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TRACKING OF CARDIOVASCULAR RISK FACTORS FROM CHILDHOOD TO ADULTHOOD AND THEIR PREDICTIVE VALUE FOR ADULT OUTCOME

Jonna Juhola

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ABSTRACT

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Tracking of cardiovascular risk factors from childhood to adulthood and their predictive value for adult outcome

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Background: Atherosclerosis is a leading cause of death worldwide. Progression of the disease is long term; even though the first signs are known to be present already in childhood symptoms do not usually appear until middle age or later.
Aims: The aim of the present thesis was to investigate tracking of cardiovascular risk factors from childhood to adult age spanning several decades. Also the aim of this thesis was to study a combination of childhood risk factors to predict adult outcomes (obesity and hypertension) controlling for multiple confounding and new genetic factors. In addition, the effect of child and adult blood pressure (BP) on subclinical atherosclerosis in adult age was examined.
Participants and Methods: This study is part of the Cardiovascular Risk in Young Finns Study launched in 1980, which is a multicentre follow-up study from childhood to adult age to evaluate risk factors and precursors of cardiovascular disease. The findings of the present study are based on data from the 21- and 27-year follow-ups in 2001 and 2007 when a total of 2,283 and 2,204 participants aged 24 to 45 years were re-examined. In addition, data for 1,987 participants from similar contemporary cohort studies in United States of America and Australia were used in the analyses.
Results: In a multivariable analysis the independent predictors of adult elevated BP included parental hypertension (P<0.0001), childhood systolic BP (P<0.0001), a genetic risk score (P<0.0001), parental occupational status (P=0.02), and childhood overweight/obesity (P=0.001). A non-laboratory risk score composed of childhood body mass index (BMI), maternal BMI, and family income predicted adult obesity in all age groups between 3-18 years (P <0.001 for all groups). Inclusion of genetic variants of obesity in the analyses did not significantly improve the prediction of adult obesity (AUC (0.779, P=0.16)). In contrast, genetic markers of BP improved the prediction of adult elevated BP with and without a family history of hypertension. Individuals with persistently elevated BP from childhood to adult age as well as individuals with normal childhood BP but elevated adult BP had an increased risk of high carotid artery intima-media thickness (cIMT) RR 1.82[1.47–2.38] and 1.57[1.22–2.02], respectively) (relative risk [95% confidence interval]) in comparison with persistently normotensive. In contrast, individuals with elevated BP during childhood but normal BP during adulthood did not have significantly increased risk of high cIMT (RR 1.24[0.92–1.67]) in comparison with persistently normotensive. In addition, these individuals had a lower risk of increased carotid artery IMT (RR 0.66[0.50–0.88]) compared with those with persistently elevated BP.
Conclusions: Tracking of cardiovascular risk factors from childhood to adult age is strong. Multiple childhood risk factors including genetic markers predict adult hypertension. Thus, a multifactorial approach may be useful in identifying children at risk for hypertension later in life. The increased risk of subclinical atherosclerosis associated with elevated childhood BP was reduced if BP was normal in adult age. A simple risk score based on childhood risk factors (child BMI, maternal BMI and low socioeconomic status) was superior in predicting adult obesity compared with the currently recommended approach of using child BMI only.

Key words: tracking, blood pressure, obesity, intima media thickness, risk factors, atherosclerosis

TIIVISTELMÄ

Jonna Juhola

Sydän- ja verisuonitautien riskitekijöiden urautuminen ja ennustearvo lapsuudesta aikuisuuteen.

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Tausta: Länsimaissa kuolleisuus sydän- ja verisuonitauteihin on korkea. Valtimokovettumataudin ehkäisy on haastavaa, sillä kliinisesti tauti ilmenee vasta keski-iällä. Valtimoseinämän muutokset ovat kuitenkin todettavissa jo lapsuus- ja nuoruusiällä.
Tavoite: Väitöskirjatutkimuksen tavoitteena oli selvittää, voidaanko lapsena mitattujen sydän- ja verisuonitautien riskitekijöiden avulla ennustaa aikuisiän riskiprofiilia. Lisäksi selvittää, mitkä lapsuuden riskitekijät ennustavat lihavuutta tai korkeaa verenpainetta aikuisiällä ja parantavatko lihavuuden tai verenpaineen geenivariantit näiden tautien kehittymisen ennustettavuutta. Lisäksi tutkimuksessa selvitettiin, onko lapsena mitatun verenpaineen vaikutus valtimokovettumataudin varhaismuutokseen (kaulavaltimoiden seinämäpaksuus) aikuisiällä palautuvaa vai pysyvää, mikäli verenpaine on aikuisena normaali.
Menetelmät: Tämä tutkimus on toteutettu osana Lasten Sepelvaltimotaudin Riskitekijät -projektia, joka on vuonna 1980 käynnistetty valtakunnallinen etenevä seurantatutkimus. Tutkimuksen tavoite on selvittää lapsuuden riskitekijöiden vaikutusta valtimokovettumataudin kehittymiseen ja sepelvaltimotaudin syntyyn myöhemmällä iällä. Vuonna 2001 seurantatutkimukseen osallistui 2283 ja vuonna 2007 2204 iältään 24-45-vuotiasta henkilöä. Lisäksi tutkimuksessa on käytetty 1987 henkilön aineistoa, joka koostuu Yhdysvalloissa ja Australiassa tehdyistä vastaavanlaisista seurantatutkimuksista.
Tulokset: Lapsuuden riskitekijöiden todettiin urautuvan aikuisuuteen. Itsenäisiä riskitekijöitä kohonneelle verenpaineelle aikuisena olivat lapsuuden systolinen verenpaine (P<0.0001), vanhempien verenpainetauti (P<0.0001), korkea geneettinen riskipiste (P<0.0001), lapsuuden ylipaino tai lihavuus (P=0.001) ja perheen matala ammattistatus (P=0.02). Kaikissa ikäryhmissä (3-18 vuotiaat) kolmesta helposti mitattavasta lapsuuden riskitekijästä (äidin painoindeksi, lapsen painoindeksi ja perheen sosioekonominen asema) laskettu riskipiste paransi lihavuuden kehittymisen ennustetta aikuisiällä verrattuna pelkkään lapsen painoindeksiin. Lihavuuden geenimarkkerit eivät merkittävästi parantaneet lihavuuden kehittymisen ennustetta aikuisiällä. Verenpaineen geenimarkkerit sen sijaan ennustivat korkean verenpaineen kehittymistä sekä erikseen että yhdessä lapsen vanhempien korkean verenpaineen kanssa. Henkilöillä, joilla verenpaine oli pysyvästi koholla lapsuudesta aikuisikään tai joilla oli normaali verenpaine lapsena, mutta kohonnut verenpaine aikuisena, oli suurempi riski suurentuneeseen kaulavaltimon seinämän paksuuteen verrattuna niihin henkilöihin, joilla verenpainetaso säilyi normaalina RR 1.82 (1.47-2.38) ja RR 1.57 (1.22-2.02) (riskisuhde ja 95% luottamusväli]). Jos verenpaine oli lapsena koholla mutta aikuisena normaali tilastollista riskiä suurentuneeseen kaulavaltimon seinämän paksuuteen ei puolestaan ollut RR 1.24 (0.92-1.67). Henkilöillä, joilla oli korkea verenpaine lapsena, mutta normaali verenpaine aikuisena, riski suurentuneeseen kaulavaltimon paksuuteen oli pienempi RR 0.66 (0.50-0.88), kuin niillä joilla verenpaine oli pysyvästi koholla.
Johtopäätökset: Sydän- ja verisuonitautien riskitekijät urautuvat lapsuudesta aikuisikään. Monet lapsuusiän tekijät ja perintötekijät ennustavat kohonneen verenpaineen kehittymistä aikuisena. Kohonneen verenpaineen aiheuttamat varhaiset valtimokovettumataudin suonimuutokset olivat osittain palautuvia, mikäli lapsen kohonnut verenpaine oli aikuisena normaali. Lapsuuden riskitekijöistä (äidin painoindeksi, lapsen painoindeksi ja perheen sosioekonominen asema) laskettu riskipiste ennustaa lihavuuden kehittymistä aikuisena paremmin kuin pelkkä nykysuositusten mukainen lapsen painoindeksi.

Avainsanat: urautuvuus, verenpaine, lihavuus, seinämäpaksuus, riskitekijät, valtimokovettumatauti

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ABBREVIATIONS

AGA = appropriate birth weight for gestational age

AHA = American Heart Association

ARYA = The Atherosclerosis Risk in Young Adults

AUC = area under receiver-operating characteristic curve

BMI = body mass index

BP = blood pressure

CAC = coronary artery calcification

CAD = coronary artery disease

CDAH = Childhood Determinants of Adult Health

CI = confidence interval

cIMT = carotid artery intima-media thickness

CRP = C-reactive protein

CT = computed tomography

CV = coefficient of variation

CVD = cardiovascular disease

DBP = diastolic blood pressure

EGIR = European Group for the Insulin Resistance

FFQ = food frequency questionnaire

FH = Familial hypercholesterolemia

FMD = flow mediated dilatation

GWAS = genome-wide association studies

HDL-C = high-density lipoprotein cholesterol

H-L = Hosmer-Lemeshow X^2 test

HR = hazard ratio

IDF = International Diabetes Federation

IDI = Integrative discrimination index

JNC7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

LDL-C = low-density lipoprotein cholesterol

LPA = apolipoprotein(a) gene

MetS = metabolic syndrome

NCEP = National Cholesterol Education Program

NHANES = National Health and Nutrition Examination Survey

NHBPEP = National High Blood Pressure Education Program

NHLBI = National Heart, Lung, and Blood Institute

NPV = negative predictive value

NRI = net reclassification index

OR = odds ratio

PCSK9 = Proprotein convertase subtilisin/kexin type 9

PDAY = Pathobiological Determinants of Atherosclerosis in Youth

PPV = positive predictive value

PWV = pulse wave velocity

r = Spearman's correlation coefficient

RR = relative risk

SBP = systolic blood pressure

SD = standard deviation

SGA = small for gestational age

SI = stiffness index

SNP = single nucleotide polymorphism

TG = triglycerides

TC = total cholesterol

T2DM = Type II diabetes mellitus

USPSTF = US Preventive Services Task Force

YEM = Young's elastic modulus

YFS = the Cardiovascular Risk in Young Finns Study

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by roman numerals I-IV.

I) **Juhola J**, Magnussen CG, Viikari JSA, Kähönen M, Hutri-Kähönen N, Jula A, Lehtimäki T, Åkerblom HK, Pietikäinen M, Laitinen T, Jokinen E, Taittonen L, Raitakari OT, Juonala M. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: The Cardiovascular Risk in Young Finns Study. *J Pediatr*. 2011;159:584-90.

II) Juonala M, **Juhola J**, Magnussen CG, Würtz P, Viikari JSA, Thomson R, Seppälä I, Hernesniemi J, Kähönen M, Lehtimäki T, Hurme M, Telama R, Mikkilä V, Eklund C, Räsänen L, Hintsanen M, Keltikangas-Järvinen L, Kivimäki M, Raitakari OT. Childhood environmental and genetic predictors of adulthood obesity: The Cardiovascular Risk in Young Finns Study. *J Clin Endocrinol Metab*. 2011;96:E1542-9.

III) **Juhola J**, Oikonen M, Magnussen CG, Mikkilä V, Siitonen N, Jokinen E, Laitinen T, Würtz P, Gidding SS, Taittonen L, Seppälä I, Jula A, Kähönen M, Hutri-Kähönen N, Lehtimäki T, Viikari JS, Juonala M, Raitakari OT. Childhood physical, environmental, and genetic predictors of adult hypertension: the cardiovascular risk in young Finns study. The Cardiovascular Risk in Young Finns Study. *Circulation.* 2012;126:402-9.

IV) **Juhola J**, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Kähönen M, Taittonen L, Urbina E, Viikari JSA, Dwyer T, Raitakari OT, Juonala M. Combined effects of child and adult elevated blood pressure on subclinical atherosclerosis. The International Childhood Cardiovascular Cohort Consortium. *Circulation.* 2013;128:217-24.

1 INTRODUCTION

Atherosclerotic diseases (coronary artery disease, stroke and peripheral artery disease) are leading causes of death worldwide. The atherosclerotic process is long-term and the origins of disease is in childhood even though clinical manifestations are usually not evident until middle age or later. Well known risk factors of atherosclerotic disease include hypertension, dyslipidemia, diabetes, family history of cardiovascular disease (CVD), obesity and smoking. These factors, except family history, are mostly modifiable and susceptible to preventive efforts. In this study the aim was to examine tracking of child risk factors of CVD to adult age in six different age groups when controlling for a comprehensive set of confounders. This information could aid in the identification of high-risk individuals with a potential for early, accurate and efficient targeting of preventive efforts. Furthermore, it has not been clear whether genetic factors could be of benefit in the identification of children at risk for adult hypertension or obesity. Previously, it has been shown that overweight or obese children who are non-obese as adults display a similar lower cardiovascular-risk profile as non-obese children (Juonala et al., 2011). Also, it has been found that recovery from metabolic syndrome has a beneficial effect on vascular properties in young adults after a six-year follow-up (Koskinen et al., 2010). The vascular effects of elevated blood pressure from child to adulthood are still, however, unclear. This study aimed to examine whether the risk of subclinical carotid atherosclerosis was reduced if elevated blood pressure during child resolved by adult age.

The Cardiovascular Risk in Young Finns Study is an on-going multicentre follow-up study of cardiovascular risk factors. The original cross-sectional survey was conducted in 1980 when 3,596 individuals aged 3-18 years participated. Large cohort studies including repeat comprehensive assessments over the life-course provide the best opportunity to elucidate connections between cardiovascular risk factors and the development of cardiovascular disease, as it is challenging to conduct clinical trials spanning more than 50 years. The follow-up studies initiated in Finland, Australia and the United states in the 1970's and 1980's were joined together in 2009 when a consortium (International Childhood Cardiovascular Cohort (i3C) Consortium) was established with improved opportunities to study long-term effects of cardiovascular risk factors in a combined data set.

2 REVIEW OF THE LITERATURE

2.1. ORIGIN AND PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Clinical atherosclerotic diseases, such as ischemic heart disease, stroke and peripheral artery disease, are among the main causes of morbidity and mortality worldwide. Though the onset of atherosclerosis is in early life, clinical manifestation of the disease occurs decades later. The progression of atherosclerosis is shown in **Figure 1**. Evidence of atherosclerosis in the young was reported in autopsies of Korean War casualties showing atherosclerotic changes in 77% of the soldiers at a mean age of 22 years (Enos, Holmes, & Beyer, 1953). Similar results were observed by McNamara et al. among casualties of the Vietnam War (McNamara, Molot, Stremple, & Cutting, 1971). These autopsy findings were later confirmed in the aorta and coronary arteries of children and young adults in the Bogalusa Heart Study and the Pathological Determinants of Atherosclerosis in Youth (PDAY) study. These studies showed that atherosclerosis in the young is associated with known ante- and post-mortem risk factors for CVD including BMI, SBP (systolic blood pressure), DBP (diastolic blood pressure), serum concentrations of total cholesterol, triglycerides, and LDL-C, as well as cigarette smoking and impaired glucose tolerance (Berenson et al., 1998; H. C. McGill, Jr. et al., 2000). In the longitudinal Bogalusa Heart Study an autopsy was performed in the young (≥ 2 years of age) who had died from accidents or homicides and whose risk factor data was available prior to death (ante-mortem). In the PDAY study the risk factor data (smoking, hypertension, obesity and impaired glucose tolerance) was obtained post-mortem from adolescents and young adults aged 15 to 39 years.

Atherosclerosis is denoted as hardening and thickening of the intima, the innermost layer of the arterial wall. Rupture of the atherosclerotic plaque often leads to the manifestation of clinical symptoms of atherosclerosis such as stroke and myocardial infarction. The American Heart Association (AHA) has described the six histological stages of the atherosclerotic process (Herbert C. Stary, 2000; H. C. Stary et al., 1994).

Initial (type I) lesion consists of lipid-laden macrophages (foam cells) appearing as isolated lesions only. In type II lesions fatty streaks consisting of foam cells begin to appear. Intermediate type III lesions contain macrophages and grow as a result of lipid accumulation. In type IV lesions (atheroma) smooth muscle cells in the intima become lipid-laden and a fibrous cap can be detected over the lipid core. In type V lesions (fibroatheroma) the lipid-laden smooth muscle cells are the primary component and extracellular matrix (collagen, glycoproteins and proteoglycans) is synthesized by these cells. Complicated type VI lesion can lead to fissure and hemorrhage or rupture of the

plaque and thrombus formation. Atheromas and complicated lesions may compromise the distal blood flow by stenosis, and subsequent thrombus formation and embolus may lead to clinical symptoms of stroke, myocardial infarction or peripheral artery disease. Size of the plaque, consistency of the lipid core and thinness of the lipid core predisposes to plaque rupture. In most people the type IV lesions do not narrow the vessel lumen much but in the presence of very high blood lipid levels large amounts of lipids may accumulate quickly causing further narrowing of the lumen.

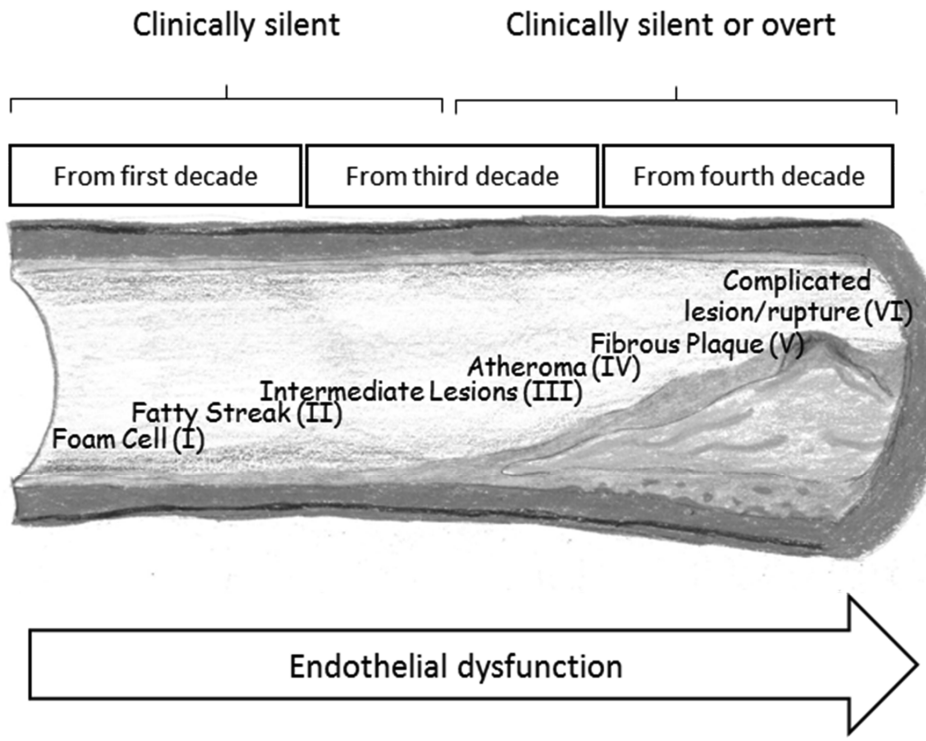

Figure 1. Progression of endothelial dysfunction and arterial stiffness.

2.2. RISK FACTORS OF ATHEROSCLEROSIS IN CHILDREN AND YOUNG ADULTS

The development and progression of atherosclerosis is associated with conventional risk factors of CVD including hypercholesterolemia, smoking, hypertension, obesity, diabetes, a positive family history, and physical inactivity. Clustering of risk factors in child has been shown to accelerate the process of atherosclerosis (Berenson et al., 1998; Juonala, Viikari, et al., 2010; H. C. McGill, Jr. et al., 2001). Moreover, these child risk factors have been associated with markers of subclinical atherosclerosis such as coronary artery calcification (CAC) and carotid artery intima-media thickness (cIMT). Both CAC and cIMT have been shown to be associated with risk factors of CVD and with

the prevalence of stenotic and ischemic myocardial lesions in adult populations (Greenland et al., 2007).

2.2.1. HYPERTENSION

It has been estimated that about 50% of stroke and ischemic heart disease worldwide and a total of 7.6 million deaths in 2001 could be attributed to high blood pressure (Lawes, Vander Hoorn, & Rodgers, 2008). An increase in SBP by 20mmHg and DBP by 10mmHg has been shown to double the risk of mortality from both ischemic heart disease and stroke. Blood pressure tends to persist (track) over time (Chen & Wang, 2008). For example, in the Bogalusa Heart Study it was shown that 40% of 5 to 14 year-old children with SBP over the 80th percentile remained in the highest quintile 15 years later (Bao, Threefoot, Srinivasan, & Berenson, 1995). The National High Blood Pressure Education Program (NHBPEP) implemented guidelines for pediatric hypertension and provided cut-points to define hypertension in children and adolescents. Hypertension was defined as SBP $\geq 95^{th}$ percentile and/or DBP $\geq 95^{th}$ percentile on repeat measurements stratified for age, sex, and height based on national data from the United States (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). A blood pressure between the 90^{th} and 95^{th} percentile was defined as prehypertension. By definition, therefore, the prevalence of essential hypertension in child would be approximately 5% but in several studies on healthy randomly selected children from the population the true prevalence of hypertension has been between 3% and 4.5% and the prevalence of prehypertension about 3% (M. L. Hansen, Gunn, & Kaelber, 2007; Sorof, Lai, Turner, Poffenbarger, & Portman, 2004). Obesity in child is associated with higher blood pressure and with the current obesity epidemic the severity and extent of child hypertension has been estimated to increase.

Autopsy studies show that hypertension in children and young adults is associated with the presence and severity of atherosclerosis in the aorta and coronary arteries. Hypertension was related with atherosclerotic lesions among 93 autopsied persons aged 2 to 39 years in the Bogalusa Heart Study (Berenson et al., 1998) and the PDAY study reported raised lesions in hypertensive young white and black adults (H. C. McGill et al., 1998). The association between child hypertension and subclinical markers of atherosclerosis has been examined in several studies. Lande et al. studied the association between child primary hypertension and vascular structure in children aged 10 to 18 years in a cross sectional design. In their study cIMT was higher in hypertensive children compared to normotensive controls and cIMT was correlated with more severe hypertension and the association was independent of obesity (Lande, Carson, Roy, & Meagher, 2006). Thus, hypertension was considered a potential marker of blood pressure induced vascular damage. Another cross-sectional study including 53

hypertensive and 33 normotensive children aged 11-18 years reported hypertension and obesity related vasculopathy (Sorof et al., 2003). cIMT was increased in hypertensive children compared to normotensive children and remained higher after controlling for gender, race, age, height, weight, and BMI. Furthermore, participants with both high SBP and DBP had higher cIMT than participants with isolated systolic hypertension. Although the authors noted that BMI was most strongly associated with cIMT they suggested that both hypertension and overweight were potentially capable of causing vascular pathology even in early age. Moreover, the longitudinal results of the Cardiovascular Risk in Young Finns study showed that LDL-C, BMI, SBP and smoking assessed at the age of 12-18 years were independently associated with cIMT 21 years later (Raitakari et al., 2003). The Muscatine study reported that adolescent SBP and DBP were statistically significantly associated with cIMT in young adulthood in univariable analyses but the association was not statistically significant when adjusted for BMI and total cholesterol (Davis, Dawson, Riley, & Lauer, 2001). The Atherosclerosis Risk in Young Adults (ARYA) study, including 750 participants in Utrecht with blood pressure assessed at a mean age of 13 years and a follow-up to 27-30 years of age, showed that adolescent SBP was positively related with cIMT in young adulthood (Vos et al., 2003).

The association of child/adolescence blood pressure levels and other indices of subclinical atherosclerosis in adulthood such as decreased flow mediated dilation (FMD), decreased carotid artery elasticity and CAC have been studied previously in the Young Finns cohort. Juonala et al. found that elevated SBP at 12 to 18 years of age predict impaired brachial endothelial function in adulthood after controlling for other child and adulthood risk factors including adult blood pressure (Juonala, Viikari, Rönnemaa, Helenius, et al., 2006). Juonala et al. furthermore reported that child SBP and child skinfold thickness were independent predictors of decreased carotid artery elasticity assessed by three different methods (carotid artery compliance, Young's elastic modulus (YEM) and stiffness index (SI)) (Juonala et al., 2005). Another study of the Young Finns cohort by Hartiala et al. (Hartiala et al., 2012) found that adolescent (12 to 18 years) LDL-C and systolic BP were independent predictors of CAC 27-years later in adults. As the findings were shown to be independent of changes in systolic BP and LDL-C over time, it was concluded that these risk factors during adolescence may have long lasting effects on the coronary arteries that can contribute to the development of CAC in adults.

Thus, elevated BP, even at early age, has been considered to potentially damage the vasculature. However, vascular effects after changes in or normalisation of blood pressure tracking over time from child to adult age is still unclear.

2.2.2. OBESITY

Obesity is associated with several comorbidities such as type 2 diabetes, CVD, hypertension, sleep apnea, and some cancers (Roberts, Dive, & Renehan, 2010). More than 40 years ago the Framingham Heart Study showed that obesity is associated with cardiovascular mortality (Kannel, Lebauer, Dawber, & McNamara, 1967). More recent studies report that adult obesity is associated with in increased all-cause mortality (Engeland, Bjorge, Sogaard, & Tverdal, 2003; Jee et al., 2006). In addition, a high child BMI has been linked with an increased risk of CVD in adulthood (Baker, Olsen, & Sorensen, 2007). Moreover, a doubling of the rate of premature death from endogenous causes has been observed from the lowest to the highest child BMI quartile (Franks et al., 2010). In the Muscatine study, Mahoney et al. linked child BMI with CAC at a mean age of 33 years (Mahoney et al., 1996). Furthermore, in a study by Juonala et al., using data from 6,328 participants compiled from four prospective follow-up studies, child overweight/obesity was associated with known risk factors of CVD in adulthood including type 2 diabetes, hypertension, high LDL-C, high HDL-C, high triglycerides, and high cIMT (Juonala et al., 2011). The risk of type 2 diabetes at adult age was more than doubled among children who were overweight or obese (Juonala et al., 2011).

Presently the US Preventive Services Task Force (USPSTF) recommend to measure BMI in all children to identify those at increased risk of obesity later in life (U. S. Preventive Services & Barton, 2010). Child obesity was defined as an age- and sex-specific BMI above the 95th percentile and overweight as a BMI between the 85th and 95th percentile. The International Obesity Task Force has provided age- and sex-specific international cut-offs for child overweight and obesity from ages 2 to 18 years. These cutoffs are considered to be stricter than the USPSTF's thresholds and to represent approximately the 99th percentile for child obesity. The prevalence of child and adolescent overweight and obesity has increased during the 1980s and 1990s in the United States but the increase has levelled off in more recent years (Ogden, Carroll, Kit, & Flegal, 2012; Y. Wang & Beydoun, 2007). Nevertheless, obesity in child and adolescent is becoming more severe (Skelton, Cook, Auinger, Klein, & Barlow, 2009; Skinner & Skelton, 2014). The tracking of BMI from child to adult age is strong (Srinivasan, Bao, Wattigney, & Berenson, 1996) with a 3 to 4-fold risk of an overweight or obese child to be obese at adult age (Juonala, Viikari, Rönnemaa, Helenius, Taittonen, & Raitakari, 2006). Furthermore, the recent study by Juonala et al. showed that 65% of overweight or obese children were obese as adults and 80% of obese children were obese also in adulthood (Juonala et al., 2011).

Several childhood determinants of adult obesity such as low socioeconomic status, parental overweight/obesity, birth weight, low childhood physical activity, age of maturation and childhood temperament have been previously identified (Parsons,

Power, Logan, & Summerbell, 1999). Earlier cohort studies have included small samples with a relatively short follow-up precluding a comprehensive control of important confounding. It is not known if the prediction of adult obesity could be improved by taking into account other child characteristics or novel risk markers such as increased inflammation or novel genetic variants. Moreover, Cole et al. proposed international cutoffs to define obesity and overweight in children (Cole, Bellizzi, Flegal, & Dietz, 2000), but the sensitivity and specificity of these cutoffs to correctly identify children at risk of adult obesity has not been previously tested longitudinally.

2.2.3. SERUM LIPIDS

Low-density lipoprotein cholesterol (LDL-C) has a central role in the development of atherosclerosis. LDL-C is related with cardiovascular events and mortality in adults, and the use of statins reduces the amount of CVD events. High-density lipoprotein cholesterol (HDL-C) is inversely related with coronary heart disease events in adults (Gordon, Kannel, Castelli, & Dawber, 1981). Triglycerides are directly associated with relative weight and development of diabetes mellitus (Castelli, 1986). Although high triglycerides are strongly associated with CVD, there is some controversy as to whether high triglycerides are a risk factor that contributes directly to CVD or whether it is a biomarker of other underlying processes (Cullen, 2000; Sarwar et al., 2007).

The Bogalusa Heart Study and the PDAY Study showed that dyslipidemias are associated with atherosclerotic lesions and accelerated atherosclerosis already during the first two decades of life. In cross-sectional studies by Järvisalo et al., hypercholesterolemia in child was directly associated with increased carotid and aortic IMT and inversely associated with brachial FMD in children aged 9 to 16 years (Järvisalo et al., 2001; Järvisalo et al., 2002). Furthermore, the longitudinal Muscatine, Bogalusa Heart, and Cardiovascular Risk in Young Finns, and CDAH studies reported child LDL-C, HDL-C and total cholesterol levels to predict subclinical atherosclerosis in adulthood (Davis et al., 2001; S. Li et al., 2003; Magnussen et al., 2009; Raitakari et al., 2003).

NCEP Expert Panel guidelines was used to define high plasma lipid levels in childhood and adolescence. High total cholesterol was defined as ≥200mg/dL (5.17mmol/l), high LDL-C as ≥130mg/dL (3.36mmol/l), and high triglycerides as ≥100mg/dL (1.13mmol/l) for those aged 0-9-years and as ≥130mg/dL (1.47mmol/l) for those aged 10-19-years. Low HDL-C was defined as <40mg/dL (1.03mmol/l). The most common dyslipidemias in childhood are familial hypercholesterolemia (FH) and combined dyslipidemia. Combined dyslipidemia characterized by elevated LDL-C and triglyceride levels is estimated to be prevalent in more than 40% of obese adolescents (Kavey, 2015). FH is an autosomal dominant disorder causing severly elevated LDL-C

levels and is most commonly due to the defects on LDL receptor gene. Other genes that may be affected are subtilisin/Kexin 9 (PCSK9) and apo B. This is related with a high CVD mortality at an early age if undiagnosed and untreated. The prevalence of the homozygous FH has previously been reported to be approximately 1:1 million and the prevalence of heterozygous FH approximately 1:500 in European populations (Goldstein, Schrott, Hazzard, Bierman, & Motulsky, 1973; Reiner et al., 2011). More lately reports from Europe and US suggests a prevalence of heterozygous FH between 1:200 and 1:250 (Benn, Watts, Tybjaerg-Hansen, & Nordestgaard, 2012; de Ferranti et al., 2016; Nordestgaard et al., 2013).

Tracking studies have provided essential information of the stability of child lipids over time. The information of the level at which child dyslipidemias track into later life is essential when considering potential benefits of early treatment or prevention. Previously, serum lipids have been examined in the Muscatine, Bogalusa Heart, The Cardiovascular Risk in Young Finns, and CDAH studies showing moderate to strong tracking from child to young adulthood for shorter follow-up times from 4 to 20 years. With total cholesterol, LDL-C, HDL-C, and triglyceride correlation coefficients of 0.42-0.72, 0.44-0.69, 0.29-0.53, and 0.11-0.57 respectively (Clarke, Schrott, Leaverton, Connor, & Lauer, 1978; Magnussen et al., 2011; Porkka, Viikari, Taimela, Dahl, & Åkerblom, 1994; Webber, Srinivasan, Wattigney, & Berenson, 1991). However, as noted in a study by Magnussen et al., a large proportion of children and adolescents identified as having high serum lipid levels do not have high levels in adulthood (Magnussen et al., 2008).

2.2.4. METABOLIC SYNDROME AND DIABETES

Diabetes is strongly associated with CVD long-term and, furthermore, glucose intolerance is associated with the risk of developing CVD. In children with type 1 diabetes endothelial dysfunction, defined as reduced FMD, was observed to be common and it was considered to predispose diabetic children to the atherosclerotic structural changes of the carotid artery (Järvisalo et al., 2004). Children with type 1 diabetes were shown to have increased cIMT compared to healthy controls (Järvisalo et al., 2002a). Clustering of risk factors in child accelerate the progression of atherosclerosis (Raitakari et al., 1995; Raitakari, Porkka, Räsänen, Rönnemaa, & Viikari, 1994; Raitakari, Porkka, Viikari, Rönnemaa, & Åkerblom, 1994). Obesity is often combined with other CVD risk factors such as hypertension, high LDL-C, high triglycerides, low HDL-C and insulin resistance, which in adults is known as metabolic syndrome (MetS). Obesity-related risk factor clustering is also seen in children and clustering is suspected to preserve into adulthood (Raitakari et al., 1995; Raitakari, Porkka, Viikari, et al., 1994). There are several somewhat different but partly overlapping definitions for MetS in adulthood and the most commonly used criteria are provided by the European

Group for the Insulin Resistance (EGIR), International Diabetes Federation (IDF) and National Cholesterol Education Panel (NCEP). Also in 2009 several major organizations published the harmonized criteria of MetS, where waist measurement would continue to be a useful preliminary screening tool and the diagnosis of MetS requires three abnormal findings out of 5 (Alberti et al., 2009). The MetS in adulthood is associated with cardiovascular and overall mortality (Lakka et al., 2002).

There is no consensus about the definition of MetS in child and adolescence and there is some controversy about the utility of the diagnosis to correctly and sufficiently identify risk individuals (Steinberger et al., 2009). Several studies have demonstrated instability of the diagnosis of the MetS in child and adolescence even in a relatively short period of time (Goodman, Daniels, Meigs, & Dolan, 2007; Gustafson et al., 2009). Also, it was noted that approximately two-thirds of the children and adolescents defined as having MetS did not meet the MetS criteria 14 to 27 years later (Magnussen et al., 2012). Child and adolescent MetS predict adult MetS, high cIMT and T2DM (Magnussen et al., 2010; Morrison, Friedman, & Gray-McGuire, 2007; Morrison, Friedman, Wang, & Glueck, 2008). On the other hand, child and adolescent BMI was as good as child and adolescent MetS in predicting adult MetS, cIMT and T2DM (Magnussen et al., 2010). Currently, as stated by American Heart Association, it has been suggested that the definition of MetS in child and adolescence may not be sufficient for cardiovascular risk stratification. A more complex score may be needed and at the moment the focus should be on all cardiovascular risk factors identifiable in child including genetic risk markers and other important individual characteristics (Steinberger et al., 2009).

2.2.5. SMOKING

Smoking is one of the major modifiable risk factors of CVD (Michael J. Pencina, D'Agostino, Larson, Massaro, & Vasan, 2009). The PDAY study showed that in the young smoking was associated with advanced lesions in the left anterior descending coronary artery (LAD) and that smoking accelerated the progression of atherosclerosis to the final stage (Zieske et al., 2005). Effects of smoking on the vasculature are not fully understood but e.g. nicotine and carbon monoxide of tobacco smoke have adverse effects on systemic inflammation markers (i.e. white blood cell counts, CRP, interleukins), platelet activation (i.e. fibrinogen), and lipid profiles (Ambrose & Barua, 2004; Rahman & Laher, 2007; Wannamethee et al., 2005). Smoking contributes to atherosclerosis by causing decreased levels of endothelial NO and increased expression of adhesion molecules related with endothelial dysfunction (D. S. Celermajer et al., 1992; Jaimes, DeMaster, Tian, & Raij, 2004; Messner & Bernhard, 2014). Smoking is associated with higher cIMT in adults (K. Hansen et al., 2016; Howard et al., 1994; Rosvall et al., 2015). Increased cIMT has even been reported in smoking adolescents (Dratva et al., 2013). Furthermore, exposure to environmental tobacco smoke is dose-

dependently related to progression of atherosclerosis and impairment of endothelium-dependent dilatation (David S. Celermajer et al., 1996; Gall et al., 2014; Howard, Wagenknecht, Burke, & et al., 1998; Juonala, Magnussen, & Raitakari, 2013; Kallio et al., 2010; Steenland, 1992). Maternal smoking is also associated with vascular structure and function of the offspring (Geerts, Bots, Grobbee, & Uiterwaal, 2008; Geerts, Bots, van der Ent, Grobbee, & Uiterwaal, 2012). Recently, novel SNPs as modifiers of the smoking effect on cIMT has been found in genome-wide interaction studies (C. Li et al., 2015; L. Wang et al., 2014). This kind of testing can clarify the individual variation in responses to tobacco smoke.

2.3. FAMILY HISTORY AND GENETICS OF CARDIOVASCULAR DISEASE, HYPERTENSION AND OBESITY

Family history of cardiovascular disease is an independent risk factor for coronary artery disease and is considered a similar risk factor as high cholesterol levels, hypertension or diabetes (Lloyd-Jones et al., 2004; Myers, Kiely, Cupples, & Kannel, 1990; Schildkraut, Myers, Cupples, Kiely, & Kannel, 1989). The risk of the offspring is related both to paternal and maternal history of cardiovascular disease as elucidated in a recent meta-analysis (Weijmans, van der Graaf, Reitsma, & Visseren, 2015). Also, family history has been independently associated with subclinical markers of atherosclerosis such as coronary artery calcium, cIMT, and vascular function (Bensen, Li, Hutchinson, Province, & Tyroler, 1999; Pandey et al., 2013). In Young Finns Study young adults with family history had greater cIMT compared to those without (Juonala, Viikari, Räsänen, et al., 2006). Recent guidelines stress the assessment of family history as an important component of primary prevention which impact on treatment decisions of hypertension or dyslipidemias (Chobanian et al., 2003; National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2002).

Identification of gene variants of common diseases and polygenic traits has been rapidly progressing after the implementation of genome-wide association studies (GWAS) (Li & Loos, 2008). The rare diseases may have large genetic effects on, for example, some monogenic forms of obesity, whereas common diseases are polygenic with small contribution of single genetic variants. Therefore, these genetic variants contribution to the cardiovascular risk overall, obesity or hypertension is challenging and the simultaneous identification of several susceptible genetic variants is needed. Several prospective cohort studies on genetic risk scores consisting of multiple single-nucleotide polymorphisms have previously reported associations with cardiovascular events and CAC in populations of European ancestry (Bjornsson et al., 2015; Ripatti et al., 2010; Thanassoulis et al., 2012). In addition, a variety of studies have linked genetic

variants at chromosome 9p21 and in the apolipoprotein(a) gene (LPA) to the risk of CAD and the severity of the disease as classified with angiography (Chan et al., 2013; Dandona et al., 2010; Helgadottir et al., 2012; Patel et al., 2014; Patel et al., 2010). Recently either a genetic risk score and/or a family history were associated with more severe CAD at angiography (Bjornsson et al., 2015; Hindieh et al., 2016). Furthermore, genetic variants are not only linked to an increased risk of CAD but also with a reduced risk of CAD such as variant *ASGR1* (Nioi et al., 2016). In a study by Nioi et al. the mutation in a *ASGR1* gene was associated with lower levels of non-HDL-C and a 34% lower risk of CAD (Nioi et al., 2016).

Heritability of obesity based on twin and family studies is considered to be high, generally in the range of 40-70% (Maes, Neale, & Eaves, 1997), but still genetic variants predisposing to obesity are poorly known and the proportion of the variance in BMI explained by the identified variants is only a few percent (Speliotes et al., 2010). With a genome-wide association study (GWAS) Frayling et al. were the first to discover a single nucleotide polymorphism (SNP), rs9939609 near FTO gene, associated with fat mass and obesity (Frayling et al., 2007). FTO gene variants rs1421085, rs9930506 and rs17817449 were also found to be associated with BMI and obesity risk in white Europeans (Dina et al., 2007; Frayling et al., 2007). A meta-analysis including data on 249,796 individuals confirmed 14 known obesity susceptibility loci and identified 18 novel genetic variants with a total of 32 SNPs associated with BMI (Speliotes et al., 2010). But the research in the area is rapidly progressing and more than 73 obesity susceptibility loci have been identified through GWAS (T. Wang, Jia, & Hu, 2015). These loci are considered to explain only 2% to 4% of obesity heritability leaving a majority of the loci influencing BMI undiscovered (T. Wang et al., 2015).

Hypertension heritability in family and twin studies varies between 30-60% (Ehret, 2010; Levy et al., 2000; van Rijn et al., 2007). In GWAS, several new genetic markers associated with blood pressure and hypertension have been revealed. Ehret et al. reported 29 novel independent SNPs associated with blood pressure with the genetic risk score based on the 29 genetic variants significantly associated with hypertension. To date GWAS have identified over 50 genetic loci influencing blood pressure in predominantly European populations (Kato et al., 2015).

The potential utility of genetic markers to predict future obesity and hypertension has not previously been examined using longitudinal child to adulthood data. Whether these genetic markers can improve the prediction of adult obesity or hypertension in addition to traditional child cardiovascular risk factors was therefore not clear.

2.4. NON-INVASIVE ASSESSMENT OF SUBCLINICAL ATHEROSCLEROSIS

Non-invasive imaging methods to quantify structural and functional characteristics of the arteries with ultrasound include measures of intima media thickness, arterial elasticity (YEM, SI and pulse wave velocity) and endothelial function (brachial artery FMD) among others. Also CAC measured with computed tomography (CT) can be used as a sign of atherosclerosis.

Carotid IMT can be measured with B-mode ultrasound as a surrogate marker of the early structural changes of atherosclerosis. Pignoli et al. demonstrated the the histological measurement of IMT in the common carotid artery correspond with the ultrasound measurement (Pignoli, Tremoli, Poli, Oreste, & Paoletti, 1986; Wong, Edelstein, Wollman, & Bond, 1993). CIMT has been shown to reflect atherosclerotic changes in more proximal vessels (e.g. coronary artery disease) in adults as well as shown to be associated with conventional cardiovascular risk factors (Bots & Grobbee, 2002; de Groot et al., 2004; Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007). Usefulness of the cIMT as a surrogate marker of atherosclerosis has also been criticised. CIMT increases with age among subjects without significant clustering of cardiovascular risk factors. As it is not possible to separately assess the media and the intima layers with non-invasive ultrasound in the subclinical phase of the disease, a high cIMT may well represent an increased media thickness due to media hypertrophy in the absence of intimal atherosclerosis (Gidding, 2008; H. C. Stary et al., 1992). However, several studies have shown increased cIMT to be a strong indicator of future cardiovascular and cerebrovascular events and cardiovascular mortality in adults (Bots & Grobbee, 2002; Chambless et al., 2000; Chambless et al., 1997; Lorenz et al., 2007). In a recent study by Polak et al., it was stated that maximum cIMT (and presence of plaque) in the internal carotid artery improves the prediction of CVD risk in addition to factors included in the Framingham risk score (Polak et al., 2011). CIMT is most widely used as an early surrogate marker of atherosclerosis in the subclinical phase of the disease in young adults.

3 AIMS OF THE STUDY

The Cardiovascular Risk in Young Finns Study is an ongoing longitudinal follow-up study of atherosclerosis risk factors in child established in 1980. At baseline 3,596 (83.2%) participants aged 3 to 18 years attended. The findings of the present study are based on the data from the 21- and 27-year follow-ups performed 2001 and 2007 when a total of 2,283 and 2,204 participants aged 24 to 45 years were re-examined. In addition, study IV includes data for 1,987 participants from the similar contemporary Bogalusa Heart, Muscatine and Childhood Determinants of Adult Health studies. The specific aims of this thesis include:

1. To examine tracking of cardiovascular risk factors from childhood to adult age and the timing of the child assessment in tracking of risk factors to adult age (I).
2. To examine childhood characteristics and genetic predictors of adult obesity and hypertension (II, III).
3. To study longitudinal effects of blood pressure on the vasculature in adulthood (IV).

4 PARTICIPANTS AND METHODS

This study includes data from four prospective cohort studies conducted in Finland (Cardiovascular Risk in Young Finns Study), Australia (Childhood Determinants of Adult Health (CDAH) Study), and the United States (Bogalusa Heart Study, Muscatine Study) (Figure 2). The description of the study cohorts is shown in (Table 1). The methods section is mainly focused on describing the Cardiovascular Risk in Young Finns Study because three of the studies (I, II and III) were based on data from this cohort and only study IV was based on data from all four cohorts.

Table 1. Overview of the study cohorts

Study	Location	Year started	Initial Cohort	Key publications
Muscatine Study	Iowa, USA	1971	N=4829, aged 8-18 y	Davis et al. 2001, Mahoney et al. 1996
Bogalusa Heart Study	Louisiana, USA	(1972) 1973	N=4238, aged 2.5-14 y, Biracial community (65% white, 35% black)	Li et al. 2003, Berenson et al. 1998
Cardiovascular Risk in Young Finns Study	Finland	(1978) 1980	N=3596, aged 3-18 y	Juonala et al. 2011, Raitakari et al. 2003
Childhood Determinants of Adult Health (CDAH) Study	Australia	1985	N=1919, aged 9-15 y	Magnussen et al. 2008, Magnussen et al. 2009

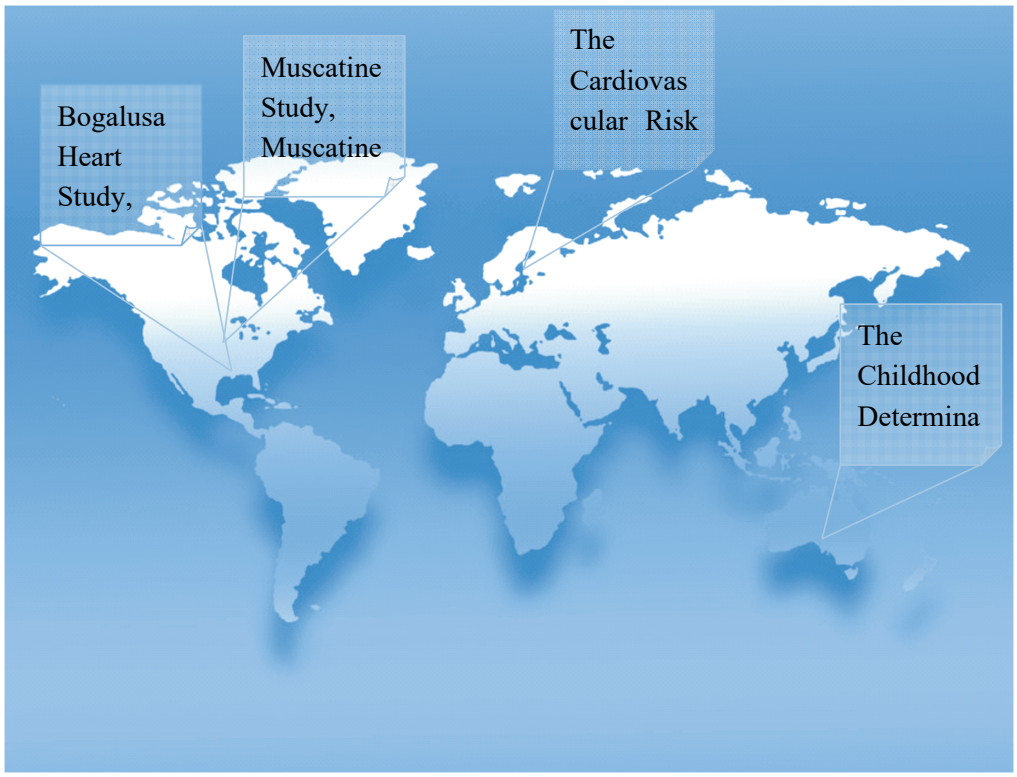

Figure 2. Cohort locations of studies that are part of the International Childhood Cardiovascular Cohort (i3C) Consortium

4.1. THE CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

4.1.1. PARTICIPANTS

The Cardiovascular Risk in Young Finns Study is a multicentre population based follow-up study from child to adulthood evaluating risk factors and precursors of cardiovascular disease. The study began in 1980 when a total of 4,320 Finnish children and adolescents aged 3, 6, 9, 12, 15, 18 years were invited and 3,596 (83.2%) of them participated in the first cross-sectional survey conducted in five university cities and their rural surrounds. The progression of the Cardiovascular Risk in Young Finns Study is shown in **Figure 3**. Subjects were randomly recruited from a national register. The follow-up studies have been performed in 1983, 1986, 2001 and 2007 with 2,991 (83.2%), 2,779 (78.3%), 2,288 (63.5%) and 2,204 (61.3%) subjects participating, respectively. Childhood data at baseline (1980) and 1986, and adulthood data at 2001 and 2007 follow-ups when participants were aged 24 to 45 years, was included in the analyses.

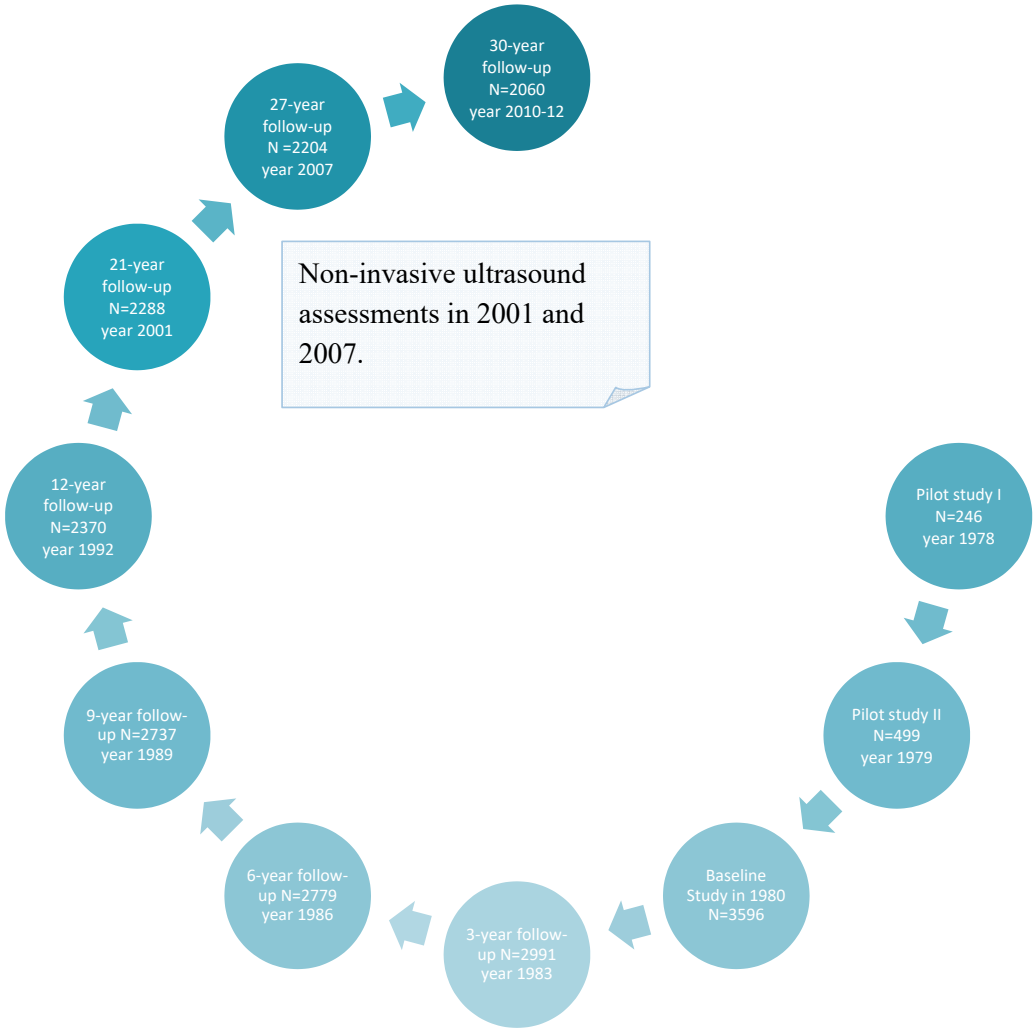

Figure 3. Progression of the Cardiovascular Risk in Young Finns Study

4.1.2. BIOCHEMICAL ANALYSES

Blood samples were collected from the right antecubital vein after a 12-hour fast (Raitakari et al., 2008). Total cholesterol and triglycerides were measured enzymatically (Olympus system Reagent; Germany) in a clinical chemistry analyser (AU400, Olympus) in 2001 and 2007. HDL-C was analysed after precipitation of very low-density lipoprotein and LDL-C with dextran sulphate 500,000. LDL-C concentration was calculated using the Friedewald-formula in subjects with triglycerides <4.0 mmol/l. In 1980, 1983, and 1986, total cholesterol concentrations were measured using a fully enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) with OLLI 3000 and Kone CD analysers (Kone Co., Espoo, Finland). During 1980-1986 serum triglycerides were determined with an enzymatic method (Boehringer Mannheim).

All lipid measurements were performed in duplicate in the same laboratory. The coefficient of variation (CV) was 2.2% for total cholesterol, 2.3 % for HDL-C and 3.8% for triglycerides.

Lipid levels from 1980, 1983 and 1986 were corrected by using following correction factor equations to correspond to the samples taken in 2001 due to changes in methods and kits over time. Triglycerides measured in 2007 were also corrected but corrections were not needed for total cholesterol, HDL-C and LDL-C levels measured in 2007. These equations were determined with linear regression analysis utilizing standardized principal component adjustments.

Total cholesterol = 1.091 x total cholesterol (1980–1986) – 0.271 mmol L^{-1}.

HDL-C = 1.068 x HDL-C (1980–1986) – 0.0277 mmol L^{-1}.

Triglycerides = 1.00756 x triglycerides (1980–1986) + 0.0582 mmol L^{-1}.

Triglycerides = (triglycerides (2007) + 0.03226)/0.9811

In 2001 and 2007 plasma glucose concentrations were analysed enzymatically and serum C-reactive protein (CRP) was analysed using a latex turbidimetric immunoassay kit (CRP-UL-assay, Wako Chemicals, Neuss, Germany) with an automated analyser (Olympus, AU400). The CV for plasma glucose was 2.0% and the interassay CV for CRP was 3.3%. Serum insulin was measured with a micro particle enzyme immunoassay kit (Abbott Laboratories, Diagnostic Division Dainabot). In 1986 serum glucose was measured with the β-D-glucose: NAD oxidoreductase method and in 1980, 1983 and 1986 serum insulin using a modification of the immunoassay method of Herbert et al. (Herbert, Lau, Gottlieb, & Bleicher, 1965). Due to changes in methods or reagents from 2001 to 2007 glucose and insulin levels were corrected with the following correction factor equations:

Glucose = (glucose (2007) – 0.0235)/0.9471

Insulin = insulin (2007) x 1.3728 – 0.8795

4.1.3. BLOOD PRESSURE MEASUREMENTS

Blood pressure was measured from right brachial artery using a standard mercury sphygmomanometer in 1980 and in 1983 and using a random zero sphygmomanometer in 1986, 2001, and 2007. In 1980, blood pressure from 3-year-olds was measured using an ultrasound device (Arteriosonde 1020, Roche). Blood pressure was measured in the sitting position following a 5 minute rest at all time-points. Korotkoff´s first phase (I) was used as the sign of SBP and fifth phase (V) as the sign of DBP. Readings were

documented to the nearest even number of millimetres at least three times on each subject. The average of these three measurements was used in the analysis.

4.1.4. QUESTIONNAIRES

Questionnaires were used to obtain data on diet (Juonala, Viikari, et al., 2010), physical activity (Telama et al., 1985), exposure to tobacco smoke, birth weight, age at menarche, family history of hypertension and childhood socioeconomic status.

Information on dietary habits was obtained with a non-quantitative food frequency questionnaire (FFQ, short 19-item non-quantitative food frequency questionnaire). Data were recorded from parents in 3–9-year-old subjects, but at the age of 12–18 years study subjects answered the questions themselves with the help of parents, if needed. To examine the frequency of vegetables and fruit consumption, participants were asked habitual dietary choices with six response categories; 1=daily, 2=almost every day, 3=a couple of times per week, 4=about once a week, 5=a couple of times per month, 6=more seldom. The response categories were converted into times of consumption per week (1->9.5; 2->6.3; 3->3; 4->1.2; 5->0.3; 6->0). The questionnaire was used to obtain data on daily milk consumption in glasses with one glass being estimated as 0.2 litres.

In child physical activity was ascertained at 9 years of age or older by assessing the frequency, intensity and duration of physical activity. Study subjects answered themselves with parental help if needed. The answers were coded as an index ranging from 5 to 14.

Parental hypertension was present if either parent reported the diagnosis of hypertension at or before the age of 55 years. Data on birth weight and height were obtained from the parents in 1983 when participants were 6–21 years old. Birth weight was analysed as a continuous variable.

Childhood socioeconomic status was determined by obtaining data on parental school years, family income and parental occupational status. Parental school years was coded into an ordinal variable (<9, 9–12, >12 years). Family income was coded as an eight-category variable and parental occupational status into three categories: manual, lower-grade non-manual and higher-grade non-manual.

Information on cigarette smoking was collected in participants aged 12 years or older at baseline, and participants with daily smoking or more often were considered as smokers. Parental smoking was defined as either parent reporting daily smoking.

4.1.5. OTHER STUDY VARIABLES

Weight (kg) and height (m) were measured and BMI calculated as weight/height^2. Preterm birth was defined as birth before 37 weeks' gestation. Individuals born at term were categorized either as small for gestational age (SGA) (birth weight < 10th percentile) or as appropriate birth weight for gestational age (AGA) (birth weight 10-90th percentile).

4.1.6. CAROTID ARTERY ULTRASOUND

B-mode ultrasound studies of the left carotid artery were performed at both 2001 and 2007 follow-ups using standardized protocols (Raitakari et al., 2003). At least four caliper measurements of the far wall were taken approximately 10 mm proximal to the bifurcation to derive mean and maximum IMT and the best-quality end-diastolic frame was selected (Raitakari et al., 2003). 57 subjects were re-examined 3 months after their initial visit to assess reproducibility (test-retest variation) of ultrasound measurements with an average absolute difference and SD between visits of 0.05±0.04 mm. An independent observer reanalysed 113 scans to evaluate inter-observer variation of the measurement with a CV of 5.2%.

4.1.7. GENETIC ANALYSES

In the present analyses, we used 29 SNPs associated with systolic and diastolic BP recently identified in GWAS (Ehret et al., 2011). Genotyping was successfully performed with the Illumina Bead Chip (Human 670K) in 1, 939 individuals. A genetic risk score was calculated as an arithmetic sum of risk alleles in these 29 SNPs. All results were essentially similar when the genetic risk score was derived with the allele count weighted by the effect sizes established in previous GWAS meta-analyses (Ehret et al., 2011).

4.2. THE MUSCATINE STUDY

4.2.1. PARTICIPANTS

Between 1970 and 1981, 11 377 school children aged 8 to 18 years in Muscatine, Iowa, underwent biennial examinations (Lauer, Clarke, & Beaglehole, 1984). 721 individuals (29% of those eligible) that had previously participated in at least one childhood survey and participated in the 1996-99 follow-up (adult age 33 to 45 years) when cIMT was measured were included in the analyses. This subset of participants has previously been demonstrated to be representative of the original cohort at baseline (Dwyer et al., 2013).

4.2.2. CLINIC MEASUREMENTS

Height was recorded to the nearest 0.5 cm using the Iowa Stadiometer. Blood pressures were measured using standard mercury sphygmomanometers at baseline and follow-up measurements were obtained using random-zero sphygmomanometers. All measurements were taken on the right arm, before blood work, and after the participant had been seated for five-minutes. Blood pressure cuffs covering at least two-thirds of the upper arm length and sufficiently long to encompass at least one-half of the arm circumference without overlapping were used. Pressures at the first, fourth and fifth Korotkoff phase were recorded. The mean of three systolic and diastolic (fifth phase) measurements obtained at baseline and follow-up were used in analyses (Clarke et al., 1978)

4.2.3. CAROTID ARTERY ULTRASOUND STUDIES

Carotid ultrasound studies were performed by one technician using the Biosound Phase 2 ultrasound machine equipped with a 10-MHz transducer (Biosound Esaote Inc., Indianapolis, IN). The protocol for bilateral carotid ultrasound assessments included maximal IMT of the near and far walls of the common carotid, carotid bifurcation, and internal carotid artery (Davis et al., 2001). A 4.4% random sample underwent repeat carotid ultrasound studies during a second visit at mean 107 days later to assess reproducibility. The mean absolute difference for the within-subject reliability was 0.058 mm with a median of 0.049 mm for the mean of the 12 maximal IMT measurements (Davis et al., 2001).

4.3. THE BOGALUSA HEART STUDY

4.3.1. PARTICIPANTS

Seven cross-sectional surveys were performed for total of 12 164 children aged 4-17 years between 1973 and 1994. 586 individuals who had blood pressure measured in either the 1981-83, 1984-85, or 1987-88 youth surveys (when aged 4-17-years) and blood pressure and cIMT measured in either the 2001-02 or 2003-07 adult surveys (then aged 23-42-years) were included in the analyses in the present study.

4.3.2. CLINIC MEASUREMENTS

Height was measured to the nearest 0.1 cm using a manual height board. The average of replicate measurements was used as the score. BP was measured at baseline and follow-up from the right arm after venepuncture with participants in a relaxed sitting position. Upper arm length and circumference were measured to select a cuff of appropriate size. Systolic and diastolic BPs were recorded at the first, fourth, and fifth Korotkoff phases

using mercury sphygmomanometers. The phase five reading was used to denote diastolic pressure in the analyses. Three BP readings were taken by each of two randomly assigned observers for a total of six measurements. The trained observers were blinded to each other's readings. The mean of the six replicate readings was used in the analyses.

4.3.3. CAROTID ARTERY ULTRASOUND STUDIES

B-mode ultrasound examinations were performed at the 2001-02 and 2003-07 follow-ups according to established protocols (S. Li et al., 2003). Maximum IMT was measured from three right and three left far walls for common carotid, carotid bifurcation, and internal carotid segments according to strict protocols. Seventy-five participants underwent repeat ultrasound examinations 10-12 days after their initial visit to determine intra-individual reproducibility. The average absolute difference and standard deviation (SD) between measurements for all carotid IMT segments was 0.05±0.03 mm.

4.4. THE CHILDHOOD DETERMINANTS OF ADULT HEALTH (CDAH) STUDY

4.4.1. PARTICIPANTS

Baseline data was collected in 1985 when 8498 school aged children (7-15 years) participated. 680 individuals who had blood pressure measured in the 1985 baseline survey (when aged 9-, 12-, or 15-years) and cIMT and blood pressure measured in the 2004-06 adult follow-up survey (then aged 27-36-years) were included in this study.

4.4.2. CLINIC MEASUREMENTS

Height was measured to the nearest 0.1 cm using a portable stadiometer. BP measurements were obtained in the sitting position and following a five-minute rest from the upper left arm using a standard mercury sphygmomanometer at baseline. Appropriate cuff size was selected according to the upper arm girth. Systolic pressure was recorded at Korotkoff's first phase and diastolic pressure was recorded at both Korotkoff's fourth and fifth phase, and fifth phase was selected to define DBP at baseline. This procedure was repeated after five-minutes and the mean of the two measurements was used in the analyses. At follow up BP was measured from the right upper arm using a digital automatic monitor (Omron HEM907, Omron Healthcare Inc, Kyoto, Japan). The mean of the three consecutive measurements of systolic and DBPs separated by a one-minute interval was used in the analyses.

4.4.3. CAROTID ARTERY ULTRASOUND

B-mode ultrasound studies of the carotid artery were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) ultrasound machine with a 7.0-MHz linear-array transducer by one technician. Vascular measurements derived with this machine compare well with those from a clinic-based machine (Magnussen, Fryer, Venn, Laakkonen, & Raitakari, 2006). Imaging followed protocols described in the Young Finns study (Raitakari et al., 2003). Several 3- to 5-second real-time image clips were recorded including the proximal carotid bulb and approximately 30 mm of the common carotid artery. The two highest-quality end-diastolic frames were selected by the reader for measurement and six measurements of the common carotid far wall were taken approximately 10 mm proximal to the carotid bulb to derive mean and maximum cIMT. Intra-rater reproducibility for maximum IMT measurements was assessed in a random sample of 30 participants with the average absolute difference and standard deviation of 0.02±0.04 mm.

4.5. CLASSIFICATION OF CHILDHOOD AND ADULTHOOD RISK FACTOR LEVELS

We used age and sex specific cut off points for BMI recommended by the IOTF (Cole et al., 2000) to define child overweight/obesity. Child prehypertension (>=90th percentile) was classified based on height, sex, and age tables from the NHBPEP (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Pediatric dyslipidemia was classified in accordance with NCEP borderline-high (borderline-low in the case of HDL-C) cut off points ("National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents," 1992). Adult obesity was defined as BMI >30 kg/m^2. Adult hypertension was defined as SBP≥140mmHg or DBP≥90mmHg or use of medication for the condition as per guidelines of the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). Also lower limits such as SBP≥130mmHg or DBP≥85mmHg and SBP≥120mmHg or DBP≥80mmHg or use of medication for the condition for the adult hypertension was used. European cut off points for high serum lipids in adulthood was applied: total cholesterol (TC) >5.0 mmol/l (190 mg/dl), LDL-C>3.0 mmol/l (115mg/dl), HDL-C: Men<1.0 mmol/l (40mg/dl), Women<1.2 mmol/l (46mg/dl), triglycerides (TG) >1.7 mmol/l (150 mg/dl) (Graham et al., 2007).

4.6. STUDY DESIGN AND STATISTICAL ANALYSES OF STUDIES I-IV

Statistical analyses were performed using Statistical Analysis System (SAS version 9.2) and STATA version 10.0. P-value of <0.05 was considered statistically significant. An attrition analysis was performed to determine if the representativeness of the baseline sample was maintained in the present cohort, baseline characteristics were compared between those who participated and those who did not participate at follow-up.

Study I

Age and sex specific Spearman's rank-order correlation coefficients were calculated to examine 27-year tracking of cardiovascular risk factors. For blood pressure analyses, the values of those aged 3 years at baseline were excluded due to differences in the method of measurement between study years 1980 and 2007. Odds ratios (OR) and 95% confidence intervals (95%CI) for having abnormal adult risk factor levels for child risk factor status are presented stratified by sex for children aged 3-, 6-, or 9-years, and children aged 12-, 15-, or 18-years. The puberty stage paralleled with age stratification. We combined age groups due to low numbers exceeding cutoffs for some strata. Odds of having the outcome in adulthood are expressed for the presence of the child risk factor (absence of child risk factor is a reference group). The cutoff points when the child factor is considered as risk factor are presented in the methods section. The performance of the high-risk child levels to predict abnormal adult levels was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity was calculated as true positives/ (true positives + false negatives) x 100; specificity as true negatives/ (true negatives + false positives) x 100; NPV as true negatives/ (true negatives + false negatives) x 100; and PPV as true positives/ (true positives + false positives) x 100. These data are presented stratified by age and sex. Subjects currently using lipid lowering medications (N=46) or antihypertensive medications (N=152) were excluded when calculating correlations for serum lipids or blood pressure, respectively, and pregnant subjects were excluded (N=37) when analysing BMI.

Study II

Age- and sex-specific z-scores for child variables were calculated to study the associations of child risk variables with adult obesity. Logistic regression was then used to examine age- and sex-adjusted odds of adult obesity. Then, a multivariable logistic regression analysis using stepwise modelling was constructed to determine the independent childhood predictors of adult obesity. As no sex*risk factor interactions were observed in logistic models, the analyses were not stratified by sex. The analyses were repeated using high-risk waist circumference (≥88 cm in females and ≥102 cm in

males) as an outcome variable. In addition, similar modelling was performed after including also the genotype data in the analyses. A risk score composed of child BMI at baseline, maternal BMI and family income using effect sizes given in Table 4A was used in age-stratified analyses.

The incremental value of adding risk variables to predict adult obesity was examined based on multivariate logistic regression models. The ability of several models to predict obesity risk was estimated using C statistics by calculating the area under the receiver operating characteristic curve (AUC), the net reclassification improvement (NRI) and integrated discrimination index (IDI) (M. J. Pencina, D'Agostino, D'Agostino, & Vasan, 2008). For NRI, participants were assigned to one of four categories (<5%, 5%-10%, 10%-20%, and >20%) that reflected their risk of adult obesity based on each model. Model calibration was tested by the Hosmer-Lemeshow X^2 test (M. J. Pencina et al., 2008).

Values for triglycerides, insulin and CRP were $\log_{10}$-transformed prior to analyses due to skewed distributions.

Study III

Age- and sex-specific z-scores for each continuous childhood variable were calculated before analyses to study the associations between childhood risk variables and adult hypertension,. Values for triglycerides, insulin and CRP were $\log_{10}$-transformed prior to analyses due to skewed distributions.

Logistic regression was used to examine age- and sex-adjusted odds of adult hypertension. The variables that were significant in age and sex specific analyses were then added to multivariable logistic regression analyses to determine the independent childhood predictors of adult hypertension. For variables showing strong intercorrelations (i.e. different blood pressure variables, adiposity variables or variables of socioeconomic metrics), only the most representative variable (the one showing the strongest age and sex adjusted association) was selected to avoid multicollinearity.

Nagelgerke's R-square values for different logistic models were calculated to estimate the contribution of parental hypertension and genetic score to the variance of the outcome adult hypertension,. The contribution of either parental hypertension or genetic score was estimated by calculating pseudo R2 values for 3 different logistic regression models with forward stepwise inclusion of either parental hypertension or genetic score to a model with all other significant predictors.

We calculated the odds of adult hypertension for each age group according to a risk score based on the independent predictors of adult hypertension to examine the strength of association between child exposures and adult hypertension across all ages at

baseline, The risk score was composed of child BP, child overweight or obesity, parental hypertension, genetic risk score and parental occupational status at baseline, and weighted by the effect size of each variable as assessed by multivariable logistic regression.

The incremental value of adding risk variables to predict adult hypertension was examined based on multivariable logistic regression models. The ability of several models to predict hypertension risk was estimated by calculating AUC, NRI and IDI. IDI represents a continuous variant of NRI and is defined as the difference in mean discrimination slopes between the two models (M. J. Pencina et al., 2008). NRI and IDI were calculated to determine the extent to which incorporation of parental hypertension and the genetic risk score in the prediction models reassigned individuals to risk categories that more correctly reflected whether or not the subjects developed adult hypertension. Participants were assigned to one of four categories (<5%, 5%-10%, 10%-20%, and >20%) according to their risk for adult hypertension as estimated by the various prediction models. The proportions of participants correctly reclassified to either higher- or lower-risk categories (by incorporation of parental hypertension and the genetic risk score/additional variables) were compared. Model calibration was tested by the Hosmer-Lemeshow X^2 test (M. J. Pencina et al., 2008).

Study IV

The study cohort consisted of the combined data set of the i3C Consortium. Comparisons of characteristics between the cohorts were conducted using chi-square tests or analysis of variance.

Relative risks (RR) and 95% confidence intervals (CI) were calculated using Poisson regression with robust standard errors to examine the associations between child-adult BP groups and adult high cIMT. All analyses were adjusted for length of follow-up, cohort, race, and adult BMI. Both data pooling and meta-analysis (DerSimonian & Laird, 1986; Pettigrew, Gart, & Thomas, 1986) techniques were used. In pooled analyses we additionally adjusted for age and sex. Cohort×BP, sex×BP, and age×BP group interaction effects were tested. There were no significant interaction effects observed in the analyses.

Several sensitivity analyses were performed to examine the influence of different child and adult BP definitions, sex, age and adiposity status on the magnitude of the associations. In cohorts with relevant available data, pooled analyses were re-run after additional adjustment for smoking status (Bogalusa, Young Finns, and CDAH), socioeconomic status (Young Finns, CDAH) and pubertal status (Young Finns) in childhood.

In order to examine the influence of BMI on change in BP status between child and adult age, we present mean (SD) change in BMI (adult minus child) of age-, sex-, cohort-, and race-specific (Bogalusa) z-scores for each BP group. BP groups were as follows: control group – participants who had a normal BP in child and had normal BP as adults; resolution group - participants who had elevated BP in child but not as adults; incident group – participants with a normal BP in child who had elevated BP as adults; and persistent group – participants who had elevated BP in child and as adults. Logistic regression analyses was used to examine differences between the control group and the remaining BP groups. The logistic regression models were adjusted for length of follow-up for analyses stratified by cohort and additionally adjusted for cohort in pooled analyses.

5 RESULTS

5.1. CHARACTERISTICS AND ATTRITION OF THE YOUNG FINNS STUDY PARTICIPANTS

5.1.1. CHARACTERISTICS

The baseline (1980) characteristics according to sex for those who participated in follow-up study in 2001 or 2007 are shown in (Table 2). The study cohort consisted of 2625 participants of which 1430 (54.5%) were females and 1195 (44.5%) were males. The mean age of the participants at baseline in 1980 was 10.6 years.

Table 2. Characteristics of participants in the Young Finns Study according to sex at baseline (1980).

Variable	Females		Males		
	Statistic*	N	Statistic	N	P-value
Age (years)	10.6±5.0	1430	10.6±5.0	1195	0.37
Systolic BP (mmHg)	111±11.2	1430	114±12.9	1195	0.0004
Diastolic BP (mmHg) (IV)	73.5±11.1	1391	73.7±11.5	1159	0.64
Diastolic BP (mmHg) (V)	68.5±9.4	1221	68.9±9.9	1007	0.34
Resting heart rate (beats/minute)	82.7±14.4	1426	78.3±14.6	1190	<0.0001
Maternal hypertension prevalence (%)	42375	1415	42466	1185	0.72
Paternal hypertension prevalence (%)	42561	1324	42593	1084	0.74
Parental hypertension prevalence (%)	42504	1430	42475	1195	0.51
Parental smoking prevalence (%)	38.2	1417	38.7	1184	0.79
Smoking prevalence (%)	42410	697	15.0	567	0.01
Childhood prehypertension prevalence (%)	47.8	1183	48.9	986	0.63
BMI (kg/m²)	17.8±3.0	1430	17.9±3.1	1195	0.25
BMI z-score‡	-0.14±0.93	1430	-0.14±1.03	1195	1.00
Parental education (%)§	39/37/24	1408	36/38/26	1182	0.82
Family income (8 levels)	4.8±2.0	1380	4.9±1.9	1160	0.76
Parental occupational status (%)‖	39/45/17	1289	40/42/18	1036	0.38
Physical activity index	10.8±3.8	1331	11.5±3.8	1102	<0.0001
Birth weight (g)	3448±517	1241	3560±568	1021	<0.0001
Triglycerides (mmol/l)	0.79±0.3	1419	0.75±0.3	1188	0.0004
LDL-C (mmol/l)	3.3±0.8	1417	3.2±0.7	1188	<0.0001
HDL-C (mmol/l)	1.5±0.3	1417	1.5±0.3	1188	0.32
Total cholesterol (mmol/l)	5.2±0.8	1419	5.0±0.8	1188	<0.0001
CRP (mg/l)	1.08±3.2	1231	0.9±2.8	990	0.26
Insulin (IU/l)	10.3±6.2	1411	8.9±5.6	1182	<0.0001
Milk consumption (dl/day)	3.1±1.6	1373	3.8±1.9	1146	<0.0001
Vegetables or fruit consumption (frequency/week)	13.5±4.5	1414	12.9±4.9	1175	0.0023
Age at menarche (years)	12.0±2.0	1305			
Small for gestational age (g)	2620±180	49	2671±268	38	0.29
Preterm birth (g)	2821±611	144	2884±615	124	0.40

*Statistics are mean±SD or proportions.
‡Z-score for body mass index-for-age according to the Centers for Disease Control and Prevention growth charts (Kuczmarski et al., 2002).
§Three categories (<9/9-12/>12 years), according to a higher educated parent.
‖Three categories according to a parental occupation (manual/lower-grade non-manual/higher-grade non-manual).

5.1.2. ATTRITION

An attrition analysis was performed to compare child baseline (in 1980) characteristics between participants and non-participants at the 2001 or 2007 adult age follow-ups. The representativeness of the study cohort is shown in Table 3. Non-participants were more often of male sex (59% vs. 46 %, P<0.0001), younger (10.0 vs. 10.6 years, P=0.0007) and more often from lower income families (family income category 4.6 vs. 4.9, P=0.001). Non-participants were also more often classified as overweight or obese (11.3 vs. 8.2 %, P=0.006) but with no difference in continuous BMI between groups.

Table 3. Baseline characteristics (in 1980) of study participants and non-participants in the Young Finns Study at the 2001 or 2007 adult follow-ups.

Variable in 1980	Participants	Non-participants
N	2625	971
Age*	10.6	10.0
Sex, male (%)†	46	59
SBP (mmHg)‡	112.6	112.4
DBP (mmHg)‡§	68.7	69.1
Parental hypertension (%)‡	14.9	14.3
Family income‖	4.9§	4.6
Overweight/Obesity (%)†	8.2	11.3
BMI (kg/m2)‡	17.9	17.8
Total cholesterol (mmol/l)‡	5.1	5.1
HDL-C (mmol/l)‡	1.5	1.5
LDL-C (mmol/l)‡	3.3	3.2
Triglycerides (mmol/l)‡	0.77	0.76

*Differences between participants and non-participants were examined with t-test, P <0.001
†Differences between participants and non-participants were tested with χ^2, P<0.01
‡Differences between participants and non-participants were examined with t-test; differences in parental hypertension was tested with χ^2, P was always > 0.05
§Three-year-olds were not included, N (participants)=2228; N (non-participants) = 772.
‖Differences in family income (eight categories) was examined with logistic regression, P <0.01

5.2. TRACKING AND PREDICTABILITY OF CARDIOVASCULAR RISK FACTORS FROM CHILDHOOD TO ADULTHOOD

5.2.1. TRACKING OF CARDIOVASCULAR RISK FACTORS OVER 27-YEARS

Spearman's correlation coefficients (r) for cardiovascular risk factors measured between 1980 and 2007 are shown in Table 4. Significant tracking was observed both in males and females across all age groups. The strong correlation between childhood and future cardiovascular risk factors was observed among 9-18 year-old males and females for LDL-C (r=0.50-0.63 (P<0.001) in females and 0.48-0.59 (P<0.001) in males), HDL-C (r=0.41-0.58 P<0.001 in females and 0.48-0.59 P<0.001 in males), total cholesterol

(r=0.52-0.57 P<0.001 in females and 0.43-0.57 P<0.001 in males) and BMI (r=0.37-0.53 P<0.001 in females and 0.33-0.59 P<0.001 in males), but especially in males the correlation was strong also among the younger children between 3 to 6 years for total cholesterol and LDL cholesterol (r=0.56-0.56 and 0.53-0.61 respectively, P<0.0001). The weakest correlations were seen for DBP (r=0.21 (P<0.0001) for females and r=0.25 for males (P<0.0001)) and TG (r=0.30 (P<0.0001) for females and r=0.27 for males (P<0.0001)).

Table 4. Age and sex specific Spearman's correlation coefficients for 27-year tracking (1980-2007) of cardiovascular risk factors in the Young Finns Study

	Age in 1980	BMI		SBP		DBP		TC		LDL-C		HDL-C		TG	
		N	r	N	r	N	r	N	r	N	r	N	r	N	r
Females															
	3	155	0.29	-	-	-	-	162	0.39	160	0.34	160	0.45	162	0.08†
	6	193	0.43	195	0.35	194	0.25*	201	0.40	200	0.44	201	0.41	201	0.34
	9	183	0.53	182	0.35	182	0.26*	190	0.52	189	0.50	190	0.41	190	0.36
	12	223	0.45	213	0.36	213	0.09†	232	0.57	231	0.63	232	0.42	232	0.28
	15	212	0.37	201	0.36	201	0.19*	214	0.56	211	0.61	214	0.58	214	0.35
	18	188	0.51	168	0.33	168	0.28*	184	0.53	184	0.57	184	0.48	184	0.38
	All	1179	0.43	1124	0.32	958	0.21	1183	0.50	1175	0.52	1181	0.46	1183	0.30
Males															
	3	153	0.36	-	-	-	-	154	0.56	151	0.53	154	0.45	154	0.22*
	6	142	0.35	139	0.33	139	0.23*	142	0.56	137	0.61	141	0.50	142	0.36
	9	172	0.54	169	0.39	167	0.29*	173	0.57	168	0.58	172	0.59	173	0.13†
	12	171	0.59	159	0.23*	158	0.11†	166	0.49	159	0.59	165	0.56	166	0.34
	15	182	0.33	155	0.28*	155	0.27*	170	0.50	168	0.55	167	0.48	170	0.32
	18	155	0.58	137	0.27*	136	0.35	148	0.43	143	0.48	147	0.49	148	0.24*
	All	975	0.46	909	0.27	755	0.25	953	0.52	919	0.56	946	0.51	953	0.27

All $P<0.0001$, unless $*P<0.01$ and † not meaningful

5.2.2. TRACKING IN CHILDHOOD AND ADOLESCENCE COMPARED WITH TRACKING IN ADULTHOOD

To compare 6-year tracking in childhood (1980-1986) and in adulthood (2001-2007) the correlation coefficients of BMI, SBP, DBP, TC, TG, LDL-C, HDL-C and non-HDL-C for 6 different age categories in childhood and in adulthood was calculated. Tracking in adulthood was stronger for BMI, SBP, DBP, and TG in both genders (Figure 4(a-h).). For TC, LDL-C, HDL-C and non-HDL-C 6-year tracking appeared to be as good in adults as in children and adolescents in both genders. The significant trend for stronger tracking with increasing age was seen in both genders. The trend for 6-year correlations in 1980-1986 (ages 3-18) and in 2001-2007 (ages 21-39) was calculated. Trend in correlation coefficients for 6-year time interval was significant for HDL-C in males (P for trend 0.0004) and for BMI, SBP, DBP and triglycerides in males and females (P for trend < 0.05).

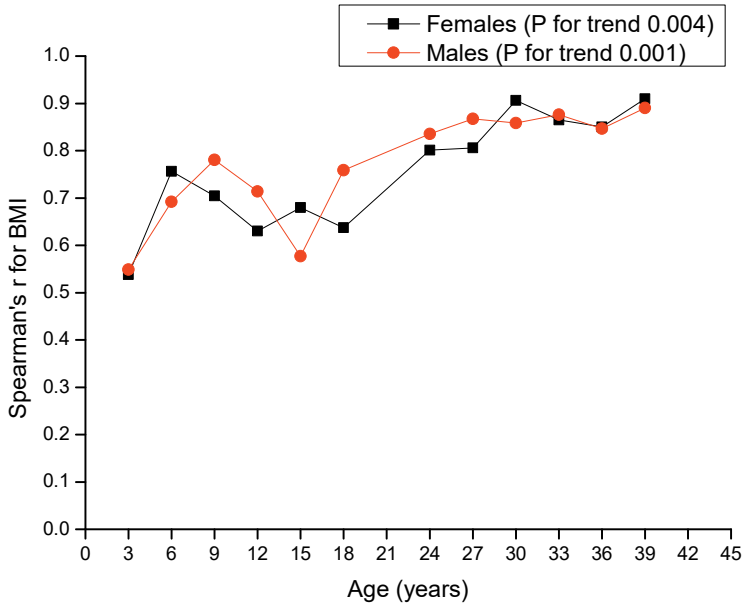

Figure 4a. 6-year tracking for BMI in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

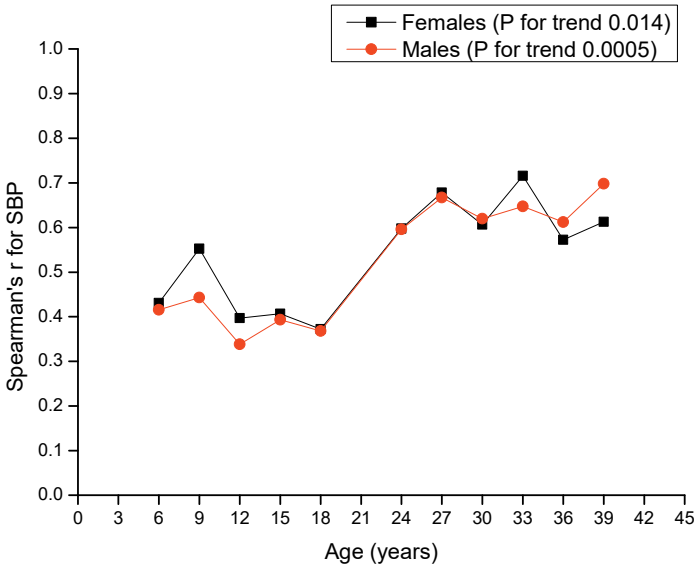

Figure 4b. 6-year tracking for SBP in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

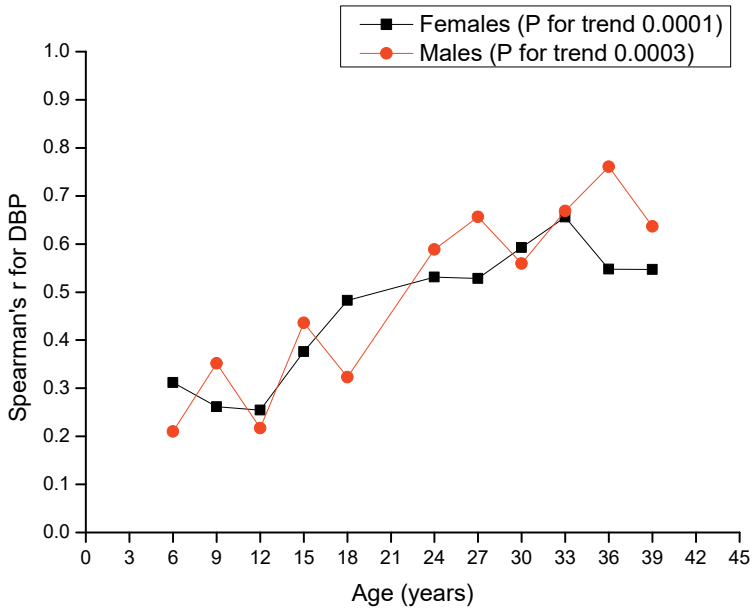

Figure 4c. 6-year tracking for DBP in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

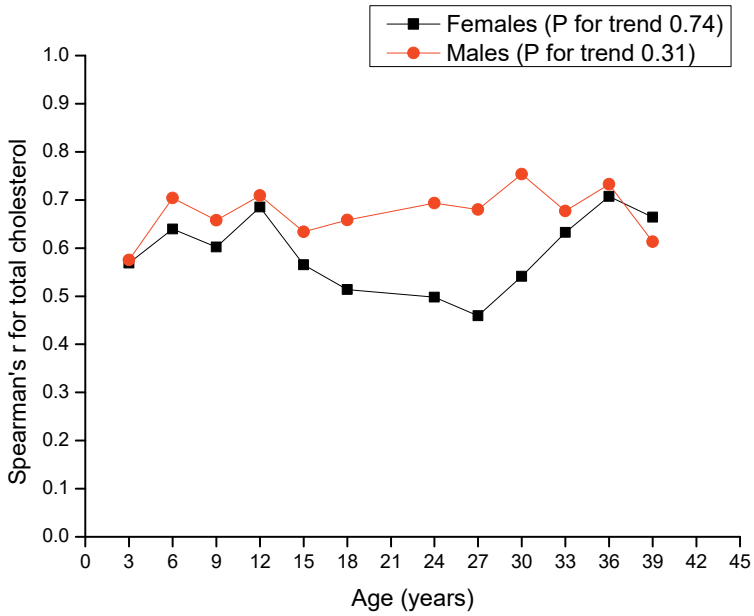

Figure 4d. 6-year tracking for total cholesterol in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

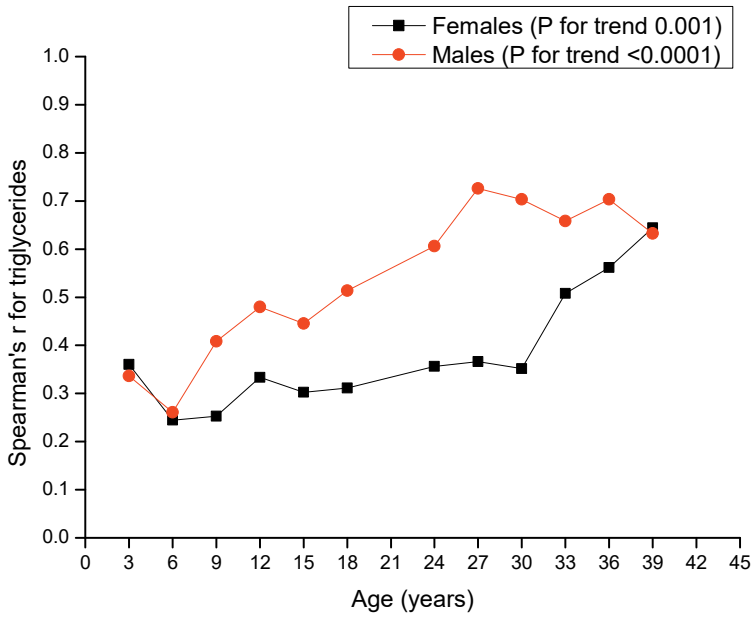

Figure 4e. 6-year tracking for triglycerides in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

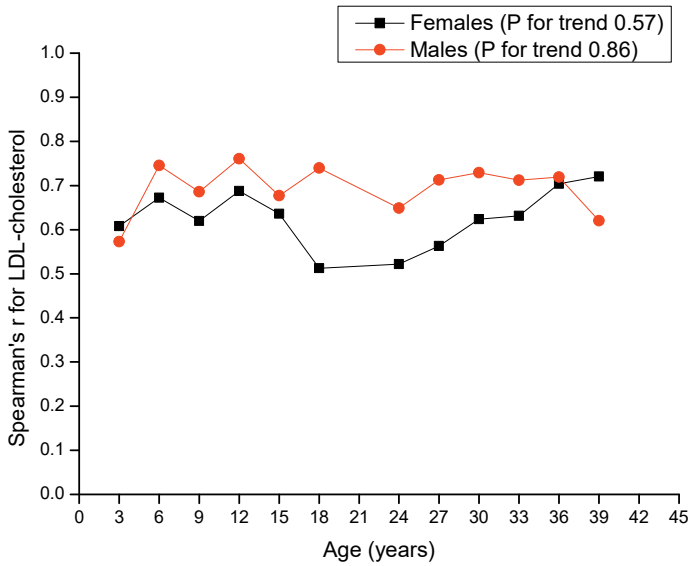

Figure 4f. 6-year tracking for LDL cholesterol in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

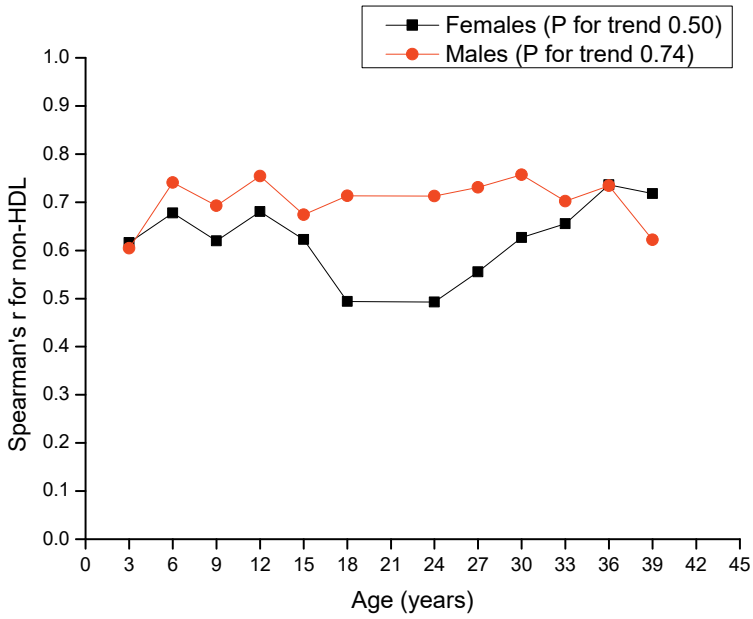

Figure 4g. 6-year tracking for non-HDL-C in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

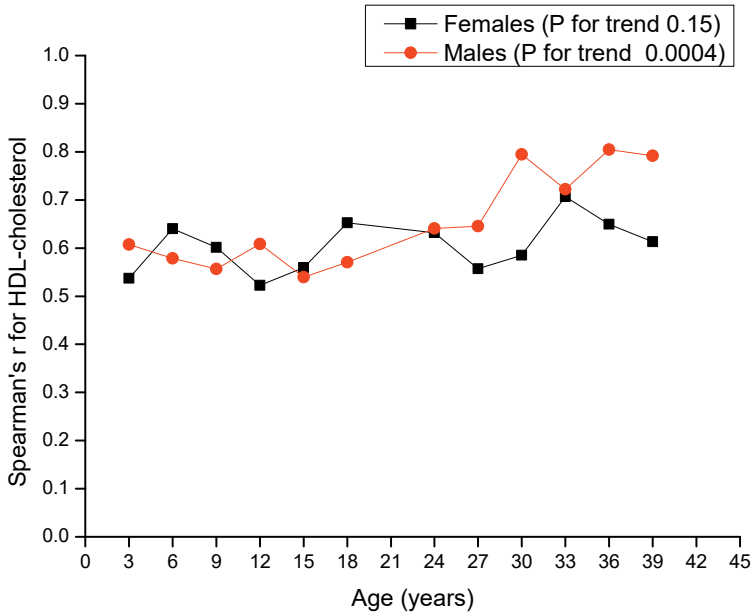

Figure 4h. 6-year tracking for HDL-C in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

Figure 4(a-h). 6-year tracking in childhood (ages 3-18) in 1980-1986 and in adulthood (ages 21-39) in 2001-2007 and trend for tracking from childhood to adulthood.

5.2.3. INFLUENCE OF FOLLOW-UP TIME ON TRACKING

Influence of time on tracking was explored by calculating the age and sex specific correlation coefficients for time intervals of 3, 6, 21 and 27 years (Figure 5). Correlations tended to decrease as time between measurements increased, but correlations remained strong between assessments performed more than two decades later. For BMI the 3-year and 27-year interval correlations were 0.78 and 0.43 ($P<0.0001$) respectively, the corresponding correlations for total cholesterol were 0.65 and 0.48 ($P<0.0001$), for LDL-C 0.70 and 0.51 ($P<0.0001$), for HDL-C 0.66 and 0.46 ($P<0.0001$), for DBP 0.31 and 0.28 ($P<0.05$).

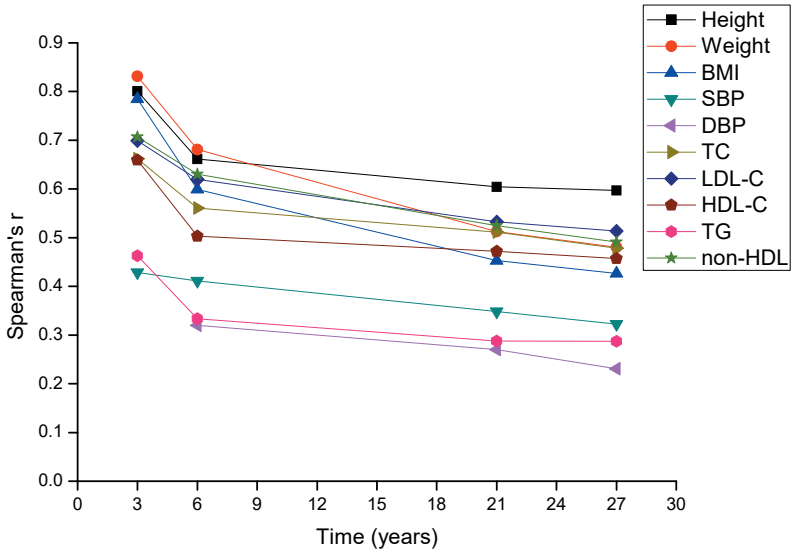

Figure 5. Influence of time on tracking

5.2.4. UTILITY OF CHILDHOOD RISK FACTOR LEVELS TO PREDICT ADULT CARDIOVASCULAR RISK PROFILE

Odds of developing abnormal adult cardiovascular risk factor levels based on childhood risk factors are presented in (Table 5). With the exception of high triglycerides in younger girls, those with high childhood risk factor levels were at significantly increased odds of developing abnormal risk factor levels 27-years later. Odds of an overweight/obese child to become an overweight/obese adult were high for both females and males. In younger male groups the odds of adult overweight/obesity were increased over 6-fold. The odds of developing adult hypertension were over 2-fold for both sexes whereas the odds of developing adult dyslipidemia was over 2- fold for females and over 4-fold for males.

Table 5. Odds ratios (OR) and 95% confidence intervals (95%CI) of abnormal CVD risk factors in adulthood given high-risk childhood levels

	Age at baseline, years			
	3, 6, and 9		12, 15 and 18	
Childhood risk factor	**OR**	**95% CI**	**OR**	**95% CI**
Females				
Overweight/Obesity	5.1	2.8-9.7	9.4	4.7-18.9
Prehypertension/Hypertension*	2.4	1.1-5.2	2.3	1.6-3.5
High TC	2.8	1.4-5.5	7.3	4.2-12.6
High LDL-C	3.1	1.7-5.8	7.8	5.1-11.8
Low HDL-C	3.6	2.3-5.6	4.1	2.7-6.2
High TG	1.4	0.8-2.6	3.0	1.8-4.9
Males				
Overweight/Obesity	6.6	3.3-13.3	18.9	9.2-38.7
Prehypertension/Hypertension*	2.8	1.5-5.1	2.1	1.5-3.1
High TC	4.5	2.4-8.4	5.3	3.4-8.3
High LDL-C	5.8	3.3-10.0	4.6	3.0-6.9
Low HDL-C	5.8	3.6-9.2	4.3	2.6-7.2
High TG	2.4	1.4-4.2	2.3	1.4-3.8
All				
Overweight/Obesity	5.7	3.6-9.1	13.6	8.3-22.3
Prehypertension/Hypertension*	2.4	1.5-3.9	2.3	1.7-3.0
High TC	3.5	2.2-5.5	5.0	3.6-6.9
High LDL-C	4.0	2.7-6.0	5.4	4.1-7.2
Low HDL-C	4.4	3.2-6.1	4.2	3.0-5.8
High TG	1.8	1.2-2.7	2.4	1.7-3.3

* Data from participants aged 3 years at baseline not included. Prehypertension in childhood was defined as SBP or DBP 90th to <95th percentile and hypertension in childhood SBP or DBP over 95th as in NHBPEP guidelines (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Overweight/obesity in childhood was defined according to age and sex specific cut off points for BMI recommended by the IOTF (Cole et al., 2000). Pediatric dyslipidemia was classified according to NCEP borderline-high (borderline-low in the case of HDL-C) cut off points ("National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents," 1992).

Adulthood obesity was defined as BMI >30 kg/m^2. Adult hypertension was defined as SBP≥140mmHg or DBP≥90mmHg or medication for the condition as per guidelines of the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). To define dyslipidemia in adulthood, European cut off points for high serum lipids was used: total cholesterol (TC) >5.0 mmol/l (190 mg/dl), LDL-C>3.0 mmol/l (115mg/dl), HDL-C: Men<1.0 mmol/l (40mg/dl), Women<1.2 mmol/l (46mg/dl), triglycerides (TG) >1.7 mmol/l (150 mg/dl) (Graham et al., 2007).

Detailed sensitivity and specificity analyses were performed and PPV and NPV calculated across the six age groups to estimate utility of childhood (age 3-18 years) risk factors to predict adult (aged 30-45 years) risk factors (Table 6). Clinical tracking of obesity from child to adulthood was strong in the sense that normal weight children often remained normal weight adults with high NPV (>80) across all age groups and for both sexes. Using current pediatric thresholds most of the overweight or obese adults were defined as normal weight in child and thus ~80% of overweight or obese females and ~70% of overweight or obese males in adulthood would not have been identified.

Overweight or obese children of any age would, on the other hand, most likely be overweight/obese in adulthood 27 years later. High specificity in child overweight/obesity (>90%) to predict adult overweight/obesity was found in all age groups in males and in females. Sensitivity was highest in females aged 6 and 9 years and in males aged 12 years. PPV was highest in 15-year-old females (86%) and males (85%). Tracking of clinical hypertension from child to adulthood was similar in all age groups and sensitivity and specificity was comparatively high. Sensitivity, specificity and PPV were highest in older age groups (12, 15 and 18 years) especially in females for total cholesterol and LDL-C. For HDL-C there were not much distinction between age groups in females with PPV=31-38% and NPV=84-93% in all age groups. In males, child HDL-C levels were most predictive in age groups of 6, 9 and 12 years. With the 95th percentile as a cut off for high child risk factor levels a higher specificity but lower sensitivity was seen among all different risk factors. Sensitivity, specificity and PPV were still highest in older age groups (12, 15 and 18) especially for BMI, hypertension, LDL-C and HDL-C (Table 6).

Table 6. Sensitivity, specificity, positive predictive value, and negative predictive value for the prediction of abnormal CVD risk factors in adulthood for high-risk childhood levels (with international cutoffs in childhood and 95th percentile cutoffs in childhood)

Age, years	**TC***					**LDL-C***				
Females	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
3	143/162	89.8	12.6	37.1	68.4	135/160	90.4	18.5	34.8	80.0
6	186/202	98.4	10.9	33.9	93.8	174/201	94.4	17.8	39.1	85.2
9	172/192	95.7	16.3	52.3	80.0	165/191	94.0	19.4	47.3	80.8
12	202/234	94.6	21.1	52.0	81.3	177/233	94.4	39.7	57.1	89.3
15	173/217	92.0	33.7	60.1	79.6	138/214	82.1	54.9	66.7	73.7
18	159/190	98.0	33.0	62.9	93.6	133/190	91.2	54.6	69.9	84.2
All	1035/1197	94.8	20.5	49.8	82.7	922/1189	90.7	33.0	52.0	81.7
Males										
3	120/155	90.6	31.9	48.3	82.9	109/151	90.1	43.8	58.7	83.3
6	129/144	96.0	17.4	55.8	80.0	117/139	92.5	27.1	63.3	72.7
9	156/176	94.4	17.4	54.5	75.0	147/171	93.8	24.3	61.9	75.0
12	155/173	95.7	22.8	71.6	72.2	129/165	87.3	40.0	74.4	61.1
15	135/181	84.7	52.0	82.2	56.5	112/175	76.2	67.4	85.7	52.4
18	110/156	82.1	59.1	83.6	56.5	102/150	76.9	54.8	81.4	47.9
All	805/985	90.0	30.5	65.7	67.2	716/951	85.1	41.0	70.4	62.6
Age, years	**HDL-C***					**TG***				
Females	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
3	105/160	88.9	41.1	30.5	92.7	23/162	10.3	85.0	13.0	81.3
6	102/202	72.3	56.1	33.3	87.0	28/202	18.2	86.7	14.3	89.7
9	81/192	66.0	65.5	38.3	85.6	26/192	23.5	88.6	30.8	84.3
12	113/234	64.8	56.7	31.0	84.3	34/234	19.5	86.5	23.5	83.5
15	100/217	80.4	63.2	37.0	92.3	29/217	33.3	90.2	37.9	88.3
18	102/190	82.1	53.6	31.4	92.1	36/190	42.9	85.2	33.3	89.6
All	603/1195	74.7	56.6	33.3	88.5	176/1197	24.6	87.1	26.1	86.2

Males										
3	85/154	77.4	50.4	28.2	89.9	23/155	24.3	88.1	39.1	78.8
6	72/143	80.5	61.8	45.8	88.7	16/144	25.5	95.9	75.0	72.7
9	52/175	68.1	84.4	61.5	87.8	22/176	13.5	87.9	31.8	70.8
12	62/172	70.0	74.2	45.2	89.1	18/173	17.1	94.2	66.7	62.6
15	112/177	81.4	42.5	31.3	87.7	30/181	22.1	87.5	56.7	60.3
18	114/153	96.7	30.9	25.4	97.4	26/156	23.3	87.5	53.9	64.6
All	497/974	78.0	57.4	36.4	89.3	135/985	20.7	90.0	52.6	68.0
Age, years	**BMI***					**Hypertension***				
Females	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
3	6/161	5.3	96.5	16.7	88.4					
6	24/200	36.0	91.1	37.5	90.9	110/203	75.0	47.6	10.9	95.7
9	20/188	30.3	93.6	50.0	86.3	99/181	71.4	47.5	15.2	92.7
12	20/228	19.2	94.3	50.0	79.8	89/219	53.7	62.4	24.7	85.4
15	7/213	23.1	99.5	85.7	90.3	69/207	46.0	69.4	24.6	85.5
18	11/189	21.6	98.0	72.7	90.3	105/190	74.5	51.1	33.3	85.9
All	88/1179	22.9	95.5	50.0	86.4	472/1000	62.4	55.7	21.4	88.5
Males										
3	5/153	18.2	99.2	80.0	87.8					
6	12/142	25.0	94.3	25.0	88.5	57/143	55.6	63.8	26.3	86.1
9	20/172	30.0	92.3	45.0	86.2	89/167	76.5	52.6	29.2	89.7
12	17/171	38.2	97.1	76.5	86.4	58/163	47.1	69.6	41.4	74.3
15	13/182	31.4	98.6	84.6	85.8	70/178	53.7	69.4	51.4	71.3
18	19/155	35.0	95.7	73.7	80.9	124/157	87.5	25.7	39.5	78.8
All	86/975	30.9	96.2	65.1	85.9	398/808	63.8	56.7	37.7	79.3
Age, y	**LDL-C†**					**HDL-C†**				
All	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
3	15/311	8.1	97.3	66.7	61.8	15/311	10.5	97.2	50.0	80.0
6	20/340	11.2	98.4	85.0	57.8	20/325	12.5	96.5	55.0	76.3
9	18/362	9.4	99.5	94.4	52.6	16/367	8.5	97.1	50.0	75.5
12	22/398	10.1	100	100	48.1	21/385	14.9	97.8	66.7	79.2
15	23/389	9.7	100	100	41.3	17/394	14.6	98.7	76.5	79.8
18	15/340	6.2	98.5	86.7	39.4	24/343	17.4	95.6	50.0	82.1
All	113/2140	9.1	98.9	90.3	49.8	112/2169	13.0	97.2	58.0	78.8
Age, y	**BMI†**					**Hypertension†**				
All	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**n/N**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
3	15/314	14.6	96.7	40.0	88.3	-	-	-	-	-
6	15/342	11.1	96.6	33.3	87.8	18/352	4.7	94.8	11.1	87.7
9	17/360	15.9	97.6	58.8	84.6	20/367	17.9	96.8	50.0	86.7
12	21/399	16.3	97.8	66.7	81.0	19/404	11.6	97.4	57.9	78.2
15	12/395	18.0	99.7	91.7	87.0	18/401	9.1	97.3	55.6	73.9
18	16/344	16.9	98.9	81.3	80.5	13/347	5.8	97.1	46.2	71.0
All	96/2154	15.8	97.9	61.5	84.7	88/1871	9.6	96.7	44.3	79.4

*International cutoffs: Overweight/obesity in childhood was defined according to age and sex specific cut off points for BMI recommended by the IOTF (Cole et al., 2000). Childhood prehypertension (>=90th percentile) was classified according to height, sex, and age tables from the NHBPEP (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Pediatric dyslipidemia was classified according to NCEP borderline-high (borderline-low in the case of HDL-C) cut off points ("National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents," 1992).

Adulthood obesity was defined as BMI >30 kg/m^2. Adult hypertension was defined as SBP≥140mmHg or DBP≥90mmHg or medication for the condition as per guidelines of the 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). To define dyslipidemia in adulthood, European cut off points for high serum lipids was used: total cholesterol (TC) >5.0 mmol/l (190 mg/dl), LDL-C>3.0 mmol/l (115mg/dl), HDL-C: Men<1.0 mmol/l (40mg/dl), Women<1.2 mmol/l (46mg/dl), triglycerides (TG) >1.7 mmol/l (150 mg/dl) (Graham et al., 2007).

†95th percentile cutoffs

5.3. GENETIC AND CONVENTIONAL CHILDHOOD PREDICTORS OF ADULT OBESITY

5.3.1. ASSOCIATIONS OF CHILDHOOD RISK AND GENETIC FACTORS WITH ADULT OBESITY

Age- and sex specific odds ratios between child risk factors and adult obesity are shown in Table 7. Of the child risk factors, BMI, CRP, maternal BMI, paternal BMI, insulin, SBP, birth weight and aggression prone negative emotionality were significantly associated with adult obesity (P<0.05). Inverse associations for adult obesity were observed for child HDL-C, parental education and family income. As shown in Table 8, polymorphisms in the proximity of the genes *TFAP2B*, *LRRN6C* and *FLJ35579*, *FANCL,* and *FTO,* as well as a genotype risk score, were significantly associated with adult obesity in age- and sex-adjusted analyses.

Table 7. Age and sex adjusted odds ratios of adult obesity in relation to different risk factors during childhood.

Variable	OR(95%CI)	P-value
Child BMI	2.51(2.21-2.85)	<0.0001
Maternal BMI	1.64(1.47-1.83)	<0.0001
Paternal BMI(N=1,868)	1.57(1.39-1.77)	<0.0001
Log-Insulin	1.51(1.33-1.71)	<0.0001
Child SBP	1.42(1.26-1.59)	<0.0001
log-CRP	1.40(1.26-1.55)	<0.0001
Family income	0.83(0.74-0.93)	0.001
HDL-C	0.86(0.77-0.97)	0.01
Parental education	0.87(0.77-0.98)	0.02
Child birth weight(N=1,853)	1.16(1.02-1.31)	0.02
Aggression prone negative emotionality(N=1,903)	1.14(1.02-1.27)	0.02
Log-Triglycerides	1.12(1.00-1.26)	0.05
Vegetables, consumption frequency	0.96(0.86-1.08)	0.49
Temperamental activity	1.03(0.92-1.15)	0.63
Fruit, consumption frequency	0.98(0.87-1.09)	0.67
Physical activity index	1.03(0.91-1.15)	0.67
LDL-C	1.02(0.91-1.14)	0.75
Age at menarche*	0.99(0.91-1.07)	0.71
Emotional warmth	0.99(0.88-1.11)	0.85

Each model includes 2,032-2,119 participants unless otherwise stated.

Odds ratios (OR) for a 1-SD increase in continuous study variables and one category change in parental school years (<9, 9-12, >12 years). Results are sorted by P-value and effect size.

*Data on 1,074 females: odds ratios for one-year change in the age of menarche.

Table 8. Age and sex adjusted odds ratios for adult obesity in relation to genotype

SNP	Nearest gene	OR (95%CI)	P-value
SNP risk score		1.07(1.03-1.11)	0.0002
*rs9930506	FTO	1.26(1.06-1.49)	0.0096
rs987237	TFAP2B	1.33(1.09-1.61)	0.005
rs2112347	FLJ35779	1.23(1.04-1.46)	0.02
*rs9939609	FTO	1.20(1.01-1.42)	0.02
rs887912	FANCL	1.23(1.02-1.47)	0.03
rs10968576	LRRN6C	1.19(1.01-1.41)	0.04
rs1558902	FTO	1.19(1.01-1.42)	0.04
*rs17817449	FTO	1.20(1.00-1.43)	0.041
*rs1421085	FTO	1.19(1.00-1.41)	0.049
rs543874	SEC16B	1.20(0.96-1.40)	0.10
rs2241423	MAP2K5	1.21(0.95-1.52)	0.12
rs7359397	SH2B1	1.12(0.95-1.33)	0.17
rs29941	KCTD15	1.13(0.94-1.34)	0.19
rs10150332	NRXN3	1.11(0.92-1.35)	0.27
rs13107325	SLC39A8	1.43(0.75-2.72)	0.27
rs7138803	FAIM2	1.09(0.92-1.29)	0.33
rs10938397	GNPDA2	1.08(0.91-1.28)	0.36
rs571312	MC4R	1.09(0.87-1.36)	0.47
rs713586	RBJ	1.06(0.90-1.25)	0.49
rs4836133	ZNF608	1.06(0.89-1.26)	0.51
rs1514175	TNNI3K	0.94(0.79-1.12)	0.51
rs206936	NUDT3	0.94(0.77-1.15)	0.54
rs13078807	CADM2	1.07(0.86-1.33)	0.56
rs2287019	QPCTL	1.06(0.87-1.29)	0.58
rs4929949	RPL27A	0.96(0.80-1.14)	0.61
rs2890652	LRP1B	0.96(0.79-1.16)	0.65
rs2867125	TMEM18	1.06(0.84-1.33)	0.65
rs1555543	PTB2	1.04(0.87-1.24)	0.66
rs3817334	MTCH2	0.96(0.81-1.15)	0.66
rs10767664	BDNF	1.05(0.84-1.32)	0.69
rs3810291	TMEM160	1.03(0.85-1.25)	0.74
rs9816226	ETV5	0.97(0.76-1.23)	0.80
rs11847697	PRKD1	1.03(0.53-2.00)	0.93
rs2815752	NEGR1	1.00(0.83-1.20)	0.99
rs4771122	MTIF3	1.00(0.83-1.22)	0.99

Each model includes 1,939 participants, except *rs9930506 N=1819, *rs1421085=1880, *rs17817449 N=1819, *rs9939609 N=1931.

Odds ratios (OR) for a 1-allele increase in gene variants and 1-point increase in risk score in age- and sex-adjusted analyses. Results are sorted by P-value.

SNP risk score is an arithmetic sum variable of risk alleles in these 31 SNPs.

In the age- and sex-specific multivariable model shown in Table 9 the independent predictors of adult obesity included child BMI, child hsCRP, family income (inverse association) and maternal BMI at baseline. Paternal BMI was not included in the model shown in Table 9 due to missing data (N=1,868), but paternal BMI was nevertheless independently associated with adult obesity (OR 1.25[1.09-1.43], P=0.01) in the sub-cohort with data available. Similar results were found when high waist circumference

was substituted for BMI-derived obesity in the multivariable model with the only exception that high insulin (P=0.02) emerged as an additional risk factor.

Polymorphisms in the proximity of the genes *TFAP2B*, *LRRN6C* and *FLJ35579* remained significantly associated with obesity. When the five different FTO SNPs were added separately to the final multivariable model none of them were significantly associated with obesity (P values = 0.12-0.33). Child BMI, CRP, maternal BMI, family income, and the SNPs near the genes *FLJ35579* and *SEC16B* were significant (P<0.05) predictors of increased adult BMI in a multivariable regression analysis using continuous BMI as the outcome variable. However, the effects of the SNPs near the genes *TFAP2B* (P = 0.12) and *LRRN6C* (P = 0.07) were not statistically significant.

Table 9. Stepwise multivariable models for associations between child risk factors, genotype and adult obesity (BMI ≥30 kg/m2).

Variable	OR(95%CI)	P-value
Child risk factors in predicting adult obesity (n=2119)		
BMI	2.28(2.00-2.59)	<0.0001
Maternal BMI	1.37(1.21-1.55)	<0.0001
Log-CRP	1.18(1.05-1.34)	0.007
Family income	0.87(0.77-0.99)	0.03
Child risk factors and genotype data in predicting adult obesity (n=1953)		
BMI	2.33(2.03-2.68)	<0.0001
Maternal BMI	1.35(1.19-1.53)	<0.0001
Log-CRP	1.17(1.03-1.33)	0.02
Family income	0.87(0.76-0.99)	0.04
rs2112347 (*FLJ35579)*	1.28(1.06-1.55)	0.01
rs10968576 (*LRRN6C)*	1.22(1.01-1.48)	0.04
rs987237 (*TFAP2B)*	1.25(1.01-1.56)	0.04

Odds ratios (OR) for a 1-SD or 1-allele increase in study variables.

5.3.2. MULTIPLE CHILD RISK FACTORS IN THE PREDICTION OF ADULT OBESITY

The ability of different logistic regression models to discriminate individuals at risk for adult obesity was estimated using AUC, NRI and IDI (Table 10). The predictive utility of a model including age, sex, child BMI, maternal BMI and family income (model 2) was superior compared with a model including age, sex and child BMI (model 1) (C-statistics 0.751 vs. 0.772, P=0.0015). Including child CRP and novel genetic variants (model 3) did not incrementally improve AUC (0.779, P=0.16) or NRI, although such a model provided significant IDI (Table 10). A simple risk score composed of child BMI, maternal BMI, and family income predicted adult obesity in all age groups between 3-18 years (P <0.001 for all groups).

Table 10. Comparison of models for prediction of adult obesity (BMI>30 kg/m^2) in 1,939 individuals.

	AUC-value (95% CI)	P-value	NRI	P-value	IDI	P-value	H-L	P-value
Model 1.								
Age, sex, BMI	0.751(0.721-0.781)	-	ref	-	ref	-	9.8	0.28
Model 2.								
Age, sex, BMI, maternal BMI, family income	0.772(0.745-0.800)	0.0015	14.1	<0.0001	1.3	0.0005	11.9	0.16
Model 3.								
Age, sex, BMI, maternal BMI, family income, CRP, rs987237, rs10968576, rs2112347	0.779(0.752-0.806)	0.16	2.0	0.45	1.2	0.001	10.5	0.23

CI, confidence interval; NRI, Net reclassification improvement; IDI, Integrative discrimination index; H-L, Hosmer-Lemeshow X^2 statistics; ref, referent model.

5.4. GENETIC MARKERS, CHILD ENVIRONMENTAL AND PHYSICAL FACTORS IN PREDICTING ADULT HYPERTENSION

Odds ratios for various child genetic, environmental and physical factors to predict future hypertension was calculated (Table 11). Elevated child blood pressure, child overweight/obesity, and parental hypertension approximately doubled the odds of adult hypertension. Also, both child systolic and diastolic BP (treated as continuous variables) were significantly associated with adult hypertension. The results were similar for child diastolic BP when either Korotkoff's fourth or fifth phase was used. Inverse associations with adult hypertension were observed for all indices of child socioeconomic status, including parental occupational status, parental school years and family income (low status predisposing to future hypertension) (Table 11). Inverse associations with adult hypertension were also observed for age at menarche and child smoking (including children over 12 years of age). Birth weight did not predict adult hypertension (Table 11), nor did preterm birth (OR 0.92, 95%CI 0.69-1.22, P=0.55, N=2287) and small for gestational age birth weight (OR 1.55, 95%CI 0.96-2.49, P=0.072, N=875).

The novel genetic risk score composed of 29 SNPs was associated with adult hypertension (Table 11). The mean value of the genetic risk score was 30.4 (median, 30.6; range, 20.2-41.2). The age and sex-adjusted effects of the individual SNPs of the score on hypertension risk are shown in Table 12. SNPs near the *CACNB2(3')* (rs1813353), *ULK4* (rs3774372), *ZNF831* (rs6015450) and *ZNF652* (rs12940887) genes were associated with adult hypertension (P<0.01) in additive models (Table 12).

Table 11. Age- and sex-adjusted odds ratios (OR) and 95% confidence intervals (95%CI) of adult hypertension for different childhood factors

Variable	OR	95%CI	P-value	N
Overweight/obesity status*	2.18	1.62-2.93	<0.0001	2625
Youth prehypertension†	2.18	1.82-2.61	<0.0001	2169
Maternal hypertension	2.14	1.52-3.01	<0.0001	2600
Parental hypertension	2.02	1.60-2.54	<0.0001	2625
Paternal hypertension	1.97	1.50-2.59	<0.0001	2408
SBP	1.67	1.53-1.82	<0.0001	2625
DBP (V)	1.42	1.30-1.56	<0.0001	2228
DBP (IV)	1.38	1.26-1.50	<0.0001	2550
Genetic risk score	1.31	1.20-1.44	<0.0001	2391
Body mass index	1.20	1.10-1.30	<0.0001	2625
Parental occupational status	0.78	0.68-0.88	<0.0001	2325
Family income	0.87	0.80-0.94	0.0007	2540
Parental education	0.82	0.73-0.92	0.0008	2590
Log triglycerides	1.15	1.03-1.21	0.008	2607
Smoking‡	0.52	0.35-0.77	0.001	1264
Age at menarche	0.85	0.74-0.98	0.02	1305
Log CRP	1.09	0.99-1.19	0.06	2221
Total cholesterol	1.08	0.99-1.17	0.07	2607
LDL-C	1.07	0.99-1.16	0.09	2605
Insulin	1.07	0.98-1.16	0.13	2593
Resting heart rate	1.06	0.97-1.14	0.19	2616
Vegetables or fruit consumption	0.96	0.89-1.04	0.35	2589
Physical activity index	0.97	0.89-1.06	0.48	2433
Parental smoking	0.94	0.79-1.12	0.51	2601
Birth weight	0.97	0.89-1.06	0.52	2262
HDL-C	0.98	0.91-1.07	0.66	2605
Milk consumption	0.99	0.91-1.08	0.81	2519

Odds ratios (OR) for a 1-SD increase in continuous study variables, one-point increase in 29 SNP risk score, and one category change in youth overweight/obesity status (yes, no), maternal hypertension (yes, no), parental hypertension (yes, no), paternal hypertension (yes, no), parental school years (three categories: <9, 9-12, >12), parental occupational status (three categories: manual, lower-grade non-manual, higher-grade non-manual), parental smoking (yes, no).

*Age and sex specific international cut-off points were used in defining childhood overweight/obesity status

†Child prehypertension was classified according to the tables from NHBPEP. 3-year old participants were excluded because of the differences in the method of DBP measurement.

‡Information on cigarette smoking was available for participants aged 12-18 years.

Hypertension in adulthood was defined as systolic SBP≥130mmHg and/or DBP≥85mmHg or use of antihypertensive medication, either in 2001 and/or 2007.

Table 12. Unadjusted odds ratios of adult hypertension for the 29 individual SNPs of the blood pressure genetic risk score*

	Nearest gene/locus	OR	95%CI	P-value	N
rs1813353	CACNB2	1.26	1.09-1.45	0.002	2402
rs3774372	ULK4	1.25	1.09-1.44	0.002	2402
rs6015450	ZNF831	1.29	1.09-1.53	0.003	2402
rs12940887	ZNF652	1.18	1.04-1.33	0.009	2402
rs13107325	SLC39A8	1.77	0.98-3.18	0.06	2402
rs805303	BAG6	1.11	0.99-1.25	0.08	2399
rs10850411	TBX3	1.11	0.98-1.26	0.11	2402
rs11953630	EBF1	1.11	0.98-1.26	0.11	2402
rs4373814	CACNB2	1.10	0.97-1.24	0.12	2402
rs11191548	NT5C2	1.19	0.95-1.49	0.14	2402
rs17608766	GOSR2	1.12	0.95-1.31	0.17	2400
rs17367504	MTHFR	1.12	0.94-1.33	0.21	2402
rs13082711	SLC4A7	1.10	0.95-1.29	0.21	2402
rs1327235	JAG1	1.08	0.96-1.22	0.21	2402
rs1173771	NPR3	1.08	0.95-1.21	0.24	2402
rs4590817	C10orf107	1.12	0.92-1.35	0.26	2402
rs2521501	FES	1.08	0.93-1.25	0.30	2402
rs932764	PLCE1	1.06	0.94-1.20	0.32	2402
rs1378942	CSK	1.05	0.93-1.18	0.44	2399
rs3184504	SH2B3	1.04	0.93-1.18	0.50	2402
rs2932538	MOV10	1.05	0.90-1.22	0.55	2402
rs1799945	HFE	0.95	0.78-1.15	0.60	2402
rs17249754	ATP2B1	0.94	0.75-1.18	0.62	2402
rs1458038	FGF5	0.98	0.86-1.11	0.72	2399
rs7129220	ADM	0.97	0.83-1.14	0.75	2402
rs419076	MECOM	1.01	0.90-1.14	0.84	2402
rs633185	ARHGAP42	1.01	0.89-1.16	0.85	2402
rs13139571	GUCY1A3	1.01	0.88-1.16	0.90	2402
rs381815	PLEKHA7	1	0.87-1.16	0.97	2402

*SNPs selected according to Ehret et al. (Ehret et al., 2011)

In a multivariable analysis the independent predictors of adult hypertension included parental hypertension, child systolic BP, the genetic risk score, parental occupational status, and child overweight/obesity (Table 13). Both parental hypertension and genetic risk score explained approximately 1% of the variation in adult hypertension as estimated by the Nagelgerke pseudo-R^2 values (for the full model shown in Table 13. Associations between child risk factors and adult hypertension. The multivariable model was adjusted for age and sex (N=2,119). Table 13 the pseudo-R^2 value was 22%). Child diastolic and systolic BP were included separately in the multivariable model due to the strong relation between these variables. When child systolic BP was replaced with diastolic BP in the final model, child diastolic BP was also an independent predictor of adult hypertension. Results were similar using child hypertension as a dichotomous variable in the analyses.

Table 13. Associations between child risk factors and adult hypertension. The multivariable model was adjusted for age and sex (N=2,119).

Variable	OR	95%CI	P-value
Parental hypertension	2.23	1.68-2.96	<0.0001
Child systolic BP	1.04	1.03-1.05	<0.0001
Genetic risk score	1.27	1.13-1.43	<0.0001
Child overweight or obesity*	1.84	1.27-2.67	0.001
Parental occupational status	0.83	0.70-0.97	0.02

Adult hypertension was defined as SBP≥140mmHg and/or DBP≥90mmHg or use of antihypertensive medication, either in 2001 and/or 2007.

Odds ratios (OR) for a 1-SD increase in continuous study variables and one category change in child overweight/obesity status (yes, no), parental hypertension (yes, no), parental occupational status (three categories).

*Age and sex specific international cutoffs were used in defining child overweight/obesity.

The utility of different child risk factor models to predict adult hypertension was examined by comparing four multivariable models. AUC, NRI and IDI were calculated (Table 14). Model 1 consisted of age, sex and child systolic BP, and was compared to model 2 that additionally included child overweight/obesity, parental hypertension, and parental occupational status. Model 2 performed better than model 1 as evidenced by significantly increased AUC, NRI, and IDI (Table 14). Parental hypertension was replaced with a genetic risk score in model 3. The prediction of model 3 was superior compared with model 1 but with no statistical difference compared with model 2. When both parental hypertension and the genetic risk score were included in the model (model 4), both AUC and IDI increased significantly compared to models 1, 2 or 3, with NRI significantly increased compared to model 1.

Nagelkerke´s pseudo R2 value was 0.2231 for the final model shown in Table 14. The pseudo R2 value was 0.1953 for model 1 including all other predictors but not "parental hypertension" or "genetic score". The pseudo R2 value increased to 0.2084 when parental hypertension was added to the model. Alternatively, adding the genetic risk score to the model increased the pseudo R2 to 0.2119. Accordingly, the inclusion of parental hypertension or the genetic risk score increased the pseudo R2 value 0.0131 and 0.0166, respectively.

Table 14. Comparison of models for prediction of adult hypertension in 2,119 individuals.

	AUC-value (95% CI)	P-value	NRI	P-value	IDI	P-value	H-L	P-value	Model Used for Comparison
Model 1									
Age, sex, child SBP	0.706 (0.678-0.735)						7.1	0.53	
Model 2									
Model 1 +child overweight/obesity status*, parental occupational status, and parental hypertension	0.730 (0.703-0.757)	0.004	0.105	<0.0001	0.026	<0.0001	5.3	0.73	1
Model 3									
Model 1 +child overweight/obesity, parental occupational status, and 29 SNP risk score	0.724 (0.697-0.752)	0.0005 0.81	0.109 -0.006	<0.0001 0.8	0.017 -0.009	<0.0001 0.024	12.2	0.14	1 2
Model 4									
Model 1 +child overweight/obesity, parental occupational status, parental hypertension, and 29 SNP risk score	0.739 (0.712-0.765)	<0.0001 0.04 0.007	0.139 0.029 0.034	<0.0001 0.18 0.11	0.033 0.006 0.016	<0.0001 0.007 <0.0001	11	0.20	1 2 3

Adult hypertension was defined as SBP≥140mmHg and/or DBP≥90mmHg, or use of antihypertensive medication, either in 2001 and/or 2007. AUC indicates area under the curve; CI, confidence interval; NRI, Net reclassification improvement; IDI, Integrative discrimination index; H-L, Hosmer-Lemeshow X^2 statistics and SNP, single-nucleotide polymorphisms

* Age and sex specific international cutoffs were used in defining child overweight/obesity.

5.5. EFFECTS OF CHILD AND ADULT ELEVATED BLOOD PRESSURE ON SUBCLINICAL ATHEROSCLEROSIS

For these analyses data from four independent international cohorts including 4,210 participants was available (Table 15). The mean follow-up time was 23 years. The mean SBP in adulthood was highest for Young Finns (120.8mmHg) and lowest in Muscatine (113.8 mmHg). The DBP in adulthood did not differ significantly between cohorts. The mean BMI in adulthood was highest in Bogalusa (30.2 kg/m^2) and lowest in CDAH (25.8 kg/m^2). 42% of the normotensive children displayed elevated blood pressures as adults whereas 60% of the children with elevated blood pressure had elevated adult blood pressures as well (Table 16). Significant tracking was observed between child and adult BP levels in all international cohorts (Table 17).

Table 15. Child and adulthood characteristics of participants in the four cohorts

	Muscatine	**Bogalusa**	**Young Finns**	**CDAH**	**P-value***
N (males/females)	721 (345/376)	586 (234/352)	2,223 (1,004/1,219)	680 (315/365)	0.03
Child					
Age, y	14.6 (1.9)	12.5 (3.4)	12.0 (4.2)	11.9 (2.4)	<0.001
Age range, y	8-18	4-18	6-18	9-15	
Blacks, N (%)	-	209 (35.7)	-	-	
SBP, mmHg	116.9 (12.7)	106.9 (10.8)	114.1 (11.3)	109.3 (12.9)	<0.001
DBP, mmHg	68.8 (10.9)	55.9 (11.6)	68.7 (9.6)	66.4 (11.8)	<0.001
BMI, kg/m^2	21.4 (3.4)	19.9 (4.3)	18.3 (3.1)	18.6 (2.9)	<0.001
Adulthood					
Age, y	38.6 (2.9)	33.9 (3.6)	38.0 (4.8)	31.8 (2.5)	<0.001
Age range, y	33-46	23-42	27-45	27-36	
SBP, mmHg	113.8 (11.8)	115.7 (14.4)	120.8 (14.3)	118.2 (13.0)	<0.001
DBP, mmHg	74.0 (9.7)	77.8 (10.6)	75.7 (11.4)	72.7 (9.5)	0.06
BMI, kg/m^2	28.2 (5.8)	30.2 (7.9)	26.1 (4.8)	25.8 (4.9)	<0.001
cIMT, mm	0.71 (0.15)	0.74 (0.16)	0.67 (0.10)	0.60 (0.10)	<0.001
Length of follow-up, y	24.0 (2.1)	21.4 (1.5)	26.0 (2.2)	19.9 (0.6)	0.009

Values are mean (SD) for continuous variables or N (%) for dichotomous variables unless stated otherwise. Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, CDAH, Child Determinants of Adult Health; cIMT, carotid intima-media thickness.

*P-values are for comparisons across cohorts with linear regression and chi-square tests.

Table 16. Blood pressure status in adulthood in relation to blood pressure status in child

		BP status in adulthood		
		Normal	Elevated	Total
Cohort	BP status in child	n (%)	n (%)	n
Muscatine	Normal	307 (70.3)	130 (29.8)	437
	Elevated	143 (50.4)	141 (49.7)	284
Bogalusa	Normal	301 (56.4)	233 (43.6)	534
	Elevated	21 (40.4)	31 (59.6)	52
Young Finns	Normal	618 (53.7)	533 (46.3)	1151
	Elevated	381 (35.5)	691 (64.5)	1072
CDAH	Normal	260 (57.0)	196 (43.0)	456
	Elevated	101 (45.1)	123 (54.9)	224
All	Normal	1486 (57.6)	1092 (42.4)	2578
	Elevated	646 (39.6)	986 (60.4)	1632

BP status in youth was classified as normal if systolic and diastolic BP (fifth phase) were <90th percentile for age, sex, and height by using the NHBPEP tables, and elevated if systolic or diastolic BP were ≥90th percentile. BP status in adulthood was classified as normal if systolic BP <120 mm Hg and diastolic BP <80 mm Hg, and elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg. In addition, adult BP status was considered elevated among those self-reporting the use of antihypertensive medications.

Table 17. Partial correlation coefficients (r) for tracking of blood pressure (BP) z-scores from child (age 4-18 years) to adulthood (age 23-46 years, mean follow-up 23 years). *

	Systolic BP	Diastolic BP
Cohort	r (N)	r(N)
Muscatine	0.26 (718)	0.23 (718)
Bogalusa	0.33 (583)	0.21 (583)
Young Finns	0.34 (2223)	0.24 (2222)
CDAH	0.31 (680)	0.17 (680
All	0.32 (4204)	0.22 (4203)

*All models adjusted for length of follow-up. All P-values <0.001. Z-scores are age-, sex-, race- (Bogalusa), and cohort-specific.

5.5.1. INFLUENCE OF ELEVATED CHILD AND ADULT BLOOD PRESSURE ON HIGH CIMT IN ADULTS

In participants with elevated child BP and normal adult BP (resolution group) the relative risk of high cIMT in adulthood was comparable to persistently normotensive participants (control group) (Table 18). The risk of high cIMT in adults was higher in adults with elevated BP (incident and persistent groups; incident group – participants with a normal BP in child who had elevated BP as adults; persistent group – participants who had elevated BP in child and as adults.) compared with the normotensive control group. The risk of high cIMT was not significantly increased in normotensive adults with elevated BP in adolescence (12-18 years) but the risk was higher in these compared with elevated BP in early child (4-11 years).

The meta-analysis results are shown in Figure 6. The results were similar to those observed using pooled analyses. Although there was no difference shown in the CDAH cohort between any of the comparator groups and the control group, heterogeneity between cohorts was not statistically significant. Findings were similar when different BP status definitions were used, e.g. defining adult hypertension utilizing a cutoff of 120/80 mmHg or using child BP cutoffs of ≥90th percentile according to NHBPEP tables. Results were consistent in analyses stratified by age, and sex (Table 18). The analyses were also repeated excluding individuals with antihypertensive medication (N=254, 6.0% of the whole cohort) with essentially similar findings.

Several approaches to adjust for the effect of BMI confounding on the results were undertaken. First, the main analyses were additionally adjusted for adult BMI, which did not essentially modify the results shown. Second, analyses were performed separately among normal weight and overweight/obese adult participants with similar results. For example, the risk of high cIMT was not significantly increased within the resolution group (elevated child BP but normal adult BP) with a normal adult weight (RR=1.39, 95%CI=0.91-2.14) nor for the overweight/obese adults (RR=1.12, 95%CI=0.73-1.71).

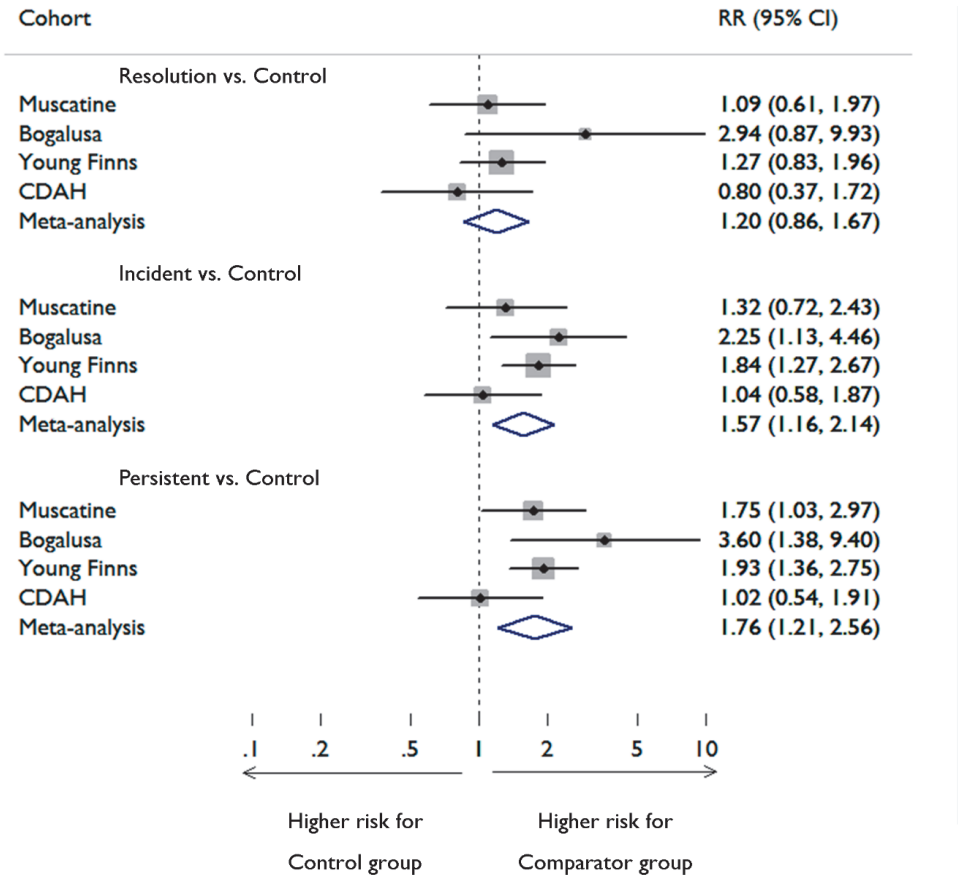

Figure 6. Forest plots showing relative risk of high carotid intima media thickness (cIMT) in the different study cohorts separately and combined.

BP status in youth was classified as normal if systolic and diastolic BP (fifth phase) were <90th percentile for age, sex, and height by using the NHBPEP tables, and elevated if systolic or diastolic BP were ≥90th percentile. BP status in adulthood was classified as normal if systolic BP <120 mm Hg and diastolic BP <80 mm Hg, and elevated if systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg. In addition, adult BP status was considered elevated among those self-reporting the use of antihypertensive medications.

Table 18. Relative risks (RR) and 95% confidence intervals (95%CI) of high cIMT (≥90th percentile) in relation to blood pressure (BP) groups* in child and adulthood

Child – adult	Participants 4-11 years			Participants 12-18 years			Males			Females			All participants		
BP group	n/N	RR	(95%CI)	n/N	RR	(95%CI)	n/N	RR	(95%CI)	n/N	RR	(95%CI)	n/N	RR	(95%CI)
Control	82/844	1.00	ref	188/1945	1.00	Ref	119/1194	1.00	ref	151/1595	1.00	ref	270/2789	1.00	ref
Resolution	27/262	0.96	(0.65-1.46)	49/371	1.31	(0.98-1.76)	33/261	1.21	(0.85-1.73)	43/372	1.21	(0.87-1.68)	76/633	1.22	(0.96-1.54)
Incident	11/101	0.88	(0.47-1.62)	66/388	1.50	(1.14-1.98)	43/290	1.16	(0.83-1.63)	34/199	1.52	(1.06-2.17)	77/489	1.33	(1.04-1.71)
Persistent	17/68	1.82	(1.12-2.95)	27/122	1.92	(1.32-2.79)	26/116	1.75	(1.17-2.61)	18/74	2.14	(1.38-3.33)	44/190	1.94	(1.45-2.61)

All analyses adjusted for length of follow-up, cohort, race, and adult BMI. The age-stratified model additionally adjusted for sex; the sex-stratified model additionally adjusted for age; and the 'All' model additionally adjusted for both age and sex.

*Child BP was classified as elevated if SBP or DBP were ≥95th percentile using the NHBPEP tables for age, sex, and height. Adult BP was classified as elevated if SBP≥140mmHg or DBP≥90mmHg. Elevated BP groups were as follows: control group – participants who had a normal BP in child and had normal BP as adults; resolution group - participants who had elevated BP in child but not as adults; incident group – participants with a normal BP in child who had elevated BP as adults; and persistent group – participants who had elevated BP in child and as adults.

6 DISCUSSION

6.1. MAIN FINDINGS OF THE STUDY

Tracking of LDL-C, HDL-C, total cholesterol, BMI, and SBP and DBP from child to adult age spanning 27-years was significant and strong. Elevated child blood pressure predicted adult hypertension and elevated child BMI predicted adult overweight when these were classified according to international cutoffs. Also high child cholesterol predicted adult dyslipidemia. The best age to assess cardiovascular risk factors in children was evaluated. Child hypertension seemed to predict adult hypertension assessed between 6 and 18 years. Child age did not seem to affect the prediction of abnormal adult lipids in male subjects, whereas in female subjects, measurements (especially LDL-C) were best predicted by assessments in the 12- to 18-year group. Adult obesity specificity rates were very good in all age groups.

The independent predictors of adult obesity included maternal BMI, family income (inversely), child BMI, CRP, and polymorphisms in the proximity of genes FLJ35779, TFAP2B, and LRRN6C. A simple risk score composed of child BMI, family socioeconomic status and maternal BMI significantly improved the prediction of adult obesity. Importantly, this was true across all age groups assessed (3-18 years).

The independent child predictors of adult hypertension were SBP, overweight/obesity, parental hypertension, parental occupational status and genetic risk score consisting of the 29 novel BP-associated SNPs. Prediction of adult hypertension was improved when the genetic risk score was included in the statistical model.

Individuals with persistently elevated BP from child to adulthood had increased risk of subclinical carotid atherosclerosis assessed by cIMT. This risk was markedly reduced in the setting of adult normotension. The main findings of the study are presented in Figure 7.

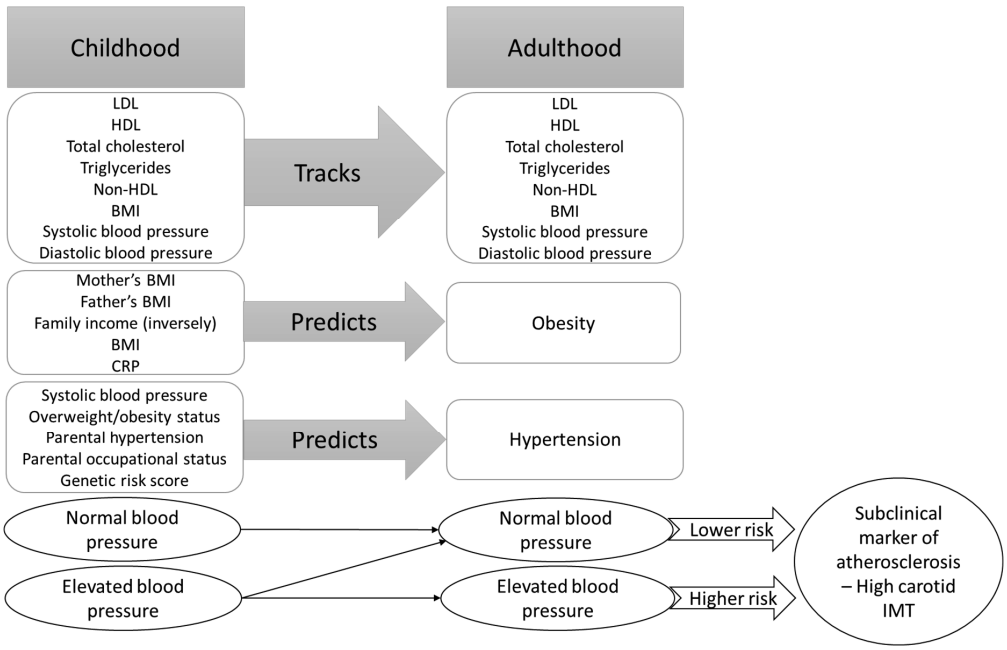

Figure 7. Main findings of the study.

6.2. STUDY COHORT

The study cohort of this thesis primarily consisted of participants from the Cardiovascular Risk in Young Finns Study. The participants were randomly selected from the national register from the five University cities and their rural surroundings. The study was launched in 1980 when 4,320 participants were invited and of those 3,596 (83.2%) participants undertook the initial examination and interviews. The baseline cohort was concluded to be representative of the total sample (Åkerblom et al., 1985). For a prospective cohort with a follow-up over decades, the number of drop-outs due to non-participation is relatively small. The participation rate for the most recent follow-up was 61.3%. Moreover, some participants who dropped out earlier on eventually re-entered the study in later follow-ups. Non-participants in 2001 and 2007 were more often of male sex, younger age, and from lower income families compared with active participants. Non-participants were also more likely to be overweight or obese (according to Cole et al.) compared with participants, even though there was no substantial difference in continuous BMI. The distribution of child risk factors assessed in 1980 were otherwise similar between participants and non-participants so the present study cohort can be considered to be representative of the original cohort.

Data from four large longitudinal cohort studies were combined in study IV. In the Muscatine Study, the 865 participants, who had repeat follow-up examinations every 2

– 4 years from the beginning of 1992, were considered similar to the original cohort for height, weight, blood pressure, triceps skinfold thickness, total cholesterol and triglycerides (adjusted for age, sex and calendar year) at baseline. Participants of the Bogalusa Heart Study who underwent an ultrasound examination of the carotid artery (635 individuals) in 1995-1996 were representative of the original cohort for race, sex, BMI, SBP, HDL-C, LDL–C, and triglycerides. The 2410 participants of the CDAH study (28% of the baseline population) were re-examined in 2004-2006. Participants were slightly older, had lower BMI and included more females, but were similar for blood pressures, total cholesterol, HDL-C and triglycerides (adjusted for age and sex) compared with non-participants. The sample size of the present combined study provide sufficient statistical power and seems representative of the original study cohorts.

6.3. METHODS

Blood pressure was measured in 1980 using a standard mercury sphygmomanometer and in 2001 and 2007 using a random zero sphygmomanometer. Generally, mercury sphygmomanometers are of a standard design with standard parts and are considered to be of similar accuracy. However, lower blood pressure readings using a random-zero sphygmomanometer compared with standard mercury sphygmomanometer have been reported (Parker et al., 1988). In the study by Parker et al. these devices were compared in 66 participants and the mean difference ranged from 2.5 to 3.3 mm Hg for SBP and 1.9 to 2.7 mm Hg for DBP (Parker et al., 1988). According to guidelines of the JNC7 the variability of blood pressure measurements can be diminished by using exacting methods (Chobanian et al., 2003). Specifically, standard validated and calibrated auscultatory devices should be used, with patients seated for at least 5 minutes prior to measurement and using cuffs of appropriate size. In this study these aspects were taken into account. In the Young Finns Study and the Muscatine Study blood pressure was measured three times with the average used in final analyses. In the Bogalusa Heart Study three measurements were obtained by each of 2 randomly assigned observers and the mean of the total 6 readings used in the analyses. In the CDAH Study the mean of two measurements was used at baseline and the mean of the three consecutive 1-minute readings obtained used in the follow-up. Finally, all risk factors measured form blood samples were analysed using standard methods.

CIM) has been shown to be related with cardiovascular risk factors and the risk of cardiovascular and cerebrovascular events (Lorenz et al., 2007; O'Leary et al., 1999; Polak et al., 2011; Polak et al., 2010). IMT has also been linked with cardiovascular mortality (Chambless et al., 1997; Lorenz et al., 2007). The measurement of cIMT is used mainly in research settings as a surrogate marker of CVD. However, in a recent

study by Polak et al. (Polak et al., 2011) it was shown that internal carotid artery maximum IMT (and presence of plaque) improved the prediction of CVD risk based on the Framingham risk score only. In this Thesis IMT was measured from the far wall of the left common carotid artery, and the measurement of IMT was also the most consistent measurement across the different cohorts. Polak et al. has shown that both common and internal carotid IMT predict cardiovascular outcomes (Polak et al., 2011). A recent meta-analysis also showed that common carotid IMT improved cardiovascular risk prediction in asymptomatic populations (Den Ruijter, Peters, & Anderson, 2012) but the added value was small and routine screening not recommended in the general population.

6.4. TRACKING OF CARDIOVASCULAR RISK FACTORS FROM CHILDHOOD TO ADULTHOOD

Findings of this study showed that tracking of cholesterol values and BMI from child to adulthood spanning 27-years was significant and strong. In comparison, tracking of blood pressure and triglyceride levels was somewhat inferior. In addition, when testing the ability of current international child lipid, overweight/obesity and blood pressure cutoffs to predict adult dyslipidemia, overweight/obesity or hypertension, it was observed that classification of abnormal LDL-C, HDL-C and blood pressure were sensitive but less specific, and classification of abnormal TG and overweight/obesity specific but less sensitive in predicting adult cardiovascular risk. Tracking over a 6-year interval was lower in child than in adulthood, with a trend for higher Spearman's correlation coefficients with increasing age. Tracking of cardiovascular risk factors seem to decline rapidly in early child but later on tracking was only slightly diminished with increasing time intervals between assessments.

Previously tracking of cardiovascular risk factors in child has been studied in other cohorts with a shorter follow-up time of 4, 6, or 8-years and the results of this study are in line with these earlier reports (Clarke et al., 1978; Freedman, Shear, Srinivasan, Webber, & Berenson, 1985; Nicklas, von Duvillard, & Berenson, 2002).

NCEP has provided cutoffs for abnormal child lipid levels, National High Blood Pressure Education Program for child blood pressure levels, and Cole et al for child BMI levels in the clinical setting (Cole et al., 2000; "National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents," 1992; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Earlier Friedman et al. have shown in approximately 900 subjects aged 5 to 19 years at

baseline and with a 30-year follow-up that the NCEP cutoffs have a 43% to 46% sensitivity and 82% to 86% specificity for abnormal adult total cholesterol and LDL-C levels (Friedman, Morrison, Daniels, McCarthy, & Sprecher, 2006). Previous data from the Young Finns, Bogalusa Heart, and Childhood Determinants of Adult Health studies including approximately 1800 subjects aged 12 to 18 years with a approximately 20 year follow-up show a 80 to 92% sensitivity and 37% to 47% specificity for abnormal adult TC, LDL-C, and HDL-C levels(Magnussen et al., 2008). The findings of this study including >2200 children followed for 27 years are in line with these earlier reports with 75% to 95% sensitivity and 20% to 57% specificity for total cholesterol, LDL-C and HDL-C levels.

Prehypertension or hypertension in child at the age 6-9 years predicted adult hypertension in both males (OR, 2.8 (95% CI, 1.5 to 5.1)) and females (OR, 2.4 (95% CI, 1.1 to 5.2)) in the present study. The results were similar in the older age groups (ages 12 to 18 years). In addition, for blood pressure cutoffs, sensitivity and specificity rates were satisfactory (62% to 64% and 56% to 57%, respectively) and when using the 95th percentile cutoffs the PPV, sensitivity and specificity were 44%, 10%, and 97%.

The Bogalusa Heart Study, including a biracial study cohort of approximately 1700 participants and a 13 to 24 year follow-up, previously reported a cohort-level sensitivity of 44% and specificity of 93% for adult overweight/obesity (Janssen et al., 2005). In the present study the sensitivity was lower (23% to 31%), but specificity similar (94% to 96%). Inferior sensitivity could be due to differences in follow-up and because BMI tracking in black women is superior to that observed in white women (Deshmukh-Taskar et al., 2006). Another explanation could be that the present child data was collected prior to the more recent obesity epidemic with the inability of current pediatric cutoffs to identify child obesity in the past.

Previous guidelines from 1992 endorsed selective screening and recommended measuring lipid levels from individuals with family history of early CVD or elevated total cholesterol levels. In an updated report, it was also recommended that children with overweight (BMI between 85th and 95th percentile), obesity (BMI >95th percentile), hypertension (blood pressure >95th percentile), cigarette smoking, or diabetes mellitus, be screened with a fasting lipid profile (Daniels, Greer, & Committee on, 2008). In the new guidelines issued by the NHLBI, universal screening of lipids for all children aged 9 to 11 years was recommended. Universal risk-factor screening may, however, impose psychosocial distress to children and family members at risk for CVD. On the other hand, a false sense of security may be conveyed to families with absence of significant risk factors preventing the maintenance of a healthy life style long term.

An important issue in the prevention of cardiovascular disease is the optimal timing of the risk assessment. Previously it was demonstrated that high levels of cardiovascular risk factors in child were highly predictive of having higher cIMT in adulthood especially in children aged ≥9 years (Juonala, Magnussen, et al., 2010). The present study adds to this and shows that blood pressure between 6 and 18 years of age seems similarly predictive of adult hypertension. The tracking of lipid levels from early age to adulthood is also relatively strong in males whereas the tracking of lipids (especially LDL-C) in female subjects is most consistent from 12- to 18-year to adult age. It has been shown in a systematic meta-analysis that overweight or obesity in school aged children is associated with other cardiovascular risk factors as well (Friedemann et al., 2012). Child overweight and obesity was specific in predicting adult obesity in all age groups. An intervention should, thus, be provided for overweight children of all ages in order to avoid adult obesity.

6.5. CHILDHOOD PREDICTORS OF ADULT OBESITY AND HYPERTENSION

This study shows that the prediction of adult obesity can be significantly improved if maternal BMI and family socioeconomic status is taken into account in addition to child BMI. Furthermore, three genetic variants were independently associated with adult obesity, but their contribution in the prediction of adult obesity was small. Child overweight/obesity, parental hypertension and family socioeconomic status improved the prediction of adult hypertension compared with child BP only. The genetic risk score consisting of 29 novel hypertension linked SNPs provided additional value to family history of hypertension only in the prediction of adult hypertension.

The reported associations between child BMI, socioeconomic status, parental BMI and adult obesity are in line with previous cohort studies (Eriksson, Forsen, Osmond, & Barker, 2003; Parsons et al., 1999; Whitaker, Wright, Pepe, Seidel, & Dietz, 1997). However, prior studies have mainly been conducted with substantially smaller samples sizes and/or without extensive baseline data on potential confounding and modifying factors. Current observations in this study indicate that most children at high-risk of adult obesity could be identified applying a simple non-laboratory based risk assessment.

Previously it has been shown that serum CRP levels correlate strongly with BMI (Visser, Bouter, McQuillan, Wener, & Harris, 1999), but it is unclear whether CRP has a causal role in the development of obesity. Such a role has been recently suggested in a study that found an association between a genetic variant in the *CRP* gene and fat mass

(Bochud et al., 2009). Child CRP levels were independent predictors of adult obesity in the present study. CRP levels are elevated in offsprings of obese parents (Lieb et al., 2009). In addition, two recent studies utilizing genetic data have supported the concept that obesity and inflammation may share a common genetic and/or pathophysiological basis (Ridker et al., 2008). Although child CRP predicted adult obesity in multivariable models, the inclusion of CRP did not significantly improve the prediction of adult obesity in a model including child BMI, maternal BMI and family income.

Blood pressure is a complex trait. Its heritability is estimated to be between 30 and 50% based on family and twin studies (Fuentes, Notkola, Shemeikka, Tuomilehto, & Nissinen, 2000; Havlik et al., 1979; Hottenga et al., 2005; Kupper et al., 2005; Padmanabhan, Caulfield, & Dominiczak, 2015; Snieder, Harshfield, & Treiber, 2003). Blood pressure is influenced by genetics, gene-environment interactions as well as environmental factors including consumption of sodium, physical inactivity and body weight (Hong, deFaire, Heller, McClearn, & Pedersen, 1994; van den Elzen et al., 2004). Parental hypertension assessed in child doubled the odds of adult hypertension in the present study. A similar association with adult hypertension was also observed for child hypertension and overweight/obesity. In combination the prediction of adult hypertension was improved even further. Parental hypertension reflects a genetic predisposition for hypertension. In previous studies, the utility of a genetic risk scores in the prediction of cardiovascular disease or type 2 diabetes mellitus has been limited (Paynter et al., 2010; Talmud et al., 2010). The present study showed an improvement in prediction of adult hypertension when either parental hypertension or the genetic risk score was added separately or simultaneously to the risk model. These results then suggest that the genetic risk score and parental hypertension provided complementary information in the prediction of adult hypertension.

In the present study several newly identified susceptibility gene loci associated with BP and hypertension were examined together with conventional child risk factors. The roles of individual genetic variants revealed in adult GWAS in the pediatric setting are not completely understood. Of the individual SNPs markers in the proximity of CACNB2 (rs1813353), ULK4 (rs3774372), and ZNF831 (rs6015450) genes were most strongly associated with adult hypertension. The pathophysiological mechanisms between the genetic variants and BP are poorly understood. There are several putative pathways for how the 3 strongest SNPs might affect BP (Ehret, 2010). The rs1813353 variant is located at 3’ in an intron region of the CACNB2 gene encoding the β-2 subunit of a voltage gated calcium channel. CACNB2 is expressed in the heart and may regulate BP through interactions between the β-2 subunit and α-1 calcium channels. The β-2 subunit has been suggested to directly influence conformational changes in the

calcium channels (Van Petegem, Clark, Chatelain, & Minor, 2004), and mutations in CACNB2 have been implicated in inherited cardiac arrhythmia syndromes (Burashnikov et al., 2010; Foell et al., 2004). The clinical significance of rs3774372 is currently unknown, but it is a missense mutation in the ULK4 (unclike kinase 4) gene encoding serine/threonine protein kinase. The rs6015450 is located 20 kb 5' from the ZNF831 (zinc finger protein 831) gene. The DNA-binding zinc finger proteins are transcription factors that modulate the expression of genes. However, there are several other genes near rs6015450 and there is no known function for this particular SNP. Further GWAS studies are needed to elucidate novel pathways in the pathophysiology of hypertension and to develop new drug therapies.

This study shows that a combined risk score including child BP, child overweight/obesity, parental hypertension, low parental occupational status, and a genetic risk score was superior to child BP only in predicting adult hypertension. Importantly, the combined risk score predicted adult hypertension in all six age groups. Altogether, the present data suggest that the identification of children at risk for adult hypertension could be improved with a multifactorial approach. Moreover, these data demonstrate that the prediction of adult hypertension was improved when novel genetic variants were included in the risk assessment.

In addition, the effects of several obesity susceptibility gene loci recently associated with BMI were examined in the present study (Dina et al., 2007; Frayling et al., 2007; Speliotes et al., 2010). Genetic risk markers in the proximity of *TFAP2B, FLJ35779* and *LRRN6C* genes were independently associated with adult obesity. These novel genetic risk markers, however, only marginally improved the prediction of adult obesity when analyzed in combination with child BMI, parental BMI and socioeconomic status.

The pathophysiological mechanisms linking the genetic variants with obesity are not completely understood. Variants near the *FTO* gene were among the first reported genetic markers associated with BMI. We found that *FTO* variants were associated with adult obesity in models adjusted for age and sex, but not in models adjusted for child and maternal BMI. The lack of an effect in multivariable models may reflect the fact that *FTO* is associated with BMI already in child (Hakanen et al., 2009). *FTO* may influence weight gain via energy intake and satiety (Hetherington & Cecil, 2010). Mice with over-expression of *FTO* had increased food intake resulting in obesity in a recently reported study (Church et al., 2010). Variants near *TFAP2B*, *LRRN6C* and *FLJ35779* genes were independently associated with obesity in the present study. The gene *TFAP2B* encodes a transcription factor expressed in adipose tissue (Frayling et al., 2007). Its over-expression leads to increased lipid accumulation (Tao et al., 2006) and decreased expression of adiponectin (Ikeda et al., 2006). Thus *TFAP2B* may have

multiple effects on fat accumulation. *LRRN6C* is a member of the gene encoding the LRR transmembrane protein family. These proteins are involved in innate immunity and nervous system development (Dolan et al., 2007). Mechanisms linking *LRRN6C* and obesity are unknown. Similarly, nothing is currently known about mechanisms linking obesity and *FLJ35779* (a.k.a. *POC5*) which codes a protein required in mitosis (Azimzadeh et al., 2009). It is possible that the identified variants near these genes modulate the transcription of some other nearby genes. For example, the rs2112347 (the non-coding variant of the *FLJ35779* gene) lies within ~400kb of the 3-hydroxy-3-methylglutaryl-CoA reductase gene, which is intimately involved in cholesterol synthesis and lipid metabolism providing a potential link with obesity. Whether genetic testing is useful in identifying children at risk of adult obesity should be addressed in future studies.

A simple risk score based on non-laboratory child risk factors (child BMI, maternal BMI, and low socioeconomic status) was superior to a model including child BMI only in predicting adult obesity. Importantly, this association was found across all age groups studied (i.e. 3, 6, 9, 12, 15 and 18 year-olds). In a recent statement by US Preventive Services Task Force a grade B recommendation was given for clinicians to screen children aged 6 years and older for obesity (U. S. Preventive Services & Barton, 2010). The screening was recommended to be performed based on BMI measurements. These results suggest that the identification of children at risk for adult obesity could be improved if parental BMI and indices of socioeconomic status such as family income would be taken into account in the assessment. Our data also suggest that child BMI predict adult obesity already at the age of 3 years.

6.6. RECOVERY FROM HYPERTENSION AND VASCULAR CHANGES

Prior studies have shown that high BP levels in child are associated with adverse arterial health later in life. The main finding in the present study based on a large combined international data set was that the effect of elevated child BP on adult cIMT is mainly reversible. The study shows that the risk for high cIMT in adults is mainly related with an elevated BP in adulthood, irrespective of the variance in child BP (elevated or normal). These results were consistently demonstrated in meta-analysis of the data, in both sexes, and across different age and adiposity groups.

The Muscatine Study (Davis et al., 2001), the Bogalusa Heart Study (S. Li et al., 2003) and the Young Finns Study (Raitakari et al., 2003) have previously shown that child BP levels are predictive of increased adult cIMT. In Young Finns (Hartiala et al.,

2012; Raitakari et al., 2003) analyses of continuous BP data showed that among individuals aged 12-18 years at baseline the association between child BP levels and adult cIMT or coronary calcification remained significant after adjustment for adult BP levels or BP change between child and adulthood. In the present analyses conducted in four cohorts using categorically-defined BP levels that are used within current guidelines, the risk of high cIMT was not significantly increased among adolescents aged 12-18 years with elevated BP in child only (P=0.18, when compared to those with persistently normal BP), even though the risk increase in this age group approached 30% and was higher than among children aged 3-9 years. Nevertheless, the risk for elevated cIMT was highest among those with persistently elevated BP. Altogether; these results suggest that the effects of elevated BP in child on accelerated atherosclerosis can be reversed if normal BP levels are achieved in adulthood. Concerning the reversibility of child risk factor effects, in Young Finns cohort among with i3CConsortium cohorts, it has been previously reported that overweight or obese children who become non-obese adults have essentially the same cardiovascular risk profile as adults who were never obese (Juonala et al., 2011). On the other hand, Tirosh et al. (Tirosh et al., 2011) has in their longitudinal cohort of over 37,000 apparently healthy 17 year-old males reported that baseline BMI was associated with risk of coronary heart disease at follow-up and that this effect was independent of adult BMI.

One plausible mechanism for the present observations is that the adverse effects of elevated child BP are due to higher risk of adult hypertension, i.e. tracking. Consistent with this, significant tracking of BP levels from child to adult age was observed within all cohorts, and the risk of elevated adult BP was strongly dependent on child BP. Adiposity is known to have a substantial effect on both BP and accelerated atherosclerosis. A prior report of the four present cohorts (Juonala et al., 2011) examined the effects of child and adult adiposity on cardiometabolic outcomes and found that especially adult BMI levels were associated with elevated BP and increased cIMT. The present study, therefore, included several analyses to account for adiposity. First, the main analyses were adjusted for adult BMI. Second, analyses were made separately among normal weight and overweight/obese participants showing essentially similar results. This supports the view that the normalization of risk for high cIMT among the BP resolution group is independent of adiposity status. Furthemore, this study found support for weight management intervention strategies by observing the most favorable changes in adiposity levels between child and adulthood in the BP resolution group.

There were considerable differences in child prevalence of elevated BP when the NHBPEP tables were applied. In addition, the prevalence of elevated BP (33-49%) was

far higher in the Muscatine, Young Finns, and CDAH cohorts than what would be expected based on the 90th percentile definition in the NHANES data which the NHBPEP tables are based on. Population, secular, and/or method differences may have contributed to this disparity. For example, Muscatine, Young Finns, and CDAH participants are predominantly of white European descent whereas the NHANES data is based on all ethnicities represented in the US. This should be taken into account when using the tables in the clinical setting. Sensitivity analyses using another definition for elevated child BP as diastolic or systolic BP $\geq 90^{th}$ percentile for age-, sex-, height-, and cohort-specific levels provided, however, similar findings when compared with those using the NHBPEP tables to define elevated BP.

6.7. LIMITATIONS

Limitations of this study include the loss of original participants during the long-term follow-up. In this study non-participants were more often male and had lower socioeconomic status during child compared with active participants. Therefore, the rates of adult hypertension in Young Finns cohort might be an underestimation of the true population rates. In 1980, when the first data was collected the importance of the abdominal adiposity was not knowledged. Thus the data on waist circumference in childhood was missing. Also, non-anthropometric measures of body composition for example densitometry, isotope dilution methods, in vivo neutron activation analysis, dual energy X-ray absorptiometry, computerized tomographic scanning or magnetic resonance imaging have not been performed. The Young Finns cohort is a large, randomly selected, cohort of young men and women prospectively followed-up for up to 27 years from child. Extensive data were available on several possible child and genetic determinants of obesity and hypertension that could be comprehensively taken into account in multivariable models. Child CRP levels were analysed from samples stored for 25 years at -20°C, but we have shown that CRP levels remain stable when stored at this temperature (Juonala, Viikari, Rönnemaa, Taittonen, et al., 2006). Differences in the acquisition of data within the cohorts did not allow adjustments for variables such as puberty and socioeconomic status in study IV. In addition, cIMT was used as a surrogate outcome as cohorts were comprised of young adults without cardiovascular events. Also, as potential limitation of lacking childhood measurements of cIMT and therefore tracking data of cIMT. CIMT has, however, been shown to predict cardiovascular events.

6.8. CLINICAL IMPLICATIONS

Serum lipids, blood pressure and body mass index tend to track from child to middle age. In addition, adult hypertension can be predicted based on assessments in all age groups between 6 and 18 years of age. Child lipids predict adult dyslipidemia in all child age groups among males and most consistently in the 12-18-year-old groups among females. Sensitivity and specificity of child BMI in predicting adult obesity was very good in all child age groups and an intervention to alter BMI could, thus, be provided whenever an overweight child is seen in the medical setting. Previously, it has been shown in four population based cohorts that child cardiovascular risk factors predict subclinical atherosclerosis in adults based on a high adult cIMT value, particularly from the age of 9 years (Juonala, Magnussen, et al., 2010). These data are important when considering the age for risk factor screening in children.

Hypertension is a major cardiovascular risk factor influenced by genetic propensity and various environmental stimuli. Independent predictors for adult hypertension were child SBP and DBPs, parental hypertension, child overweight/obesity, low parental occupational status, and a high genetic risk score. An additive effect of family history and genetics on adult hypertension was observed suggesting a complementary effect of these variables. The present data suggest that a multifactorial approach, if implemented, could improve the identification of children with a high risk of adult hypertension. These data, furthermore, emphasize the importance of overweight as a potential modifiable risk factor in the care of patients with elevated blood pressure.

This thesis demonstrates that child BMI, CRP, family income (inversely) maternal BMI and certain polymorphisms were independently related with adult obesity. Including information on genetic variants and inflammation (CRP) in the prediction models, however, only marginally improved the prediction. Newly identified genetic variants may give insights into the biology of obesity, but seem not to add much to obesity prediction overall. Similar observations with novel genetic risk factors have been made for cardiovascular end points (Ripatti et al., 2010). Therefore, from the perspective of health policy, the most important finding was that 3 easily measurable risk factors (high child BMI, high maternal BMI and low socioeconomic status) can be used to identify children at risk of adult obesity. A simple risk score based on these 3 risk factors was superior in predicting adulthood obesity compared with the currently recommended approach of using child BMI only (U. S. Preventive Services & Barton, 2010).

This thesis demonstrated that the effect of elevated child BP on adult cIMT is mostly reversible. Furthermore, the results suggest that the reduction of the risk for high cIMT in the BP resolution group is independent of adiposity. However, the most favorable

changes in adiposity levels between child and adulthood were found in the BP resolution group. This highlights the importance of weight management from early life. Clearly maintaining a normal BMI accompanied with normal BP from child to adulthood is beneficial, and maintaining a low or optimum risk status throughout life is associated with a very low lifetime risk of CVD (Lloyd-Jones, 2012). However, the results of this study indicate that when increased BMI or BP are detected in children or adolescents, interventions should be implemented to reduce the risk of atherosclerosis development as tracking of these factors is associated with increased carotid IMT.

6.9. FUTURE RESEARCH DIRECTIONS

The heritability of hypertension in family and twin studies is high but GWAS have so far been able to explain only a small amount of blood pressure variability. More focused novel approaches are needed. Novel pathways of BP regulation involving genes and genetic variants may well improve our understanding of the pathophysiology of essential hypertension and lead to the development of more targeted drug therapies with less adverse effects.

Clustering of cardiovascular risk factors has previously been observed in epidemiological studies, but less is known about the pleiotropic effects of the genome and genetic variants on cardiovascular risk and disease. Evidence of a shared genetic basis of blood pressure regulation, body composition and lipid metabolism has been reported previously, but more research is needed in this area.

Other more recent non-invasive imaging technologies including very high resolution ultrasound, MRI (magnetic resonance imaging) and PET/CT (positron emission tomography – computed tomography) could improve the understanding of the cardiovascular system and potentially aid in the identification of risk individuals developing coronary artery disease at an early age. More research is needed to explore the potential of these technologies in clinical and research settings as well as in the cardiovascular risk assessment.

Studying associations between cardiovascular risk and clinical events or disease was not possible due to the young age of the study cohorts. Research on the effects of lifetime burden of risk factors for the development of events and disease severity will, however, be possible in the near future making the identification and early treatment of high risk individuals possible.

7 SUMMARY

1. Tracking of serum lipids, SBP and BMI from child to adult age spanning 27-years was significant and strong. In addition, child BP predicted adult hypertension from six years of age. Child lipids predicted adult dyslipidemia in all age groups in males and most consistently from adolescence in females. Sensitivity and specificity of child body mass index to predict adult obesity was very good in all age groups. These data are important when considering age of risk factor screening in children.

2. The prediction of hypertension in adults can be improved significantly by including information on child overweight or obesity, parental hypertension, and family socioeconomic status compared with child BP only. Including a genetic risk score, consisting of the 29 novel BP-associated SNPs, further improved the prediction of adult hypertension. Child BMI, CRP, family income (inversely), maternal BMI, and polymorphisms in the proximity of FLJ35779, TFAP2B, and LRRN6C genes were independently associated with adult obesity. The impact of genetics in the prediction of adult obesity was, however, low. A simple risk score including high child BMI (regardless of age), high maternal BMI, and low socioeconomic status was superior in predicting adult obesity compared with the currently recommended child BMI only.

3. Elevated BP from child to adult age was associated with an increased risk of subclinical carotid atherosclerosis assessed by cIMT. The risk was markedly reduced in the setting of adult normotension.

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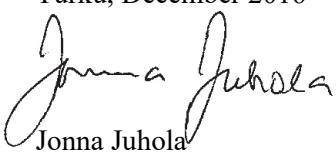

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9 REFERENCES

Alberti, K. G., Eckel, R. H., Grundy, S. M., Zimmet, P. Z., Cleeman, J. I., Donato, K. A., et al. (2009). Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation, 120*(16), 1640-1645.

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: An update. *Journal of the American College of Cardiology, 43*(10), 1731-1737.

Azimzadeh, J., Hergert, P., Delouvee, A., Euteneuer, U., Formstecher, E., Khodjakov, A., et al. (2009). hPOC5 is a centrin-binding protein required for assembly of full-length centrioles. *J Cell Biol, 185*(1), 101-114.

Baker, J. L., Olsen, L. W., & Sorensen, T. I. A. (2007). Childhood body-mass index and the risk of coronary heart disease in adulthood. *New England Journal of Medicine, 357*(23), 2329-2337.

Bao, W., Threefoot, S. A., Srinivasan, S. R., & Berenson, G. S. (1995). Essential hypertension predicted by tracking of elevated blood pressure from childhood to adulthood: the Bogalusa Heart Study. *American journal of hypertension, 8*(7), 657-665.

Benn, M., Watts, G. F., Tybjaerg-Hansen, A., & Nordestgaard, B. G. (2012). Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication. *The Journal of Clinical Endocrinology & Metabolism, 97*(11), 3956-3964.

Bensen, J. T., Li, R., Hutchinson, R. G., Province, M. A., & Tyroler, H. A. (1999). Family history of coronary heart disease and pre-clinical carotid artery atherosclerosis in African-Americans and whites: the ARIC study: Atherosclerosis Risk in Communities. *Genet Epidemiol, 16*(2), 165-178.

Berenson, G. S., Srinivasan, S. R., Bao, W. H., Newman, W. P., Tracy, R. E., & Wattigney, W. A. (1998). Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *New England Journal of Medicine, 338*(23), 1650-1656.

Bjornsson, E., Gudbjartsson, D. F., Helgadottir, A., Gudnason, T., Gudbjartsson, T., Eyjolfsson, K., et al. (2015). Common Sequence Variants Associated With Coronary Artery Disease Correlate With the Extent of Coronary Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 35*(6), 1526-1531.

Bochud, M., Marquant, F., Marques-Vidal, P. M., Vollenweider, P., Beckmann, J. S., Mooser, V., et al. (2009). Association between C-reactive protein and adiposity in women. *J Clin Endocrinol Metab, 94*(10), 3969-3977.

Bots, M. L., & Grobbee, D. E. (2002). Intima media thickness as a surrogate marker for generalised atherosclerosis. *Cardiovascular Drugs and Therapy, 16*(4), 341-351.

Burashnikov, E., Pfeiffer, R., Barajas-Martinez, H., Delpon, E., Hu, D., Desai, M., et al. (2010). Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm., 7*(12), 1872-1882.

Castelli, W. P. (1986). The Triglyceride Issue - A View from Framingham. *American Heart Journal, 112*(2), 432-437.

Celermajer, D. S., Adams, M. R., Clarkson, P., Robinson, J., McCredie, R., Donald, A., et al. (1996). Passive Smoking and Impaired Endothelium-Dependent Arterial Dilatation in Healthy Young Adults. *New England Journal of Medicine, 334*(3), 150-155.

Celermajer, D. S., Sorensen, K. E., Gooch, V. M., Spiegelhalter, D. J., Miller, O. I., Sullivan, I. D., et al. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet, 340*, 1111-1115.

Chambless, L. E., Folsom, A. R., Clegg, L. X., Sharrett, A. R., Shahar, E., Nieto, F. J., et al. (2000). Carotid wall thickness is predictive of incident clinical stroke - The Atherosclerosis Risk in Communities (ARIC) Study. *American Journal of Epidemiology, 151*(5), 478-487.

Chambless, L. E., Heiss, G., Folsom, A. R., Rosamond, W., Szklo, M., Sharrett, A. R., et al. (1997). Association of Coronary Heart Disease incidence with carotid arterial wall thickness and major risk factors: The Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *American Journal of Epidemiology, 146*(6), 483-494.

Chan, K., Patel, R. S., Newcombe, P., Nelson, C. P., Qasim, A., Epstein, S. E., et al. (2013). Association between the chromosome 9p21 locus and angiographic coronary artery disease burden: a collaborative meta-analysis. *J Am Coll Cardiol, 61*(9), 957-970.

Chen, X., & Wang, Y. (2008). Tracking of blood pressure from childhood to adulthood: a systematic

review and meta-regression analysis. *Circulation, 117*(25), 3171-3180.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., et al. (2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA : the journal of the American Medical Association, 289*(19), 2560-2572.

Church, C., Moir, L., McMurray, F., Girard, C., Banks, G. T., Teboul, L., et al. (2010). Overexpression of Fto leads to increased food intake and results in obesity. *Nat Genet, 42*(12), 1086-1092.

Clarke, W. R., Schrott, H. G., Leaverton, P. E., Connor, W. E., & Lauer, R. M. (1978). Tracking of blood lipids and blood pressures in school age children: the Muscatine study. *Circulation, 58*(4), 626-634.

Cole, T. J., Bellizzi, M. C., Flegal, K. M., & Dietz, W. H. (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ (Clinical research ed.), 320*(7244), 1240-1243.

Cullen, P. (2000). Evidence that triglycerides are an independent coronary heart disease risk factor. *The American Journal of Cardiology, 86*(9), 943-949.

Dandona, S., Stewart, A. F., Chen, L., Williams, K., So, D., O'Brien, E., et al. (2010). Gene dosage of the common variant 9p21 predicts severity of coronary artery disease. *J Am Coll Cardiol, 56*(6), 479-486.

Daniels, S. R., Greer, F. R., & Committee on, N. (2008). Lipid screening and cardiovascular health in childhood. *Pediatrics, 122*(1), 198-208.

Davis, P. H., Dawson, J. D., Riley, W. A., & Lauer, R. M. (2001). Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation, 104*(23), 2815-2819.

de Ferranti, S. D., Rodday, A. M., Mendelson, M. M., Wong, J. B., Leslie, L. K., & Sheldrick, R. C. (2016). Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation, 133*(11), 1067-1072.

de Groot, E., Hovingh, G. K., Wiegman, A., Duriez, P., Smit, A. J., Fruchart, J. C., et al. (2004). Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation, 109*(23), 33-38.

Den Ruijter, H. M., Peters, S. E., & Anderson, T. J. (2012). Common carotid intima-media thickness measurements in cardiovascular risk prediction: A meta-analysis. *JAMA : the journal of the American Medical Association, 308*(8), 796-803.

DerSimonian, R., & Laird, N. (1986). Metaanalysis in Clinical-Trials. *Controlled Clinical Trials, 7*(3), 177-188.

Deshmukh-Taskar, P., Nicklas, T. A., Morales, M., Yang, S. J., Zakeri, I., & Berenson, G. S. (2006). Tracking of overweight status from childhood to young adulthood: the Bogalusa Heart Study. *European journal of clinical nutrition, 60*(1), 48-57.

Dina, C., Meyre, D., Gallina, S., Durand, E., Korner, A., Jacobson, P., et al. (2007). Variation in FTO contributes to childhood obesity and severe adult obesity. *Nature Genetics, 39*(6), 724-726.

Dolan, J., Walshe, K., Alsbury, S., Hokamp, K., O'Keeffe, S., Okafuji, T., et al. (2007). The extracellular leucine-rich repeat superfamily; a comparative survey and analysis of evolutionary relationships and expression patterns. *BMC Genomics, 8*, 320.

Dratva, J., Probst-Hensch, N., Schmidt-Trucksäss, A., Caviezel, S., de Groot, E., Bettschart, R., et al. (2013). Atherogenesis in youth – Early consequence of adolescent smoking. *Atherosclerosis, 230*(2), 304-309.

Dwyer, T., Sun, C., Magnussen, C. G., Raitakari, O. T., Schork, N. J., Venn, A., et al. (2013). Cohort Profile: The International Childhood Cardiovascular Cohort (i3C) Consortium. *International journal of epidemiology, 42*(1), 86-96.

Ehret, G. B. (2010). Genome-wide association studies: contribution of genomics to understanding blood pressure and essential hypertension. *Curr.Hypertens.Rep., 12*(1), 17-25.

Ehret, G. B., Munroe, P. B., Rice, K. M., Bochud, M., Johnson, A. D., Chasman, D. I., et al. (2011). Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature, 478*(7367), 103-109.

Engeland, A., Bjorge, T., Sogaard, A. J., & Tverdal, A. (2003). Body mass index in adolescence in relation to total mortality: 32-year follow-up of 227,000 Norwegian boys and girls. *American Journal of Epidemiology, 157*(6), 517-523.

Enos, W. F., Holmes, R. H., & Beyer, J. (1953). Coronary Disease Among United-States Soldiers Killed in Action in Korea. *JAMA: the journal of the American Medical Association, 152*(12), 1090-1093.

Eriksson, J., Forsen, T., Osmond, C., & Barker, D. (2003). Obesity from cradle to grave. *Int J Obes Relat Metab Disord, 27*(6), 722-727.

Foell, J. D., Balijepalli, R. C., Delisle, B. P., Yunker, A. M., Robia, S. L., Walker, J. W., et al. (2004). Molecular heterogeneity of calcium channel beta-subunits in canine and human heart: evidence for differential subcellular localization. *Physiol Genomics, 17*(2), 183-200.

Franks, P. W., Hanson, R. L., Knowler, W. C., Sievers, M. L., Bennett, P. H., & Looker, H. C. (2010). Childhood Obesity, Other Cardiovascular Risk Factors, and Premature Death. *New England Journal of Medicine, 362*(6), 485-493.

Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., et al. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science, 316*(5826), 889-894.

Freedman, D. S., Shear, C. L., Srinivasan, S. R., Webber, L. S., & Berenson, G. S. (1985). Tracking of serum lipids and lipoproteins in children over an 8-year period: the Bogalusa Heart Study. *Preventive medicine, 14*(2), 203-216.

Friedemann, C., Heneghan, C., Mahtani, K., Thompson, M., Perera, R., & Ward, A. M. (2012). Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *Bmj, 345*, e4759.

Friedman, L. A., Morrison, J. A., Daniels, S. R., McCarthy, W. F., & Sprecher, D. L. (2006). Sensitivity and specificity of pediatric lipid determinations for adult lipid status: findings from the Princeton Lipid Research Clinics Prevalence Program Follow-up Study. *Pediatrics, 118*(1), 165-172.

Fuentes, R. M., Notkola, I. L., Shemeikka, S., Tuomilehto, J., & Nissinen, A. (2000). Familial aggregation of blood pressure: a population-based family study in eastern Finland. *J Hum Hypertens, 14*(7), 441-445.

Gall, S., Huynh, Q. L., Magnussen, C. G., Juonala, M., Viikari, J. S., Kahonen, M., et al. (2014). Exposure to parental smoking in childhood or adolescence is associated with increased carotid intima-media thickness in young adults: evidence from the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health Study. *Eur Heart J, 35*(36), 2484-2491.

Geerts, C. C., Bots, M. L., Grobbee, D. E., & Uiterwaal, C. S. (2008). Parental smoking and vascular damage in young adult offspring: is early life exposure critical? The atherosclerosis risk in young adults study. *Arterioscler Thromb Vasc Biol, 28*(12), 2296-2302.

Geerts, C. C., Bots, M. L., van der Ent, C. K., Grobbee, D. E., & Uiterwaal, C. S. (2012). Parental smoking and vascular damage in their 5-year-old children. *Pediatrics, 129*(1), 45-54.

Gidding, S. S. (2008). Noninvasive cardiac imaging: Implications for risk assessment in adolescents and young adults. *Annals of Medicine, 40*(7), 506-513.

Goldstein, J. L., Schrott, H. G., Hazzard, W. R., Bierman, E. L., & Motulsky, A. G. (1973). Hyperlipidemia in coronary heart disease, II: genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *The Journal of Clinical Investigation, 52*(7), 1544-1568.

Goodman, E., Daniels, S. R., Meigs, J. B., & Dolan, L. M. (2007). Instability in the Diagnosis of Metabolic Syndrome in Adolescents. *Circulation, 115*(17), 2316-2322.

Gordon, T., Kannel, W. B., Castelli, W. P., & Dawber, T. R. (1981). Lipoproteins, cardiovascular disease, and death: The framingham study. *Archives of Internal Medicine, 141*(9), 1128-1131.

Graham, I., Atar, D., Borch-Johnsen, K., Boysen, G., Burell, G., Cifkova, R., et al. (2007). European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, 14 Suppl 2*, S1-113.

Greenland, P., Bonow, R. O., Brundage, B. H., Budoff, M. J., Eisenberg, M. J., Grundy, S. M., et al. (2007). ACCF/AHA 2007 Clinical Expert Consensus Document on Coronary Artery Calcium Scoring By Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients With Chest Pain: A Report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) Developed in Collaboration With the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *Journal of the American College of Cardiology, 49*(3), 378-402.

Gustafson, J. K., Yanoff, L. B., Easter, B. D., Brady, S. M., Keil, M. F., Roberts, M. D., et al. (2009). The Stability of Metabolic Syndrome in Children and Adolescents. *The Journal of Clinical Endocrinology & Metabolism, 94*(12), 4828-4834.

Hakanen, M., Raitakari, O. T., Lehtimaki, T., Peltonen, N., Pahkala, K., Sillanmaki, L., et al. (2009). FTO genotype is associated with body mass index after the age of seven years but not with energy intake or leisure-time physical activity. *J Clin Endocrinol Metab, 94*(4), 1281-1287.

Hansen, K., Ostling, G., Persson, M., Nilsson, P. M., Melander, O., Engstrom, G., et al. (2016). The effect of smoking on carotid intima-media thickness progression rate and rate of lumen diameter reduction. *Eur J Intern Med, 28*, 74-79.

Hansen, M. L., Gunn, P. W., & Kaelber, D. C. (2007). Underdiagnosis of hypertension in children and

adolescents. *JAMA : the journal of the American Medical Association, 298*(8), 874-879.

Hartiala, O., Magnussen, C. G., Kajander, S., Knuuti, J., Ukkonen, H., Saraste, A., et al. (2012). Adolescence Risk Factors Are Predictive of Coronary Artery Calcification at Middle Age: The Cardiovascular Risk in Young Finns Study. *Journal of the American College of Cardiology, 60*(0), 1364-1370.

Havlik, R. J., Garrison, R. J., Feinleib, M., Kannel, W. B., Castelli, W. P., & McNamara, P. M. (1979). Blood pressure aggregation in families. *American Journal of Epidemiology, 110*(3), 304-312.

Helgadottir, A., Gretarsdottir, S., Thorleifsson, G., Holm, H., Patel, R. S., Gudnason, T., et al. (2012). Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. *J Am Coll Cardiol, 60*(8), 722-729.

Herbert, V., Lau, K. S., Gottlieb, C. W., & Bleicher, S. J. (1965). Coated charcoal immunoassay of insulin. *J Clin Endocrinol Metab, 25*(10), 1375-1384.

Hetherington, M. M., & Cecil, J. E. (2010). Gene-environment interactions in obesity. *Forum Nutr, 63*, 195-203.

Hindieh, W., Pilote, L., Cheema, A., Al-Lawati, H., Labos, C., Dufresne, L., et al. (2016). Association Between Family History, a Genetic Risk Score, and Severity of Coronary Artery Disease in Patients With Premature Acute Coronary Syndromes. *Arteriosclerosis, Thrombosis, and Vascular Biology*.

Hong, Y. L., deFaire, U., Heller, D. A., McClearn, G. E., & Pedersen, N. (1994). Genetic and Environmental-Influences on Blood-Pressure in Elderly Twins. *Hypertension, 24*(6), 663-670.

Hottenga, J. J., Boomsma, D. I., Kupper, N., Posthuma, D., Snieder, H., Willemsen, G., et al. (2005). Heritability and stability of resting blood pressure. *Twin Res Hum Genet, 8*(5), 499-508.

Howard, G., Burke, G. L., Szklo, M., Tell, G. S., Eckfeldt, J., Evans, G., et al. (1994). Active and passive smoking are associated with increased carotid wall thickness. The Atherosclerosis Risk in Communities Study. *Arch Intern Med, 154*(11), 1277-1282.

Howard, G., Wagenknecht, L. E., Burke, G. L., & et al. (1998). Cigarette smoking and progression of atherosclerosis: The atherosclerosis risk in communities (aric) study. *JAMA, 279*(2), 119-124.

Ikeda, K., Maegawa, H., Ugi, S., Tao, Y., Nishio, Y., Tsukada, S., et al. (2006). Transcription factor activating enhancer-binding protein-2beta. A negative regulator of adiponectin gene expression. *J Biol Chem, 281*(42), 31245-31253.

Jaimes, E. A., DeMaster, E. G., Tian, R.-X., & Raij, L. (2004). Stable Compounds of Cigarette Smoke Induce Endothelial Superoxide Anion Production via NADPH Oxidase Activation. [10.1161/01.ATV.0000127083.88549.58]. *Arteriosclerosis, Thrombosis, and Vascular Biology, 24*(6), 1031-1036.

Janssen, I., Katzmarzyk, P. T., Srinivasan, S. R., Chen, W., Malina, R. M., Bouchard, C., et al. (2005). Utility of childhood BMI in the prediction of adulthood disease: comparison of national and international references. *Obesity research, 13*(6), 1106-1115.

Jee, S. H., Sull, J. W., Park, J., Lee, S., Ohrr, H., Guallar, E., et al. (2006). Body-mass index and mortality in Korean men and women. *New England Journal of Medicine, 355*(8), 779-787.

Juonala, M., Järvisalo, M. J., Mäki-Torkko, N., Kähönen, M., Viikari, J. S., & Raitakari, O. T. (2005). Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation, 112*(10), 1486-1493.

Juonala, M., Magnussen, C. G., Berenson, G. S., Venn, A., Burns, T. L., Sabin, M. A., et al. (2011). Childhood Adiposity, Adult Adiposity, and Cardiovascular Risk Factors. *New England Journal of Medicine, 365*(20), 1876-1885.

Juonala, M., Magnussen, C. G., & Raitakari, O. T. (2013). Parental smoking produces long-term damage to vascular function in their children. *Curr Opin Cardiol, 28*(5), 569-574.

Juonala, M., Magnussen, C. G., Venn, A., Dwyer, T., Burns, T. L., Davis, P. H., et al. (2010). Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. *Circulation, 122*(24), 2514-2520.

Juonala, M., Viikari, J. S., Rönnemaa, T., Helenius, H., Taittonen, L., & Raitakari, O. T. (2006). Elevated blood pressure in adolescent boys predicts endothelial dysfunction: the Cardiovascular Risk in Young Finns Study. *Hypertension, 48*(3), 424-430.

Juonala, M., Viikari, J. S., Rönnemaa, T., Taittonen, L., Marniemi, J., & Raitakari, O. T. (2006). Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 26*(8), 1883-1888.

Juonala, M., Viikari, J. S. A., Kähönen, M., Taittonen, L., Laitinen, T., Hutri-Kähönen, N., et al. (2010). Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular

Risk in Young Finns study. *European Heart Journal, 31*(14), 1745-1751.

Juonala, M., Viikari, J. S. A., Räsänen, L., Helenius, H., Pietikäinen, M., & Raitakari, O. T. (2006). Young Adults With Family History of Coronary Heart Disease Have Increased Arterial Vulnerability to Metabolic Risk Factors: The Cardiovascular Risk in Young Finns Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 26*(6), 1376-1382.

Järvisalo, M. J., Jartti, L., Nanto-Salonen, K., Irjala, K., Rönnemaa, T., Hartiala, J. J., et al. (2001). Increased aortic intima-media thickness - A marker of preclinical atherosclerosis in high-risk children. *Circulation, 104*(24), 2943-2947.

Järvisalo, M. J., Rönnemaa, T., Volanen, I., Kaitosaari, T., Kallio, K., Hartiala, J. J., et al. (2002). Brachial artery dilatation responses in healthy children and adolescents. *American Journal of Physiology-Heart and Circulatory Physiology, 282*(1), H87-H92.

Kallio, K., Jokinen, E., Saarinen, M., Hämäläinen, M., Volanen, I., Kaitosaari, T., et al. (2010). Arterial Intima-Media Thickness, Endothelial Function, and Apolipoproteins in Adolescents Frequently Exposed to Tobacco Smoke. [10.1161/CIRCOUTCOMES.109.857771]. *Circulation: Cardiovascular Quality and Outcomes, 3*(2), 196-203.

Kannel, W. B., Lebauer, J. E., Dawber, T. R., & McNamara, P. M. (1967). Relation of Body Weight to Development of Coronary Heart Disease: The Framingham Study. *Circulation, 35*(4), 734-744.

Kato, N., Loh, M., Takeuchi, F., Verweij, N., Wang, X., Zhang, W., et al. (2015). Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNA methylation. *Nat Genet, 47*(11), 1282-1293.

Kavey, R.-E. W. (2015). Combined dyslipidemia in childhood. *Journal of Clinical Lipidology, 9*(5), S41-S56.

Koskinen, J., Magnussen, C. G., Taittonen, L., Rasanen, L., Mikkila, V., Laitinen, T., et al. (2010). Arterial structure and function after recovery from the metabolic syndrome: the cardiovascular risk in Young Finns Study. *Circulation, 121*(3), 392-400.

Kupper, N., Willemsen, G., Riese, H., Posthuma, D., Boomsma, D. I., & de Geus, E. J. (2005). Heritability of daytime ambulatory blood pressure in an extended twin design. *Hypertension, 45*(1), 80-85.

Lakka, H., Laaksonen, D. E., Lakka, T. A., Niskanen, L. K., Kumpusalo, E., Tuomilehto, J., et al. (2002). The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA, 288*(21), 2709-2716.

Lande, M. B., Carson, N. L., Roy, J., & Meagher, C. C. (2006). Effects of childhood primary hypertension on carotid intima media thickness - A matched controlled study. *Hypertension, 48*(1), 40-44.

Lauer, R. M., Clarke, W. R., & Beaglehole, R. (1984). Level, Trend, and Variability of Blood-Pressure During Childhood - the Muscatine Study. *Circulation, 69*(2), 242-249.

Lawes, C. M. M., Vander Hoorn, S., & Rodgers, A. (2008). Global burden of blood-pressure-related disease, 2001. *Lancet, 371*(9623), 1513-1518.

Levy, D., DeStefano, A. L., Larson, M. G., O'Donnell, C. J., Lifton, R. P., Gavras, H., et al. (2000). Evidence for a gene influencing blood pressure on chromosome 17 - Genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension, 36*(4), 477-483.

Li, C., Chen, W., Jiang, F., Simino, J., Srinivasan, S. R., Berenson, G. S., et al. (2015). Genetic association and gene-smoking interaction study of carotid intima-media thickness at five GWAS-indicated genes: the Bogalusa Heart Study. *Gene, 562*(2), 226-231.

Li, S., Chen, W., Srinivasan, S. R., Bond, M. G., Tang, R., Urbina, E. M., et al. (2003). Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA : the journal of the American Medical Association, 290*(17), 2271-2276.

Lieb, W., Pencina, M. J., Lanier, K. J., Tofler, G. H., Levy, D., Fox, C. S., et al. (2009). Association of parental obesity with concentrations of select systemic biomarkers in nonobese offspring: the Framingham Heart Study. *Diabetes, 58*(1), 134-137.

Lloyd-Jones, D. M. (2012). Improving the Cardiovascular Health of the US Population. *JAMA : the journal of the American Medical Association, 307*(12), 1314-1316.

Lloyd-Jones, D. M., Nam, B., D'Agostino, R. B., Levy, D., Murabito, J. M., Wang, T. J., et al. (2004). Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: A prospective study of parents and offspring. *JAMA, 291*(18), 2204-2211.

Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M., & Sitzer, M. (2007). Prediction of clinical cardiovascular events with carotid intima-media thickness - A systematic review and meta-analysis. *Circulation, 115*(4), 459-467.

Maes, H. H. M., Neale, M. C., & Eaves, L. J. (1997). Genetic and environmental factors in relative body weight and human adiposity. *Behavior Genetics, 27*(4), 325-351.

Magnussen, C. G., Fryer, J., Venn, A., Laakkonen, M., & Raitakari, O. T. (2006). Evaluating the use of a portable ultrasound machine to quantify intima-media thickness and flow-mediated dilation: Agreement between measurements from two

ultrasound machines. *Ultrasound in Medicine and Biology, 32*(9), 1323-1329.

Magnussen, C. G., Koskinen, J., Chen, W., Thomson, R., Schmidt, M. D., Srinivasan, S. R., et al. (2010). Pediatric Metabolic Syndrome Predicts Adulthood Metabolic Syndrome, Subclinical Atherosclerosis, and Type 2 Diabetes Mellitus but Is No Better Than Body Mass Index Alone: The Bogalusa Heart Study and the Cardiovascular Risk in Young Finns Study. *Circulation, 122*(16), 1604-1611.

Magnussen, C. G., Koskinen, J., Juonala, M., Chen, W., Srinivasan, S. R., Sabin, M. A., et al. (2012). A Diagnosis of the Metabolic Syndrome in Youth That Resolves by Adult Life Is Associated With a Normalization of High Carotid Intima-Media Thickness and Type 2 Diabetes Mellitus Risk: The Bogalusa Heart and Cardiovascular Risk in Young Finns Studies. *Journal of the American College of Cardiology, 60*(17), 1631-1639.

Magnussen, C. G., Raitakari, O. T., Thomson, R., Juonala, M., Patel, D. A., Viikari, J. S., et al. (2008). Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: evidence from the Childhood Determinants of Adult Health (CDAH) study, Cardiovascular Risk in Young Finns Study, and Bogalusa Heart Study. *Circulation, 117*(1), 32-42.

Magnussen, C. G., Thomson, R., Cleland, V. J., Ukoumunne, O. C., Dwyer, T., & Venn, A. (2011). Factors affecting the stability of blood lipid and lipoprotein levels from youth to adulthood: evidence from the Childhood Determinants of Adult Health Study. *Arch.Pediatr.Adolesc.Med., 165*(1), 68-76.

Magnussen, C. G., Venn, A., Thomson, R., Juonala, M., Srinivasan, S. R., Viikari, J. S., et al. (2009). The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood evidence from the cardiovascular risk in Young Finns study, the Bogalusa Heart study, and the CDAH (Childhood Determinants of Adult Health) study. *Journal of the American College of Cardiology, 53*(10), 860-869.

Mahoney, L. T., Burns, T. L., Stanford, W., Thompson, B. H., Witt, J. D., Rost, C. A., et al. (1996). Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *Journal of the American College of Cardiology, 27*(2), 277-284.

McGill, H. C., Jr., McMahan, C. A., Zieske, A. W., Malcom, G. T., Tracy, R. E., & Strong, J. P. (2001). Effects of nonlipid risk factors on atherosclerosis in youth with a favorable lipoprotein profile. *Circulation, 103*(11), 1546-1550.

McGill, H. C., Jr., McMahan, C. A., Zieske, A. W., Sloop, G. D., Walcott, J. V., Troxclair, D. A., et al. (2000). Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arteriosclerosis, Thrombosis, and Vascular Biology, 20*(8), 1998-2004.

McGill, H. C., McMahan, C. A., Tracy, R. E., Oalmann, M. C., Cornhill, J. F., Herderick, E. E., et al. (1998). Relation of a postmortem renal index of hypertension to atherosclerosis and coronary artery size in young men and women. *Arteriosclerosis Thrombosis and Vascular Biology, 18*(7), 1108-1118.

McNamara, J. J., Molot, M. A., Stremple, J. F., & Cutting, R. T. (1971). Coronary artery disease in combat casualties in Vietnam. *JAMA : the journal of the American Medical Association, 216*(7), 1185-1187.

Messner, B., & Bernhard, D. (2014). Smoking and Cardiovascular Disease: Mechanisms of Endothelial Dysfunction and Early Atherogenesis. [10.1161/ATVBAHA.113.300156]. *Arteriosclerosis, Thrombosis, and Vascular Biology, 34*(3), 509-515.

Morrison, J. A., Friedman, L. A., & Gray-McGuire, C. (2007). Metabolic Syndrome in Childhood Predicts Adult Cardiovascular Disease 25 Years Later: The Princeton Lipid Research Clinics Follow-up Study. [10.1542/peds.2006-1699]. *Pediatrics, 120*(2), 340-345.

Morrison, J. A., Friedman, L. A., Wang, P., & Glueck, C. J. (2008). Metabolic Syndrome in Childhood Predicts Adult Metabolic Syndrome and Type 2 Diabetes Mellitus 25 to 30 Years Later. *The Journal of Pediatrics, 152*(2), 201-206.

Myers, R. H., Kiely, D. K., Cupples, L. A., & Kannel, W. B. (1990). Parental history is an independent risk factor for coronary artery disease: The Framingham Study. *American Heart Journal, 120*(4), 963-969.

National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. (1992). *Pediatrics, 89*(3), 495-501.

National Cholesterol Education Program Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. (2002). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation, 106*(25), 3143-3421.

National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. (2004). The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics, 114*(2 Suppl 4th Report), 555-576.

Nicklas, T. A., von Duvillard, S. P., & Berenson, G. S. (2002). Tracking of serum lipids and lipoproteins from childhood to dyslipidemia in adults: the Bogalusa Heart Study. *International Journal of Sports Medicine, 23 Suppl 1*, S39-S43.

Nioi, P., Sigurdsson, A., Thorleifsson, G., Helgason, H., Agustsdottir, A. B., Norddahl, G. L., et al. (2016). Variant ASGR1 Associated with a Reduced Risk of Coronary Artery Disease. *New England Journal of Medicine*.

Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., Descamps, O. S., et al. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. [10.1093/eurheartj/eht273]. *European Heart Journal, 34*(45), 3478-3490.

O'Leary, D. H., Polak, J. F., Kronmal, R. A., Manolio, T. A., Burke, G. L., & Wolfson, S. K. (1999). Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *New England Journal of Medicine, 340*(1), 14-22.

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2012). Prevalence of obesity and trends in body mass index among us children and adolescents, 1999-2010. *JAMA : the journal of the American Medical Association, 307*(5), 483-490.

Padmanabhan, S., Caulfield, M., & Dominiczak, A. F. (2015). Genetic and Molecular Aspects of Hypertension. *Circulation Research, 116*(6), 937-959.

Pandey, A. K., Pandey, S., Blaha, M. J., Agatston, A., Feldman, T., Ozner, M., et al. (2013). Family history of coronary heart disease and markers of subclinical cardiovascular disease: Where do we stand? *Atherosclerosis, 228*(2), 285-294.

Parker, D., Liu, K., Dyer, A. R., Giumetti, D., Liao, Y. L., & Stamler, J. (1988). A comparison of the random-zero and standard mercury sphygmomanometers. *Hypertension, 11*(3), 269-272.

Parsons, T. J., Power, C., Logan, S., & Summerbell, C. D. (1999). Childhood predictors of adult obesity: a systematic review. *International Journal of Obesity, 23*, S1-S107.

Patel, R. S., Asselbergs, F. W., Quyyumi, A. A., Palmer, T. M., Finan, C. I., Tragante, V., et al. (2014). Genetic variants at chromosome 9p21 and risk of first versus subsequent coronary heart disease events: a systematic review and meta-analysis. *J Am Coll Cardiol, 63*(21), 2234-2245.

Patel, R. S., Su, S., Neeland, I. J., Ahuja, A., Veledar, E., Zhao, J., et al. (2010). The chromosome 9p21 risk locus is associated with angiographic severity and progression of coronary artery disease. *Eur Heart J, 31*(24), 3017-3023.

Paynter, N. P., Chasman, D. I., Pare, G., Buring, J. E., Cook, N. R., Miletich, J. P., et al. (2010). Association Between a Literature-Based Genetic Risk Score and Cardiovascular Events in Women. *JAMA: the journal of the American Medical Association, 303*(7), 631-637.

Pencina, M. J., D'Agostino, R. B., Larson, M. G., Massaro, J. M., & Vasan, R. S. (2009). Predicting the 30-Year Risk of Cardiovascular Disease. [10.1161/CIRCULATIONAHA.108.816694]. *Circulation, 119*(24), 3078-3084.

Pencina, M. J., D'Agostino, R. B., Sr., D'Agostino, R. B., Jr., & Vasan, R. S. (2008). Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat.Med., 27*(2), 157-172.

Pettigrew, H. M., Gart, J. J., & Thomas, D. G. (1986). The Bias and Higher Cumulants of the Logarithm of A Binomial Variate. *Biometrika, 73*(2), 425-435.

Pignoli, P., Tremoli, E., Poli, A., Oreste, P., & Paoletti, R. (1986). Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation, 74*(6), 1399-1406.

Polak, J. F., Pencina, M. J., Pencina, K. M., O'Donnell, C. J., Wolf, P. A., & D'Agostino, R. B. (2011). Carotid-Wall Intima-Media Thickness and Cardiovascular Events. *New England Journal of Medicine, 365*(3), 213-221.

Polak, J. F., Person, S. D., Wei, G. S., Godreau, A., Jacobs, D. R., Harrington, A., et al. (2010). Segment-Specific Associations of Carotid Intima-Media Thickness With Cardiovascular Risk Factors The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Stroke, 41*(1), 9-15.

Porkka, K. V., Viikari, J. S., Taimela, S., Dahl, M., & Åkerblom, H. K. (1994). Tracking and predictiveness of serum lipid and lipoprotein measurements in childhood: a 12-year follow-up. The Cardiovascular Risk in Young Finns study. *American Journal of Epidemiology, 140*(12), 1096-1110.

Rahman, M. M., & Laher, I. (2007). Structural and functional alteration of blood vessels caused by cigarette smoking: an overview of molecular mechanisms. *Curr Vasc Pharmacol, 5*(4), 276-292.

Raitakari, O. T., Juonala, M., Kähönen, M., Taittonen, L., Laitinen, T., Mäki-Torkko, N., et al. (2003). Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA : the journal of the American Medical Association, 290*(17), 2277-2283.

Raitakari, O. T., Juonala, M., Rönnemaa, T., Keltikangas-Järvinen, L., Räsänen, L., Pietikäinen, M., et al. (2008). Cohort profile: the Cardiovascular Risk in Young Finns Study. *International journal of epidemiology, 37*(6), 1220-1226.

Raitakari, O. T., Porkka, K. V., Rönnemaa, T., Knip, M., Uhari, M., Åkerblom, H. K., et al. (1995). The role of insulin in clustering of serum lipids and blood pressure in children and adolescents. The

Cardiovascular Risk in Young Finns Study. *Diabetologia, 38*(9), 1042-1050.

Raitakari, O. T., Porkka, K. V. K., Räsänen, L., Rönnemaa, T., & Viikari, J. S. A. (1994). Clustering and six year cluster-tracking of serum total cholesterol, HDL-cholesterol and diastolic blood pressure in children and young adults The cardiovascular risk in young finns study. *Journal of Clinical Epidemiology, 47*(10), 1085-1093.

Raitakari, O. T., Porkka, K. V. K., Viikari, J. S. A., Rönnemaa, T., & Åkerblom, H. K. (1994). Clustering of risk factors for coronary heart disease in children and adolescents. The Cardiovascular Risk in Young Finns Study. *Acta Pediatrica, 83*(9), 935-940.

Reiner, Ž., Catapano, A. L., De Backer, G., Graham, I., Taskinen, M.-R., Wiklund, O., et al. (2011). ESC/EAS Guidelines for the management of dyslipidaemias. [10.1093/eurheartj/ehr158]. *European Heart Journal, 32*(14), 1769-1818.

Ridker, P. M., Pare, G., Parker, A., Zee, R. Y., Danik, J. S., Buring, J. E., et al. (2008). Loci related to metabolic-syndrome pathways including LEPR,HNF1A, IL6R, and GCKR associate with plasma C-reactive protein: the Women's Genome Health Study. *Am J Hum Genet, 82*(5), 1185-1192.

Ripatti, S., Tikkanen, E., Orho-Melander, M., Havulinna, A. S., Silander, K., Sharma, A., et al. (2010). A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet, 376*(9750), 1393-1400.

Roberts, D. L., Dive, C., & Renehan, A. G. (2010). Biological Mechanisms Linking Obesity and Cancer Risk: New Perspectives. *Annual Review of Medicine, 61*, 301-316.

Rosvall, M., Persson, M., Ostling, G., Nilsson, P. M., Melander, O., Hedblad, B., et al. (2015). Risk factors for the progression of carotid intima-media thickness over a 16-year follow-up period: the Malmo Diet and Cancer Study. *Atherosclerosis, 239*(2), 615-621.

Sarwar, N., Danesh, J., Eiriksdottir, G., Sigurdsson, G., Wareham, N., Bingham, S., et al. (2007). Triglycerides and the Risk of Coronary Heart Disease: 10 158 Incident Cases Among 262 525 Participants in 29 Western Prospective Studies. *Circulation, 115*(4), 450-458.

Schildkraut, J. M., Myers, R. H., Cupples, L. A., Kiely, D. K., & Kannel, W. B. (1989). Coronary risk associated with age and sex of parental heart disease in the Framingham Study. *American Journal of Cardiology, 64*(10), 555-559.

Skelton, J. A., Cook, S. R., Auinger, P., Klein, J. D., & Barlow, S. E. (2009). Prevalence and Trends of Severe Obesity Among US Children and Adolescents. *Academic Pediatrics, 9*(5), 322-329.

Skinner, A., & Skelton, J. A. (2014). Prevalence and trends in obesity and severe obesity among children in the united states, 1999-2012. *JAMA Pediatrics, 168*(6), 561-566.

Snieder, H., Harshfield, G. A., & Treiber, F. A. (2003). Heritability of blood pressure and hemodynamics in African- and European-American youth. *Hypertension, 41*(6), 1196-1201.

Sorof, J. M., Alexandrov, A. V., Garami, Z., Turner, J. L., Grafe, R. E., Lai, D. J., et al. (2003). Carotid ultrasonography for detection of vascular abnormalities in hypertensive children. *Pediatric Nephrology, 18*(10), 1020-1024.

Sorof, J. M., Lai, D., Turner, J., Poffenbarger, T., & Portman, R. J. (2004). Overweight, Ethnicity, and the Prevalence of Hypertension in School-Aged Children. *Pediatrics, 113*(3), 475-482.

Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., et al. (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nature Genetics, 42*(11), 937-U953.

Srinivasan, S. R., Bao, W. H., Wattigney, W. A., & Berenson, G. S. (1996). Adolescent overweight is associated with adult overweight and related multiple cardiovascular risk factors: The Bogalusa heart study. *Metabolism-Clinical and Experimental, 45*(2), 235-240.

Stary, H. C. (2000). Natural History and Histological Classification of Atherosclerotic Lesions: An Update. *Arteriosclerosis, Thrombosis, and Vascular Biology, 20*(5), 1177-1178.

Stary, H. C., Blankenhorn, D. H., Chandler, A. B., Glagov, S., Insull, W., Richardson, M., et al. (1992). A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arteriosclerosis, Thrombosis, and Vascular Biology, 12*(1), 120-134.

Stary, H. C., Chandler, A. B., Glagov, S., Guyton, J. R., Insull, W., Rosenfeld, M. E., et al. (1994). A definition of initial, fatty streak, and intermediate lesions of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arteriosclerosis, Thrombosis, and Vascular Biology, 14*(5), 840-856.

Steenland, K. (1992). Passive smoking and the risk of heart disease. *JAMA, 267*(1), 94-99.

Steinberger, J., Daniels, S. R., Eckel, R. H., Hayman, L., Lustig, R. H., McCrindle, B., et al. (2009). Progress and Challenges in Metabolic Syndrome in Children and Adolescents: A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. *Circulation, 119*(4), 628-647.

Talmud, P. J., Hingorani, A. D., Cooper, J. A., Marmot, M. G., Brunner, E. J., Kumari, M., et al. (2010). Utility of genetic and non-genetic risk factors in prediction of type 2 diabetes: Whitehall II prospective cohort study. *British Medical Journal, 340*.

Tao, Y., Maegawa, H., Ugi, S., Ikeda, K., Nagai, Y., Egawa, K., et al. (2006). The transcription factor AP-2beta causes cell enlargement and insulin resistance in 3T3-L1 adipocytes. *Endocrinology, 147*(4), 1685-1696.

Telama, R., Viikari, J., Välimäki, I., Sirentiusanen, H., Åkerblom, H. K., Uhari, M., et al. (1985). Atherosclerosis Precursors in Finnish Children and Adolescents .10. Leisure-Time Physical-Activity. *Acta Paediatrica Scandinavica*, 169-180.

Thanassoulis, G., Peloso, G. M., Pencina, M. J., Hoffmann, U., Fox, C. S., Cupples, L. A., et al. (2012). A Genetic Risk Score Is Associated With Incident Cardiovascular Disease and Coronary Artery Calcium: The Framingham Heart Study. *Circulation: Cardiovascular Genetics, 5*(1), 113-121.

Tirosh, A., Shai, I., Afek, A., Dubnov-Raz, G., Ayalon, N., Gordon, B., et al. (2011). Adolescent BMI Trajectory and Risk of Diabetes versus Coronary Disease. *New England Journal of Medicine, 364*(14), 1315-1325.

U. S. Preventive Services, & Barton, M. (2010). Screening for obesity in children and adolescents: US preventive services task force recommendation statement. *Pediatrics, 125*(2), 361-367.

van den Elzen, A. P. M., de Ridder, M. A. J., Grobbee, D. E., Hofman, A., Witteman, J. C. M., & Uiterwaal, C. S. P. M. (2004). Families and the natural history of blood pressure - A 27-year follow-up study. *American journal of hypertension, 17*(10), 936-940.

Van Petegem, F., Clark, K. A., Chatelain, F. C., & Minor, D. L., Jr. (2004). Structure of a complex between a voltage-gated calcium channel beta-subunit and an alpha-subunit domain. *Nature, 429*(6992), 671-675.

van Rijn, M. J. E., Schut, A. F. C., Aulchenko, Y. S., Deinum, J., Sayed-Tabatabaei, F. A., Yazdanpanah, M., et al. (2007). Heritability of blood pressure traits and the genetic contribution to blood pressure variance explained by four blood-pressure-related genes. *Journal of Hypertension, 25*(3), 565-570.

Visser, M., Bouter, L. M., McQuillan, G. M., Wener, M. H., & Harris, T. B. (1999). Elevated C-reactive protein levels in overweight and obese adults. *Jama, 282*(22), 2131-2135.

Vos, L. E., Oren, A., Uiterwaal, C., Gorissen, W. H. M., Grobbee, D. E., & Bots, M. L. (2003). Adolescent blood pressure and blood pressure tracking into young adulthood are related to subclinical atherosclerosis: The Atherosclerosis Risk in Young Adults (ARYA) Study. *American journal of hypertension, 16*(7), 549-555.

Wang, L., Rundek, T., Beecham, A., Hudson, B., Blanton, S. H., Zhao, H., et al. (2014). Genome-wide interaction study identifies RCBTB1 as a modifier for smoking effect on carotid intima-media thickness. *Arterioscler Thromb Vasc Biol, 34*(1), 219-225.

Wang, T., Jia, W., & Hu, C. (2015). Advancement in genetic variants conferring obesity susceptibility from genome-wide association studies. *Front Med, 9*(2), 146-161.

Wang, Y., & Beydoun, M. A. (2007). The obesity epidemic in the United States - Gender, age, socioeconomic, Racial/Ethnic, and geographic characteristics: A systematic review and meta-regression analysis. *Epidemiologic Reviews, 29*, 6-28.

Wannamethee, S. G., Lowe, G. D., Shaper, A. G., Rumley, A., Lennon, L., & Whincup, P. H. (2005). Associations between cigarette smoking, pipe/cigar smoking, and smoking cessation, and haemostatic and inflammatory markers for cardiovascular disease. *Eur Heart J, 26*(17), 1765-1773.

Webber, L. S., Srinivasan, S. R., Wattigney, W. A., & Berenson, G. S. (1991). Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study. *American Journal of Epidemiology, 133*(9), 884-899.

Weijmans, M., van der Graaf, Y., Reitsma, J. B., & Visseren, F. L. J. (2015). Paternal or maternal history of cardiovascular disease and the risk of cardiovascular disease in offspring. A systematic review and meta-analysis. *International Journal of Cardiology, 179*, 409-416.

Whitaker, R. C., Wright, J. A., Pepe, M. S., Seidel, K. D., & Dietz, W. H. (1997). Predicting obesity in young adulthood from childhood and parental obesity. *N Engl J Med, 337*(13), 869-873.

Wong, M., Edelstein, J., Wollman, J., & Bond, M. G. (1993). Ultrasonic-pathological comparison of the human arterial wall. Verification of intima-media thickness. *Arteriosclerosis, Thrombosis, and Vascular Biology, 13*(4), 482-486.

Zieske, A. W., McMahan, C. A., McGill, H. C., Jr., Homma, S., Takei, H., Malcom, G. T., et al. (2005). Smoking is associated with advanced coronary atherosclerosis in youth. *Atherosclerosis, 180*(1), 87-92.

Åkerblom, H. K., Viikari, J., Uhari, M., Räsänen, L., Byckling, T., Louhivuori, K., et al. (1985). Atherosclerosis precursors in Finnish children and adolescents. I. General description of the cross-sectional study of 1980, and an account of the children's and families' state of health. *Acta paediatrica Scandinavica.Supplement, 318*, 49-63.