Indigenous citizens, the risk was estimated to 44.2%. There is considerable undertreatment with lipid-lowering and blood pressure medication in the Indigenous populations, indicating a potential to prevent many of these cases with appropriate risk management. (Calabria et al., 2018) CVD was the second leading cause of death, after cancer, among Indigenous Australians in 2014-2018. Indigenous adults reported CVD rates about double those of non-Indigenous Australians in both remote and non-remote areas in all age-groups in 2018-19 (**Figure 1**). (Australian Institute of Health and Welfare, 2020a)

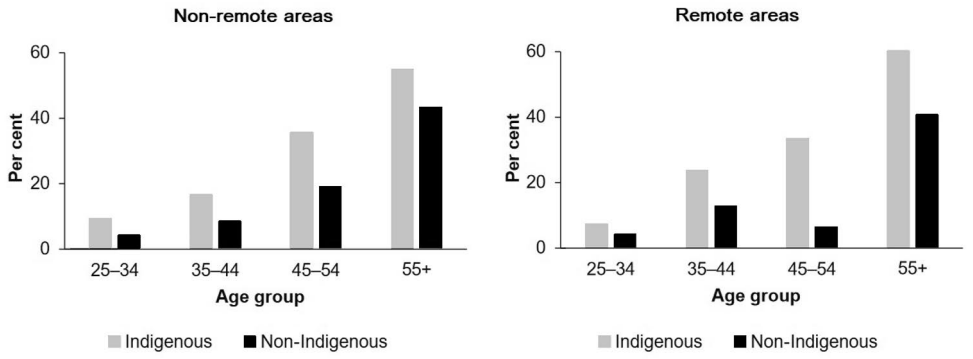

Figure 1. Self-reported cardiovascular conditions in 2018-19 by age group and indigenous status. Adapted and modified from Aboriginal and Torres Strait Islander Health Performance Framework 2020 summary report (p. 34) by Australian Institute of Health and Welfare 2020.

2.3 Risk factors for cardiovascular disease

Specific risk factors for atherosclerosis and CHD were first described in the Framingham Heart Study in 1957, as Dawber et al. proposed that individuals with hypercholesterolemia, hypertension, obesity, and signs of left ventricular hypertrophy on the ECG were more likely to suffer from cardiovascular events. This led to the realization that prevention of CHD must focus on these risk factors and should begin much before any clinical manifestations. (Dawber et al., 1957) In 1981, Hopkins and Williams proposed a total of 246 risk factors associated with CVD. These included factors that have since then been well studied and acknowledged, such as obesity, diabetes and dyslipidaemia, but also more controversial suggestions such as slow beard growth and earlobe crease. (Hopkins & Williams, 1981) To date, an extensive amount of research has been done to shed light on the multifactorial pathophysiology of CVD that is today seen as a product of risk factor accumulation. The risk factors that are considered of clinical relevance include behavioural, metabolic, environmental, genetic, socioeconomic and psychosocial aspects. (Yusuf et al., 2020)

2.3.1 Modifiable risk factors

Many of the identified CVD risk factors are modifiable. The PURE (Prospective Urban Rural Epidemiology) study is a large, prospective cohort study that has examined CVD risk factors and their associations with CVD mortality in over 150 000 participants from 21 nations, including low, middle, and high-income countries. The study found that over 70% of CVD cases were attributable to a small amount of modifiable risk factors, namely hypertension, high non-HDL cholesterol, tobacco consumption, air pollution, poor diet, low education, abdominal obesity and diabetes. (Yusuf et al., 2020) Improvements in these risk factors have been shown to cause dramatic changes in CVD mortality. In eastern Finland, following the North Karelia project, CVD mortality decreased by more than 80% from 1972 to 2012. Almost two thirds of this mortality reduction could be explained by changes in blood pressure, tobacco use and cholesterol levels. (Jousilahti et al., 2016)

2.3.1.1 Dyslipidaemia

LDL-cholesterol is a well-established risk factor for atherosclerotic CVD. (Ference et al., 2017) In 1954, Gofman et al. discovered that LDL-cholesterol levels were much higher and HDL-cholesterol levels were lower in the plasma of individuals who had suffered a heart attack compared with healthy individuals. (Goldstein & Brown, 2015) This association between cholesterol levels and atherosclerotic heart disease has been replicated in numerous epidemiological studies, among others in the Framingham

Heart Study (Castelli, 1984), the Seven Countries Study (Verschuren et al., 1995) and the Bogalusa Heart Study (Berenson & Srinivasan, 2003).

The atherosclerotic process typically starts at sites in the arterial system where there are perturbations in blood flow. The shear stress at the arterial wall, together with other pathophysiological stimuli of endothelial cell dysfunction such as aging, inflammation, and hormonal factors, cause disruptions in the endothelial integrity, leading to activation of proinflammatory factors and allowing circulating lipoproteins to start to accumulate in the subendothelial space. (Gimbrone & García-Cardeña, 2016) This accumulation is well documented for LDL-cholesterol. In the intimal layer, LDL-cholesterol gets in contact with reactive oxygen species leading to formation of oxidized LDL. This promotes inflammation in the arterial wall as well as the uptake of oxidized LDL into macrophages, which in turn leads to the formation of foam cells that form the plaque. (Wolf & Ley, 2019)

Elevated triglyceride levels have also been associated with elevated cardiovascular risk in epidemiological studies and reaching target levels of triglycerides seems to reduce CVD risk. (Budoff, 2016; Miller et al., 2011)

In 2012-2013, 65% of Indigenous Australian adults had dyslipidaemia, defined as having abnormal levels of cholesterol and/or triglycerides or taking cholesterol-lowering medication. Indigenous adults were 1.1 times more likely to have dyslipidaemia than their non-Indigenous counterparts. (Australian Institute of Health and Welfare, 2015b) Several studies have shown that Indigenous Australians, especially those living in remote and rural areas, have a more atherogenic lipid profile with very low HDL-cholesterol levels. (Lyons et al., 2014) Another typical feature of Indigenous Australians lipid profiles is the presence of very small LDL-cholesterol particles. (O'Neal et al., 2008)

2.3.1.2 Hypertension

There is a strong, direct association between high blood pressure and cardiovascular morbidity including ischemic heart disease, stroke and other vascular morbidities for all age groups and independent of ethnicity. (Lewington et al., 2002) For adults, a continuous relationship holds true at least for levels above 110-115 mmHg systolic blood pressure (SBP) and 70-75 mmHg diastolic blood pressure (DBP), under which there is little evidence of cardiovascular risk. (Mancia et al., 2013)

High blood pressure relates to CVD via several mechanisms. The increased pressure at the arterial walls causes mechanical stress and increases endothelial permeability. This can mitigate the deposition of lipids and the formation of atherosclerotic plaques. Hypertension also leads to remodeling of coronary arteries, left ventricular hypertrophy and increased vascular resistance at the microvascular level, all leading to worsening of the cardiac function. (Escobar, 2002)

In Australia, about one third of the adult population suffers from hypertension, defined as SBP greater or equal to 140 mmHg, DBP greater or equal to 90 mmHg or receiving medication for blood pressure control. (Australian Institute of Health and Welfare, 2019) Indigenous Australians aged 18 and over were 1.2 times as likely to have high blood pressure when compared to the non-Indigenous population. (Australian Bureau of Statistics, 2013a)

2.3.1.3 Obesity and overweight

The WHO defines overweight as a body mass index (BMI) greater than or equal to 25 kg/m^2 and obesity as BMI greater than or equal to 30 kg/m^2. Global obesity rates are on the rise and were about three times as high in 2016 as in 1975. Of the world's adult population, 39% were overweight and 13% were obese in 2016, whereas 18% of children aged 5-19 years were overweight or obese. Rates of overweight and obesity are especially rising in low- and middle-income countries. The reasons why obesity has reached pandemic dimensions include increased intakes of energy-dense foods and the declining need for physical effort in work and transportation. (World Health Organization, 2020) Apart from being a substantial risk factor for CVD, obesity increases the risk for many other non-communicable diseases such as Alzheimer disease, depression and cancer. (Blüher, 2019)

Obesity relates to CVD risk both directly and indirectly. Direct effects include adaptations of the cardiovascular system related to the increased body weight and the pro-inflammatory and pro-thrombotic environment that is found in obese individuals. Indirect effects include obesity-related disorders that also increase CVD risk, such as insulin resistance, hypertension and dyslipidaemia. (Koliaki et al., 2019) However, it seems like obesity is also an independent risk factor for CVD, which persists even after adjusting for comorbidities such as hypercholesterolemia, diabetes and hypertension. (Hubert et al., 1983; Kenchaiah et al., 2002)

Childhood obesity tends to persist to adulthood. This so-called tracking of obesity has been shown in many populations. (de Wilde et al., 2018; Evensen et al., 2016; Singh et al., 2008) However, there is evidence that if childhood prevention is able to stop obesity from tracking into adulthood, the risk for later type 2 diabetes, hypertension, dyslipidaemia and atherosclerosis is similar to those who were never obese. (Juonala et al., 2011)

There is a pattern of a dual burden of malnutrition seen in Indigenous Australia with high rates of both underweight and overweight in children and adults. In 2012-13, Indigenous Australians were 1.2 times more likely to be overweight and 1.6 times more likely to be obese than their non-Indigenous counterparts, with 66% of the Indigenous population being either overweight (29%) or obese (37%). On the other hand, 8% of Indigenous children aged 2-14 years were underweight, compared to

4.8% of non-Indigenous children. Indigenous people over 15 years of age were 1.6 times as likely to be underweight compared with non-Indigenous peers. (**Figure 2**) (Australian Institute of Health and Welfare, 2015b)

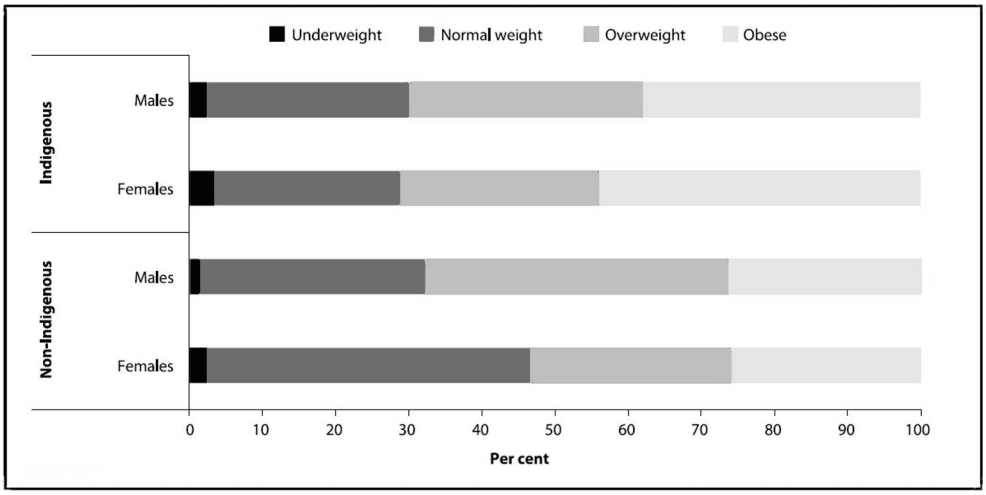

Figure 2. Body weight categories in Indigenous and non-Indigenous Australian people aged 15 and over, 2012-2013. Adapted and modified from The Health and Welfare on Australia's Aboriginal and Torres Strait Islander Peoples 2015 (p. 66), by Australian Institute of Health and Welfare, 2015.

2.3.1.4 Diabetes

In 1979, Kannel et al. observed an association between diabetes and atherosclerosis, describing a two- to threefold increase in atherosclerotic disease in diabetic individuals in the Framingham Heart Study. (Kannel, 1979) Diabetes is a chronic state of hyperglycaemia that is associated with early and rapidly progressing atherosclerosis. There are two major subtypes of diabetes with type 2 accounting for the majority of cases. Both type 1 and type 2 increase cardiovascular risk, albeit via slightly different mechanisms. (Colom et al., 2021) Mortality rates from CVD are 2-4 times higher in adults with diabetes compared to normoglycemic individuals. (Rubin et al., 2012) Diabetes raises CVD risk significantly more in women than in men. (Emerging Risk Factors Collaboration et al., 2010) Hyperglycaemia is associated with changes in both the macrovasculature, manifested as increased arterial stiffness and greater intima-media-thickness, as well as dysfunction of the microcirculation, all contributing to greater CVD risk. (Strain & Paldánius, 2018)

In 2012-13, 11% of Indigenous adults suffered from diabetes. Diabetes was 3.3 times more common in the Indigenous population, when compared with the non-Indigenous population. (Australian Institute of Health and Welfare, 2015b).

2.3.1.5 Smoking

In 2015, 11.5% of global deaths were attributable to tobacco smoking (Reitsma et al., 2017), making it the second leading risk factor for early death worldwide, even though smoking rates are declining in most parts of the world (Forouzanfar et al., 2016). Tobacco smoke predisposes to a variety of cardiovascular syndromes, from stable angina pectoris to acute coronary syndromes and peripheral atherosclerosis. The mechanisms through which smoking causes CVD include vasomotor dysfunction due to decreased nitric oxide availability, increased endothelial inflammation, modification of lipid profiles as well as thrombotic events caused by platelet dysfunction and alterations in thrombotic and fibrinolytic factors (Ambrose & Barua, 2004).

Smoking has a strong social gradient worldwide and it is more prevalent in low-income settings on all continents. (Ciapponi, 2011) In Australia, smoking among Indigenous people is much more common in all age groups (**Figure 3**), and it is thought to be the leading risk factor contributing to the immense health disparities between the Indigenous and non-Indigenous populations. (Australian Institute of Health and Welfare, 2015a) Smoking during pregnancy is also common in the Indigenous population; 43% of Indigenous mothers who gave birth in 2018 had smoked during pregnancy, compared to 11% in the non-Indigenous population. (Australian Institute of Health and Welfare, 2020b)

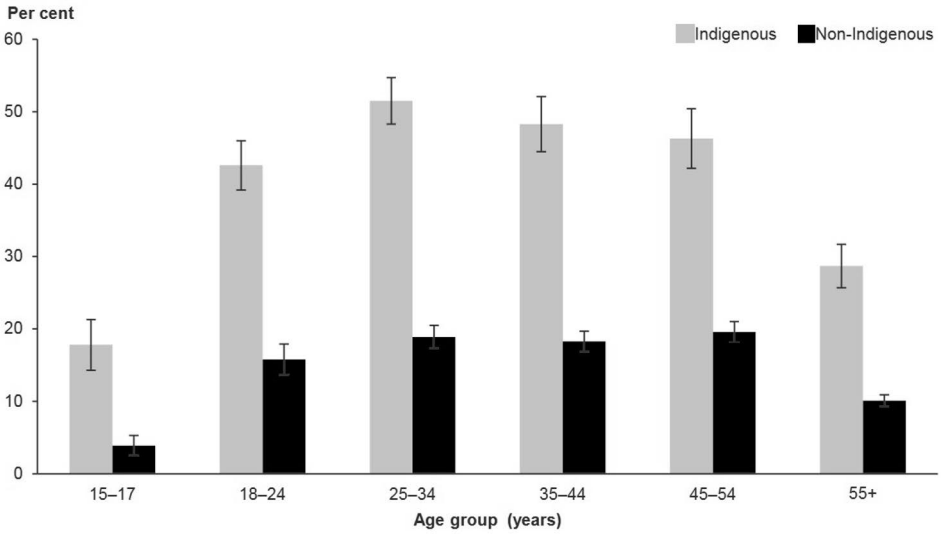

Figure 3. Current smokers in Australia in 2011-2013 by age group and Indigenous status. Adapted and modified from Cardiovascular Disease, Diabetes and Chronic Kidney Disease – Australian Facts (p.8) by Australian Institute of Health and Welfare.

2.3.1.6 Unhealthy dietary patterns

According to the Global Burden of Disease Study in 2017, dietary risks were a major factor increasing the global burden of disease, accounting for 10.9 million deaths and 255 million disability adjusted life years (DALYs). The largest dietary contributors to the disease burden worldwide were high intake of sodium and low intake of whole grains. Diets including large amounts of sugar-sweetened beverages are increasingly adding to the global burden of disease. (GBD 2017 Risk Factor Collaborators, 2018)

Dietary factors can reduce CVD incidence but also support secondary prevention among those who have suffered from myocardial infarction. Avoiding excess energy intake promotes normal body weight but also improves insulin sensitivity, glucose levels and reduces inflammation. (Yu et al., 2018) Fruit and vegetable consumption is associated with reduced risk of CVD and cancer. (Aune et al., 2017) Other food groups that favour good cardiovascular health include seafood, nuts, legumes, and whole grains, whereas processed meats, refined grains, sugar sweetened beverages, trans fats and sodium may be deleterious. Alcohol is thought to have a U-shaped relationship with moderate consumers having the lowest CVD risk. (Yu et al., 2018)

Dietary interventions may have notable effects on cardiovascular health both in adults and children. As an example, the Special Turku Coronary Risk Factor Intervention Project (STRIP) is a longitudinal intervention study that has provided half of its participants with biannual dietary counselling from infancy for a time period of 20 years. The dietary intervention promoting a heart-healthy diet has resulted in e.g. a lower intake of saturated fat and a more favourable cardiometabolic risk profile. In the group that received dietary counselling, a larger proportion had good total- and LDL-cholesterol levels and lower glucose levels as well as less insulin resistance than the control group at the age of 26 years, six years after the intervention had ended. (Pahkala et al., 2020) Another example is the North Karelia project. It was a community-based intervention programme that was launched in 1972 with the aim of lowering the high cardiovascular mortality rates with lifestyle changes in the Finnish province of North Karelia. Largely due to smoking cessation and improvements in diet, the annual age-adjusted cardiovascular disease mortality was reduced by more than 80% among middle aged men in the area from 1969 to 2011. (Puska & Jaini, 2020)

In 2012-2013, Indigenous Australians consumed significantly less vegetables, fruits, and dairy products than non-Indigenous Australians and failed to meet the national recommendations for these food groups. Indigenous Australians consumed more of so called discretionary foods, including alcoholic beverages, soft drinks, chips and fries, pastries, cakes and muffins and confectionary than non-Indigenous Australians. (Australian Bureau of Statistics, 2016)

2.3.1.7 Physical inactivity

Sedentary behaviour and physical inactivity are major CVD risk factors. The AHA recommends at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per weeks for adults. (Arnett et al., 2019) Physical activity increases cardiac output both by increasing stroke volume and heart rate. Longstanding physical activity can lead to morphological and physiological adaptations of the cardiovascular system, including left ventricular dilation and hypertrophy, as well as improved contractility and increased myocardial relaxation and preload. (Lavie et al., 2015) Sedentary behaviour and physical inactivity, on the other hand, have been linked with increased CVD risk. (Lavie et al., 2019) A meta-analysis including over 700 000 participants examined the dose-response association between sedentary time and CVD risk, and found that high levels of sedentary time were directly associated with the risk for adverse cardiovascular events, independent of physical activity. (Pandey et al., 2016) Nonetheless, another large meta-analysis (n=1 005 791) showed that high levels of physical activity eliminate the increased mortality risk associated with prolonged sitting times. (**Figure 4**) (Ekelund et al., 2016)

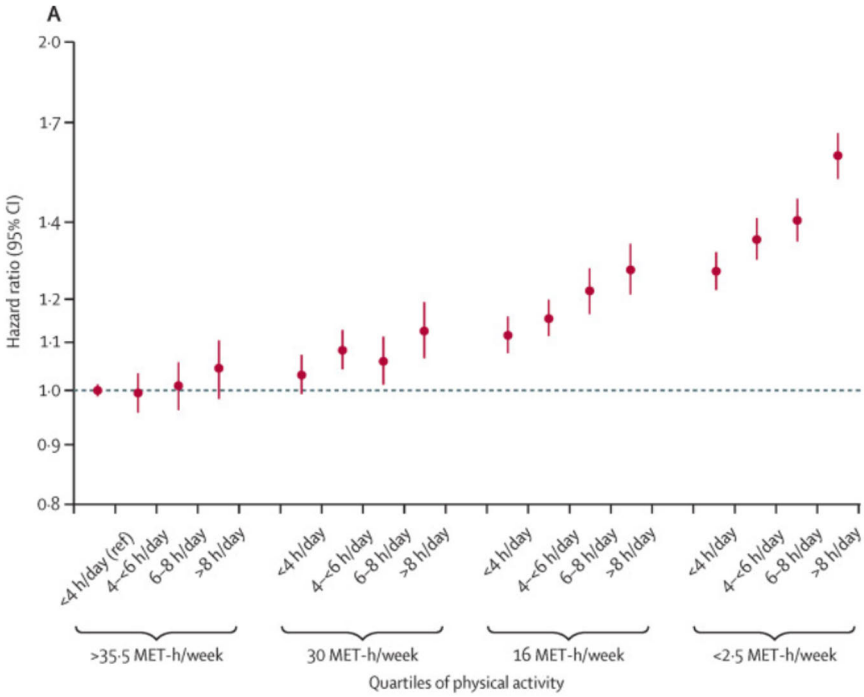

Figure 4. Hazard ratios for all-cause mortality according to sitting time (h/day) and physical activity (MET-h/week) in a meta-analysis by Ekelund et al. The reference group is the group with the highest levels of physical activity (>35.5 MET-h/week) and least sitting time per day (<4h/day). Reprinted from the Lancet (Ekelund et al. 2016) with permission from Elsevier.

In 2012-13, Indigenous Australians were 1.1 times more likely to be sedentary or to exercise at low intensity, compared with non-Indigenous Australians according to the Australian Aboriginal and Torres Strait Islander Health Survey. Of the Indigenous people living in non-remote areas, 61% of adults reported being physically inactive or having low levels of exercise in the week before the survey. (Australian Bureau of Statistics, 2013b)

2.3.2 Non-modifiable risk factors

Some population groups are more susceptible to CVD than others. Sex, age, and race/ethnicity are often considered non-modifiable risk factors for CVD.

CVD prevalence is higher for men than women, especially before menopause. This is partly because of oestrogen and partly because of differences in risk factors. Oestrogen induces changes in serum lipid concentrations but also acts directly to protect the vasculature by increasing vasodilation and preventing the formation of atherosclerotic plaques. (Mendelsohn & Karas, 1999) After menopause, CVD becomes more prevalent in women, in part reflecting a longer life expectancy than men. (Elias-Smale et al., 2015)

CVD increases with age in all populations due to age-related changes in the heart and vasculature. Atrial and ventricular dilation, hypertrophy and fibrosis all increase with age. Conduction in the pacemaker system slows down. The valves of the heart experience thickening, lipid accumulation and calcification with advancing age. There is also age-related remodelling of the arteries, manifested as thickening of the arterial walls, seen as increased carotid intima-media-thickness (cIMT) and arterial stiffening because of high collagen content, calcification, and elastin degradation. Endothelial dysfunction increases with age, increasing the susceptibility for plaque formation. (**Figure 5**) (Costantino et al., 2016; Kane & Howlett, 2018)

There are large racial disparities in the incidence and outcomes of many illnesses, including CVD. Many ethnic minorities globally experience poorer overall health with earlier onset of illness, more severe courses of disease and suboptimal treatment, compared to the majority populations. (Williams et al., 2010) Racial health inequities have been extensively studied in the U.S. population, where African Americans continue to experience a considerably larger burden of CVD. (Ferdinand et al., 2020; Sidney et al., 2016)

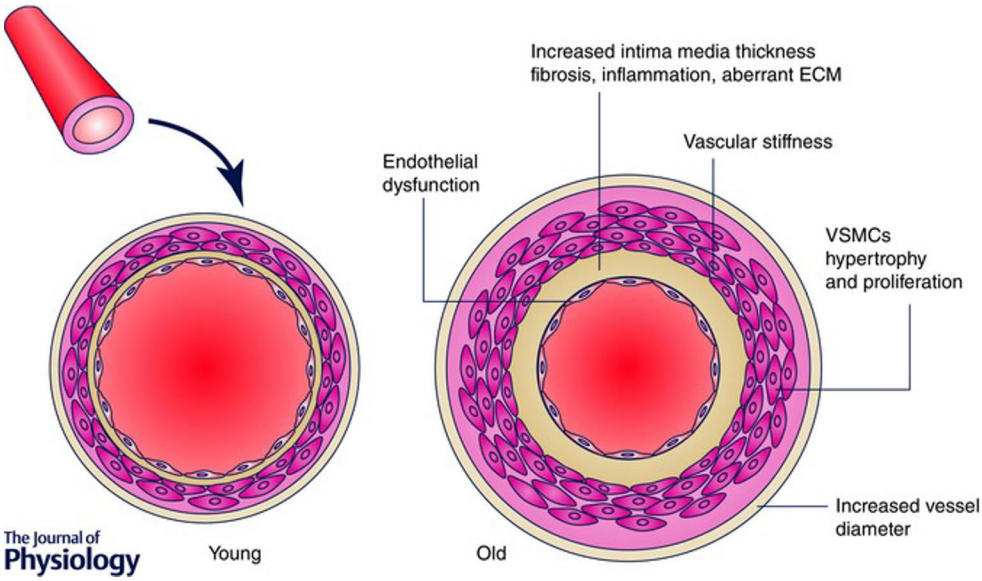

Figure 5. Structural changes in the ageing vasculature. On the left, a cross-section of a young artery and on the right, a cross-section of an aged artery. ECM=Extracellular matrix, VSMC=vascular smooth muscle cell. Reprinted from the Journal of Physiology (Constantino et al. 2016) with permission from John Wiley and Sons.

The relationship between ethnicity and health is complex. Ethnicity, health, and SES are closely intertwined, and the racial inequalities in health reflect larger inequalities in society. (Williams et al., 2010) The suggestion that genes alone could explain the racial disparities is not supported by evidence, as alleles that affect genetic susceptibility do not seem to be strongly determined by ethnicity. (Cooper et al., 2003).

2.3.3 Early life predictors

Predisposition to CVD is thought to exist already in the foetus, with factors such as birth size and maternal obesity before or during pregnancy correlating strongly with the individual's future CVD risk. Other risk factors in infancy and childhood include SES and education as well as areal disadvantage and remoteness.

2.3.3.1 Birth size

The relationship between birth weight and later CVD was first described in 1989, when Barker et al. examined mortality outcomes in 15 000 individuals born in Hertfordshire between 1911 and 1930. It was found that individuals with low birth weight had an increased risk of dying from CVD compared to those with higher birth weight. (Barker

et al., 1989) Later analyses from the same study revealed that low birth weight infants had, in addition to an increased CVD risk, an increased risk of developing other chronic diseases such as type 2 diabetes (Hales et al., 1991), metabolic syndrome (Barker et al., 1993), and osteoporosis (Cooper et al., 1997). These findings led to the development of the so-called Developmental Origins of Health and Disease (DOHaD) theory that suggests that malnutrition *in utero* leads to foetal programming that causes permanent changes in the organ structure, making the foetus susceptible to chronic disease later in life. Since then, the association between birth size and later cardiovascular risk has been studied extensively, and several associations have been found between small size at birth and later cardiovascular risk markers. These include metabolic markers such as insulin resistance (Tian et al., 2019), high lipid levels and SBP as well as subclinical markers of atherosclerosis such as thickening of the aortic and carotid walls. (Martyn et al., 1998; Skilton et al., 2005, 2011)

More recently, it has been suggested that, rather than inverse, the relationship between birth size and cardiovascular risk could be U- or J-shaped, indicating that both large and small size at birth predispose to later CVD. (Knop et al., 2018; Lai et al., 2019) High birth weight has been associated with childhood obesity (Yuan et al., 2015) and metabolic syndrome (Boney, 2005).

In 2011, 11.9% of the babies born to Indigenous mothers in Australia were of low birth weight, making Indigenous mothers twice as likely to give birth to a low birth weight infant compared to non-Indigenous mothers. High birth weight was less common in the Indigenous population (1.4% vs. 1.7%). Various factors are thought to affect this gap in birth weight. Indigenous mothers were more likely to smoke during pregnancy (50% vs. 12%) and were younger when having their first child (21.5 vs. 28.6 years). Low birth weight was more common in lower socioeconomic settings and with increasing remoteness. Although most Indigenous mothers had access to prenatal care, the access was still worse than for non-Indigenous mothers: 95% of non-Indigenous mothers had more than five antenatal care visits – for Indigenous mothers the rate was 83%. (Australian Institute of Health and Welfare, 2017b)

2.3.3.2 Maternal factors

In addition to maternal smoking that is associated with lower birth weight (Abraham et al., 2017), maternal nutritional status and lipid profiles play, among other factors, a role in subsequent CVD risk development.

The nutritional environment *in utero*, and thus the nutrition of the mother, has an impact on the later risk for metabolic disturbances and CVD in the offspring. It is thought that altered nutrition during so called critical phases in the foetal development may lead to permanent physiological changes that may manifest much later in the life course. (Hoet & Hanson, 1999)

Undernutrition in pregnancy is linked to poor foetal growth and later disease susceptibility. A cohort study that examined 2414 people born during the Dutch famine in the 1940's, found that maternal exposure to undernutrition was associated with glucose intolerance and increased rates of CHD and obesity in the offspring, as well as with adverse lipid profiles and disturbances in blood coagulation. (Roseboom et al., 2006)

Today, maternal malnutrition is especially affecting poor women and their children both in developing and developed countries. Women are more often affected by food insecurity and malnutrition than men and this gender inequality in nutrition leads to intergenerational inheritance of disease susceptibility. (FAO et al., 2020)

On the other hand, prevalence of obesity during pregnancy is rising all over the world and the long-term effects of maternal obesity on the offspring are gaining increasing interest. Excessive body weight in pregnancy increases the immediate risks for pregnancy outcomes but is also associated with long-term risks for the offspring, such as increased susceptibility for insulin resistance, obesity and CHD. (Yu et al., 2013) Maternal obesity without or in combination with gestational diabetes increases the risks for metabolic syndrome in the offspring. (Boney, 2005)

The FELIC study compared the progression of foetal fatty streaks in the aorta in children of normocholesterolemic and hypercholesteraemic mothers and showed that the atherosclerotic lesions progressed significantly faster in children of mothers with high cholesterol levels during pregnancy. This finding indicates a higher long-term susceptibility for atherosclerosis in the offspring of mothers with hypercholesterolemia in pregnancy. (Napoli et al., 1999)

The notion that metabolic and nutritional circumstances *in utero* impact later long-term disease susceptibility in the offspring has led to the suggestion that there is an epigenetic component in foetal programming that responds to changes in nutrient availability, affecting DNA methylation, histone modification and microRNA, thus altering gene expression in the offspring. (Vickers, 2014)

Compared with non-Indigenous Australian mothers, Indigenous mothers were 1.6 times as likely to be obese and four times as likely to have pre-existing diabetes in 2018. (Australian Institute of Health and Welfare, 2020b)

2.3.3.3 Areal disadvantage and remoteness

There are large national disparities in CVD morbidity between people living in rural and remote locations compared to those living in urban environments. The disparities keep widening in many countries, such as China (Liu, 2020) and the US (Cross et al., 2020).

Mortality rates from CVD in Australia are higher for people, especially males, living outside of major cities. (Jacobs et al., 2018) About one in five Indigenous Australians live in remote and very remote areas, compared with less than one in 50 non-Indigenous people. (Australian Institute of Health and Welfare, 2017a) There are large health inequalities between Indigenous Australians living in remote areas and those living in urban surroundings. In 2010-2012, diabetes and chronic kidney disease were twice as common and CVD was 1.4 times as common among Indigenous people living in remote Australia compared with those living in urban surroundings. (Australian Institute of Health and Welfare, 2015a)

2.3.3.4 Socioeconomic status

Low SES has been linked to increased CVD risk. Higher prevalence of biological, behavioural, environmental, and psychosocial risk factors in lower socioeconomic settings are largely responsible for this gradient. In high-income countries, income level, education, employment and neighbourhood factors are commonly used SES markers and have demonstrated an association with CVD risk. (Schultz et al., 2018) In impoverished and rural settings, traditional SES measurements can be difficult to apply. Possible surrogate markers for SES measurements include data on housing (e.g. resident ownership status, number of bedrooms or overcrowding), consumption of items such as food, clothing and furniture, or ownership of articles such as a car or a bed. (Somi et al., 2008; Wi et al., 2016)

There are many factors indicating sociodemographic disadvantage in the Indigenous population in Australia. Families are larger, and 23% of indigenous households consist of 5 or more people compared with 10% of non-Indigenous households. In 2015-16, Indigenous children received child protection services at a 7-fold rate compared with their non-Indigenous counterparts. Although Indigenous youth aged 10-17 years only account for 6% of all Australians in that age group, 59% of young people in youth detention were Indigenous. Imprisonment rates in 2016 were 13 times that for non-Indigenous people. Employment rates are lower in the Indigenous population, as are household incomes. More young Indigenous people fail to meet national education targets. (Australian Institute of Health and Welfare, 2017a)

2.4 Quantifying cardiovascular risk

Quantification of individual cardiovascular risk is needed for identification of individuals who could benefit from medical interventions. In addition to traditional risk scoring, novel genetic and biomedical markers have been found to improve CVD prediction.

2.4.1 Cardiovascular health scoring

There are several multivariable risk algorithms that are used to estimate cardiovascular risk. These usually incorporate commonly acknowledged risk factors such as age, sex, blood pressure, smoking, diabetes and dyslipidaemia to produce estimates of an individual's 10-year risk for CVD events. Some of the most widely used risk scores include the Framingham score (D'Agostino et al., 2008) and the Systematic Coronary Risk Evaluation (SCORE) model (Conroy et al., 2003; SCORE2 working group and ESC Cardiovascular risk collaboration et al., 2021)

In addition to risk, cardiovascular health can also be quantified. Measures of cardiovascular health can be used as targets guiding public health interventions and the proportion of people meeting the goal metrics can represent the overall cardiovascular health in a population. One such scoring is the American Heart Association's (AHA) impact goals that were introduced in 2010. The score incorporates seven measures of ideal cardiovascular health, including four ideal health behaviours (non-smoking, ideal BMI, physical activity at target levels and ideal diet according to guidelines) and three ideal health factors (ideal cholesterol, blood pressure and blood glucose levels). (Lloyd-Jones et al., 2010)

2.4.2 Biomarkers

Biomedical markers can be used to quantify atherosclerosis and CHD risk in individuals. These include among others high-sensitivity C-reactive protein (hsCRP), a marker of chronic inflammation. HsCRP has been the most promising biomarker of preclinical atherosclerosis, and its usefulness for CVD prediction has been shown in numerous trials. (Möhlenkamp et al., 2011) Ceramides, a class of bioactive lipids that are involved in chronic apoptosis and inflammation in the vasculature, have recently been identified as novel biomarkers that seem to predict cardiovascular events and possibly even subclinical atherosclerosis. (McGurk et al., 2021; Mishra et al., 2021) Other biomarkers with potential future benefit in risk prediction include serum amyloid A and different cytokines, adhesion molecules and markers of oxidative stress, among many others. (Tibaut et al., 2019)

2.4.3 Imaging

Ultrasound can be used to detect atherosclerotic changes much before symptoms occur. To detect CVD risk, ultrasound is most widely used to measure cIMT, an indicator of subclinical atherosclerotic disease. It is measured with B-mode ultrasound at the far wall of the carotid artery with the combined thickness of the intimal and medial layers of the artery constituting this measure. (**Figure 6**) Subclinical atherosclerotic changes do not automatically lead to clinical CVD events,

but they increase the risk, thus identifying individuals who could benefit from medical intervention. Elevated cIMT, defined as ≥ 75th percentile for age and sex, is significantly associated with elevated risk of myocardial infarction, stroke and death from CHD. (Stein et al., 2008; Su et al., 2007) Because of its non-invasiveness and relatively simple technique, cIMT can be used for large-scale population studies. (Lorenz et al., 2007)

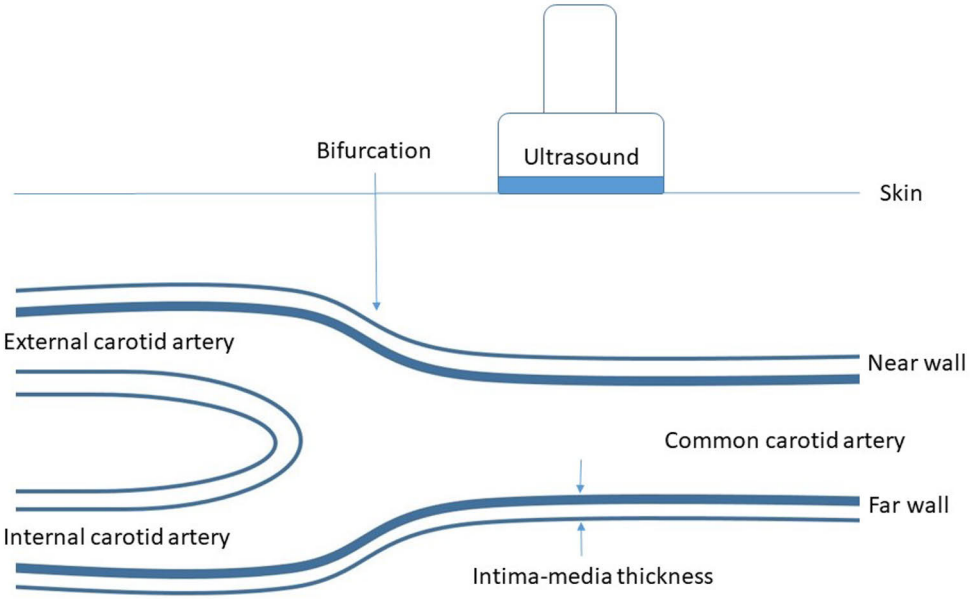

Figure 6. Schematic presentation of the site of cIMT measurement. Adapted and modified from Journal of Medical Ultrasound vol. 15 (p. 118) by Su et al. 2007.

Computed tomography can be used to quantify coronary artery calcium, which represents an estimate of overall coronary artery plaques. It is an independent predictor of coronary events and mortality, and its prediction value improves when combined with biomarkers of inflammation. (Möhlenkamp et al., 2011)

2.4.4 Genetic testing

Family history is an independent risk factor for premature CHD. (Chow et al., 2011) To date, genetic testing has been mainly used for monogenic disorders, although most diseases are polygenically determined. (Khera et al., 2018) Numerous single nucleotide polymorphisms (SNPs) that have been found in genome-wide-association studies are known to affect cardiovascular risk. (Ripatti et al., 2010) Combining these SNPs to form genetic risk scores for quantification of inherited CVD susceptibility

have been shown to improve cardiovascular risk prediction. (Iribarren et al., 2016; Lluis-Ganella et al., 2012). However, when polygenic risk scores are used in a clinical setting, they do not function as an alternative but rather as a possible addition to clinical risk modelling. (Lewis & Vassos, 2020) Even though genetic risk is an independent predictor of CVD, healthy lifestyle choices are associated with significant risk reductions even in individuals at high genetic risk. (Khera et al., 2016)

3 Aims

This thesis is based on findings from the Australian ABC and the Finnish STRIP studies. The purpose was to examine the impact of early life factors on later cardiovascular health and risk factor development in the cohorts (**Figure 7**).

The specific aims were:

1. To determine prevalences for markers of ideal cardiovascular health in the ABC according to the AHA guidelines as well as to assess the associations between early life socioeconomic factors and birth weight and cardiovascular health in adulthood. (**Study I**)
2. To examine how socioeconomic factors in early life affect the longitudinal development of cardiovascular risk factors, including BMI, lipid levels and blood pressure in the ABC. (**Study II**)
3. To examine if two measures of nutritional status, BMI and WHtR, track from childhood to adulthood, and to examine the impact of socioeconomic status and remoteness at birth on these measures in the ABC. (**Study III**)
4. To examine the relationship between birth weight for gestational age and longitudinal cardiovascular risk factor development in the ABC and the STRIP cohort. (**Study IV**)

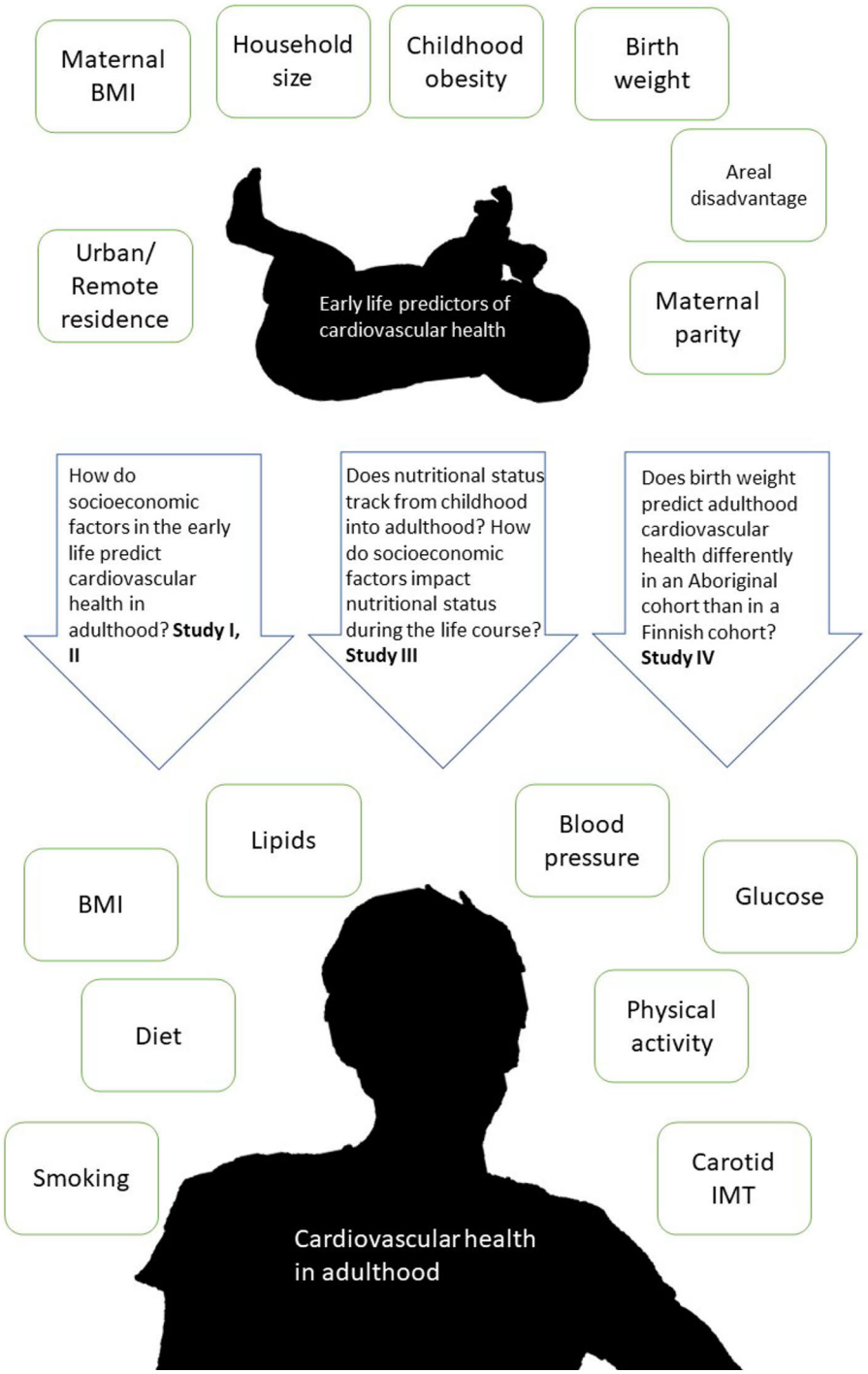

Figure 7. Schematic representation of the aims of the thesis.

4 Materials and Methods

4.1 Subjects

The study population comprised of participants from the ABC (**studies I-IV**) and the Finnish STRIP cohort (**study IV**).

4.1.1 The Aboriginal Birth Cohort

4.1.1.1 Setting and background

The Northern Territory (NT) is the jurisdiction with the lowest population density and the highest proportion of Indigenous residents in Australia. (Australian Institute of Health and Welfare, 2015b) The northern part of the territory is called the Top End (TE) and it includes the territory's capital Darwin. The Indigenous population in the NT forms clusters in Darwin and its suburbs, but much of the Indigenous population is distributed across the remote and very remote areas in the territory (**Figure 8**). (Sayers et al., 2003)

The Royal Darwin Hospital (RDH) is the only government hospital for the vast Darwin Health Region that covers an area of 120 000 square kilometres. At the time of recruitment, most Indigenous mothers (90%) in the Darwin Health Region delivered their babies at the RDH, and it is also a tertiary referral hospital for the region. (Sayers et al., 2003)

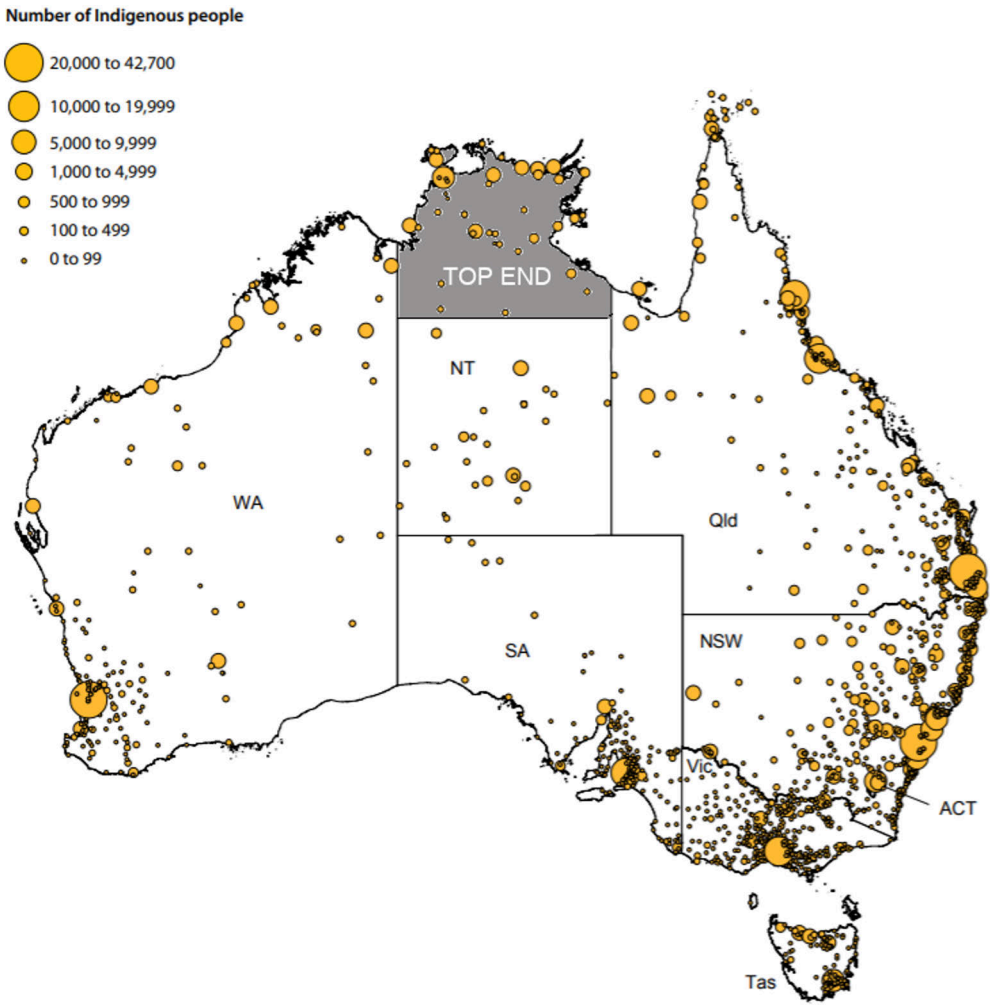

Figure 8. Clusters of Indigenous people in the Australian Jurisdictions. NT refers to the Northern Territory. The Top End is colored gray. Adapted and modified from The Health and Welfare on Australia's Aboriginal and Torres Strait Islander Peoples 2015 (p. 14), by Australian Institute of Health and Welfare, 2015.

There are logistical and cultural/linguistic difficulties related to communication and data collection in the study. Poor communication and transport infrastructure pose challenges. The contact with participants can be challenging as remote areas may not have mobile phone coverage and there are limited numbers of telephone lines and individual household postal services. Road access to many places is poor and researchers had to be trained in four-wheel driving to be able to manage the unsealed roads. Some locations were only accessible via air travel. The area experiences 3-4 months of wet season yearly, when monsoon rains flood the roads and airstrips.

In addition to the cultural differences between the researchers and the study participants, there is large cultural and linguistic diversity within the cohort. There are over 30 languages and dialects used and English is a second language for 70% of the cohort participants. Frequent name changes also complicated localizing participants: at four years of age, 30% of participants had changed their name from the time of recruitment. (Lawrance et al., 2014)

4.1.1.2 Recruitment

Singleton babies born at the Royal Darwin Hospital (RDH) between January 1987 and March 1990 to a mother who self-identified as either Aboriginal or Torres State Islander were eligible for enrolment to the ABC. Recruitment was not randomized but rather depended on whether the neonatal paediatrician was in town, and also if the mother could be located in the hospital surroundings. An Aboriginal research assistant approached the families to invite them to enrol in the study. All mothers who were found and interviewed agreed to participate. Of 1238 eligible babies, 686 were recruited. Recruitment depended on the availability of the paediatrician and the ability to locate the mothers. Despite the fact that participants were not selected at random, there were no significant differences in mean birth weight or sex ratio between those recruited and not recruited. (Sayers et al., 2003, 2017)

4.1.1.3 Follow-ups

There have been three follow-ups to date, referred to as Wave 2, Wave 3 and Wave 4. Data collection for Wave 5 commenced in 2019 and is currently under process. In addition to the variables used in this thesis and depicted in **Figure 9**, a plethora of anthropometric, biomedical, cognitive, social, emotional and ultrasonographic data were collected at each follow-up. (Sayers et al., 2017)

Wave 2 took place between 1998 and 2001. At Wave 2, 570 of the original 686 children were examined, representing 85.4% of living participants. The mean age was 11.4 years. Wave 3 took place between 2006 and 2008. At Wave 3, 467 participants with a mean age of 18.2 years were examined, representing 71.0% of living participants. Wave 4 took place between 2014 and 2016, when 70.9% (n=459) of living participants were examined. The mean age was 25.4 years. (Sayers et al., 2017)

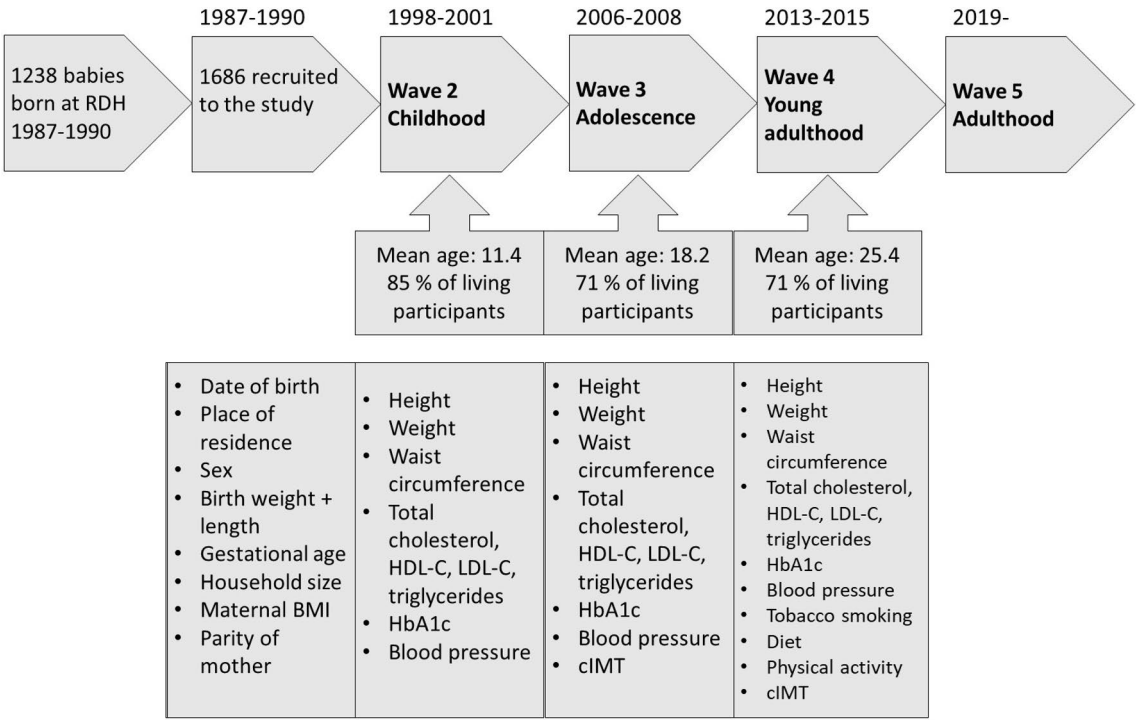

Figure 9. Flow chart depicting the follow-ups of the study as well as the variables collected at each follow-up that were used in the studies included in this thesis.

4.1.1.4 Ethical considerations

The study was approved by Human Research Ethics Committee of NT Department of Health and Community Services and Menzies School of Health Research, including the Aboriginal Ethical Sub-committee which has the power of veto. All procedures contributing to the study comply with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent to participate in the study.

4.1.1.5 Community involvement

The Australian National Health and Medical Research Council (NHMRC) has published a guideline for ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities that has a strong focus on community involvement. It highlights the responsibility of the research group to engage with Indigenous people and recommends the involvement of participants and communities in all steps of the research process. (National Health and Medical Research Council (Australia), 2018)

In the ABC, community involvement was important at all phases of the study. Before the first follow-up, community council members were contacted, and letters of endorsement were obtained from Indigenous leaders and elders. At recruitment, an Aboriginal research assistant explained the study to the mother. (Sayers et al., 2003) Key community members were identified to foster community relationships, and these members were important in all steps during and between the follow-ups. They helped with practical issues, such as community consultation, local navigation issues and language, and sometimes worked as paid assistants. (Lawrance et al., 2014)

Indigenous researchers have been involved in all aspects of the study at all follow-ups, including investigators, data collection team and local research assistants. This has encouraged and facilitated research training. Information about the study is published in community newsletters and in the national Aboriginal and Islander Health Worker Journal and provided to local community groups, stakeholders and governance groups.

4.1.2 The Special Turku Coronary Risk Factor Intervention Project

The STRIP study is an ongoing dietary intervention trial that was launched in 1989 in Turku, an urban area in southwest Finland. The aim of the intervention was to promote cardiovascular health by introducing a heart-healthy diet beginning from infancy. Recruitment of the children and their parents was done at well-baby clinics by nurses during a 5-month visit. Between February 1990 and June 1992, 1062 babies were enrolled and equally allocated to an intervention or control group. Thereafter, the intervention was continued for 20 years, and extensive data focusing on diet and cardiovascular health were obtained at least annually to the age of 20 years. Dietary counselling by a nutritionist was given to the participants in the intervention group at 3- to 12-month intervals. The aim was to promote a diet based on Nordic nutrition recommendations, including a 30-35 % proportion of daily energy intake from fat with optimal proportions of polyunsaturated fatty acids and a cholesterol intake restriction. Use of vegetables, fruits, low salt and whole-grain products was promoted. (Simell et al., 2009) After the intervention period, the first follow-up of the cohort was completed at age 26 years (n=551). (Pahkala et al., 2020)

In this thesis, data from the STRIP study was used in **Study IV**.

4.2 Data acquisition in the ABC

4.2.1 Birth weight and gestational age

Infant birth weight was measured within two hours of delivery. Birth weights were recorded to the nearest gram using a balance scale. Following agreement to participate, a neonatal paediatrician visited the mother within four days of delivery. The mother was interviewed, and a physical examination of the baby was undertaken, including an estimation of gestational age using the Dubowitz scoring system. The Dubowitz system is based on 10 neurological and 11 external characteristics (Dubowitz et al., 1970) and it gives a satisfactory estimation of the gestational age of the baby, allowing identification of preterm and small for gestational age babies.

4.2.2 Laboratory testing

Venous blood samples were collected for assessing serum lipid levels including total, LDL- and HDL-cholesterol, and triglycerides, by enzymatic methods (analytic devices employed: waves 2 and 3, Hitachi 917, Roche; wave 4, XPand Plus, Siemens). A local anaesthetic cream (EMLA) was applied 30 minutes before venepuncture. The blood samples were either centrifuged within a few hours of collection or frozen as whole blood and transported to testing laboratories. (Sayers et al., 2009)

4.2.3 Physical examination

At each follow-up, a small group of trained researchers conducted physical examinations to acquire values for blood pressure and anthropometric measurements. Blood pressure was measured three times during each follow-up (right arm, sitting after resting) with an automatic oscillatory unit (LifeSign 420, Welch Allyn) and the mean systolic and diastolic values were included in the analyses. Weight was measured to 0.1 kg with a digital scale (TBF-521, Tanita) while the participant was barefoot and in light clothing. Height was measured with a portable stadiometer to the nearest millimetre. Waist circumference was measured to the nearest millimetre using a flexible tape measure at the midpoint between the lowest rib and iliac crest at the end of exhalation. At recruitment, after delivery, height and weight of the mothers were recorded to calculate maternal BMI.

4.2.4 Ultrasonography

At Waves 3 and 4, cIMT was measured using external B-mode ultrasound with the patient lying in a supine position. The measurements were taken by the same observer. A SonoHeart Elite System (Sonosite Incorporated, Bothell, WA, USA) with a 10.5 MHz linear array transducer was used. Two readings from both common carotid arteries were averaged to calculate mean IMT. Readings were taken at end-diastole, using a simultaneously recorded 3-lead ECG tracing to locate the R wave. (Juonala et al., 2016)

4.2.5 Questionnaires

Questionnaires were used to assess factors related to lifestyle, such as tobacco use, alcohol consumption, dietary habits, and exercise, as well as to assess emotional well-being. (Sayers et al., 2009)

4.3 Definition of ideal cardiovascular health

The definition of ideal cardiovascular health used in **Study I** is based on the AHA 2010 guidelines. According to the guideline, ideal cardiovascular health is defined as the simultaneous presence of four favourable health behaviours and three health factors. The health behaviours include abstinence from smoking within the last year, BMI < 25 kg/m^2, at least 150 minutes of moderate or 75 minutes of vigorous intensity physical activity per week, and achieving 4-5 components from a 5-component diet score, comprising goal intakes for fruit and vegetables, whole-grain, fish, as well as upper limits for sodium and sugar-sweetened beverages. The health factors include untreated total cholesterol < 5.17 mmol/L, untreated fasting plasma glucose < 5.6 mmol/L and untreated blood pressure < 120 / < 80mmHg. (Lloyd-Jones et al., 2010)

The seven cardiovascular health metrics are depicted in **Figure 10**, together with the modifications that were needed when applying the guideline to the ABC. Due to lacking fasting samples, glycated haemoglobin (HbA1c) was used instead of fasting plasma glucose. Ideal HbA1c was defined as untreated HbA1c < 5.7%, meaning that no glucose-lowering medication was used, according to a definition by the American Diabetes Association. (American Diabetes Association, 2017) Due to a significant number of underweight participants in the cohort, additional analyses were conducted, including only those with a healthy BMI (18.5-24.99 kg/m^2). Because of lacking data, a modified diet score was used with possible values between 0 and 4, including target intakes for fruits and vegetables and fish as well as upper limits for soft drinks and processed meats. A total score of 3 or 4 was defined as ideal. Ideal

physical activity was defined as > 5 hours of self-reported exercise per week. (**Figure 10**)

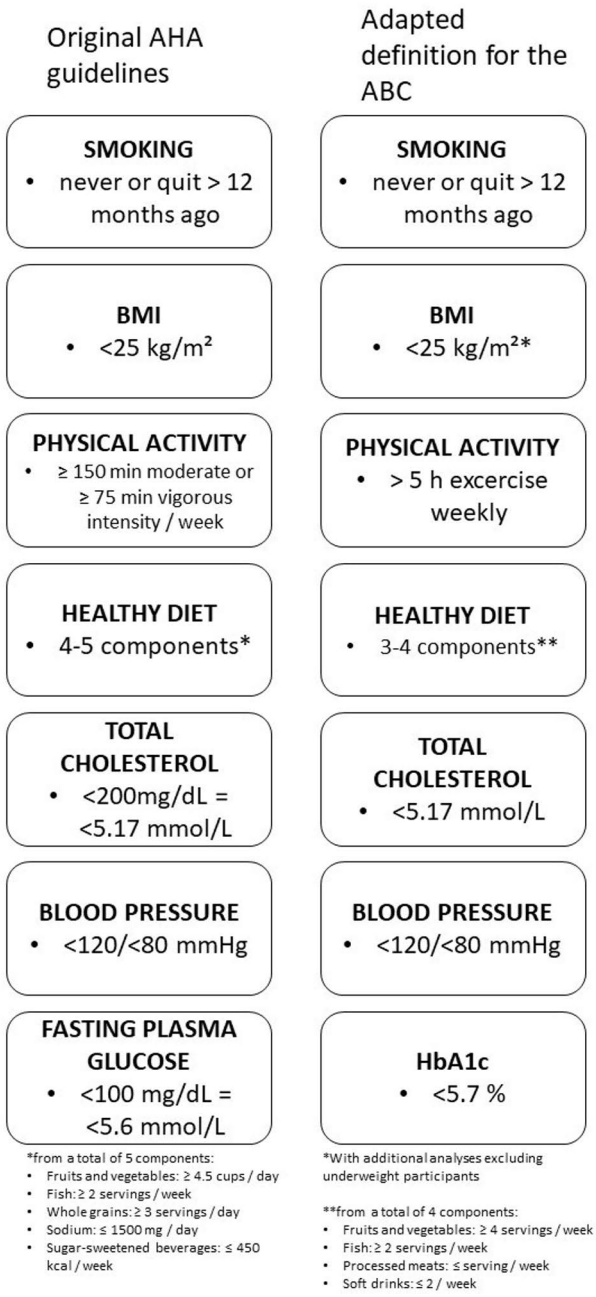

Figure 10. Components of ideal cardiovascular health as defined by the AHA and the adapted version for the ABC. The adapted version was used in **Study I**.

4.4 Categories for birth weight, areal disadvantage, remoteness, household size, maternal parity, and nutritional status

4.4.1 Birth weight categories

In **Study I**, birth weight was transformed into Z-scores and assigned into 5 categories: <-2, -2 to -1, -1 to +1, +1 to +2 and >+2.

In **Study IV**, an international growth reference, Intergrowth-21st, was used to classify the participants according to birth weight and gestational age. The categories were small for gestational age (SGA; <10th percentile of birthweight for gestational age), appropriate for gestational age (AGA; 10-90th percentile for gestational age), or large for gestational age (LGA; >90th percentile of birthweight for gestational age) according to sex. (Villar et al., 2014)

4.4.2 Areal disadvantage and remoteness

For areal disadvantage, the Indigenous Relative Socioeconomic Outcomes (IRSEO) index was used. It is a score calculated at the Indigenous Area level and it is based on 9 variables including 3 related to employment, 3 to education, 2 to housing and 1 to income using information derived from the 2011 Census of Population and Housing. Each area is assigned to one of 100 percentiles, 1 for the most advantaged and 100 for the most disadvantaged. (Biddle, 2013)

Based on their reported addresses at birth, the participants were assigned an IRSEO score. The scores were categorised into four groups: least disadvantage (range 13 to 37), mid-high disadvantage (range 43 to 79), high disadvantage (range 81 to 89) and highest disadvantage (range 91 to 99).

Based on the housing information in the questionnaires, families living in urban areas were classified as urban, and those in remote locations as not urban.

In addition to IRSEO, Accessibility and Remoteness Index of Australia (ARIA) values were calculated based on information obtained at Wave 2. ARIA is used to provide an estimate of remoteness as accessibility to service centres based on road distances. ARIA values are grouped into five categories:

1. Highly Accessible (ARIA score 0-1.84) - relatively unrestricted accessibility to a wide range of goods and services and opportunities for social interaction;
2. Accessible (ARIA score >1.84-3.51) - some restrictions to accessibility of some goods, services and opportunities for social interaction;

3. Moderately Accessible (ARIA score >3.51-5.80) - significantly restricted accessibility of goods, services and opportunities for social interaction;
4. Remote (ARIA score >5.80-9.08) - very restricted accessibility of goods, services and opportunities for social interaction;
5. Very Remote (ARIA score >9.08-12) - very little accessibility of goods, services and opportunities for social interaction. (Department of Health and Aged Care & Information and Research Branch, 2001)

As less than 4% of the participants belonged to groups 1 and 3, group 1 was combined with group 2 (Accessible) and group 3 with group 4 (Moderately accessible) for analyses.

4.4.3 Household size and parity of mother

Household size was assessed using a questionnaire to ask the participants how many persons slept in their house the night before. The number was put into four categories: 1-2, 3-5, 6-8 and 9 or more. Parity of the mother was recorded at birth and put into four categories: 1, 2-3, 4-5 and 6 or more.

4.4.4 Nutritional status

BMI and WHtR were used as markers of nutritional status.

4.4.4.1 Body mass index

Weight and height measurements were used to calculate BMI for the participants. BMI was calculated as weight divided by the square of height. (Keys et al., 1972)

BMI values were then categorized into the following categories: underweight (<18.5 kg/m²) normal weight (18.5-24.99 kg/m²), overweight (25-29.99 kg/m²) and obese (≥30 kg/m²). These BMI categories were used in **Study I** and **Study III.** For participants who were under 18 years of age at time of follow-up in **Study III**, age and sex specific cut-off points were used for categories of weight status (underweight, normal weight, overweight and obese) as defined by the International Obesity Task Force. (Cole, 2000; Cole et al., 2007)

4.4.4.2 Waist-to-Height ratio

Waist-to-Height ratio (WHtR), a tool for identifying abdominal obesity, is calculated as waist circumference in centimetres divided by height in centimetres. A cut-off value of 0.5 has been commonly used for screening for cardiometabolic risk.

(Ashwell et al., 2012) The same cut-off values can be applied to individuals irrespective of age, gender and ethnicity. (Browning et al., 2010; Khoury et al., 2013; Kuba et al., 2013). There is no consensus on a lower normal limit, but a value of less than 0.4 has been used. (Zhang et al., 2016) In **Study III**, WHtR was categorised as low (<0.4), normal (0.4-0.49) or high (≥0.5).

4.5 Data acquisition in the STRIP

In the STRIP study, data on gestational age and birth weight were collected from records of well-baby clinics. Established clinical laboratory methods were used to measure serum lipid levels (total and HDL-cholesterol, and triglycerides) from venous blood samples taken after an overnight fast (Niinikoski et al., 2012). LDL-cholesterol concentration was calculated according to the Friedewald formula. (Friedewald et al., 1972) Sitting blood pressure was measured two to four times at each visit using an oscillometric device observing appropriate rest time (15 min) and cuff sizes. (Niinikoski et al., 2009) In the 26-year follow-up, three blood pressure measurements were taken and the mean value was used for analyses. (Pahkala et al., 2020) Weight was measured to the nearest 0.1 kg with an electronic scale (S10, Soehnle, Murrhardt, Germany) and height to the nearest millimetre with a stadiometer. (Niinikoski et al., 2007) Waist circumference was measured midway between the iliac crest and the lowest rib at the midaxillary line to the nearest 0.5 cm with a flexible measuring tape (Nupponen et al., 2015). Ultrasonography was used to assess cIMT (Acuson Sequoia 512 mainframe; Acuson, Mountain View, CA). At age 19 years, the far wall of the distal common carotid arteries on both sides 1 to 2 cm from the bulb were scanned from anterior oblique and lateral angles using a 13-MHz linear-array transducer. (Laitinen et al., 2020) Two end-diastolic frames from both interrogation angles on both sides were analysed. Four measures were obtained in each image; the mean indicated average carotid IMT.

4.6 Statistical methods

Characteristics of study participants are reported as means with standard deviations (SDs) for continuous variables and as proportions for categorical variables. Attrition analyses compared baseline characteristics for participants and non-participants in each study using Student t tests for continuous variables and $\chi 2$ tests for categorical variables.

The statistical tests were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC). Statistical significance was inferred at a 2-tailed P-value < 0.05.

4.6.1 Study I

In **Study I**, the associations between socioeconomic factors (IRSEO, parity of mother, household size, and remoteness), birth weight, and maternal BMI and cardiovascular health in adulthood was examined. AHA guidelines were used to construct an index of ideal cardiovascular health with possible values between 0 and 7, one point for each metric. The index was applied to the ABC cohort in adulthood and for the total score, we excluded participants missing data on 1 or more of the metrics. Prevalences for the total score and all the individual health behaviours and factors were calculated. Associations between socioeconomic factors and ideal cardiovascular health metrics were analysed using multivariable logistic regression. First, univariate analyses adjusted for age and sex were performed. Then, multivariate models adjusted for age, gender, urban/not urban as well as categories for birthweight, maternal BMI, IRSEO score, household size and parity were analysed. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated for all variables. The sex difference regarding the total AHA score was assessed with a t-test and the sex differences for the individual ideal cardiovascular health metrics with $\chi 2$-tests.

4.6.2 Study II

Study II examined the associations between three socio-economic measures at birth (IRSEO, remoteness and parity of mother) and longitudinal levels in cardiovascular risk factors including BMI, blood pressure and lipid levels. The main analyses examined whether associations between socio-economic factors at birth and longitudinal data on cardiovascular risk factors were statistically significant. To assess these associations and to calculate point estimates (with 95% confidence intervals [CIs]) of risk factor levels for each study wave, linear mixed models were used to account for intra-subject correlation arising from the repeated measures. Models included one of the socio-economic variables (IRSEO score, residence, mother's parity at the birth of the participant) as the variable of interest, and sex, BMI (except in BMI models), and study wave as covariates. To provide adjusted means (with 95% CIs) for each follow-up wave, terms for interactions between the socio-economic variables and study wave were also included. Age was not included as a factor in the main analyses because it was collinear with study wave (variance inflation factor, 30); as age variability in each wave was limited, study wave was included as a factor in the models rather than continuous age. However, we also performed sensitivity analyses that included age as a factor. To assess the influence of missing data, data limited to participants who had participated in all three follow-ups was also analysed.

In addition to the variables measured at birth and used for the longitudinal analysis in **study II**, the impact of ARIA as an indicator of remoteness at Wave 2 on the longitudinal BMI, blood pressure and lipid values was assessed with linear mixed models.

4.6.3 Study III

In **Study III**, tracking of categories of nutritional status (BMI and WHtR) from childhood to adulthood was explored. Additionally, the association between socioeconomic status and remoteness at birth and later nutritional status was assessed. Participants who were pregnant at wave 3 and/or wave 4 were excluded from the analyses. Only participants who had height, weight and waist circumference recorded at all follow-ups were included (n=315). Overweight and obesity were combined into one category due to small numbers. $\chi 2$ tests were used to assess the association of weight status and categories of remoteness, socioeconomic status, maternal BMI and birth weight at all follow-ups separately. Tracking of nutritional status (underweight, overweight/obese and WHtR, low and high) was analysed using logistic regression and reported as OR of status being constant across time: status in childhood continuing into adolescence and adulthood and status in adolescence continuing into adulthood. Regression analyses were adjusted for age at follow-up, sex and time between compared follow-ups as well as IRSEO category that was used as a proxy for socioeconomic status. To assess the changes over time, Cochran's Q tests and McNemar's tests were used to analyse the differences in the proportions of nutritional status categories by sex over the course of the three follow-ups. To test for bias due to the large number of dropouts, sensitivity analyses were performed for tracking analyses for all plausible values for the whole cohort.

4.6.4 Study IV

The main analyses in **Study IV** examined the associations between birthweight category (SGA, AGA, LGA) and data on cardiovascular markers, including BMI, WHtR, blood pressure and lipid levels at three follow-ups, as well as cIMT at age 18 to 19 years. For this purpose, a repeated measures ANOVA was used. Compound symmetry was used as covariance structure. In each model, one of the cardiovascular markers was included as the outcome variable along with birth weight category (SGA, AGA or LGA), sex and assessment time point (study wave in the ABC and assessment age in STRIP). Finally, an interaction term between assessment time point and birth weight category was included in the model to calculate least square means (adjusted means) with 95% confidence intervals for each assessment time point and to yield group-wise comparisons between the birth weight categories.

Additionally, to assess potential mediation, all models were adjusted for BMI. Linear regression analysis adjusted for sex was used to analyse effect of birth weight on cIMT and differences in cIMT between the birth weight categories. Differences between the two cohorts and between the STRIP intervention and control groups in birth weight and gestational age were analysed using t-tests, while for birth weight category, the Cochran-Mantel-Haenszel method was applied.

5 Results

5.1 Characteristics of the participants

Characteristics at baseline of the participants are presented in **Table 1.**

Table 1. Baseline characteristics of the participants expressed as means with standard deviations or proportions (%).

		ABC	STRIP
Birth weight, g		3043 ± 600	3582 ± 501
Gestational age, wk		38.9 ± 1.5	39.4 ± 1.5
Birth weight category, %	SGA	22.4	2.4
	AGA	69.3	68.4
	LGA	8.3	29.2
Maternal BMI, kg/m^2		22.3 ± 4.1	
IRSEO, %	Least disadvantage	21.1	
	Mid-high disadvantage	5.3	
	High disadvantage	35.2	
	Highest disadvantage	28.4	
Residence, %	Urban	17.7	
	Remote	82.3	
Mother's parity, %	1 child	33.5	
	2-3 children	39.8	
	4-5 children	19.3	
	≥ 6 children	7.5	

5.1.1 Study I

The total AHA score with no missing variables was available for 204 participants, representing 29.7% of the study population. Of the studied baseline socioeconomic characteristics, females had a larger household size. Ten individuals used glucose lowering medication and were not considered having ideal glucose status. Eight individuals had blood pressure lowering medication and were considered having non-ideal blood pressure status. The attrition analyses revealed that those

participating in the follow-up at a mean age of 25.4 years were more often females and had higher IRSEO scores, compared to non-participants.

5.1.2 Study II

There was some mobility from childhood to adulthood between urban and remote areas: at wave 4, 8.7% of participants who had lived in remote areas in childhood had moved to urban areas, and 19% of participants who had lived in urban areas had moved to remote locations.

Attrition analyses showed that among non-participants, a larger proportion was male at waves 3 and 4, lived in less disadvantaged areas and lived in urban areas.

5.1.3 Study III

There was complete data (height, weight, and waist circumference) at all follow-ups available for 315 participants. Mean values with SDs for the anthropometric measurements are shown in **Table 2**. There were no differences in sex, birth weight, and maternal BMI between participants and non-participants. In line, there were no differences between participants and non-participants in BMI or WHtR at any follow-up (for BMI: P=0.48 for waves 2 and 3, P=0.47 for wave 4; for WHtR: P=0.5, 0.46 and 0.52 respectively). The participants were more often from remote and more disadvantaged areas compared with non-participants.

Table 2. Characteristics (mean ± SD) at waves 2-4 for participants in **Study III**.

	Wave 2		**Wave 3**		**Wave 4**	
	Male	Female	Male	Female	Male	Female
Age, years	11.1±1.1	10.8±1.1	17.9±1.1	17.7±1.1	25.4±1.1	25.2±1.2
Weight, kg	34.3±11.5	32.5±11.5	64.1±20.2	53.7±13.0	71.1±21.2	60.6±16.0
Height, cm	143.1±10.1	143.0±10.5	173.3±6.9	161.3±5.2	174.3±7.0	161.4±5.6
BMI, kg/m²	16.4±3.5	16.8±3.4	21.2±5.6	20.7±4.9	23.3±6.0	23.3±6.2
Waist cirumference, cm	63.8±9.5	63.9±9.0	78.8±14.5	77.7±12.6	85.7±16.0	86.2±15.1
WHtR	0.45±0.05	0.45±0.05	0.45±0.08	0.48±0.08	0.49±0.09	0.54±0.1

5.1.4 Study IV

Mean gestational age was lower in the ABC compared to the STRIP participants (38.9±1.5 weeks vs. 39.4±1.5 weeks, P<0.0001) (**Table 1**). Mean birth weight was also lower in the ABC participants (3043±600 grams vs. 3582±502 grams, P<0.0001). Furthermore, there were more SGA babies (22.4% vs 2.4%) and less LGA babies (9.1% vs. 29.2%) in the ABC than in the STRIP cohort (P<0.0001).

5.2 AHA indicators of ideal cardiovascular health

The mean ideal cardiovascular score was 4.7 ± 1.3 for males and 3.6 ± 1.5 for females (P<0.0001). The distribution of the total AHA score is presented in **Figure 11** and the prevalence of the seven ideal cardiovascular health metrics is presented in **Figure 12**. Only five participants met all seven ideal cardiovascular health metrics and one person met none of the metrics. The most common metrics met were ideal glucose (83.6%), cholesterol (74.9%) and blood pressure (73.2%) levels. The least common ideal metrics achieved were related to health behaviours: non-smoking, ideal diet and ideal levels of physical activity were met by less than half of the cohort (28.8%, 44.1% and 49.7%, respectively). Sixty-two percent had an ideal BMI when defining BMI as < 25. When healthy BMI was defined between 18.5 and 25 (i.e. dismissing underweight participants from the analyses), only 41% had an ideal BMI.

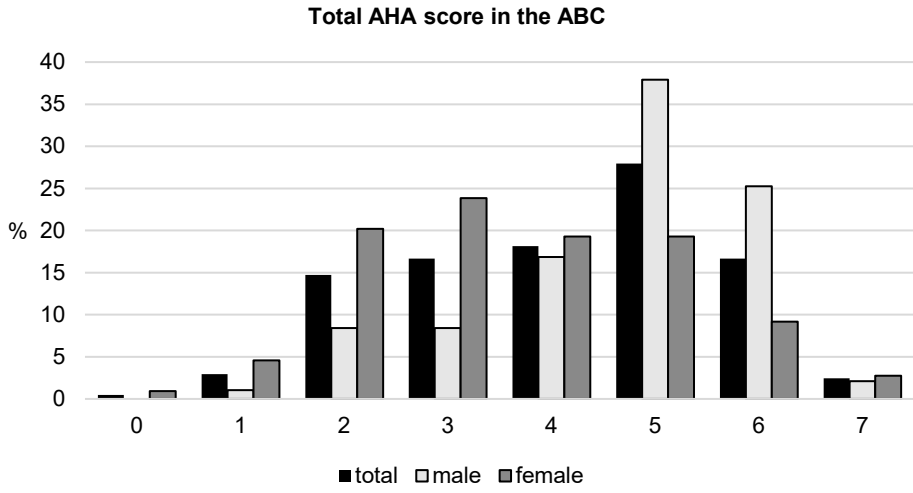

Figure 11. Distribution of the ideal cardiovascular health score in the cohort. Values are presented as percentages for the total cohort and for males and females separately.

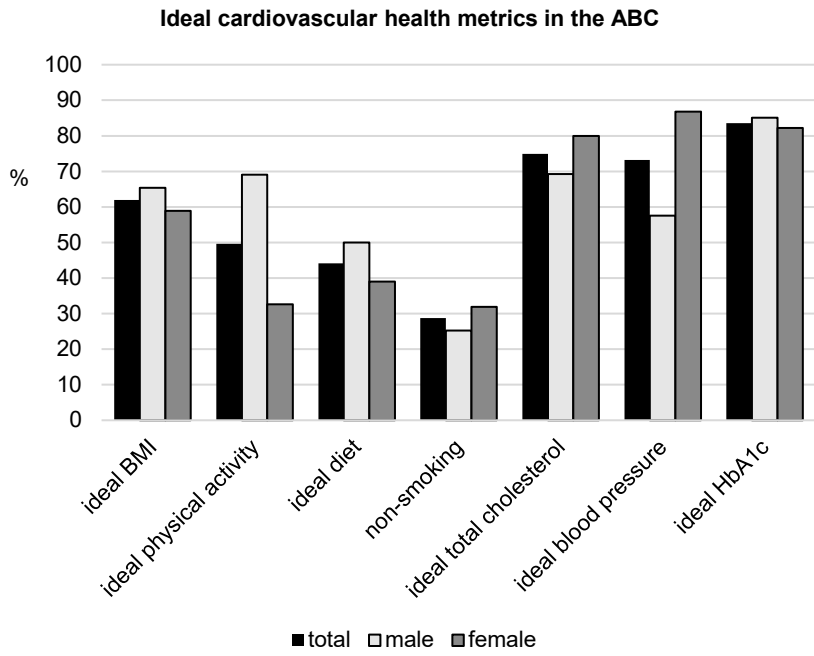

Figure 12. Prevalences for participants meeting individual health metrics. Values are presented in percentages for the total cohort, and for males and females separately.

Significant sex differences were seen in ideal physical activity (69.1% vs. 32.6%, P<0.0001), ideal blood pressure (56.8% vs. 86.0%, P<0.0001) and ideal cholesterol (69.2% vs. 80.0%, P=0.01). There were no sex differences in ideal glucose, diet, BMI or non-smoking. When analysing only participants with a BMI between 18.5 and 25, there was a significant difference between the sexes for ideal BMI: 48.1% of males and 35.3% of females (P=0.005) met the target. When analysing only those with a healthy BMI, the mean total AHA score was 4.5 for males and 3.4 for females (P<0.0001).

5.3 Socioeconomic variables and ideal cardiovascular health in adulthood

In univariate analyses sex, areal disadvantage, urban residence, and household size were associated with most of the ideal cardiovascular health metrics. The results from the multivariate analyses are presented in **Table 3**. After adjusting for age, gender, urban/not urban as well as categories for birthweight, maternal BMI, IRSEO score, household size and parity, females were less likely to report ideal levels of physical activity (OR 0.19, 95% CI [0.11-0.33]) but more likely to have ideal blood

pressure (OR 5.51, [2.84-10.71]). No significant associations were found between birth weight and the seven ideal cardiovascular health metrics. Areal disadvantage was associated with ideal physical activity and ideal blood pressure: participants from the least disadvantaged areas had significantly lower odds for presenting ideal levels than participants from more disadvantaged areas (OR 0.13 [0.02-0.76] for physical activity and OR 0.05 [0.01-0.32] for blood pressure). Participants from urban areas had lower odds for having ideal blood pressure (OR 0.11 [0.02-0.76]) than participants from non-urban areas.

Being born to a family with more than six children was directly associated with ideal BMI levels (OR 3.75 [1.10-12.80]). When disregarding underweight participants in the analyses, this association became non-significant (OR 1.81 [0.70-4.72]). Household size was associated with ideal smoking status: participants who slept in houses with more than nine people had lower odds of being non-smokers as adults (OR 0.22 [0.06-0.76]). Compared to children of normal weight mothers, offspring of underweight mothers (BMI<18.5 kg/m^2) had higher odds for having ideal BMI in adulthood (OR 2.93 [1.19-7.21]). When leaving underweight participants out of the analyses, this association was non-significant (OR 1.07 [0.51-2.03]). Children of obese mothers (BMI>30 kg/m^2) had lower odds for having ideal blood pressure (OR 0.13 [0.03-0.62]) and cholesterol levels (OR 0.13 [0.03-0.58]) in adulthood than children of normal weight mothers.

Table 3. Multivariate analyses between variables at birth and AHA index in adulthood. *P < 0.05, ** P < 0.01 ***P < 0.0001. ǂ Referent category. ǂ Adjusted for age, sex, urban/remote, categories for birthweight, areal disadvantage, household size, maternal BMI and parity of mother at the time of birth of the participant. Definitions: Least disadvantage, IRSEO score 13-37; mid-high disadvantage, IRSEO score 43-79; high disadvantage, IRSEO score 81-89; highest disadvantage, IRSEO score 91-99; number of children, number of children of mother (dead or alive) at birth of participant. Sample size was not sufficient to make logistic regression analysis between HbA1c and household size.

Predictor	Ideal BMI		Ideal physical activity		Ideal diet		Non-smoking		Ideal total cholesterol		Ideal blood pressure		Ideal Hba1c	
	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)	n(%)	AORǂ (95% CI)
Sex														
Male ǂ	140 (65.4)	1.00	145 (69.1)	1.00	53 (50.0)	1.00	49 (25.3)	1.00	135 (69.2)	1.00	117 (56.8)	1.00	164 (84.1)	1.00
Female	142 (58.9)	0.66 (0.37-1.15)	78 (32.6)	0.19 (0.11-0.33)***	48 (39.0)	0.53 (0.26-1.09)	68 (31.9)	1.41 (0.76-2.61)	172 (80.0)	1.78 (0.95-3.36)	202 (86.0)	5.51 (2.84-10.71)***	175 (81.4)	0.52 (0.26-1.04)
Birthweight (Z-score)														
<-2	23 (69.7)	0.89 (0.30-2.64)	19 (55.9)	1.54 (0.53-4.45)	9 (47.4)	1.53 (0.36-6.47)	11 (34.4)	1.76 (0.57-5.37)	23 (74.2)	0.91 (0.27-3.15)	24 (77.4)	0.1 (0.23-2.90)	26 (83.9)	1.43 (0.28-7.36)
-2 to -1	68 (76.4)	1.63 (0.77-3.45)	43 (48.3)	1.17 (0.59-2.29)	19 (38.0)	0.72 (0.29-1.78)	20 (25.6)	1.09 (0.50-2.37)	62 (78.5)	1.07 (0.47-2.48)	68 (77.3)	0.93 (0.41-2.10)	65 (82.3)	0.87 (0.37-2.07)
-1 to +1 ǂ	146 (57.9)	1.00	115 (46.6)	1.00	52 (44.8)	1.00	65 (28.9)	1.00	173 (75.6)	1.00	184 (75.7)	1.00	190 (83.3)	1.00
+1 to +2	24 (58.5)	0.92 (0.37-2.31)	24 (60.0)	0.81 (0.33-2.03)	12 (48.0)	1.66 (0.53-5.14)	7 (19.4)	0.53 (0.15-1.86)	27 (69.2)	0.91 (0.33-2.52)	20 (51.3)	0.50 (0.19-1.32)	32 (82.1)	0.94 (0.30-2.97)
>+2	6 (46.2)	0.54 (0.12-2.46)	5 (38.5)	0.54 (0.12-2.31)	2 (40.0)	-	2 (18.2)	0.43 (0.07-2.56)	6 (54.6)	0.78 (0.14-4.28)	6 (50.0)	0.64 (0.12-3.41)	8 (72.7)	0.30 (0.05-1.80)
Areal social disadvantage														
Least disadvantage	30 (37.5)	0.09 (0.02-0.54)	27 (34.6)	0.13 (0.02-0.76)*	21 (65.6)	-	35 (44.9)	0.86 (0.18-4.18)	37 (58.7)	0.23 (0.05-1.02)	47 (60.3)	0.05 (0.01-0.32)*	56 (88.9)	0.58 (0.10-3.48)
Mid-high disadvantage	11 (45.8)	0.18 (0.03-0.44)	10 (41.7)	0.78 (0.23-2.67)	4 (40.0)	1.46 (0.25-8.58)	7 (38.9)	2.10 (0.53-8.40)	13 (61.9)	0.70 (0.17-2.96)	12 (54.6)	0.12 (0.03-0.49)	15 (71.4)	0.35 (0.08-1.53)
High disadvantage	98 (60.1)	0.48 (0.25-0.90)	80 (49.7)	0.86 (0.47-1.55)	37 (46.8)	2.24 (1.05-4.80)	33 (22.6)	0.74 (0.36-1.51)	105 (73.4)	0.90 (0.44-1.87)	107 (69.0)	0.38 (0.18-0.79)	125 (86.8)	1.86 (0.85-4.07)
Highest disadvantage ǂ	143 (76.06)	1.00	106 (57.0)	1.00	39 (36.1)	1.00	42 (25.5)	1.00	152 (83.1)	1.00	153 (82.3)	1.00	143 (78.6)	1.00
Urban residence														
Urban ǂ	27 (40.9)	1.00	24 (37.5)	1.00	18 (64.3)	1.00	31 (47.7)	1.00	32 (62.8)	1.00	44 (68.8)	1.00	46 (90.2)	1.00
Not urban	255 (65.6)	0.18 (0.03-1.20)	199 (51.7)	0.69 (0.10-4.84)	83 (41.3)	-	86 (25.2)	0.65 (0.11-3.74)	275 (76.6)	0.45 (0.08-2.62)	275 (72.9)	0.11 (0.02-0.76)*	293 (81.6)	0.27 (0.03-2.96)
Number of children														
1 ǂ	101 (64.3)	1.00	78 (50.3)	1.00	38 (50.0)	1.00	42 (30.7)	1.00	103 (72.5)	1.00	111 (75.0)	1.00	118 (82.5)	1.00
2 or 3	92 (55.1)	1.00 (0.54-1.88)	84 (50.91)	0.95 (0.52-1.75)	38 (42.7)	0.92 (0.40-2.10)	43 (28.9)	0.79 (0.39-1.58)	112 (75.2)	1.83 (0.88-3.82)	114 (69.9)	1.39 (0.68-2.86)	114 (77.0)	0.56 (0.26-1.21)
4 or 5	62 (66.7)	1.37 (0.62-3.05)	47 (51.7)	0.98 (0.46-2.11)	18 (40.9)	0.80 (0.28-2.28)	26 (29.9)	0.92 (0.40-2.13)	67 (79.8)	1.74 (0.70-4.33)	65 (70.7)	1.30 (0.53-3.20)	75 (89.3)	1.77 (0.60-5.23)
6 or more	27 (71.1)	3.75 (1.10-12.80)*	14 (36.8)	0.51 (0.18-1.45)	7 (35.0)	0.38 (0.09-1.62)	6 (17.7)	0.11 (0.01-0.94)	25 (71.4)	1.65 (0.49-5.48)	29 (76.3)	2.47 (0.69-8.83)	32 (91.4)	1.54 (0.35-6.75)
Household size														
1-2	23 (63.9)	1.00	18 (51.4)	1.00	10 (58.8)	1.00	16 (48.5)	1.00	23 (74.2)	1.00	23 (67.7)	1.00	30 (96.8)	1.00
3-5	92 (60.5)	1.05 (0.35-3.16)	76 (50.7)	0.58 (0.20-1.74)	38 (49.4)	1.15 (0.30-4.49)	49 (35.0)	0.68 (0.24-1.98)	93 (71.5)	0.62 (0.17-2.18)	98 (67.6)	0.53 (0.16-1.78)	115 (88.5)	-
6-8	84 (62.7)	1.87 (0.61-5.74)	69 (52.7)	0.61 (0.20-1.85)	30 (44.1)	0.72 (0.18-2.83)	29 (24.8)	0.35 (0.11-1.07)	100 (80.0)	1.04 (0.29-3.82)	87 (66.9)	0.58 (0.17-2.01)	95 (76.0)	-
9 or more	56 (63.6)	0.96 (0.29-3.20)	45 (51.1)	0.71 (0.22-2.28)	20 (32.3)	0.67 (0.15-2.91)	12 (15.8)	0.22 (0.06-0.76)**	67 (79.8)	0.88 (0.22-3.60)	77 (87.5)	1.24 (0.30-5.10)	64 (78.1)	-
Maternal BMI														
Underweight	44 (78.6)	2.93 (1.19-7.21)**	26 (47.3)	0.83 (0.40-1.75)	9 (29.0)	0.64 (0.23-1.75)	18 (34.6)	1.45 (0.65-3.27)	38 (79.2)	1.88 (0.68-5.21)	42 (77.8)	0.79 (0.32-1.94)	42 (87.5)	1.96 (0.66-5.84)

5.4 Socioeconomic factors and longitudinal BMI, blood pressure and lipid levels

The association between socioeconomic factors at birth and longitudinal BMI, blood pressure and lipid levels, was examined in **Study II.**

5.4.1 BMI

IRSEO (P<0.001), remoteness (P<0.0001) and maternal parity (P=0.039) were all associated with longitudinal BMI levels. As shown in **Figure 13**, participants from most disadvantaged and remote areas, as well as those with a higher maternal parity, tended to have the lowest BMI values in the follow-ups.

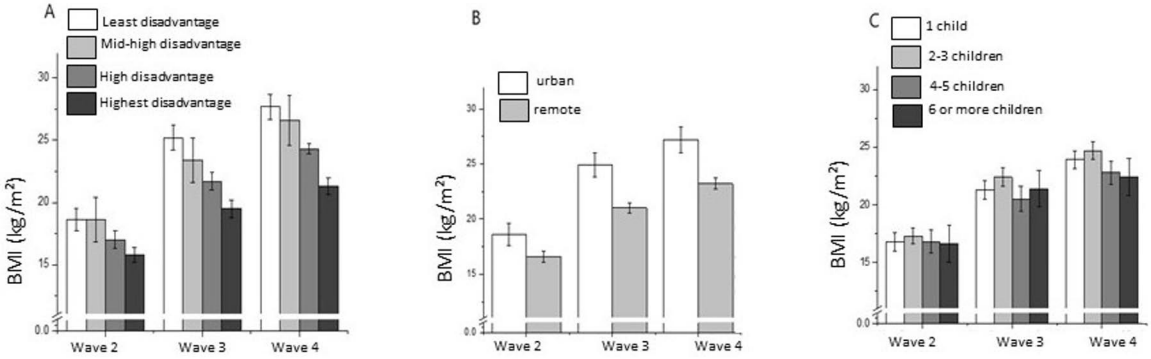

Figure 13. Relationship between socioeconomic variables and body mass index in three prospective follow-ups. A. IRSEO indicates areal disadvantage at birth; B. Urban or remote residence at birth and C. Mother's parity at birth. Bars indicate adjusted means and brackets 95% confidence intervals. Linear mixed models also included sex and study wave. Interactions: wave*IRSEO, P < 0.001; wave*remoteness, P < 0.001; wave*parity, P = 0.036.

5.4.2 Blood pressure

Figure 14 shows the associations between socioeconomic variables at birth and later SBP levels. Of the three socioeconomic variables examined, only IRSEO showed a significant association with SBP (P=0.024), while remoteness (P=0.32) and parity (P=0.54) did not. There were no associations between the socioeconomic variables and DBP (IRSEO, P=0.07; remoteness, P=0.93; parity, P=0.23).

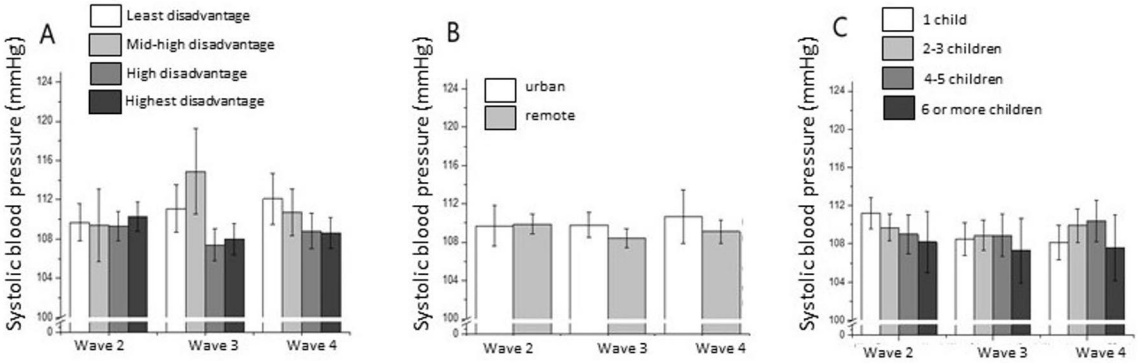

Figure 14. Relationship between socioeconomic variables and SBP in three prospective follow-ups. A. IRSEO indicating areal disadvantage at birth; B. Urban or remote residence at birth and C. Mother's parity at birth. Bars indicate least square means and brackets 95% confidence intervals. Linear mixed models also included sex, study wave, and body mass index as variables. Interactions: wave*IRSEO, P = 0.022; wave*remoteness, P = 0.46; wave*parity, P = 0.17.

5.4.3 Lipid levels

The relationships between the socioeconomic variables and LDL-cholesterol, HDL-cholesterol and triglyceride levels are depicted in **Figure 15**.

5.4.3.1 LDL-cholesterol

LDL-cholesterol was associated with IRSEO (P=0.010), but not with remoteness (P=0.21) or parity (P=0.30). The lowest LDL-cholesterol levels were seen in the most disadvantaged areas.

5.4.3.2 HDL-cholesterol

HDL-cholesterol was associated with IRSEO (P<0.001) and remoteness (P<0.001) but not with parity (P=0.53). The lowest HDL-levels were found in remote and more disadvantaged locations.

5.4.3.3 Triglycerides

Triglyceride levels were linked with remoteness (P=0.043), but not with IRSEO (P=0.42) or parity (P=0.25). Triglyceride levels were higher in the remote locations and lower in urban areas.

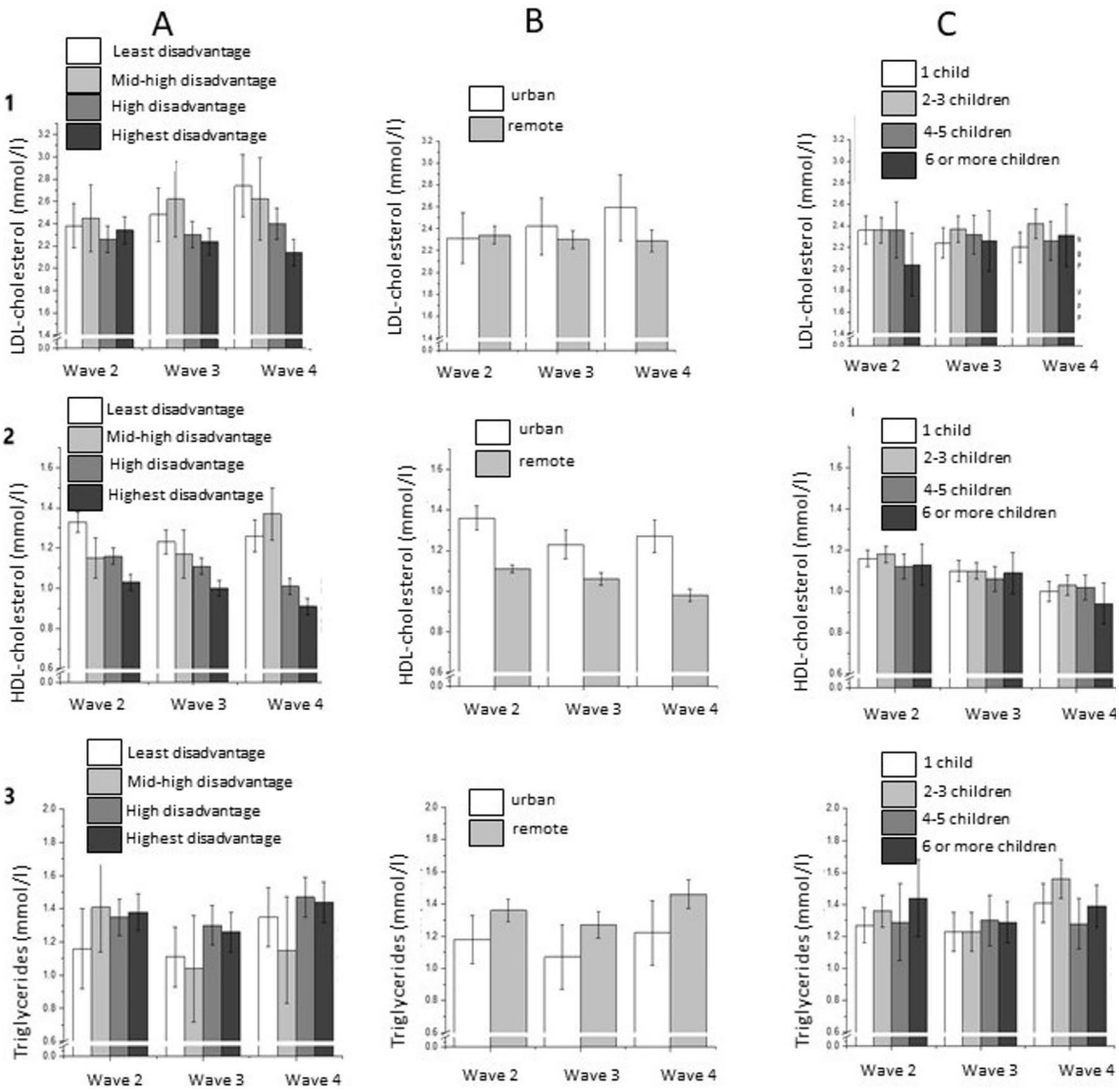

Figure 15. Association between socioeconomic variables and levels of LDL-cholesterol (1), HDL-cholesterol (2) and triglycerides (3) in three prospective follow-ups. A. IRSEO indicating areal disadvantage at birth; B. Urban or remote residence at birth and C. Mother's parity at birth. Bars indicate adjusted means and brackets 95% confidence intervals. Linear mixed models also included sex, study wave, and body mass index. Interactions: LDL: wave*IRSEO, P < 0.001; wave*remoteness, P = 0.13; wave*parity, P = 0.17; HDL: wave*IRSEO, P < 0.001; wave*remoteness, P = 0.014; wave*parity, P = 0.60; and triglycerides: wave*IRSEO, P = 0.36; wave*remoteness, P = 0.85; wave*parity, P = 0.022.

5.4.4 Impact of ARIA

ARIA, measured at Wave 2, as an indicator of remoteness was associated with several cardiovascular health markers in the longitudinal analyses. Participants in more remote areas had lower BMI, SBP, LDL-cholesterol, and HDL-cholesterol concentrations, compared with those from less remote regions. (**Figure 16**)

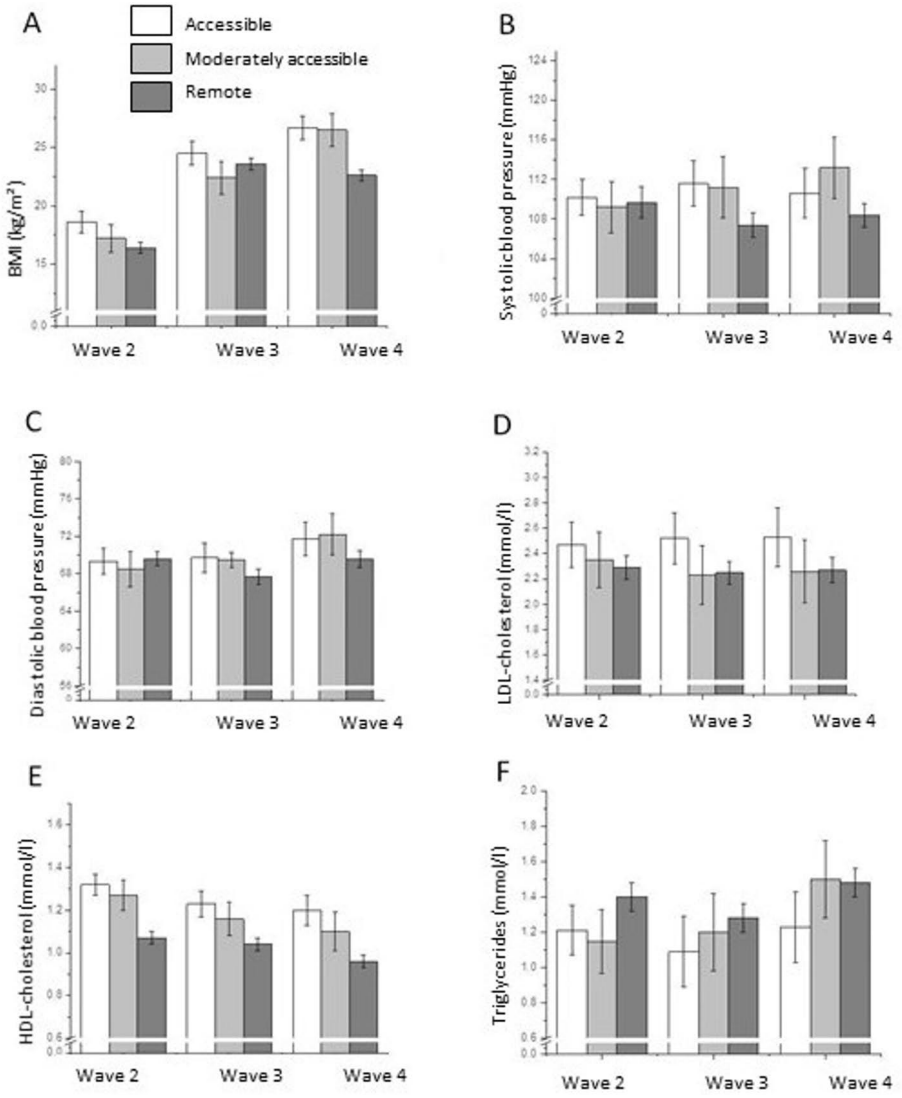

Figure 16. Relationship between ARIA and BMI (A), SBP (B), DBP (C), LDL-cholesterol (D), HDL-cholesterol (E) and triglycerides (F) in three prospective follow-ups. Linear mixed models also included sex and study wave as variables.

5.5 Nutritional status

In **Study III**, the focus was on nutritional status with WHtR and BMI used as markers of interest. First, prevalence of the BMI and WHtR categories were determined and the influence of IRSEO, remoteness, maternal BMI and birth weight on these categories was assessed. Secondly, tracking of categories of nutritional status from childhood to adulthood was examined.

5.5.1 Nutritional status categories in the cohort

Prevalence of weight categories according to BMI according to sex are presented in **Figure 17**. High rates of underweight were seen at all three follow-ups: 38.1% at wave 2, 38.1% at wave 3 and 23.5% at wave 4. Overweight and obesity increased over time: for overweight; 8.9% at wave 2, 12.1% at wave 3, and 22.9% at wave 4, and for obesity, 2.9%, 6.4% and 11.8%, respectively.

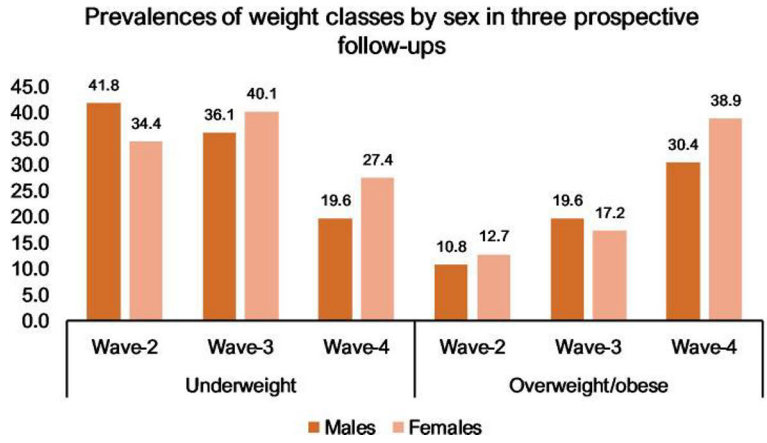

Figure 17. Percentages of underweight and overweight/obese participants by sex. For classification, age and sex specific cut-off points were used for participants under 18 years of age at follow-up. For participants aged 18 years and over, underweight was classified as BMI <18.5 kg/m^2; normal weight as 18.5–24.99 kg/m^2; overweight as 25–29.99 kg/m^2; and obesity as ≥30 kg/m^2.

There were no significant differences between the sexes in the prevalence of underweight, overweight or obesity. The differences in weight status over the course of the three follow-ups were significant with rates of underweight decreasing and rates of overweight/obesity rising ($P<0.0001$ for underweight and overweight/obesity for both sexes). There was no difference in the rate of underweight between wave 2 and wave 3 ($P=0.56$ for men and $P=0.76$ for women) but a significant difference in the prevalence of underweight between wave 2 and

wave 4 (P<0.0001 for both sexes) as well as between wave 3 and wave 4 (P<0.0001 for both sexes) was found. For the prevalence of overweight/obesity, there was a difference between wave 2 and wave 3 for male participants but not for women (P=0.002 for men and P=0.16 for women). Between wave 2 and wave 4, the difference was statistically significant for both sexes (P<0.0001) as well as between wave 3 and wave 4 (P=0.0007 for men and P<0.0001 for women).

Prevalence for WHtR classes (low/high) are presented in **Figure 18**. There were no differences between the sexes at wave 2. In later follow-ups, male participants more often had a low WHtR (22.2% vs 10.2% at wave 3 (p=0.004) and 13.9% vs 5.1% at wave 4 (p=0.008)), while female participants more often had a high WHtR (34.4% vs 20.9% at wave 3 (p=0.007) and 58.6% vs 36.1% at wave 4 (p<0.0001)). The changes in WHtR over the course of the three follow-ups were significant with rates of low WHtR decreasing and rates of high WHtR rising (p=0.002 for men and p=0.03 for women for low WHtR and p<0.0001 for both sexes for high WHtR). Between wave 2 and wave 3, there was a statistically significant difference between the rates for low WHtR for men (p=0.003) but not for women (p=0.4). Between wave 2 and wave 4, the difference was significant for women (p=0.01) but not for men (p=0.4). For high WHtR, the difference was significant between wave 2 and wave 3 (p=0.002 for men and p<0.0001 for women) and between wave 2 and wave 4 (p<0.0001 for both sexes).

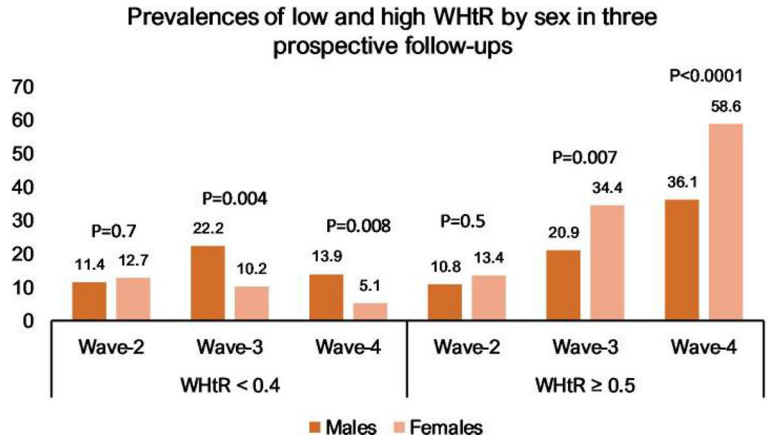

Figure 18. Prevalence of low and high waist-to-height ratio (WHtR) at three time points according to sex. P values were calculated with $\chi 2$ tests and represent differences between sexes. Values are in percentages.

5.5.2 Influence of areal disadvantage, remoteness, maternal BMI and birth weight on weight class

The associations between weight class and remoteness, maternal BMI, IRSEO and birth weight are presented in **Figure 19.** Urban participants were more likely to be overweight/obese and less likely to be underweight than remote participants in all follow-ups. Areal socioeconomic disadvantage, i.e. IRSEO, was associated with weight class in all follow-ups: participants from more disadvantaged areas were more often underweight and less often overweight/obese than participants from less disadvantaged areas. Maternal weight status was also associated with offspring weight status in all follow-ups with children of underweight mothers being more often underweight and children of overweight and obese mothers more often presenting with overweight and obesity. Birth weight was also associated with later weight status: smaller babies were more often underweight and less often overweight or obese in all follow-ups. The association was significant in all follow-ups except for overweight status at wave 2 (P=0.06) and underweight status at wave 3 (P=0.06).

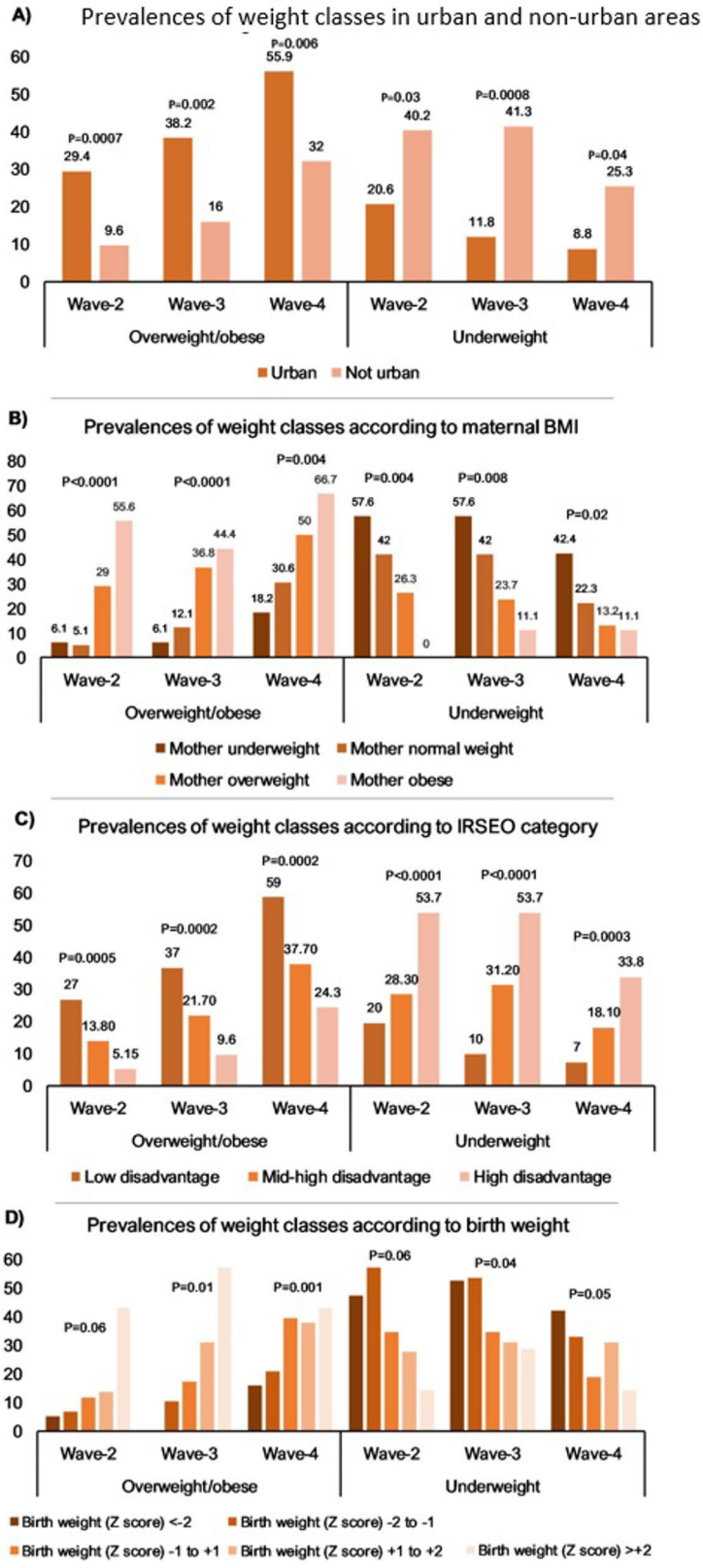

Figure 19. Prevalence of overweight/obesity and underweight in participants according to urban residence (A), maternal BMI (B), areal disadvantage (C) and birth weight (D). $\chi 2$ tests were used to assess association between weight status and presented weight classes.

5.5.3 Tracking of BMI category

Analyses of tracking of weight status according to BMI categories are presented in **Table 4**. Tracking was significant between age groups for all BMI categories, and sex was not a significant confounder in any of the analyses. Of the participants who were overweight/obese at wave 2, 67.6% remained in the same weight status category at wave 3 (OR 12.9, 95% CI [5.7-29.4]) and 83.8% at wave 4 (OR 10.9, [4.3-27.8]). Of the participants who were overweight/obese at wave 3, 86.2% continued to be overweight/obese at wave 4 (OR 21.3, [9.1-49.9]). Conversely, of the participants who were overweight/obese at wave 4, only 28.4% had been overweight/obese already at wave 2, and 45.9% at wave 3. Underweight status also showed significant tracking throughout the follow-ups. Of the participants who were underweight at wave 2, 76.7% were underweight at wave 3 (OR 20.5, [10.9-38.7]) and 46.7% remained underweight at wave 4 (OR 8.8, [4.6-17.0]). Of underweight participants at wave 3, 83.8% were underweight at wave 4 (OR 15.9, [7.6-32.9]).

Table 4. Tracking of weight classes from childhood and adolescence to adolescence and adulthood. OR adjusted for age (years) at earlier follow-up, time (years) between follow-ups and sex.

Weight status in childhood	Underweight in adolescence	Overweight / obese in adolescence	Underweight in adulthood	Overweight / obese in adulthood
Underweight	77%, OR 20.5	0%	47%, OR 8.8	8%, OR 0.1
Normal weight	18%, OR 0.2	21%, OR 1.3	11%, OR 0.2	43%, OR 2.1
Overweight /obese	0%	68%, OR 12.9	3%, OR 0.1	84%, OR 10.9

5.5.4 Tracking of WHtR category

There was significant tracking of both low and high WHtR in all follow-ups. Sex was a significant confounder in most analyses with tracking of low WHtR being more likely for male participants and tracking of high WHtR more likely for female participants. Of the participants who had a low WHtR at wave 2, 44.7% remained in the same category at wave 3 (OR 8.5, [3.6-20.2]) and 23.7% at wave 4 (OR 4.7, [1.8-12.5]), while 45.1% of participants with a low WHtR at wave 3 had a low WHtR at wave 4 (OR 21.3, [8.0-56.7]). Of the participants with a high WHtR at wave 2, 71.1% had a high WHtR at wave 3 (OR 8.3, [3.8-18.3]) and 94.7% at wave 4 (OR 25.0, [5.8-108.1]). Of the participants with a high WHtR at wave 3, 85.1% remained in the same category at wave 4 (OR 10.3, [5.3-20.1]). Of the participants who had a high WHtR in adulthood, 24.2% had a high WHtR already in childhood and 49.7% in adolescence. (**Study III**)

5.6 Birth weight category and later cardiovascular health

In **Study IV**, the influence of birth weight category (SGA, AGA, LGA) on cardiovascular health factors was examined both in the ABC and the STRIP cohorts.

5.6.1 Birth weight category and nutritional status

The associations between birth weight category and later nutritional status are presented in **Figure 20**. Birth weight category was associated with BMI in a step-wise manner from childhood to adulthood in both cohorts (P<0.0001 for ABC and P=0.003 for STRIP) with higher BMI found for higher birth weight category. Group-wise comparisons of the birth weight categories showed that participants who were LGA had higher BMI compared to the SGA participants at all follow-ups in both the ABC (age 11: P=0.0004, age 18: P<0.0001, age 25: P=0.0002) and the STRIP study (age 11: P=0.018, age 18: P=0.016 and age 26: P=0.003). AGA participants in the ABC study had higher BMI than the SGA participants at ages 18 (P=0.010) and 25 (P=0.0005), while in the STRIP study, higher BMI in the AGA participants compared to the SGA participants was found only at age 26 (P=0.024). In the ABC study, LGA participants had higher BMI than the AGA participants at ages 11 (P=0.0027) and 18 (P=0.0002), and in the STRIP at ages 18 (P=0.025) and 26 (P=0.022) (**Figure 20**).

Similar to BMI, birth weight category was associated in a step-wise manner with WHtR in the ABC (P=0.004) with higher WHtR levels found for higher birth weight category. This association persisted after adjusting for BMI (P=0.004). In contrast, there was no association between birth weight category and WHtR in the STRIP study (P=0.33).

In the ABC, group-wise comparisons between the birth weight categories showed that WHtR was higher in the LGA participants compared to the SGA participants at ages 11 (P=0.007) and 18 (P=0.0007). Similarly, the LGA participants had higher WHtR than the AGA participants at ages 11 (P=0.030) and 18 (P=0.006). There were no differences in WHtR between the SGA and AGA participants at any studied age and no differences between any of the birth weight categories were found at age 25. (**Figure 20**).

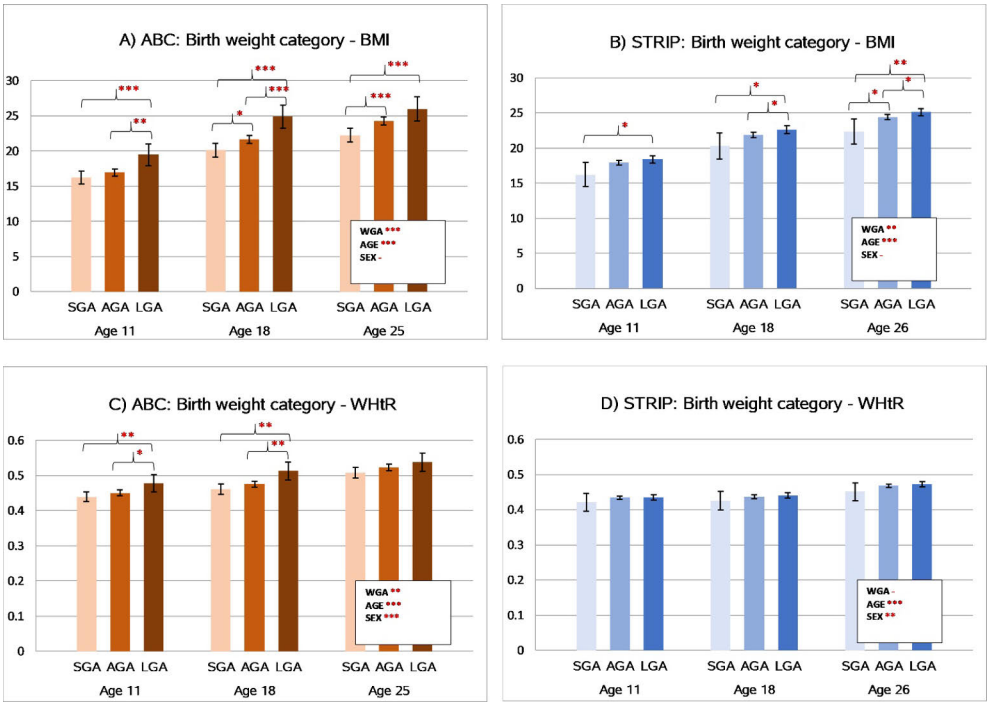

Figure 20. Associations between birthweight category and nutritional status in the ABC and STRIP cohorts. Bars indicate adjusted means with error bars for 95% confidence intervals. The values in the boxes refer to the longitudinal analyses with WGA referring to birth weight category and AGE to assessment time point. Significant intracohortal differences between the birthweight categories at each follow-up are indicated with brackets. N indicates number of participants. Unit for BMI is kg/m2. BMI=Body Mass Index; WHtR=Waist-to-Height-Ratio; SGA=Small for Gestational Age; AGA=Appropriate for Gestational Age; LGA=Large for Gestational Age; WGA=Weight for Gestational Age category. Asterisks indicate statistical significance with P < 0.05 *, P < 0.01** and P < 0.001 ***

5.6.2 Birth weight category and lipid levels

The associations between birth weight category and serum lipid levels are summarized in **Figure 21**. The longitudinal analyses revealed that there were no associations between birthweight category and total, HDL-, LDL-cholesterol, or triglyceride levels in the cohorts. Group-wise comparisons between the birth weight categories indicated that in the ABC at age 11, the LGA participants had higher triglyceride levels compared to SGA (P=0.013) and AGA (P=0.041) participants. These associations did not persist after adjusting for BMI.

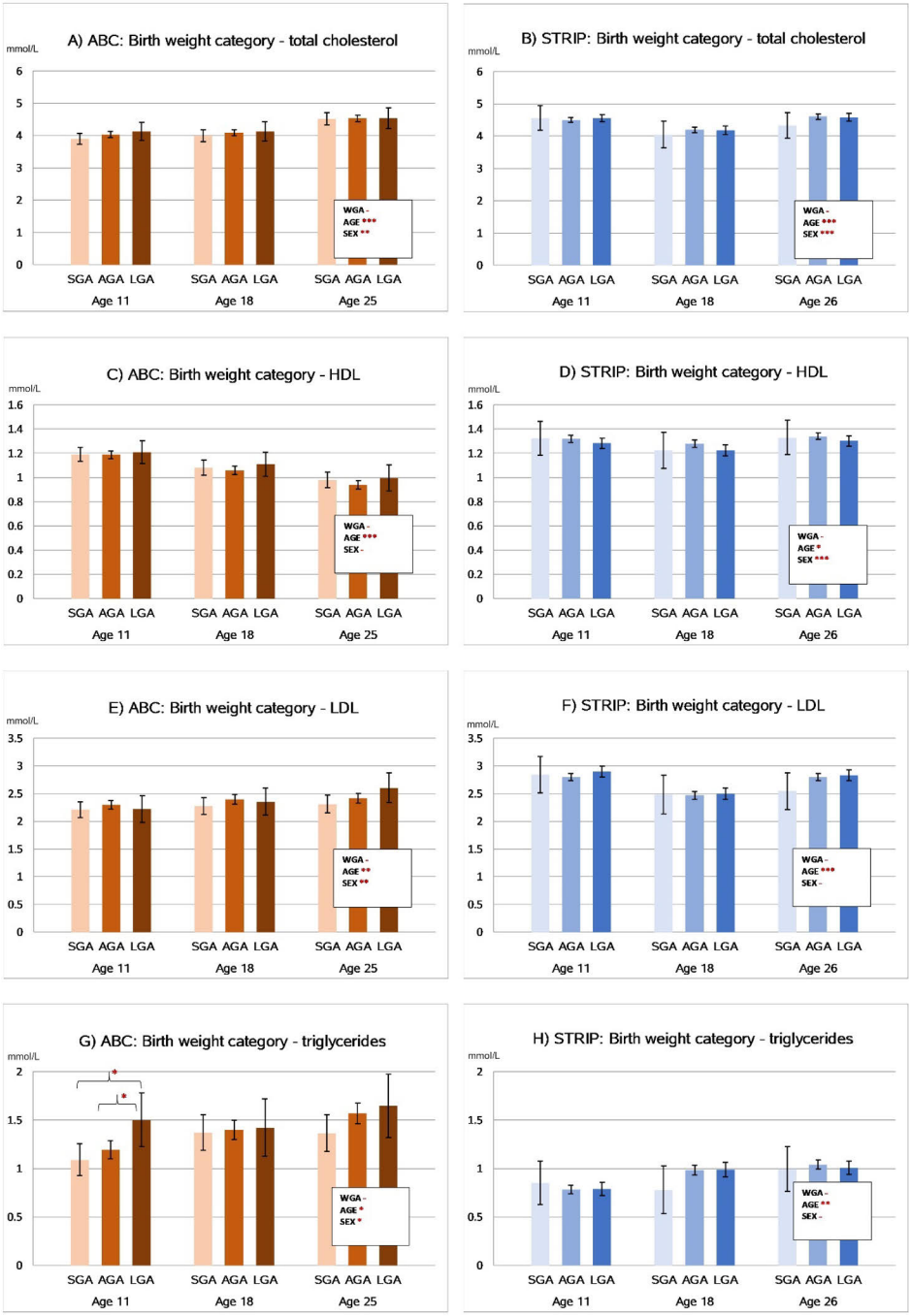

Figure 21. Associations between birthweight category and serum lipid levels in the ABC and STRIP cohorts. Bars indicate adjusted means with error bars for 95 % confidence intervals. The values in the boxes refer to the longitudinal analyses with WGA referring to birth weight category and AGE to assessment time point. Significant intracohortal differences between the birthweight categories at each follow-up are indicated with brackets.

5.6.3 Birth weight category and blood pressure

The associations between birth weight category and blood pressure levels are presented in **Figure 22**.

The longitudinal analyses revealed that birth weight category was not associated with SBP levels in either cohort. Group-wise comparisons of the birth weight categories however showed, that in the ABC cohort, SGA participants had lower SBP compared to LGA (P=0.046) and AGA participants (P=0.028) at age 25. In the STRIP study, LGA participants had higher SBP than AGA participants at age 11 (P=0.037). These associations did not persist after adjusting for BMI.

In the longitudinal analyses, birth weight category was also not associated with DBP levels in the ABC or STRIP cohorts. In the group-wise analyses, AGA participants had higher DBP than SGA participants in the ABC at age 25 (P=0.027). In the STRIP study, LGA participants had higher DBP than AGA participants at age 11 (P=0.031). These associations did not persist after adjusting for BMI.

There were no associations between birth weight category and pulse pressure in either cohort (**Figure 22**).

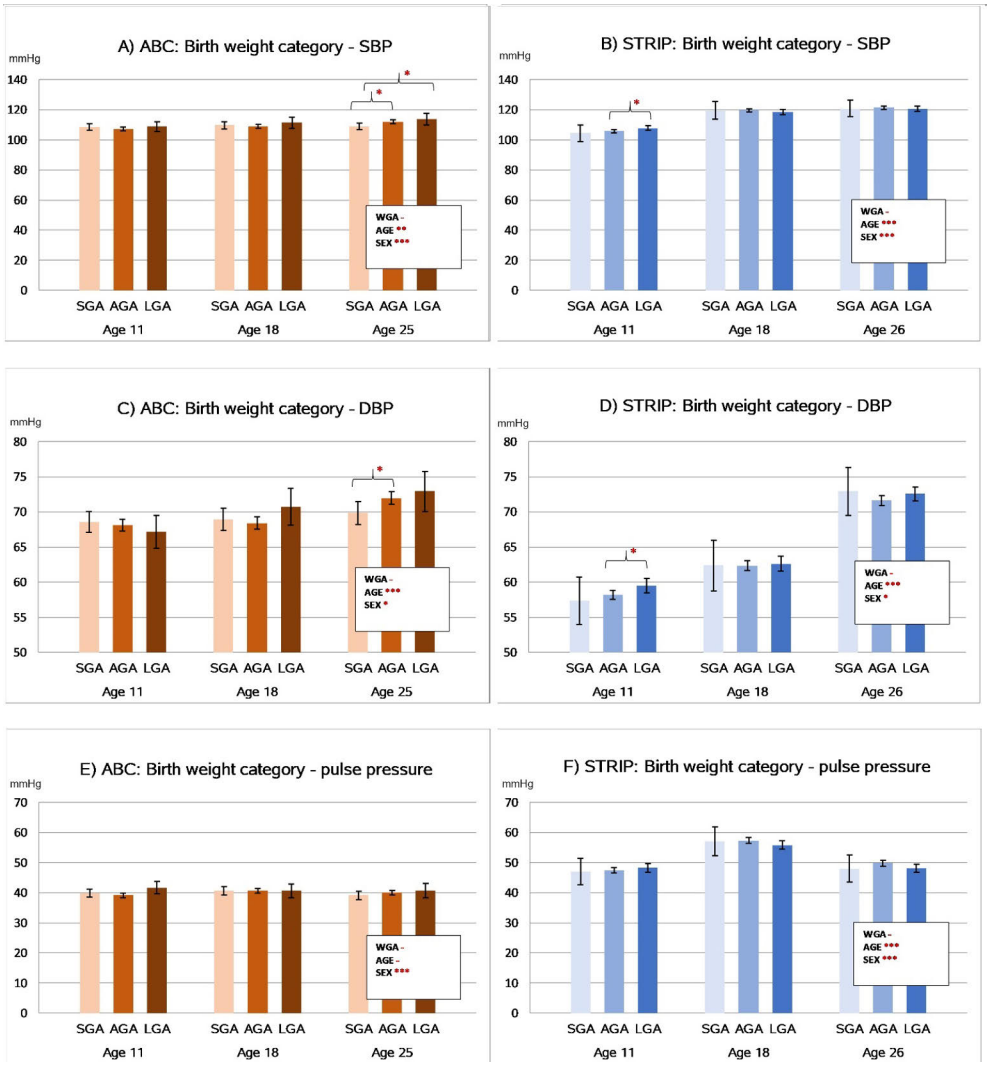

Figure 22. Associations between birthweight category and longitudinal trends in blood pressure levels in the ABC and STRIP cohorts. Bars indicate adjusted means with error bars for 95 % confidence intervals. The values in the boxes refer to the longitudinal analyses with WGA referring to birth weight category and AGE to assessment time point. Significant intracohortal differences between the birthweight categories at each follow-up are indicated with brackets. Unit for SBP, DBP and pulse pressure is mmHg. SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; SGA=Small for Gestational Age; AGA=Appropriate for Gestational Age; LGA=Large for Gestational Age; WGA=Weight for Gestational Age category. Asterisks indicate statistical significance with $P < 0.05$ *, $P < 0.01$** and $P < 0.001$ ***.

5.6.4 Birth weight category and cIMT

Mean values for cIMT with 95% confidence intervals at age 18/19 years for each birth weight category are presented in **Figure 23**. In the ABC, there was no association between birth weight category and cIMT (P=0.72). Similarly, group-wise comparisons revealed no differences in cIMT between the birth weight categories.

In the STRIP study, there was no association between birth weight category and cIMT (P=0.19). However, in the group-wise comparisons, SGA participants had a tendency for lower cIMT than AGA (P=0.085) or LGA participants (P=0.024).

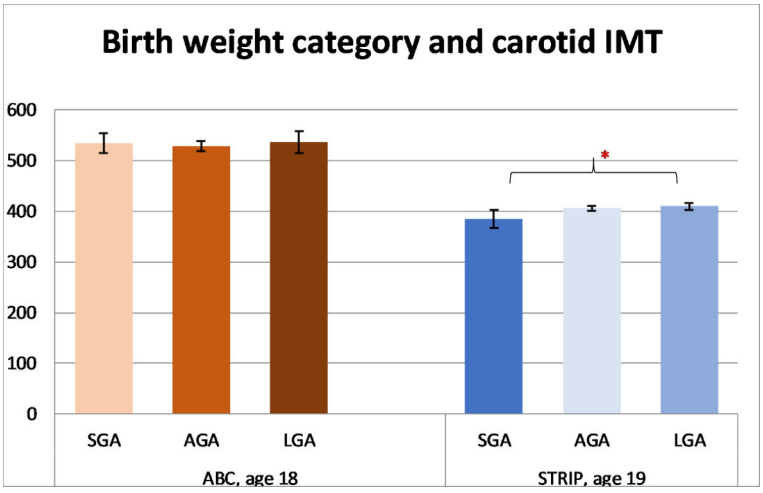

Figure 23. Carotid intima media thickness (IMT) according to birth weight category in the cohorts. Significant intracohortal differences between the birthweight categories at each follow-up are indicated with brackets. Asterisks indicate statistical significance with P < 0.05 *, P < 0.01** and P < 0.001 ***. Values are in µm.

6 Discussion

Ideal cardiovascular health in the ABC study was rare. Several early life determinants were found to independently predict future cardiovascular health, including family size, areal disadvantage and urban living environments (**Study I**). Areal disadvantage was a strong predictor of future longitudinal cardiovascular health metrics (**Study II**). There was significant tracking of nutritional status from childhood to adulthood in the ABC, both when assessed with BMI or with WHtR categories. Areal disadvantage and non-urban residence were associated with low rates of overweight/obesity and high rates of underweight (**Study III**). Birth weight for gestational age was associated with later cardiovascular health in both the ABC and the STRIP cohorts. The strongest associations were found between birth weight and BMI, with SGA infants having lower BMI and LGA infants higher BMI throughout the follow-ups in both cohorts. Birth weight category was associated with cIMT only in the STRIP cohort, where SGA participants had lower cIMT than LGA participants at age 19 (**Study IV**). The main findings of this thesis are depicted in **Figure 24**.

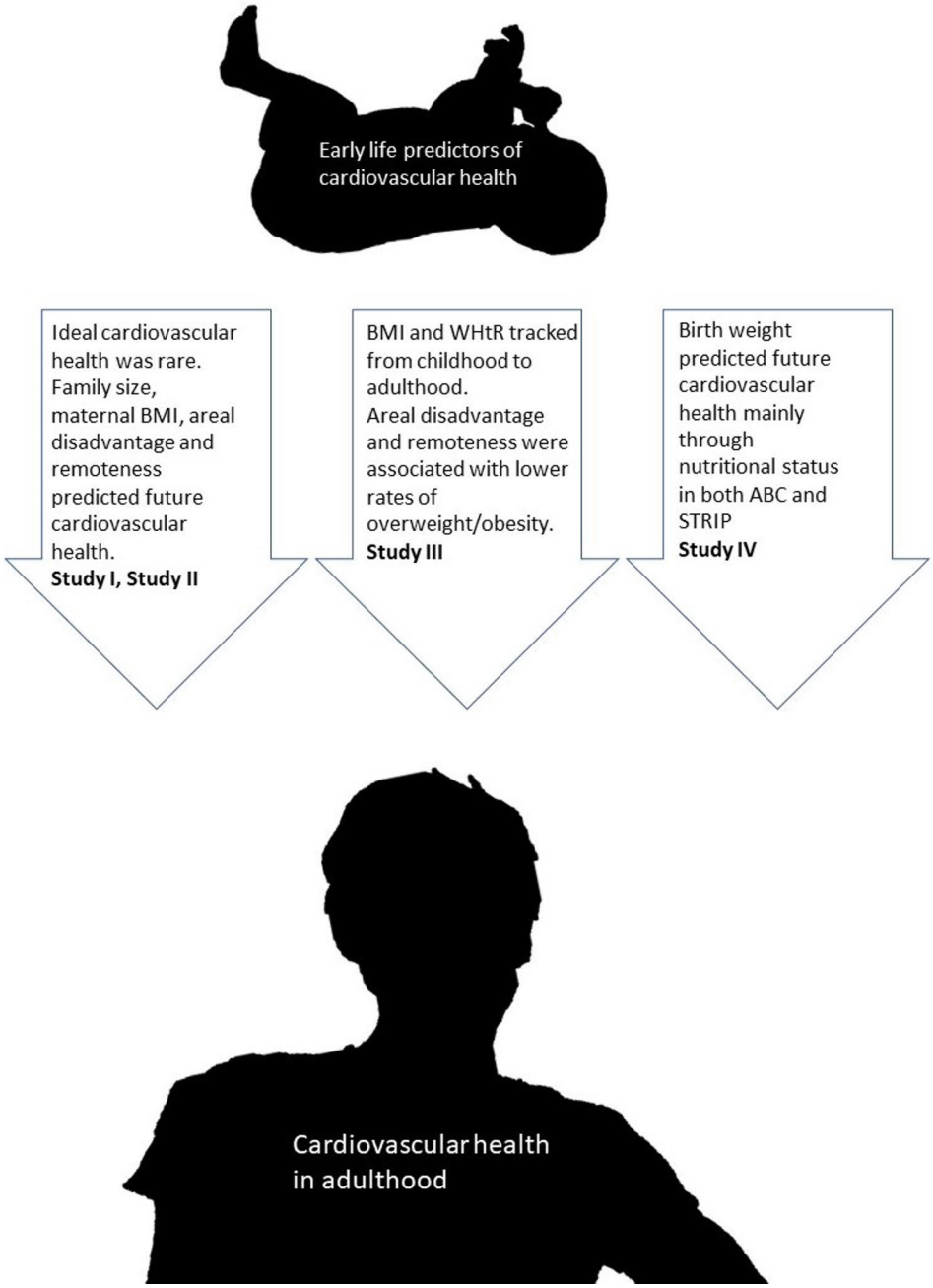

Figure 24. Schematic representation of the main findings of this thesis.

6.1 Participants

Despite the geographical challenges related to data collection, the retention rates in the ABC have been good (85%, 71% and 71% of living participants at Wave 2, 3 and 4 respectively), and the results in this thesis are generalizable to the Indigenous population residing in the NT. However, generalization of these results to other Indigenous populations, even in Australia, may be challenging as sociodemographic and geographical conditions may vary considerably.

The unique opportunity to be able to compare two almost simultaneously recruited longitudinal birth cohorts from opposite sides of the world, the ABC and the STRIP studies, provided a global health perspective to the thesis, even though direct statistical comparisons between the cohorts could not be made.

6.2 Methods

6.2.1 Cardiovascular health

The factors used to describe cardiovascular health in this thesis, i.e. BMI and WHtR, lipid levels, HbA1c, cIMT and blood pressure, are well established markers of CVD risk and applicable to different populations. The methods for collecting these data were well standardized and generalizable between the follow-ups. The data on health behaviours including smoking, sedentary lifestyle and dietary patterns were collected using questionnaires, causing a potential bias related to potential communication barriers as well as a possible response bias. A more objective way to measure cardiorespiratory fitness would be with clinical tests, such as cardiopulmonary exercise tests. (Kaminsky et al., 2019) The criteria for ideal cardiovascular health set by the AHA could not be fully met due to lack of data, and thus comparison possibilities to other studies are limited.

6.2.2 Birth weight

There are several ways to categorise birth weight and most nations have their own foetal and neonatal growth references. However, it has been debated that foetal growth does not depend on maternal nationality, ethnicity, or political borders. Therefore, an international growth reference should be possible to use to compare foetal outcomes between populations. For this purpose, the growth reference Intergrowth-21st was used to assess birth weight in the two different cohorts that were analysed. (Papageorghiou et al., 2018) Using an international growth reference revealed large differences in birth weight categories between the cohorts. In this thesis, only birth weight was used as a marker of fetal growth. However, other studies

have used measures like birth length and neonatal ponderal index to assess fetal growth. (Mayer & Joseph, 2013)

6.2.3 Socioeconomic status

The indicators of SES used in this thesis did not include the traditional variables of education and income, as there was no data available. Rather proxies, namely indicators of areal disadvantage, remoteness and family factors (household size, parity) were used. This causes some limitations to the interpretation of the results. However, the indicators used can be perceived to represent the socioeconomic disadvantage of the participants, as the areal indicator that was used (IRSEO) was specifically designed for assessment of Indigenous circumstances and household size and remoteness reflect socioeconomic disadvantage in general.

6.3 Results

6.3.1 Cardiovascular health metrics in the ABC

Only 2.5% of the individuals in **Study I** met all of the seven ideal cardiovascular health metrics according to the AHA criteria. The most common metrics met were ideal glucose (83.6%), cholesterol (74.9%) and blood pressure (73.2%). The least common metrics were related to health behaviours: non-smoking, ideal diet and ideal levels of physical activity were met by less than half of the cohort (28.8%, 44.1% and 49.7%, respectively). Sixty-two percent had an ideal BMI when defining BMI as < 25 kg/m^2. When healthy BMI was defined between 18.5-25 kg/m^2, only 41% had an ideal BMI. Significant sex differences were observed in both the total score as well as regarding blood pressure and physical activity. Several early life determinants were found to independently predict future ideal cardiovascular health. Family size and maternal BMI predicted BMI in adulthood and areal disadvantage was associated with future blood pressure and levels of physical activity. Urban living environment was also associated with non-ideal blood pressure levels, and household size was associated with smoking status in adulthood.

The AHA definition of ideal cardiovascular health builds on the concept of promoting favourable health behaviours to reduce the burden of disease presented CVD. (Lloyd-Jones et al., 2010) However, several studies show that only few individuals meet these criteria for ideal cardiovascular health (Benjamin et al., 2017; Daviglus et al., 2004; Folsom et al., 2011; Stamler et al., 1999). In an international multicohort study including 5785 participants from the i3C consortium, ideal cardiovascular health was rare with only 1% of participants meeting all seven ideal cardiovascular health targets. In the i3c, ideal glucose, ideal cholesterol and non-

smoking were the metrics that were most often met (73%, 64% and 64% respectively). (Oikonen et al., 2013) Previous epidemiological studies indicate that individuals who meet a larger number of ideal cardiovascular health behaviours or metrics have a lower risk of CVD mortality (Canto et al., 2011; Laitinen et al., 2012; Patel et al., 2014).

6.3.1.1 Impact of maternal BMI and family size

The adverse effects of high maternal BMI on offspring cardiovascular health is consistent with previous findings (Gaillard, 2015; Kahn et al., 2020). In the Generation R study, it was found that maternal obesity is associated with adverse cardiometabolic risk profiles including obesity, higher SBP and adverse lipid levels in the offspring (Gaillard et al., 2014) In the Avon Longitudinal Study of Parents and Children (ALSPAC), a linear trend between maternal pre-pregnancy BMI and offspring adiposity levels was found: offspring of underweight mothers had lower rates and offspring of overweight mothers had higher rates of adiposity with epigenetic mechanisms suggested mediating factors. (Sharp et al., 2015) In **Study I**, the observed associations between maternal underweight, large family size and offspring ideal BMI are possibly related to food insecurity and malnutrition, as these differences were only evident when ideal BMI was defined as < 25 kg/m^2 and no longer found, when underweight participants were excluded. This assumption is supported by existing data that suggests an association between household size and food insecurity in the Aboriginal population. (Markwick et al., 2014) Household size was also associated with smoking status. We found that smoking was more common in large households (> 9 people sleeping in the house) than in smaller ones. Previous studies show that smoking is particularly common in low-income Aboriginal households. (Thomas et al., 2008)

6.3.1.2 Impact of socioeconomic status, remoteness, and areal disadvantage

In line with the findings of this thesis, both family and areal socioeconomic status have been shown to be important determinants of cardiometabolic risk factors. (Clark et al., 2013; Kakinami et al., 2017; Kivimäki et al., 2018) In the i3C consortium, data from longitudinal cohorts in Australia, Finland, and USA showed that parental education and occupation are associated with the ideal cardiovascular health index among offspring in adulthood. (Laitinen et al., 2013) Neighborhood factors have been shown to be associated with the prevalence of CVD and its risk factors among adults in several studies. (Clark et al., 2013; Kakinami et al., 2017; Kivimäki et al., 2018) A Canadian study reported that children from disadvantaged

neighborhoods were more likely to have CVD risk factors or events during 34 years of follow-up compared to peers from less disadvantaged areas. (Kakinami et al., 2017) In the Cardiovascular Risk in Young Finns study, neighborhood socio-economic disadvantage across life was associated with higher blood pressure and triglyceride levels in midlife. (Kivimäki et al., 2018) In **Study II**, in contrast, it was found that in the ABC study, SBP and LDL-cholesterol levels were lower among people from areas of highest disadvantage. Remoteness as defined with the ARIA index showed similar results, with the participants from the most remote locations presenting with the lowest BMI, cholesterol and blood pressure levels. The finding that HDL-cholesterol and triglyceride levels were most favourable in people from least disadvantaged areas (HDL-cholesterol) and from urban places of residence (triglycerides) are consistent with previous studies. (Kivimäki et al., 2018; McCarthy et al., 2015)

The association of geographical location and cardiovascular risk profiles in Aboriginal Australians has been previously studied in the Heart of the Heart study. (Brown et al., 2014) In the study, it was found that participants from urban environments (Alice Springs) had higher blood pressure, elevated lipid levels and poorer kidney function than their remote living counterparts. Higher income was found to be associated with elevated risk of CVD in town camps but not in Alice Springs or in remote communities. Similar findings were seen in the ABC cohort, where urban residents had higher blood pressure. Participants from socially more advantaged areas according to the IRSEO score also had higher blood pressure and poorer levels of physical activity in this study. Similar mechanisms could lie behind these findings as the urban areas tended to score better in the IRSEO ranking.

In **Study III**, both areal disadvantage and non-urban residence were associated with lower prevalence of overweight/obesity and higher rates of underweight. This is in contrast to a study from New South Wales, where Aboriginal people from more advantaged and urban surroundings had lower prevalence of obesity and overweight than those from remote and disadvantaged areas. (Thurber et al., 2018) The spatial trend in obesity in this cohort seems to be similar to that traditionally seen in low and middle income countries, where obesity is more concentrated in cities and wealthier regions and underweight is more common in remote and rural areas. (Popkin et al., 2012) The dual burden of malnutrition and the urban-remote differential in nutritional status has been previously described in the cohort at an average age of 25 years. (Davison et al., 2019)

The findings of the associations between socioeconomic disadvantage, remoteness and cardiovascular risk have several potential explanations. Dietary factors could explain a large part of the health gap, as Indigenous Australians overall have poorer dietary patterns than non-Indigenous Australians. (Australian Bureau of Statistics, 2016) Relatively high food prices in remote communities, combined with

low incomes, cause food insecurity. (Brimblecombe & O'Dea, 2009) In studies from the U.S, food insecurity has been associated with lower blood pressure and cholesterol levels. (Saiz et al., 2016; Shin et al., 2015) Even short periods of scant income worsen dietary quality among remote living Indigenous Australians. The most notable differences between periods of high and low income are in energy intake, the proportions of energy provided by fats and carbohydrates, and the ratio of sodium to potassium intake. (Wycherley et al., 2017) Factors related to housing and infrastructure, such as limited food storage facilities and transport, also affect dietary choices. (Brimblecombe et al., 2014) Social factors including education, inequities in resource allocation, employment opportunities and physical infrastructure also play a role in the urban-remote health difference. (Smith et al., 2008)

6.3.2 Tracking of nutritional status

In the ABC, underweight was common from childhood through to adolescence and young adulthood. Overweight/obesity was relatively not as common but increased over time. This is in contrast to the general Australian Indigenous population, where rates of overweight and obesity are higher. It may reflect the cohort demographics with many people residing in remote and very remote communities.

In contrast to BMI, there were significant differences between the sexes for both tracking and prevalence of WHtR categories with females more often presenting with central adiposity in adolescence and adulthood. This finding is consistent with previous studies that show that Aboriginal women in general have greater waist circumference than their non-Aboriginal counterparts. (Adegbija & Wang, 2014; Piers et al., 2003) As demonstrated in **Study I**, females in this cohort have lower levels of physical activity compared with males, which may be a possible contributing factor. Central adiposity is a known risk factor for cardiovascular morbidity which accounts for a substantial part of the disparity in health outcomes between Indigenous and non-Indigenous Australians. Therefore, women could be at particular risk for chronic disease due to their body fat composition. (Adegbija & Wang, 2014)

6.3.3 Birth weight for gestational age and cardiovascular health

Findings from **Study IV** indicate that birth weight for gestational age is associated with later cardiovascular health both in the ABC and the STRIP – two distinct cohorts from different parts of the world. The strongest associations were found between birth weight category and BMI, with SGA infants having lower BMI and

LGA infants higher BMI throughout the follow-ups in both cohorts. Interestingly, WHtR, an indicator of central adiposity, was associated with birth weight category in the Indigenous Australian ABC cohort - but not in the Finnish STRIP study. Future lipid levels showed to be largely independent of birth weight category in both cohorts. However, in the ABC at age 11, LGA participants had higher triglyceride levels than SGA and AGA participants. Birth weight category was also associated with blood pressure levels in both cohorts. In the STRIP cohort, LGA participants had higher SBP and DBP than AGA participants at age 11. In the ABC, differences in blood pressure were only seen at age 25 when SGA participants had lower SBP than AGA and LGA participants and lower DBP than AGA participants. When adjusting for BMI, the associations found for blood pressure and lipid levels did not persist, indicating that BMI likely mediates these associations. Birth weight category was associated with cIMT only in the STRIP cohort, where SGA participants had lower cIMT than LGA participants at age 19.

The observed association between birth weight and BMI from childhood to adulthood is in line with prior studies showing that high birth weight may lead to obesity later in life. (Kang et al., 2018; Shi et al., 2013; Yuan et al., 2015) In a cross-sectional study on Korean adolescents (N=1304), higher birth weight was associated with both higher BMI and higher fat mass index (Kang et al., 2018). A study on 6 to 11-year-old Canadians showed that every 100 g increase in birth weight was associated with a 5% increase in a child's obesity risk. (Shi et al., 2013)

There is also growing evidence that obesity and the association between birth weight and future BMI could at least in part be explained by polygenic inherited susceptibility to obesity. As an example, a genome-wide polygenic score to quantify the genetic risk for future obesity was generated in a genome-wide association study and it was found that this genetic risk score was associated with only small differences in birth weight but that these differences grew in size with time reaching a gradient of 12 kg by the age of 18 between top and bottom risk score deciles. (Khera et al., 2019) A large multi-cohort study from Finland and the UK examined the role of birth weight adjusted for gestational age on later metabolic profile and found that lower birth weight was adversely associated with cardiometabolic biomarkers such as lipid levels and inflammatory markers in adulthood. (Würtz et al., 2016) The magnitude of this association, however, was modest, similar to that caused by high BMI in adulthood. It was suggested that similar molecular pathways may underlie both low birth weight and adulthood overweight. (Würtz et al., 2016)

In contrast to the findings from **Study IV,** where only few associations between birth weight category and blood pressure or lipid levels were found, previous studies have reported inverse associations between these variables. In the Bogalusa Heart Study (Louisiana), lower birth weight was associated with both higher blood pressure levels (SBP, DBP and pulse pressure) (Mzayek et al., 2007) from childhood

to adulthood as well as higher LDL-cholesterol and triglyceride levels in adolescence (Mzayek et al., 2004). A large (N=300.000) genome-wide association study using data from the EGG consortium and the UK biobank found evidence to support that the inverse association between birth weight and blood pressure is attributable both directly to the fetal genotype and indirectly to maternal genetic factors that produce an adverse intrauterine environment. According to the study, it is possible that some of the same alleles that are associated with lower birth weight might also cause higher blood pressure later in life. (EGG Consortium et al., 2019)

In the ABC study, no associations between birth weight and cIMT were found, whereas SGA infants in the STRIP study seemed to have lower cIMT than AGA and LGA infants. Some earlier studies have found higher cIMT in SGA infants (Stergiotou et al., 2014), whereas other studies have found higher cIMT in LGA infants (Dratva et al., 2013). It is possible that the sample sizes were too small to detect significant differences in cIMT or that these differences were not yet evident but may be seen in later follow-ups. Previous studies have found that cIMT can predict cardiovascular outcomes, but it seems to improve cardiovascular risk classification only modestly. (Polak et al., 2011)

The finding that birth weight was associated with WHtR in the ABC but not in the STRIP cohort, may be explained by different patterns of fat accumulation in the populations. In a previous study examining the prevalence of metabolic syndrome in the ABC, it was noted that large waist circumference was quite common despite low rates of overweight defined by BMI and the relative underweight nature of the cohort. It was suggested that there could be a susceptibility for central fat accumulation in the population and that central adiposity could serve as a better predictor of metabolic and cardiovascular disorders than BMI also in Indigenous Australians. (Sellers et al., 2008) Another study compared body fat distribution between adults of Aboriginal and European ancestry in Australia and concluded that there were significant differences in body shape with Aboriginal women having larger waist circumferences than their European Australian counterparts. (Piers et al., 2003) The finding that especially females tend to be affected by central obesity was confirmed in **Study III**.

6.4 Strengths and limitations

Overall, the strengths of the ABC study include its longitudinal nature and well-structured follow-ups with relatively good retention rates (85%, 71% and 71% of living participants at Wave 2, 3 and 4 respectively), particularly given the accessibility problems that make data collection in remote areas challenging. The study population however is relatively small causing some limitations to the interpretation of the results. Other limitations of the study include the difficult

definition of SES, as the traditional variables of household income and education were not available and may not always be well-suited in the remote communities. The IRSEO score describes the areal level socioeconomic situation and does not necessarily reflect the individual SES of the participants. In a relatively small cohort, these differences may be of even larger significance.

Although the retention rates remained high, sample sizes for some of the described health metrics in **Study I** remained low, reducing the power of the analyses. This was particularly evident for the total ideal cardiovascular health score. Due to lacking data, the total score was available only for 204 participants (29.7%). Due to the modifications made to the original AHA definition of ideal cardiovascular health regarding diet and glucose levels, the results may not be directly comparable to other similar studies. The follow-up study population may not completely represent the original birth cohort, as follow-up participants were more often females and had higher IRSEO scores compared to non-participants.

Attrition analyses identified differences between non-participants and participants also in **Study II**, as a larger proportion of the participants was male at waves 3 and 4, lived in less disadvantaged areas and more often came from urban areas, leading to limitations in the generalizability of the study population.

As only participants with data from all follow-ups were included in **Study III**, the missing data were quite substantial, leading to an evident decrease in the number of participants compared to the entire cohort. However, results from the sensitivity analyses where all data points were analysed were similar to the main analyses. There were significant geographical differences between participants and non-participants in **Study III**, with non-participants being more often from urban and less disadvantaged areas. This potential bias may exaggerate the prevalence of underweight in the cohort as underweight was more prevalent in the remote and disadvantaged regions. It is also acknowledged that the presented associations between weight status and socioeconomic status, remoteness, maternal BMI and birth weight are merely descriptive analyses presented separately for each follow-up as the data was not analysed in a longitudinal fashion and correlation over time was not assessed.

A particular strength of **Study IV** was that it compared two unique cohorts that were established almost simultaneously on opposite sides of the globe in very different socioeconomic and cultural settings. Both of these longitudinal studies began in infancy and have had good retention rates and systematically structured follow-ups and data collections. The comparisons between the cohorts remain observational as the methodologies to assess anthropometrics and blood pressure, blood sampling and carotid ultrasonography were not standardized across the cohorts to allow for statistical comparisons. As the number of SGA infants in the STRIP cohort and the number of LGA infants in the ABC were quite low, it is possible that

some existing associations were not found. Parental effects on birth weight were not analysed although especially maternal risk factors such as gestational diabetes and maternal BMI could add important information about the intergenerational inheritance of cardiovascular risk.

6.5 Clinical and public health considerations

Concerning the clinical and public health point of view, the results from **Study I** and **II** provide important background information on the early life determinants of cardiometabolic health within an Aboriginal community. To construct useful intervention strategies for positive health changes in this population based on these findings, it is essential to take Indigenous perspectives into account. Main tools in this process are culture-centered approach, community engagement, systems thinking, and integrated knowledge translation. (Oetzel et al., 2017)

The impact of blood pressure and lipid control on mortality outcomes has been well documented. It has been estimated that each 20 mmHg rise in SBP in people aged 40–69 years is associated with a doubling of cardiovascular mortality. (Lewington et al., 2002) An increase of 1 mmol/L in LDL-cholesterol levels has been associated with a 62% prospective increase in CHD. (Emerging Risk Factors Collaboration et al., 2009) The largest differences by IRSEO group found in **Study II** were 3.5 mmHg for SBP and 0.6 mmol/L for LDL-cholesterol (in Wave 4). From the public health perspective, the results from this thesis indicate that intervention strategies for preventing CVD in Indigenous Australian communities must take the perspectives and socio-economic conditions of the residents into account.

The results from **Study III** present further evidence that dietary interventions need tailored approaches, as there exist large variations within the Aboriginal community regarding nutritional status and its tracking over time. Interventions need to be delivered within critical time windows and the gender perspective is essential: pre-pregnant women and girls in general should receive special attention. (Vaivada et al., 2017) The reasons behind the dual burden of malnutrition, particularly the high rates of underweight in the remote and more disadvantaged communities, are multifactorial and include high food prices, low incomes, overcrowded households, and rudimentary cooking facilities. (Ferguson et al., 2016; Pholeros et al., 2013) Approaches that have been suggested to improve diet in the remote communities include eliminating socioeconomic constraints by reducing prices on fruits and vegetables in the community stores and enhancing nutrition-related consumer education and thus improving food security and self-efficacy to cook. (Brimblecombe et al., 2018) Nutrition education including cooking skills workshops, group education sessions and store interventions have been reported to have some positive effect on obesity in Indigenous communities according to a review study

that included both remote and urban communities in Australia. (Schembri et al., 2016) Multisector participatory approaches to strengthen food systems in remote Indigenous communities are needed (Brimblecombe et al., 2017) with a special focus on nutrition in early life.

As found in **Study IV**, larger babies, although born in completely different global contexts, tend to have larger BMIs already in childhood, putting these individuals at greater risk for obesity-related disorders such as type 2 diabetes and cancer. (Expert Panel Members et al., 2014; Franks et al., 2010) As was demonstrated in **Study III**, overweight children in the ABC have a tendency to remain overweight as adults – a phenomenon seen in many other populations as well. (Evensen et al., 2016) With the proportion of newborns with high birth weight increasing in many populations (Hadfield et al., 2009; Kramer et al., 2002; Surkan et al., 2004), and the obesity pandemic posing a major global health threat (Blüher, 2019), the effect of birth weight on future BMI is of evident importance. The rising rates of high birth weight infants have been explained by maternal factors such as pre-pregnancy obesity, gestational weight gain, and gestational diabetes (Kaul et al., 2019), indicating a need to focus on maternal health to prevent childhood obesity and help tackle the obesity pandemic. On the other hand, there is evidence that if childhood obesity discontinues into adulthood, the risk for later type 2 diabetes, hypertension, dyslipidemia, and atherosclerosis is similar to those who were never obese (Juonala et al., 2011), implicating the benefits of interventions in childhood or even earlier.

6.6 Future considerations

The participants were still young adults during the last applied follow-up. After future follow-ups, cardiovascular morbidity and clinical events could be analysed for even better understanding of the clinical relevance of the cardiovascular risk profiles seen in these cohorts.

Achieving a larger prevalence of individuals meeting ideal cardiovascular health metrics in the Aboriginal population in Australia could have significant effects on cardiovascular morbidity and mortality as well as reduce the related healthcare costs. The results presented in this thesis show that special attention needs to be put on health behaviours such as smoking and dietary habits as well as on gender equality in health to achieve these goals. Possible malnutrition must also be taken into account in future studies when analysing ideal BMI, as a significant number of participants showed to be underweight.

This thesis presents strong evidence on tracking of nutritional status from childhood to adulthood in the ABC. Socioeconomic status and remoteness factors were associated with weight status in all follow-ups. The differences in central

adiposity between males and females that seem to arise after childhood indicate a need for targeted and successfully timed approaches in dietary interventions. The high prevalence of underweight across all age groups requires special attention in the process of improving nutritional health overall in the remote Indigenous communities.

Findings presented in this thesis also suggest that birth weight category is associated with later cardiovascular risk profile with the most robust associations seen for nutritional status indicated by BMI and WHtR. This finding supports targeted prevention strategies for those individuals at risk to improve cardiovascular health worldwide.

7 Conclusions

In summary, the present study shows associations between early life predictors related to socioeconomic and family status as well as birth weight and future cardiovascular health in the Aboriginal population.

Firstly, ideal cardiovascular health according to the AHA 2010 criteria was rare in the ABC and several early life determinants were found to independently predict future cardiovascular health. For instance, family size and maternal BMI predicted BMI in adulthood, and IRSEO as an indicator of areal disadvantage was associated with future blood pressure and levels of physical activity. Furthermore, urban living environment was associated with non-ideal blood pressure levels, and household size was associated with smoking status in adulthood. (**Study I**)

Secondly, areal disadvantage was a stronger predictor of future cardiovascular health than urban residence or maternal parity at birth. Mean BMI, blood pressure, and LDL-cholesterol were at healthier levels among individuals born in highly disadvantaged and remote areas whereas mean HDL-cholesterol and triglyceride levels were least favourable in these people. (**Study II**)

Thirdly, there was significant tracking of nutritional status from childhood to adulthood in the ABC, both when assessed with BMI and with WHtR categories. In contrast to BMI, there were significant differences between the sexes for both tracking and prevalence of WHtR categories with females more often presenting with central adiposity in adolescence and adulthood. Both areal disadvantage and non-urban residence were associated with lower rates of overweight/obesity and higher rates of underweight. (**Study III**).

Fourthly, birth weight for gestational age was associated with later cardiovascular health in both the ABC and the STRIP cohorts. The strongest associations were found between birth weight category and BMI with SGA infants having lower BMI and LGA infants higher BMI throughout the follow-ups in both cohorts. Birth weight category was associated with cIMT only in the STRIP cohort where SGA participants had lower cIMT values at age 19. (**Study IV**)

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