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CARDIOVASCULAR HEALTH FROM CHILDHOOD TO ADULTHOOD - WITH SPECIAL REFERENCE TO EARLY VASCULAR CHANGES

The Cardiovascular Risk in Young Finns Study

Tomi Laitinen

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University of Turku

Faculty of Medicine
Institute of Clinical Medicine
Departments of Internal Medicine and Clinical Physiology and Nuclear Medicine
Doctoral Programme of Clinical Investigation
Research Centre of Applied and Preventive Cardiovascular Medicine
Paavo Nurmi Centre, Sports & Exercise Medicine Unit
Turku University Hospital

Supervised by

Professor Markus Juonala, MD, PhD
Department of Medicine, University of Turku and Division of Medicine, Turku University Hospital, Turku, Finland

Docent Costan Magnussen, PhD
Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland, and Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

Docent Katja Pahkala, PhD
Research Centre of Applied and Preventive Cardiovascular Medicine and Paavo Nurmi Centre, Sports & Exercise Medicine Unit, Department of Health and Physical Activity, University of Turku, Turku, Finland.

Reviewed by

Professor Heikki Tikkanen, MD, PhD
Institute of Biomedicine, School of Medicine, University of Eastern Finland, Kuopio, Finland, Department of Sports and Exercise Medicine, University of Helsinki, Helsinki, Finland, and Foundation for Sports and Exercise Medicine, Helsinki, Finland

Docent Jari Laukkanen, MD, PhD
Department of Medicine, Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland, and Central Finland Central Hospital, Jyväskylä, Finland

Opponent

Professor Jussi Huttunen, MD, PhD
Finnish Medical Journal Duodecim,
Helsinki, Finland

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To My Family

ABSTRACT

Tomi Laitinen

From the Faculty of Medicine, Institute of Clinical Medicine, Departments of Internal Medicine and Clinical Physiology and Nuclear Medicine, Doctoral Programme of Clinical Investigation, Research Centre of Applied and Preventive Cardiovascular Medicine, Paavo Nurmi Centre, Sports & Exercise Medicine Unit, University of Turku and Turku University Hospital, Turku, Finland.

Cardiovascular health from childhood to adulthood – with special reference to early vascular changes. The Cardiovascular Risk in Young Finns Study.

Background: Recent recommendations aim to improve cardiovascular health (CVH) by encouraging the general population to meet positive and modifiable ideal CVH metrics: not smoking, being physically active, and maintaining normal weight, blood pressure, blood glucose and total cholesterol levels and a healthy diet.

Aims: The aim of the present study was to report the prevalence of ideal CVH in children and young adults and study the associations of CVH metrics with markers of subclinical atherosclerosis.

Participants and methods: The present thesis is part of the Cardiovascular Risk in Young Finns Study (Young Finns Study). Data on associations of CVH metrics and subclinical atherosclerosis were available from 1,898 Young Finns Study participants. In addition, joint analyses were performed combining data from the International Childhood Cardiovascular Cohort (i3C) Consortium member studies from Australia and the USA.

Results: None of the participants met all 7 CVH metrics and thus had ideal CVH in childhood and only 1% had ideal CVH as young adults. The number of CVH metrics present in childhood and adulthood predicted lower carotid artery intima-media thickness, improved carotid artery distensibility and lower risk of coronary artery calcification. Those who improved their CVH status from childhood to adulthood had a comparable risk of subclinical atherosclerosis to participants who had always had a high CVH status.

Conclusions: Ideal CVH proved to be rare among children and young adults. A higher number of ideal CVH metrics and improvement of CVH status between childhood and adulthood predicted a lower risk of subclinical atherosclerosis.

Keywords: Cardiovascular health, health behaviors, atherosclerosis, health promotion

TIIVISTELMÄ

Tomi Laitinen

Lääketieteellinen tiedekunta, kliininen laitos, sisätautioppi sekä kliininen fysiologia ja isotooppilääketiede, Sydäntutkimuskeskus, Paavo Nurmi – keskus, Turun yliopisto ja Turun yliopistollinen keskussairaala, Turku, Suomi

Sydänterveys lapsuudesta aikuisuuteen – yhteys varhaisiin valtimomuutoksiin. Lasten Sepelvaltimotaudin Riskitekijät (LASERI) -tutkimus.

Tausta: Sydänterveys on myönteisten asioiden summa ja sen osatekijöihin voi vaikuttaa terveillä elämäntavoilla. Tuoreen määritelmän mukaisesti ihanteellista sydänterveyttä kuvastavat normaalipaino, tupakoimattomuus, riittävä liikunta, terveellinen ruokavalio sekä suositusten mukaiset verenpaineen, kolesterolin ja verensokerin tasot.

Tavoite: Väitöskirjatutkimuksen tavoitteena oli selvittää ihanteellisen sydänterveyden esiintyvyys lapsilla ja nuorilla aikuisilla sekä tutkia, miten sydänterveyden osatekijät ovat yhteydessä valtimokovettumataudin varhaisiin valtimomuutoksiin.

Menetelmät: Väitöskirjatutkimus on osa Lasten Sepelvaltimotaudin Riskitekijät (LASERI) – tutkimusta, josta oli käytettävissä tiedot 1 898 tutkittavan sydänterveystekijöistä ja varhaisista valtimomuutoksista. Tutkimukseen yhdistettiin lisäksi kansainvälisiä i3C-konsortion aineistoja australialaisesta ja yhdysvaltalaisista seurantatutkimuksista.

Tulokset: Nuorilla aikuisilla ihanteellisen sydänterveyden, jossa kaikki osatekijät toteutuivat, esiintyvyys oli vain 1 %. Tutkituista lapsista ihanteelliseen sydänterveyteen ei yltänyt kukaan. Sydänterveyden osatekijöiden lukumäärä lapsena ja aikuisena oli yhteydessä valtimoiden terveyteen aikuisiällä. Mitä enemmän ihanteellisia sydänterveyden osatekijöitä yksilöllä oli, sitä ohutseinäisemmät ja joustavammat olivat kaulavaltimot ja sitä pienempi oli sepelvaltimoiden kalkkeuman riski. Niillä tutkittavilla, jotka paransivat sydänterveyttään lapsuudesta aikuisuuteen, valtimokovettumataudin varhaismuutosten riski pieneni samalle tasolle kuin niillä, joilla oli koko ajan hyvä sydänterveys.

Johtopäätökset: Ihanteellisen sydänterveyden määritelmä ei täyty lapsilla ja nuorilla aikuisilla. Suurempi ihanteellisen sydänterveyden osatekijöiden lukumäärä ja sydänterveyden parantaminen lapsuudesta aikuisuuteen olivat yhteydessä alhaisempaan varhaisten valtimomuutosten riskiin.

Avainsanat: Sydänterveys, terveyskäyttäytyminen, valtimokovettumatauti, terveyden edistäminen

CONTENTS

ABBREVIATIONS

AHA	American Heart Association
BHS	Bogalusa Heart Study
BMI	body mass index
CAC	coronary artery calcification
CDAH	Childhood Determinants of Adult Health Study
CHD	coronary heart disease
CI	confidence interval
CT	computed tomography
CV	coefficient of variation
CVD	cardiovascular disease
CVH	cardiovascular health
FFQ	food frequency questionnaire
HDL	high-density lipoprotein
IMT	intima-media thickness
INS	Obesity/Insulin Resistance Study
i3C	International Childhood Cardiovascular Cohort
LDL	low-density lipoprotein
LRC	National Heart, Lung, and Blood Institute Lipid Research Clinics
MetS	metabolic syndrome
Minnesota	Minneapolis Childhood Cohort Studies
NaKs	Sodium-Potassium Blood Pressure Trial
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PFS	Princeton Follow-up Study
PHBPC	Prevention of High Blood Pressure in Children Study
RR	relative risk
SD	standard deviation
SE	standard error
STRIP	Special Turku Coronary Risk Factor Intervention Project
T2DM	type 2 diabetes mellitus
VLDL	very low-density lipoprotein
Young Finns Study	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. Additional unpublished data is also presented.

I **Laitinen TT**, Pahkala K, Magnussen CG, Viikari JSA, Oikonen M, Taittonen L, Mikkilä V, Jokinen E, Hutri-Kähönen N, Laitinen T, Kähönen M, Lehtimäki T, Raitakari OT, Juonala M. Ideal Cardiovascular Health in Childhood and Cardiometabolic Outcomes in Adulthood. The Cardiovascular Risk in Young Finns Study. *Circulation* 2012;125:1971-8

II Oikonen M, **Laitinen TT**, Magnussen CG, Steinberger J, Sinaiko AR, Dwyer T, Venn A, Smith KJ, Hutri-Kähönen N, Pahkala K, Mikkilä V, Prineas R, Viikari JSA, Morrison JA, Woo JG, Chen W, Nicklas T, Srinivasan SR, Berenson G, Juonala M, Raitakari OT. Ideal Cardiovascular Health in Young Adult Populations From the United States, Finland, and Australia and its Association with Carotid Intima-Media Thickness: The International Childhood Cardiovascular Cohort Consortium. *J Am Heart Assoc* 2013;2:e000244

III **Laitinen TT**, Pahkala K, Venn A, Woo JG, Oikonen M, Dwyer T, Mikkilä V, Hutri-Kähönen N, Smith KJ, Gall SL, Morrison JA, Viikari JSA, Raitakari OT, Magnussen CG, Juonala M. Childhood Lifestyle and Clinical Determinants of Adult Ideal Cardiovascular Health. The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Princeton Follow-up Study. *Int J Cardiol* 2013;169:126-32

IV **Laitinen TT**, Pahkala K, Magnussen CG, Oikonen M, Viikari JSA, Sabin MA, Daniels SR, Heinonen OJ, Taittonen L, Hartiala O, Mikkilä V, Hutri-Kähönen N, Laitinen T, Kähönen M, Raitakari OT, Juonala M. Lifetime Measures of Ideal Cardiovascular Health and their Association with Subclinical Atherosclerosis: The Cardiovascular Risk in Young Finns Study. *Int J Cardiol* 2015;185:186-191.

1. INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in developed and developing countries (World Health Organization 2011). Atherosclerosis is a gradual process involving the thickening and stiffening of arteries that begins early in life. The clinical manifestations of CVD, such as myocardial infarction and stroke, are end-points of long-term atherosclerosis progression. There are several important clinical and lifestyle risk factors such as increased blood lipids, high blood pressure, diabetes mellitus, cigarette smoking, and obesity that increase the risk of CVD outcomes (Berenson et al. 1998; Grundy et al. 1999; Raitakari et al. 2003, Wilson et al. 1998). Because of an increasingly suboptimal lifestyle of unhealthy diet, excess adiposity, physical inactivity, and smoking among children, atherosclerotic CVDs may present at younger ages (Mozaffarian et al. 2011).

Prevention of CVDs has traditionally been focused on primary prevention, namely modification of established risk factors. Another strategy that has gained more recent attention is the prevention of risk factors before they establish, or primordial prevention (Lloyd-Jones et al. 2006), first presented by Strasser (Strasser 1978). Observational studies have demonstrated the power of primordial prevention by showing that individuals who maintain a low-risk profile from childhood through middle age have a very low future risk of CVD and a substantially longer life expectancy (Lloyd-Jones et al. 2006; Stamler et al. 1999). However, it is not known how common a low-risk CVD profile is among children and young adults; the childhood factors that promote a low-risk CVD profile; and the relation of a low-risk profile to early vascular changes.

The Cardiovascular Risk in Young Finns Study (Young Finns Study) is an ongoing, multicenter follow-up of 3,596 participants that was initiated to assess biological and lifestyle factors underlying CVD and its risk factors in children and young adults. In this thesis, the main objectives were to: 1) study the prevalence and determinants of a low-risk profile containing optimal health behaviors and clinical factors in children and young adults in the Young Finns Study and in a large international cohort consortium of young adults; and 2) investigate the associations of a low-risk profile on subclinical atherosclerosis and cardiometabolic outcomes.

2. REVIEW OF THE LITERATURE

A large proportion of CVDs are preventable, but their prevalence continues to rise especially among developing countries (World Health Organization 2011). The final end-points of gradual progression of atherosclerosis are clinical CVD events. The atherosclerotic process begins early in life but the clinical manifestations tend to occur several decades later (Barker 1995; Berenson et al. 1998; Reynolds et al. 2013). CVDs are multifactorial diseases affected by different environmental and genetic factors and their interactions. In addition to lifestyle factors, familial factors such as socioeconomic disadvantage and parental smoking have also been associated with future cardiovascular risk (Gall et al. 2014; Poulton et al. 2002). In 1981, over 200 factors were suggested to associate with CVD (Hopkins et al. 1981).

2.1. Defining cardiovascular health

Since the 1960s it has been established that smoking, hypertension, and hypercholesterolemia constitute major risk factors for cardiovascular morbidity and mortality (Kannel et al. 1968). During the last decades, research has mainly focused on identifying and treating high-risk to determine how risk for cardiovascular events increases due to the presence of adverse levels of risk factors. However, this focus has gradually shifted as evidence increasingly demonstrated that low-risk cardiovascular risk factor profiles are associated with large reductions in cardiovascular morbidity and mortality (Stamler et al. 1999). Instead of the traditional risk-focused and adverse-outcomes-oriented approach, more research is having a low-risk emphasis. That is, to preserve and promote attributes which are associated with a healthy, CVD-free life.

In 2010, the American Heart Association (AHA) published the first formal definition of cardiovascular health (CVH) as part of their 2020 impact goals (Lloyd-Jones et al. 2010). The definition was derived from a broad review of the literature that aimed to determine groups of factors associated with excellent prognosis in long-term CVD-free survival and quality of life. CVH was ultimately characterized as seven CVH metrics that consisted of three physiologic health factors and four health behaviors. For each of the seven metrics, ideal, intermediate and poor levels were defined (Lloyd-Jones et al. 2010). Ideal CVH was defined as simultaneous presence of all of the seven metrics at ideal levels: normal blood pressure, total cholesterol, and fasting glucose, non-smoking, adequate physical activity, normal body mass index (BMI), and healthy diet (Table 1). Appropriate levels for children were also provided.

Table 1. Definition of ideal cardiovascular health according to the American Heart Association

Goal/Metric	Definition
Health Behaviors	
Smoking	
Adults	Never or quit >12 months ago
Children	Never tried/never smoked whole cigarette
Physical Activity	
Adults	≥150 min per week moderate intensity or ≥75 min per week vigorous intensity or combination (≥150 min per week moderate + vigorous intensity)
Children	≥60 min of moderate- or vigorous-intensity activity every day
Healthy diet*	
Adults and children	4–5 Components
	Fruits and vegetables: ≥450 g per day
	Fish: ≥two 100 g servings per week (preferably oily fish)
	Fiber-rich whole grains: ≥three 30 g servings per day
	Sodium: <1500 mg per day
	Sugar-sweetened beverages: ≤450 kcal per week
Body mass index	
Adults	<25 kg/m^2
Children	<85th percentile for age and sex
Health Factors	
Blood pressure**	
Adults	<120/<80 mmHg
Children	<90th percentile for age and sex
Total cholesterol**	
Adults	<5.2 mmol/l (<200 mg/dl)
Children	<4.4 mmol/l (<170 mg/dl)
Fasting plasma glucose**	
Adults and children	<5.6 mmol/l (<100mg/dl)

Modified from Lloyd-Jones et al. 2010
*Intake goals are expressed for a 2000-kcal diet and should be scaled accordingly for other levels of caloric intake. **untreated values

As perception of changes in physiologic risk factors and behaviors have traditionally been viewed as means to prevent adverse cardiometabolic outcomes, the purpose of the new goal is to make promoting better levels of these factors and behaviors important targets in themselves. The definition of CVH was designed to be simple and easy to measure and monitor over time (Lloyd-Jones et al. 2010). Moreover, it was meant to be accessible and actionable and allow all patients, clinicians, and communities to focus on and develop capacity in improving CVH.

2.2. Components of cardiovascular health

Of the potential factors associated with CVDs, seven metrics including three health factors and four health behaviors were included in the definition of CVH. All of these seven metrics are modifiable, and strongly associated with good prognosis in long-term CVD-free survival and longevity (Lloyd-Jones et al. 2010). In the following section, the evidence base of these metrics is reviewed.

2.2.1. Cardiovascular health factors

Blood pressure

The relationship between blood pressure and cardiovascular events has been addressed in a large number of observational studies. Blood pressure has an independent continuous relationship with the incidence of stroke, myocardial infarction, sudden death, heart failure and peripheral artery disease (Britton et al. 2009; Lewington et al. 2002). Hypertension is known to induce atherogenesis in several mechanisms (Chobanian et al. 1996). It has been estimated that the risk of coronary heart disease (CHD) begins at 115/75 mmHg and doubles with each increment of 20/10 mmHg (Lewington et al. 2002). Diastolic blood pressure is a more potent cardiovascular risk factor than systolic blood pressure until age of 50 years, but thereafter, systolic blood pressure is more important (Franklin et al. 2001). The relationship between blood pressure and cardiovascular morbidity and mortality is modified by the simultaneous presence of other cardiovascular risk factors. Metabolic risk factors are more common when blood pressure is high than when it is low (Kannel 2000; Thomas et al. 2001). Lowering elevated blood pressure has been shown to be beneficial, with antihypertensive therapy associated with a 35-40% reduction in stroke incidence and 20-25% reduction in myocardial infarction (Neal et al. 2000).

Epidemiologic studies over the past 20 years have shown blood pressure levels in children and adolescents to have increased, explained partially by the rise in obesity (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011). In prospective studies, elevated blood pressure in children and adolescents have been associated with post-mortem fatty streaks and fibrous lesions, increased carotid intima-media thickness (IMT), coronary artery calcium (CAC), decreased carotid elasticity and impaired endothelial function (Berenson et al. 1998; Hartiala et al. 2012; Juonala et al. 2006; Li et al. 2003; Mahoney et al. 1996; McGill et al. 2000; Raitakari et al. 2003). Already at the age of 6 years, systolic blood pressure level has been associated with adult carotid IMT (Juonala et al. 2010). However, a recent report showed that the risk of carotid atherosclerosis was reduced if elevated blood pressure during childhood was resolved by adulthood (Juhola et al. 2013).

Glucose homeostasis

Type 2 diabetes mellitus (T2DM) confers about a two-fold increase in risk for coronary heart disease, major stroke subtypes, and deaths attributed to other vascular causes (Emerging Risk Factors Collaboration et al. 2010). It has been shown that diabetic patients without previous myocardial infarction have an equal risk for myocardial infarction as nondiabetic patients who previously had a myocardial infarction (Haffner et al. 1998). In a recent meta-analysis, a normal fasting plasma glucose concentration of less than 5.60 mmol/l was unrelated to CVD risk. The risk of CHD was modestly higher in non-diabetic persons with impaired fasting glucose (fasting plasma glucose concentration >5.60 mmol/l) (Emerging Risk Factors Collaboration et al. 2010).

Hyperglycemia and insulin resistance have been shown to be associated with the development of atherosclerosis and its complications. A large body of evidence suggests that metabolic abnormalities cause overproduction of reactive oxygen species that are important in precipitating diabetic vascular disease by causing endothelial dysfunction and inflammation (Paneni et al. 2013). Children and young adults with diabetes have decreased arterial elasticity and increased aortic and carotid IMT (Berry et al. 1999; Järvisalo et al. 2001). BMI and metabolic syndrome (MetS) in childhood and also maternal BMI in childhood are independently associated with increased future risk of developing T2DM (Juonala et al. 2013; Magnussen et al. 2010). It has been shown that T2DM can be prevented by lifestyle changes (Tuomilehto et al. 2001). In addition, lifestyle intervention is more effective than metformin in the prevention of T2DM in persons at high risk (Knowler et al. 2002).

Serum cholesterol

An elevated serum total cholesterol concentration contributes to coronary atherosclerosis throughout life. Studies across different populations reveal that those with higher cholesterol concentrations have more CVD than do those having lower concentrations (Keys et al. 1984). Low serum cholesterol concentration in midlife predicts not only better survival but also better physical function and quality of life in old age (Strandberg et al. 2004). The majority of cholesterol circulating in blood stream is contained in low-density lipoprotein (LDL) particles. The robust relationship between total cholesterol and CVD strongly implies that an elevated LDL-cholesterol is a powerful risk factor. Indeed, it has been shown that LDL-cholesterol is the most abundant and clearly evident atherogenic lipoprotein and that any LDL-cholesterol above 2.5 mmol/l (100mg/dl) appears to be atherogenic (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2002). Apart from LDL-cholesterol, high concentrations of triglycerides and a low concentration of high-density lipoprotein cholesterol (HDL) also raise CVD risk (Gordon et al. 1977; Hulley et al. 1980). In population studies, serum total cholesterol is a good surrogate for LDL-cholesterol concentrations. A primary initiating event in atherogenesis is the accumulation of LDL-cholesterol in the subendothelial matrix (Lusis 2000). Multiple randomized trials have demonstrated that lowering LDL-cholesterol by treatment with a statin significantly reduces the risk of major coronary events (Cholesterol Treatment Trialists' Collaboration et al. 2010). In a meta-analysis, prolonged exposure to lower LDL-cholesterol beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-cholesterol with statin beginning later in life (Figure 1). In addition, this effect appears to be independent of the mechanism by which LDL-cholesterol is lowered, suggesting diet and physical activity are probably as effective at reducing the risk of CHD as are statins when started early in life (Ference et al. 2012).

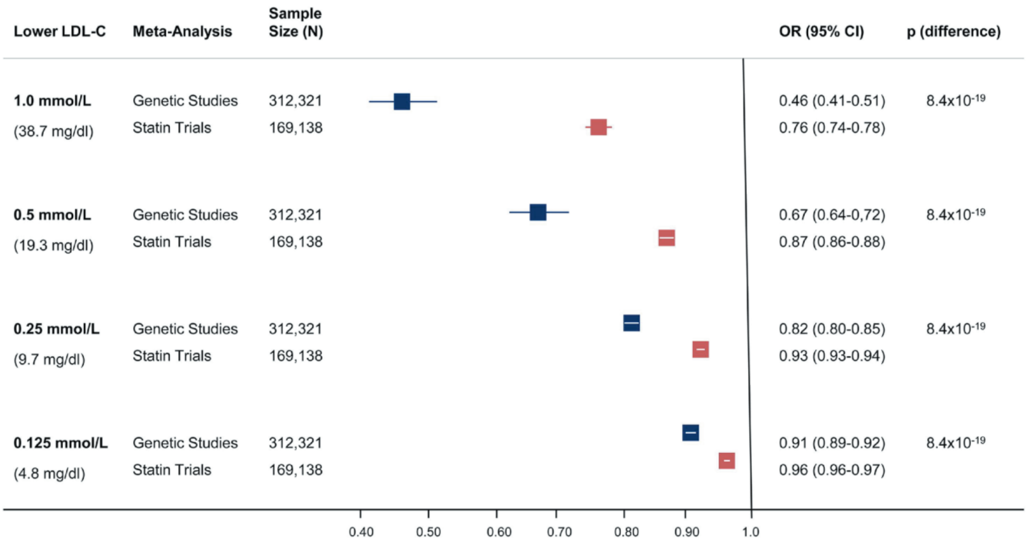

Figure 1. Comparative coronary heart disease (CHD) risk reduction of earlier and later LDL-cholesterol (LDL-C) lowering. Boxes represent the summary point estimate of the odds ratio (OR) for the association between each unit lower LDL-cholesterol and the risk of CHD, for both meta-analyses combining data from Mendelian randomization studies adjusted per unit lower LDL-cholesterol and meta-analyses of statin trials adjusted per unit lower LDL-cholesterol. Bars represent 95% confidence interval (CI). (Ference et al. 2012)

In childhood, serum cholesterol concentration has been shown to associate with subclinical atherosclerosis (Leeson et al. 2000). In adolescents with marked elevation of LDL-cholesterol due to familial hypercholesterolemia, abnormal levels of coronary calcium, increased carotid IMT, and impaired endothelial function have been demonstrated (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011). The concentration of LDL-cholesterol in childhood and young adulthood was associated with the occurrence of fatty streaks and fibrous plaques in autopsy data from the Bogalusa Heart Study (Berenson et al. 1998). In addition, childhood cholesterol levels have been associated with adult carotid IMT and CAC (Davis et al. 2001; Hartiala et al. 2012; Li et al. 2003; Magnussen et al. 2009; Raitakari et al. 2003). For adult carotid IMT, this association for total cholesterol appears at or after 12 years of age (Juonala et al. 2010).

2.2.2. Cardiovascular health behaviors

Physical activity

The cardiovascular health benefits of physical activity are well established and occur at all ages, in males and females, irrespective of race or ethnicity (Physical Activity Guidelines Advisory Committee report 2008; Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011). Insufficient physical activity and low cardiorespiratory fitness are independent risk factors for CVD (Khan et al. 2014; Lakka et al. 1994; Lee et al. 2012; Manson et al. 2002; Sesso et al. 2000) and CVD mortality (Gupta et al. 2011; Kujala et al. 1998). The risk of CVD mortality associated with low cardiorespiratory fitness is at least similar to several other established risk factors (Blair et al. 1996). The mechanisms through which physical activity ameliorates CVH are numerous: glucose homeostasis, lipids, blood pressure, and low-grade inflammation (Booth et al. 2012). Physical activity also enhances endothelial function (Vona et al. 2009), slows the progression of age-related arterial stiffening (Physical Activity Guidelines Advisory Committee report 2008) and decreases the progression of IMT (Thijssen et al. 2012). Children's CVH also benefits from physical activity (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011). In childhood, physical activity is favorably associated with cardiometabolic risk factor profile (Ekelund et al. 2012), endothelial function, and carotid IMT (Pahkala et al. 2011; Watts et al. 2004). A moderate increase in physical activity is related to decreased progression of IMT during adolescence (Pahkala et al. 2011).

For CVH, any physical activity appears to be better than none, and additional benefits may be obtained as the intensity, frequency and/or duration of physical activity increases (Lloyd-Jones et al. 2010). However, it appears that regular physical activity of 150 minutes/week of at least moderate intensity is sufficient to reduce the risk of numerous chronic diseases including CVD, preserve both physical and mental health and function into old age, and subsequently extend longevity (Blair et al. 2009).

Smoking

For more than 50 years, evidence has accrued indicating that exposure to tobacco smoke is causally related to CHD, stroke, atherosclerosis, aortic aneurysm, peripheral vascular disease, and subclinical CVD (National Center for Chronic

Disease Prevention and Health Promotion Office on Smoking and Health 2014). Cigarette smoke is an aerosol that contains >4,000 chemicals, including nicotine, carbon monoxide, acrolein, and oxidant compounds (Csordas et al. 2013). Smoking has many unfavorable effects on the vascular wall (Ambrose et al. 2004). It is associated with increased levels of inflammatory markers and contributes to endothelial dysfunction by decreasing nitric oxide bioavailability. It interferes adversely with all stages of atherosclerotic plaque formation and development and pathological thrombus formation. Exposure to cigarette smoke results in platelet activation, stimulation of the coagulation cascade, and impairment of fibrinolysis. Many cigarette-smoke-mediated prothrombotic changes are quickly reversible upon smoking cessation (Csordas et al. 2013). Among adult populations, smoking bans in public places and workplaces are associated with significant reductions in ischemic heart disease incidence (Meyers et al. 2009).

Smoking has been associated with increased carotid IMT also in young adults and atherosclerotic lesions were more prevalent in the coronary arteries of smoking adolescents and young adults (PDAY research group 1990; Knoflach et al. 2003). Exposure to cigarette smoking in childhood appears to have a pervasive effect on long-term vascular health. For example, children exposed to their parents' smoking have been shown to have reduced endothelial function and increased carotid IMT in adulthood (Gall et al. 2014; Juonala et al. 2012). In addition, serum cotinine levels, a biomarker of smoke exposure, was shown to associate with impaired brachial endothelial function, decreased aortic elasticity, and increased aortic IMT in healthy children (Kallio et al. 2009; Kallio et al. 2010).

Excess body weight - overweight and obesity

Overweight and obesity predispose to numerous cardiac complications such as CHD, heart failure, and sudden death (Poirier et al. 2006). Overweight is associated with an adverse lipid profile, hypertension and insulin resistance in childhood (Dahlström et al. 1985; Ylitalo 1981). Indeed, overweight is crucial in the pathophysiology of T2DM and MetS that are both strong risk factors for CVD morbidity and mortality (Haffner et al. 1998; Lakka et al. 1994). Excessive adipose tissue accumulation is often accompanied with a proinflammatory and prothrombotic state, which may be one link between increased risk of stroke among those who are obese (Poirier et al. 2006; Rost et al. 2001). In addition to an unfavorable risk factor profile, it is apparent that a variety of adaptations and alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of hypertension or underlying organic heart disease (Poirier et al. 2006).

It has been shown that being overweight or obese as a child predicts the development of T2DM and CVD in adulthood (Baker et al. 2007; Juonala et al. 2011). In cross-sectional studies, obese children have been reported to have increased carotid IMT and stiffness compared with healthy control children (Iannuzzi et al. 2004). BMI measured as young as 3 years of age has been associated with adult carotid IMT (Juonala et al. 2010). Importantly, a high BMI in childhood is known to associate with a high risk of obesity later in adulthood (Singh et al. 2008). As such, it has been suggested that intervention should occur whenever an overweight child is seen in medical settings (Juhola et al. 2011). In a recent report from four longitudinal cohort studies, childhood overweight-related risks for various outcomes (hypertension, high-risk carotid IMT, dyslipidemia, T2DM) appeared to be reversible among those individuals who became nonobese adults (Juonala et al. 2011).

Diet

Diet is a powerful determinant of CVD (Mozaffarian et al. 2011). Natural experiments have shown rapid reductions in CVD after dietary improvement (Capewell et al. 2011). In contrast to individual nutrients, health effects of foods likely represent the synergy of composite effects and interactions of multiple factors, including carbohydrate quality, fiber content, specific fatty acids and proteins, preparation methods and food structure (Mozaffarian et al. 2011).

The dietary goals included in the AHA's definition of CVH include recommended intake levels of five dietary metrics: fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages (Table 1). Many epidemiological studies have indicated a protective role for a diet rich in fruits and vegetables against the development and progression of CVD (Napoli et al. 2007). Higher consumption of fish and omega-3 fatty acids is also associated with a lower risk of CVD (Daviglus et al. 1997; Hu et al. 2002). Excess intake of salt (sodium chloride) has a major role in the pathogenesis of elevated blood pressure. Independent of its effect on blood pressure, excess salt intake also promotes left ventricular hypertrophy and fibrosis in the heart and arteries (Appel et al. 2011; Frohlich 2007; Whelton et al. 2012).

There is a consistent, inverse association between consumption of whole grains and incident CVD in epidemiological studies (Liu et al. 1999; Mellen et al. 2008). Consumption of sugar-sweetened beverages is associated with increased risk of CVD (de Koning et al. 2012) while high added sugar consumption is linked with increased risk for CVD mortality (Yang et al. 2014).

In addition to these five dietary goals included in the definition of CVH, several other dietary factors have shown to be protective against CVD. Consuming more nuts, dairy products, and vegetable oils and avoidance of partially hydrogenated fat (trans fat), saturated fat, processed meats and excessive alcohol consumption have established cardiometabolic benefits (Mozaffarian et al. 2011). Appropriate energy balance is also essential for CVH.

Childhood diet pattern has been shown to be a significant determinant of diet pattern in adulthood (Mikkila et al. 2004; Mikkila et al. 2005). Unhealthy diet in childhood, i.e. a diet poor in vegetables and fruits is associated with MetS, and increased carotid IMT and arterial stiffness in adulthood (Aatola et al. 2010; Jääskeläinen et al. 2012; Kaikkonen et al. 2013). An increase in the consumption of sugar-sweetened beverages from childhood to adulthood is associated with BMI and overweight in women (Nissinen et al. 2009). The effects of dietary intervention initiated in infancy and maintained until age 20 years on atherosclerosis risk factors have been studied in the Special Turku Coronary Risk Factor Intervention Project (STRIP) (Simell et al. 2009). The aim of the intervention was to counsel study participants toward a diet beneficial for CVH. The dietary counseling led to lower saturated fat intake, LDL-cholesterol concentration, blood pressure (Niinikoski et al. 2009; Niinikoski et al. 2012), improved insulin sensitivity (Oranta et al. 2013), and enhanced endothelial function in the intervention group (Raitakari et al. 2005). In addition, the dietary counseling is associated with higher number of ideal CVH metrics in adolescence (Pahkala et al. 2013).

2.3. Prevalence of ideal cardiovascular health

Since the publication of the AHA definition of ideal CVH in 2010, numerous studies have reported the prevalence of ideal CVH to be low (Table 2). Among nearly 2,000 US participants, the prevalence of ideal CVH, meeting all seven metrics, was only 0.1% (Bambs et al. 2011). An important disparity was highlighted, with the prevalence of ideal CVH being significantly lower in non-Hispanic blacks and Hispanics compared to non-Hispanic whites (Dong et al. 2012). In an Italian population, only 1 in 10 of the participants met more than five ideal CVH metrics, and the prevalence of meeting all seven metrics was 1.7% (Vetrano et al. 2013). Among a population of 9,962 Chinese participants, 0.5% met ideal levels of all sevenCVH metrics (Zeng et al. 2013). Del Brutto et al. compared CVH of two distinct populations that had similar ethnic backgrounds, Hispanic participants living in rural coastal Ecuador and Northern Manhattan. Meeting all seven metrics was scarce in both populations; 2.1% in participants living in rural costal Ecuador and 0% in those living in Northern Manhattan. Overall CVH status in participants living in rural costal Ecuador was better, as 36.4% of them had 4 or more ideal CVH metrics compared with 14.1% of the participants living in Northern Manhattan (Del Brutto et al. 2013). Data on CVH in children and adolescents is scarce. Of the 4673 US adolescents in the selected National Health and Nutrition Examination Survey (NHANES) sample, no males or females exhibited ideal levels of all 7 CVH metrics; less than half of the adolescents were classified as having ≥5 ideal CVH metrics (Shay et al. 2013). Similarly, in the STRIP study none of the adolescents met all 7 ideal CVH metrics. Moreover, the proportion of participants meeting at least 5 ideal metrics decreased with age, with 60.2%, 45.5%, and 34.2% at 15, 17, and 19 years of age, respectively (Pahkala et al. 2013).

Considering these data as a collective, ideal CVH is rare despite the majority of children being born with the potential of ideal CVH (Shay et al. 2013). Fewer than half of adolescents preserve at least five of the seven metrics. After adolescence the prevalence of ideal CVH steadily declines, until it is almost nonexistent above age 60 years (Go et al. 2013).

2.4. Association of cardiovascular health status with the risk of cardiovascular outcomes

Several prospective studies have shown that the greater the number of ideal CVH metrics, the lower the risk of cardiovascular outcomes (Table 2). In the Atherosclerosis Risk in Communities study, CVD incidence rates were one-tenth as high among those with 6 ideal metrics compared with zero ideal metrics (Folsom et al. 2011). In the Northern Manhattan study, a strong graded relationship between the number of ideal CVH metrics and risk for stroke, myocardial infarction, and vascular death among different ethnicities living in the same community was demonstrated (Dong et al. 2012).

Table 2. Prospective studies examining the relationship between number of ideal cardiovascular health (CVH) metrics and cardiovascular outcomes.

Study	N	Age (years)	Prevalence of ideal CVH (%)	Follow-up (years)	CV outcomes associated with the number of CVH metrics
Atherosclerosis Risk in Communities (Folsom et al. 2011)	12,744	45-64	0.1%	18.7	MI, coronary death, stroke
Coronary Artery Calcification in Type 1 Diabetes study (Alman et al. 2014a)	546 with T1DM, 631 without T1DM	37±9 39±9	0%	6.1	CAC
The Framingham Offspring Study (Xanthakis et al. 2014)	2,680	58±10	0.7%	maximum 16	Incident CHD, stroke or TIA, intermittent claudication and heart failure.
Kailuan Study (Wu et al. 2012)	101,510	18-98	0.1%	4	CVD events incl. MI, cerebral infarction, and cerebral hemorrhage
The National Health and Nutrition Examination Survey (Yang et al. 2012)	44,959	≥20	2.0% in 1988-1994 1.2% in 2005-2010	14.5	Mortality from CVD and ischemic heart disease
The National Health and Nutrition Examination Survey (Ford et al. 2012)	7,622	≥20	1.1% in 1999-2002	5.8	CVD mortality
Northern Manhattan Study (Dong et al. 2012)	2,981	69±10	0%	11	MI, stroke, vascular death
Reasons for Geographic and Racial Differences in Stroke study (Kulshreshtha et al. 2013)	22, 914	≥45	0%	4.9	Stroke
The SEARCH CVD Study (Alman et al. 2014b)	190	13-17	0%	5	arterial stiffness
Special Turku Coronary Risk Factor Intervention Project (Pahkala et al. 2013)	298-394	15-19	0%	4	aortic IMT and distensibility

Ideal CVH = all 7 CVH metrics at ideal levels, MI = myocardial infarction, T1DM = type 1 diabetes mellitus, CAC = coronary artery calcification, CHD = coronary heart disease. TIA= transient ischemic attack, CVD = cardiovascular disease, IMT=intima-media thickness

Potential mechanisms underlying the inverse association between CVH and CVD incidence are not completely clear. However, the health promoting benefits of each of the health behaviors and health factors have been, individually, well-established (Lloyd-Jones et al. 2010). In prospective studies, the number of ideal CVH metrics have been shown to associate with CAC in adults (Alman et al. 2014a) and with IMT and arterial stiffness in childhood (Alman et al. 2014b; Pahkala et al. 2013) (Table 2). Moreover, change in CVH status between childhood and adulthood is associated with arterial stiffness (Aatola et al. 2014). Two cross-sectional studies of middle-aged participants have recently shown an inverse association between the number of CVH metrics and carotid IMT (Kulshreshtha et al. 2014; Xanthakis et al. 2014). However, data on longitudinal associations of CVH status and carotid IMT as well as data on associations of CVH status and carotid IMT or distensibility in young adults are lacking.

Greater CVH has also been associated with modestly lower blood concentrations of cardiometabolically adverse serum biomarkers; plasminogen activator inhibitor-1, aldosterone, C-reactive protein, D-dimer, fibrinogen, homocysteine, and growth differentiation factor-15 (Xanthakis et al. 2014). Subclinical disease and these serum biomarkers both represent likely intermediary factors in the transition of low CVH to CVD. However, the association of CVH status and incident CVD has been shown to be only partly mediated by measures of subclinical disease and cardiometabolic serum biomarkers (Xanthakis et al. 2014).

2.5. Other associations of cardiovascular health status

Yang et al. reported that those with 6 or more ideal metrics had 51% lower risk for all-cause mortality compared with individuals with 0 or 1 metrics at ideal levels. Risk reductions were similar for older ages, both sexes, and all race/ethnicity and educational attainment groups (Yang et al. 2012). In another study, participants who met at least 5 ideal CVH metrics had a reduction of 78% in the risk for all-cause mortality compared to those who met none of the 7 ideal metrics (Ford et al. 2012). In the Atherosclerosis Risk in Communities study, there was an inverse association between the number of ideal CVH metrics at baseline and combined cancer incidence during the 17-19 years of follow-up (Rasmussen-Torvik et al. 2013). Ideal CVH in young adulthood and its maintenance to middle age is also associated with better psychomotor speed, executive function, and verbal memory in midlife, suggesting that maintenance of ideal CVH has implications for cognitive outcomes later in life (Reis et al. 2013). Accordingly, a recent report showed that people with poor CVH have a substantially higher incidence of cognitive impairment compared to those with intermediate or ideal CVH (Thacker et al. 2014). In addition, ideal CVH metrics, especially health behaviors, have an inverse relationship with depressive symptoms (Espana-Romero et al. 2013).

2.6. Measurement of subclinical atherosclerosis

The atherosclerotic process is lifelong, but clinical symptoms and events usually do not occur until middle age (Figure 2). However, early subclinical changes in vascular structure and function can be reliably measured noninvasively (Detrano et al. 2008; Raitakari et al. 2003). Thickening and stiffening of large artery walls, coronary artery calcification (CAC), and endothelium-dependent vasoactivity are four currently used markers of subclinical atherosclerosis. In the present thesis, subclinical atherosclerosis was studied by arterial wall IMT and arterial distensibility assessed by ultrasound, and CAC assessed by computed tomography (CT).

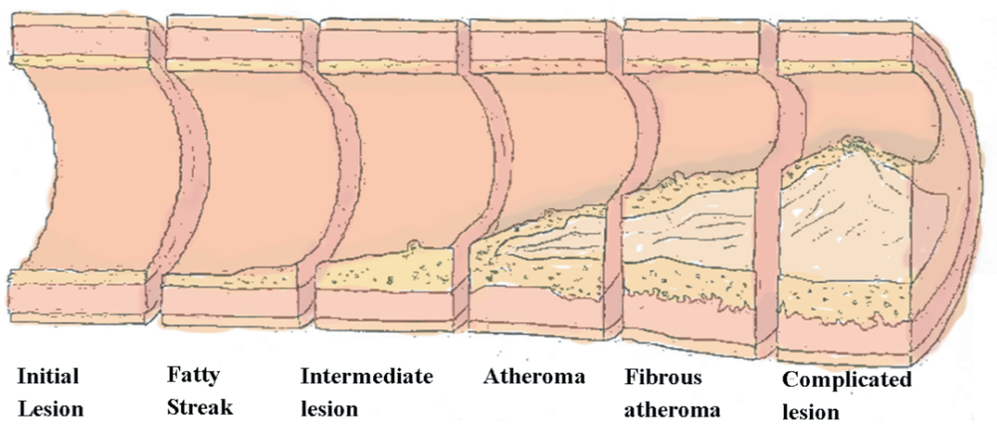

Figure 2. Development of atherosclerosis. Blocks indicate decades of life. The initial lesions contain atherogenic lipoproteins that elicit an increase in macrophages in the arterial wall causing adaptative intimal thickening. Later fatty streaks can be found. Finally, atheromas and fibroatheromas are potentially symptom producing lesions.

2.6.1. Arterial wall intima-media thickness

Measurement of arterial wall IMT was first described in 1986, when Pignoli et al. showed a close correlation between ultrasonically measured aortic IMT and the same thickness measured by light microscopy (Pignoli et al. 1986). Assessment of IMT involves a simple distance measurement between the leading edges of the lumen-intima and media-adventitia ultrasound interfaces (Figure 3). Carotid IMT can be measured relatively simply due to its size and attainable anatomy; it therefore quickly became the vessel of choice for ultrasonic examination of IMT. Today, carotid IMT is recognized as a surrogate marker of atherosclerosis (de Groot et al. 2004).

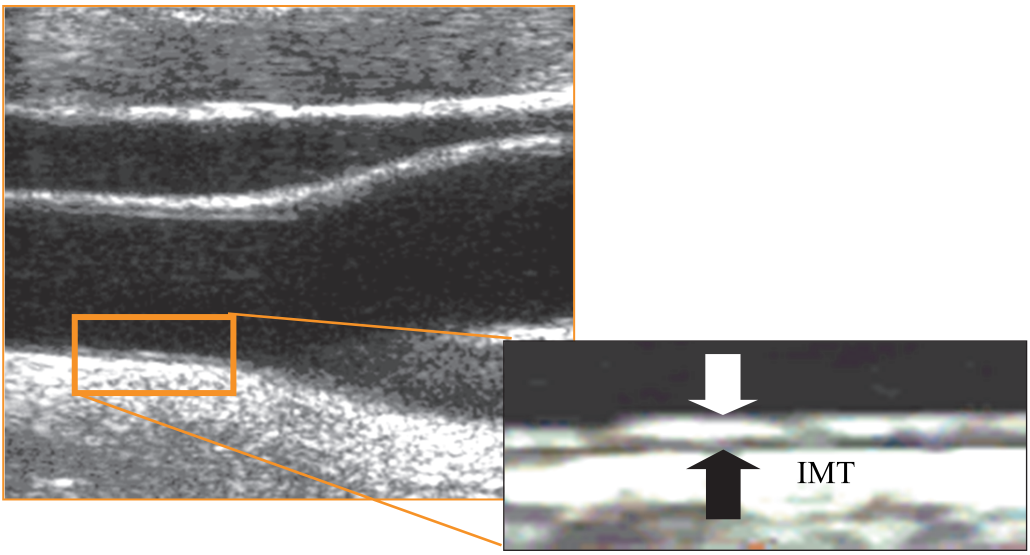

Figure 3. Carotid intima-media thickness. The layers between the white (lumen-intima interface) and the black arrow (media-adventitia interface) represent the intima-media layers in the ultrasound image.

Increased carotid IMT is strongly associated with current and childhood cardiovascular risk factor levels (Davis et al. 2001; Raitakari et al. 2003) and relates to the extent and severity of coronary artery disease (Burke et al. 1995). Several longitudinal studies have shown that increased carotid IMT is an independent predictor of myocardial infarction and stroke (Bots et al. 1997; O'Leary et al. 1999). In addition, mean carotid IMT has been shown to predict the presence of complex coronary artery lesions and also associate with lesion complexity (Ikeda et al. 2012). In a meta-analysis, the future risk of myocardial infarction was shown to increase by 10% to 15%, and stroke risk by 13% to 18% for each 0.1 mm increase in carotid IMT (Lorenz et al. 2007).

2.6.2. Arterial distensibility

Decreased elasticity has been considered as an early pathophysiological change in arteries relevant to the development of atherosclerosis (Oliver et al. 2003). Elasticity of proximal large arteries, such as carotid artery is a consequence of a high elastin to collagen ratio in their walls. The elasticity of an artery can be estimated by measuring its distensibility. Ultrasonic assessment of carotid artery distensibility measures the ability of the artery to expand as the response to pulse pressure caused by cardiac contraction and relaxation, reflecting the mechanical load of the artery wall (Figure 4) (Juonala et al. 2005). Arterial distensibility decreases with age largely due to progressive degeneration of arterial elastin fibers and increases in collagen (Avolio et al. 1998). However, cardiovascular risk factors are shown to associate with decreased arterial distensibility in childhood (Aggoun et al. 2000; Tounian et al. 2001) and childhood risk factors predict decreased carotid distensibility in young adulthood (Juonala et al. 2005). In addition, spontaneous recovery from MetS was favorably associated with carotid distensibility in young adults (Koskinen et al. 2010). In adults, decreased carotid distensibility is implicated as a predictor of cardiovascular events (Haluska et al. 2010). In a recent report, ultrasound measures of carotid arterial stiffness were independently associated with incident ischemic stroke but not with incident CVD events (Yang et al. 2012).

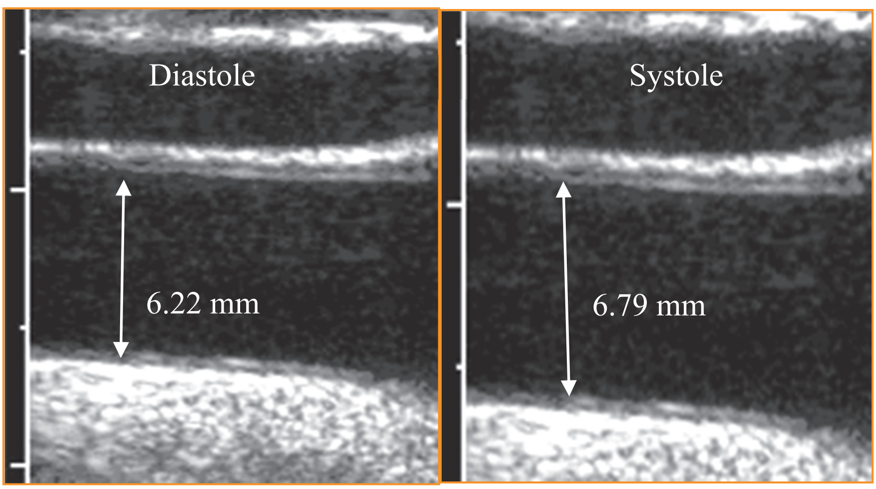

Figure 4. Carotid distensibility defined by the difference in arterial diameter in end-diastole and end-systole.

2.6.3. Coronary artery calcification

Coronary artery calcification (CAC) detected in CT is a marker of subclinical CHD (Detrano et al. 2008; Rumberger et al. 1994). The presence of atherosclerotic plaque is confirmed by a positive scan finding (Figure 5), whereas the absence of detectable CAC on CT among asymptomatic subjects implies that the presence of atherosclerotic plaque is substantially less likely (Greenland et al. 2007; Wexler et al. 1996). CAC is found more frequently in advanced coronary lesions and older individuals. The amount of calcified plaque correlates with the total amount of atherosclerotic plaque and it has been shown that plaques with evidence of mineralization are larger and associated with larger coronary arteries (Wexler et al. 1996). CAC is a predictor of incident CHD and coronary events in different populations and provides predictive information beyond that provided by standard risk factors (Detrano et al. 2008; Secci et al. 1997; Taylor et al. 2005).

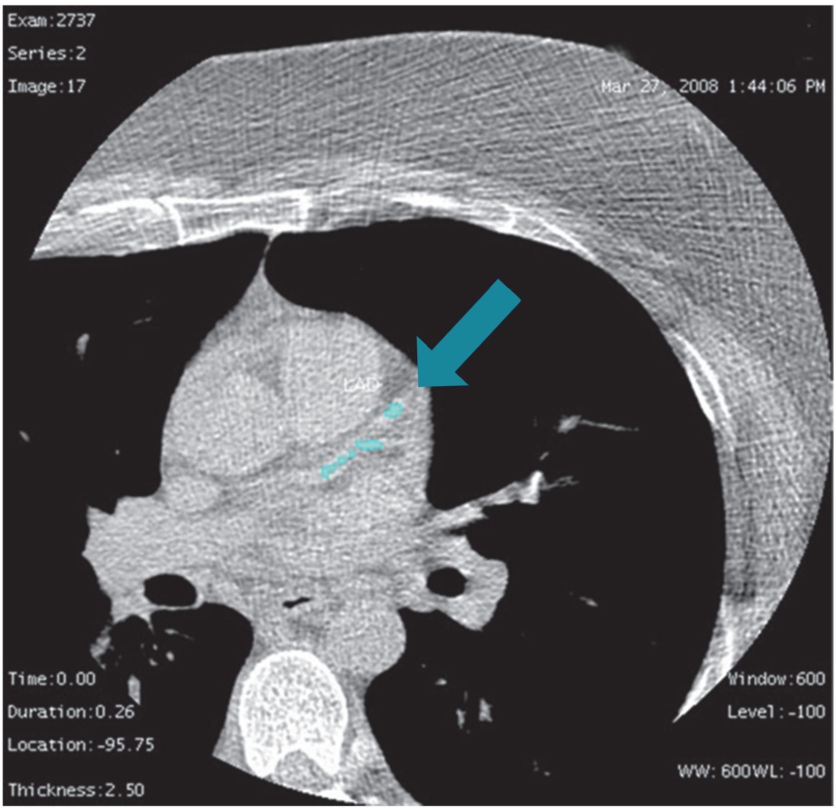

Figure 5. A Cardiac computed tomography scan for calcium scoring showing coronary artery calcification of the left anterior descending artery.

It has been demonstrated that cardiovascular risk factors in early adulthood are associated with increased CAC in middle age independently of contemporary risk factors (Loria et al. 2007). It has also been shown that changes in continuous composite healthy lifestyle factor score (5 factors: not overweight/obese, low alcohol intake, healthy diet, physically active, nonsmoker) in young adults, was associated with CAC and IMT 20 years later (Spring et al. 2014). In addition, elevated BMI, LDL-cholesterol and systolic blood pressure levels in childhood and adolescence independently predict adulthood CAC (Hartiala et al. 2012; Mahoney et al. 1996).

3. AIMS OF THE STUDY

This thesis is predominantly based on findings from the Cardiovascular Risk in Young Finns Study. In addition, participants from four other prospective epidemiological studies, the Childhood Determinants of Adult Health Study, Princeton Follow-up Study, Bogalusa Heart Study, and Minneapolis Childhood Cohort Studies, all members of the International Childhood Cardiovascular Cohort (i3C) Consortium, were included in the analyses for some of the aims. The purpose was to examine the prevalence and childhood predictors of ideal CVH, and to determine the association of ideal CVH with early vascular changes and cardiometabolic outcomes (Figure 6).

The specific aims were:

1. to report the prevalence of ideal CVH in Finnish children and young adults and also in a large international cohort of young adults (Study I, II).

2. to investigate the childhood determinants of adult ideal CVH (Study III).

3. to study whether the number of ideal CVH metrics in childhood and adulthood is associated with subclinical atherosclerosis and cardiometabolic outcomes (Study I, II, IV)

4. to investigate the effect of longitudinal change in CVH on subclinical atherosclerosis (Study IV).

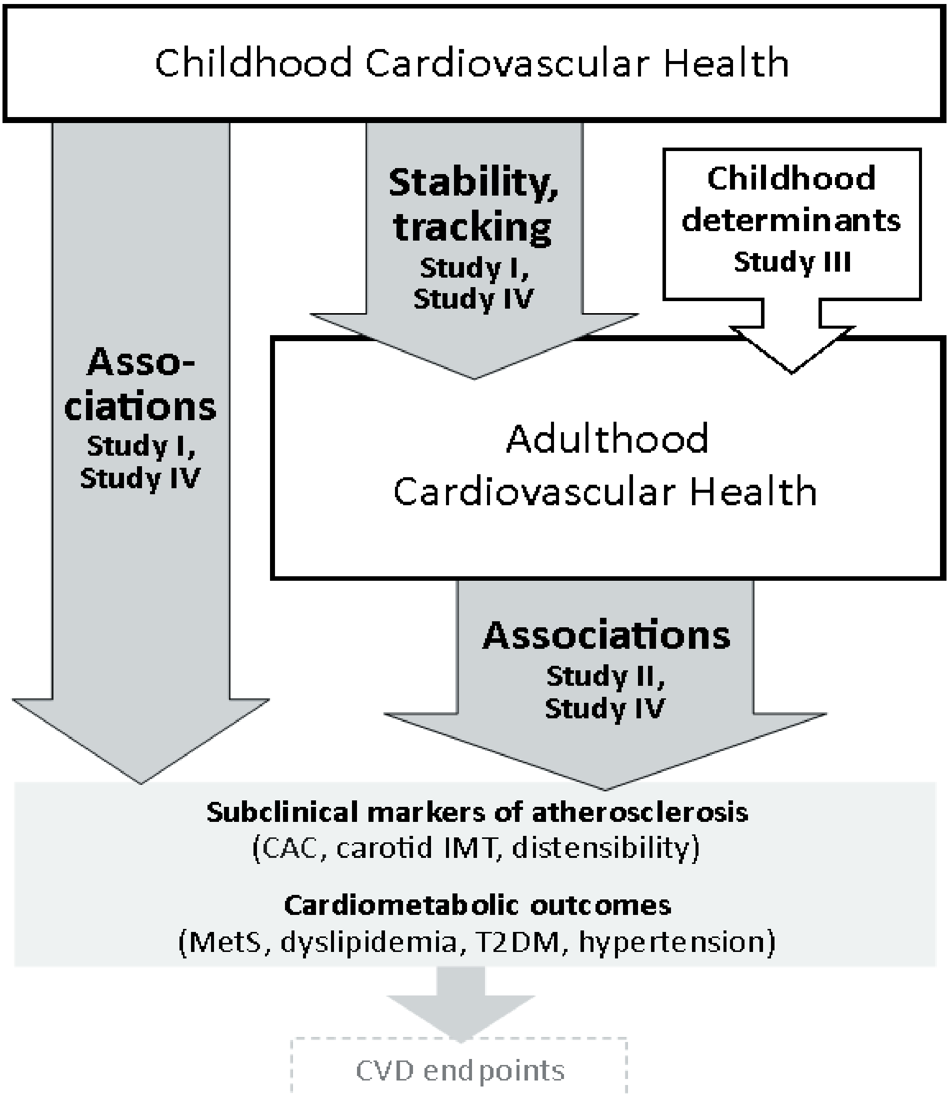

Figure 6. Schematic presentation of the aims of the study.

4. SUBJECTS AND METHODS

4.1. Description of the study cohorts

All of the cohort studies used protocols approved by local ethics committees, with signed informed consent from participants or their parents. All cohorts collected data on participants' age, sex, race, height and weight, blood pressure, total cholesterol, and glucose. Self-reported questionnaires were used to derive data on tobacco smoking, physical activity, and diet. Summary of the study cohorts is presented in Table 3.

4.1.1. The Cardiovascular Risk in Young Finns Study

The Cardiovascular Risk in Young Finns Study (Young Finns Study) is an on-going multicentre follow-up study to assess risk factors underlying CVD. The Young Finns Study was designed as a collaborative effort between five university hospitals in Finland (Turku, Tampere, Helsinki, Kuopio and Oulu). Pilot studies were performed in 1978 (N=264, aged 8 years) and in 1979 (N=634, aged 3, 12 and 17 years). The first cross-sectional study was conducted in 1980. Altogether 4,320 children and adolescents aged 3, 6, 9, 12, 15 and 18 years were randomly chosen from the population register of these areas to produce a representative sample of Finnish children. Of these individuals, 3,596 (83%) participated in the original study. Since then, regular follow-ups have been performed. The participation rates in the follow-up studies among Young Finns participants are shown in Figure 7. Follow-ups in 2001 and 2007 included non-invasive ultrasound studies to assess carotid artery IMT and distensibility. In 2008, a cardiac CT study to measure CAC was conducted for a subsample of the Young Finns Study participants (N=589), then 40 to 46 years of age. The latest follow-up of the Young Finns Study was performed in 2010-2012. In this thesis, data from the 1980, 1986, 2001 and 2007 follow-ups were used (Figure 7).

Year	N	Age cohorts
1980	3596	3 6 9 12 15 18
1983	2991	6 9 12 15 18 21
1986	2779	9 12 15 18 21 24
1989	2737	12 15 18 21 24 27
1992	2730	15 18 21 24 27 30
2001	2283	24 27 30 33 36 39
2007	2204	30 33 36 39 42 45
2011/12	2063	34 37 40 43 46 49

Figure 7. Study design and participation rates at each stage of the Young Finns Study.

4.1.2. The Childhood Determinants of Adult Health Study

The Childhood Determinants of Adult Health (CDAH) study was established to examine childhood predictors of adult cardiovascular disease and diabetes. Baseline data were collected in 1985 on a representative sample of 8,498 school children 7 to 15 years of age as part of the Australian Schools Health and Fitness Survey. Lifestyle and biological risk factors were measured, including lipoproteins on a subsample of children 9, 12, and 15 years of age (n=1,919). In 2004–2006, a total of 5,170 participants (61%) from the original cohort provided data to the follow-up study. Of these, 2,410 participants were reexamined at 34 field-work clinics across Australia when aged 26 to 36 years. In the follow-up study, a total of 2,049 participants underwent non-invasive ultrasound studies of carotid artery.

4.1.3. The Princeton Follow-up Study

The Princeton Follow-up Study (PFS) was conducted in 1998-2003 to re-examine lipids and other risk factors of CVD in an established cohort during their fourth decade of life. The participants were originally seen in 1973-1978 as schoolchildren, 5-19 years of age, in the Princeton City School District (Cincinnati, OH, USA) as part of the National Heart, Lung, and Blood Institute Lipid Research Clinics (LRC). The student population in LRC was 72% white and 28% black, with a mean age of 12.4±3.3 years. In 1998, eligible former schoolchildren with a mean age of 38.6±3.6 years were invited to participate in the PFS, 22 to 30 (median 26) years after their initial LRC sampling. There had been no contact with the former schoolchildren during intervals in these studies.

4.1.4. The Bogalusa Heart Study

The Bogalusa Heart Study (BHS) began in 1973 as an epidemiological investigation of cardiovascular risk factors and their environmental determinants in a black (35%) and white (65%) pediatric population of the semi-rural community of Washington Parish, Bogalusa (LA, USA). Seven cross-sectional surveys of children aged 4 to 17 years, each including more than 3,500 children, were conducted between 1973 and 1988. In addition, five cross-sectional surveys of young adults aged 18 to 32 years who had been previously examined as children and remained accessible were conducted between 1979 and 1991. In the 2001 to 2002 survey, 1,143 participants (mean age 36.4±4.4 years; 70% white; 43% men) underwent non-invasive ultrasound studies of the carotid artery. In the 2003 to 2007 survey, IMT was measured in 958 participants (39.0±4.3 years old). The participation rate was approximately 80% for children to approximately 60% for the young adult cohort.

4.1.5. The Minneapolis Childhood Cohort Studies

The Minneapolis Childhood Cohort Studies (Minnesota) consist of three separate cohort recruitments (ages 6-19), all sampled from school screening. The Prevention of High Blood Pressure in Children (PHBPC) study was initiated in 1977-78 with blood pressure screening of 10,423 6-8 year olds. A cohort of 1,207 children was then selected for long-term evaluation and seen twice yearly through grade school and once yearly through high school for anthropometric and blood pressure measures. An examination at age 19 (N=817) included blood analyses, as did examinations at age 24 (N=679) and age 40 (N=400). The sodium-potassium blood pressure trial (NaKs) was initiated in 1985-86 with the screening of 19,452 children aged 11-14 years of which 295 were entered into a sodium-potassium trial and seen in clinic four times per year for three years. At ages 14-17 blood analyses were performed. At mean age 26 years, 179 members of the cohort had a clinic examination and blood tests. The Obesity/Insulin Resistance study (INS) was initiated in 1995. After school screening of 12,000 11-19 year olds, 678 were recruited for detailed cardiovascular evaluation and insulin clamp studies at mean ages 13, 15, 19 and 22.

Table 3. Summary of the international childhood cohort studies used in the present thesis.

Cohort	Study	Data	Adult measures	Population Source	First visit year	Total enrolled	Baseline age	Mean age at follow-up	Race (% White)
Young Finns Study	I,II, III,IV	childhood, adulthood	CVH, IMT, CAC, distensibility	Random	1980	3,596	3-18	37.8	100%
CDAH	II, III	childhood, adulthood	CVH, IMT	Schools	1985	8,498	7-15	31.0	97%
PFS	II, III	childhood, adulthood	CVH	Schools	1973	6,775	4-20	38.5	73%
BHS	II	adulthood	CVH, IMT	Schools	1973	12,164	3-18	29.5	65%
Minnesota	II	adulthood	CVH, IMT						
PHBPC				Schools	1977	1,207	6-8	39.2	80%
NaKs				Schools	1985	295	11-14		86%
INS				Schools	1995	678	11-19		80%

CVH = cardiovascular health, IMT = carotid artery intima-media thickness, CAC = coronary artery calcification, distensibility = carotid artery distensibility. Young Finns Study = the Cardiovascular Risk in Young Finns Study; CDAH = Childhood Determinants of Adult Health Study. PFS = Princeton Follow-up Study; BHS = Bogalusa Heart Study; Minnesota = Minneapolis Childhood Cohort Studies; PHBPC= Prevention of High Blood Pressure in Children Study; NaKs= Sodium-Potassium Blood Pressure Trial; INS= Obesity/Insulin Resistance Study

4.2. Study design and participants

Study I examined the prevalence of ideal CVH in children and investigated whether the number of CVH metrics in childhood is associated with hypertension, dyslipidemia, MetS, T2DM, and carotid IMT 21 years later in adulthood. This study included 856 participants from the Young Finns Study aged 12-18 years (mean age 15.0 ± 2.5 years) that had complete risk factor data available from baseline, had undergone ultrasound examinations and laboratory measurements during the 2007 survey, and therefore had data available concerning cardiometabolic outcomes in adulthood.

Study II examined the prevalence of ideal CVH in young adults and the relation between ideal CVH metrics and ultrasonographically measured carotid IMT cross-sectionally in 5 international cohort studies, the Young Finns Study, CDAH, BHS, PFS, and Minnesota. A total of 5,785 young adults (mean age 36.6 ± 3.2 years) comprising 1,898 participants from the Young Finns Study; 1,848 from CDAH; 981 from the BHS; 723 from the PFS; and 335 from Minnesota were included in the analyses.

In Study III, childhood lifestyle and clinical determinants of adult ideal CVH were studied. This study included a total of 4,409 participants aged 3-19 years at baseline from the Young Finns Study (N=1,883), CDAH (N=1,803) and PFS (N=723). Participants were re-examined 19-31 years later when aged 30-48 years.

Study IV examined among 1,465 participants from the Young Finns Study aged 12-24 years (mean age 17.5±4.1 years) who were followed up for 15-21 years whether average lifetime CVH, and change in CVH status from childhood and young adulthood to middle age, were associated with CAC, carotid distensibility, and carotid IMT.

4.3. Data acquisition in the Young Finns Study

4.3.1. Physical examination and questionnaires

Physical examination included measurements of height, weight, waist and hip circumference and systolic and diastolic blood pressure. Height and weight were measured in light clothes without shoes with a digital scale, to the nearest 0.5

cm and 0.1 kg. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference, collected since 2001, was assessed midway between the iliac crest and the lowest rib and hip circumference at the level of the greater trochanters as the average of two measurements to the nearest 0.1 cm. In 1980, blood pressure was measured with a standard mercury sphygmomanometer. In 1986, 2001 and 2007, blood pressure was measured using a random zero sphygmomanometer in sitting position after 5 minutes rest. Korotkoff´s first sound was used as the sign of systolic blood pressure and fifth sound as the sign of diastolic blood pressure. Readings to the nearest even number of mmHg were performed. The average of three systolic and diastolic readings was used as the measure of blood pressure in analyses.

Information on dietary habits, smoking, physical activity, parental smoking in childhood and family socioeconomic status were obtained with questionnaires. The length of parent's education (in years), parental occupation, and family annual income were considered as indicators of socioeconomic status in childhood and participants own annual income was considered as an indicator of socioeconomic status in adulthood. Parental occupation was coded from 1 to 5 (1=farmers, 2=lower manual, 3=upper manual, 4=lower non-manual 5=upper non-manual). Family income in 1980 was converted into its present-day value in euros and three income groups were formed: low (<16000 EUR), medium (>16000 EUR to ≤35000 EUR), or high (>35000 EUR). Parental smoking was considered positive if either parent had smoked daily for at least 12 months.

4.3.2. Biochemical analyses

All venous blood samples were drawn from the right antecubital vein of recumbent participants after a 12-hour fast. Serum or plasma was separated and stored at -70 ºC until analysis. Venous blood was sampled for the measurement of plasma concentrations of glucose, and serum concentrations of total cholesterol, HDL-cholesterol, triglycerides, and C-reactive protein. Details of methods in 1980 and 1986 have been presented elsewhere (Viikari et al. 1991). In 2001, all analyses were performed in the laboratory of the Research and Development Unit of the Social Insurance Institution, Turku, and in 2007, in the laboratory for the Population Research of the National Institute for Health and Welfare, Turku.

All lipid determinations were done in duplicate in the same laboratory. Standard enzymatic methods (Olympus System Reagent; Germany) were used for serum cholesterol and triglycerides. Serum HDL-cholesterol concentration was measured from the serum supernatant after precipitation of very low density lipoprotein (VLDL) and LDL with dextrane sulphate-$MgCl_2$. LDL-cholesterol concentration was calculated by using the Friedewald formula in samples where triglyceride level was below 4 mmol/l (Friedewald et al. 1972). Because of changes in determination methods and reagents, lipid levels from 1980, 1986 and triglycerides from 2007 were corrected to correspond to the samples taken in 2001 (Juonala et al. 2004). No correction equations were needed for the 2007 total cholesterol, LDL-cholesterol and HDL-cholesterol levels.

Total cholesterol = 1.091 * total cholesterol (1980-1986) – 0.271 mmol/l.
HDL-cholesterol = 1.068 * HDL-cholesterol (1980-1986) – 0.0277 mmol/l.
Triglycerides = 1.00756 * triglycerides (1980-1986) + 0.0582 mmol/l.
Triglycerides = (triglycerides (2007) + 0.03226)/0.9811

In 2001 and 2007, glucose concentrations were analyzed enzymatically and serum insulin was measured by microparticle enzyme immunoassay kit (Abbott Laboratories, Diagnostic Division, Dainabot). In 1986, serum glucose was measured with the β-D-glucose:nicotinamide adenine dinucleotide oxidoreductase method. Due to changes in methods or reagents from 2001 to 2007 glucose levels were corrected by using the following correction factor equation: Glucose = (glucose (2007) – 0.0235)/ 0.9471.

4.3.3. *Defining metabolic syndrome, type 2 diabetes, dyslipidemia and hypertension*

In 2007, the harmonized definition for MetS was used (Alberti et al. 2009). MetS was diagnosed if participants had at least 3 of the following 5 factors: 1) waist circumference ≥102 cm for males and ≥88 cm for females, 2) raised triglycerides: >1.7 mmol/l (>150 mg/dl), or specific treatment for this lipid abnormality, 3) reduced HDL-cholesterol: <1.036 mmol/l (<40 mg/dl) in males and <1.3 mmol/l (<50 mg/dl) in females, or specific treatment for this lipid abnormality, 4) raised blood pressure: blood pressure ≥130/85 mmHg, or treatment of previously diagnosed hypertension, and 5) raised fasting plasma glucose ≥5.6 mmol/l (100 mg/dl), or previously diagnosed T2DM. In the absence of a consensus on pediatric MetS definition (Steinberger et al. 2009), the definition that was previously shown to predict adult outcomes was used (Magnussen et al. 2010). Participants were categorized as having MetS if they had any three of the following five components: BMI ≥75th percentile, systolic or diastolic blood pressure ≥75th percentile, HDL-cholesterol ≤25th percentile, triglycerides ≥75th percentile, or glucose ≥75th percentile.

Participants were classified as having T2DM if they had fasting plasma glucose of 7.0 mmol/l or greater, reported use of oral glucose-lowering medication or insulin but had not reported having type 1 diabetes, or reported a diagnosis of T2DM by a physician. Participants were also classified as having T2DM if they had HbA1c ≥6.5% (48 mmol/mol). Participants were classified as having hypertension if they had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, or if they reported use of blood-pressure lowering medication. National Cholesterol Education Program (NCEP) guidelines for LDL-cholesterol (4.14 mmol/l [160 mg/dl] or higher), HDL-cholesterol (<1.036 mmol/l [40 mg/dl]) and triglycerides (<2.26 mmol/l [200 mg/dl] were used to define dyslipidemia (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) 2002).

4.4. Assessing the ideal cardiovascular health metrics in the Young Finns Study

The childhood CVH metrics were used for participants aged 12-18 years (Lloyd-Jones et al. 2010). In children, BMI and health factors such as blood pressure normally change with age, growth and development. Therefore, a single threshold to identify elevated risk across childhood is not appropriate. Hence, the use of percentiles is recommended to define higher risk levels for BMI and blood pressure in childhood (Lloyd-Jones et al. 2010). All percentile limits used in the present study are age- and sex-specific.

4.4.1. Ideal health factors

In childhood, ideal total cholesterol status was defined as <4.40 mmol/l (<170mg/dl) and in adulthood as ideal <5.17 mmol/l (<200mg/dl). The ideal blood pressure status was classified in childhood as systolic blood pressure <90th percentile and diastolic blood pressure <90th percentile and in adulthood as systolic blood pressure<120 mmHg and diastolic blood pressure< 80 mmHg Ideal fasting plasma glucose concentration was classified in childhood and adulthood as <5.6 mmol/l (<100mg/dl).

4.4.2. Ideal health behaviors

Ideal BMI was classified in childhood as <85th percentile and in adulthood as <25 kg/m^2. In 1986 and 2001, information on dietary habits was obtained with a non-quantitative food frequency questionnaire (FFQ). To examine the frequency of consumption of fruits, vegetables, fish or fish products and soft drinks the subjects were asked to complete a questionnaire on habitual dietary choices for the past month with 6 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, and 6=more seldom. Subjects were classified as having an ideal fruit and vegetable consumption if they consumed both fruits and vegetables daily. Subjects who consumed fish or fish products a couple of times per week or more frequently were classified as having ideal fish consumption. Subjects who consumed soft drinks a couple of times per week or less frequently were classified as having ideal soft drink consumption. Subjects who had 2-3 of these 3 ideal diet components were categorized as having an ideal diet. In 2007, a more detailed quantitative FFQ that provided an estimate of food consumption in grams per day was introduced. Intake goals defined by the AHA are expressed for a diet containing 2000 kilocalories (Lloyd-Jones et al. 2010). Therefore the intake goals were first scaled according to subjects' energy intake. The achievement of the 5 ideal dietary goals was the categorized: ≥450g per day of fruits and vegetables, ≥two 100 g servings per week of fish, ≥three 30 g servings per day of whole grains, sodium<1500 mg per day and ≤450 kcal of sugar-sweetened beverages per week. Subjects who had 4-5 of these 5 ideal diet components were categorized as having an ideal diet. Smoking data were collected in connection with the medical examination in a solitary room where participants could respond confidentially and undisturbed. Children who reported that they had never smoked a whole cigarette were categorized as having an ideal smoking status. In adulthood, never or former smokers were classified to have ideal smoking status.

Physical activity was assessed by a self-report questionnaire. In childhood and adulthood, the physical activity questionnaire consisted of the following variables: intensity of physical activity, frequency of moderate or vigorous intensity activity, and hours spent on moderate or vigorous intensity activity per week. The AHA's definition of ideal physical activity in childhood is ≥60min of moderate or vigorous activity every day (approximated as ≥7 hours of moderate or vigorous activity per week in the present study) and in adulthood, ≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or ≥150 min/week moderate + vigorous intensity activity (approximated as ≥1 hour/week vigorous intensity or ≥2-3 hours/week moderate intensity or ≥2-3 hours/week moderate + vigorous in the present study).

4.4.3. Indices of ideal cardiovascular health

From the individual ideal health factors and behaviors described above, the corresponding CVH indices were generated. The CVH index in childhood corresponds to the number of ideal health factors and behaviors present at the 1986 follow-up. The ideal CVH index in adulthood corresponds to the number of ideal health factors and behaviors present at the 2007 survey. In Study IV, additional data from the 2001 survey were used (N=334, 22.8%) if complete ideal CVH index data were not available from the 2007 survey. In the analyses, the ideal CVH indices were used as continuous variables (index 0 to 7). Change in ideal CVH index indicates change in indices between childhood and adulthood.

4.5. Ultrasound studies and measurement of coronary artery calcification

4.5.1. Carotid artery intima-media thickness

A high-resolution ultrasound system (Sequoia 512, Acuson, CA, USA) with 13.0 MHz linear array transducer was used to perform carotid ultrasound studies in 2001 and 2007. Ultrasound studies were performed for 2,264 participants in

2001 and for 2,197 participants in 2007. Physicians and ultrasound technicians performed all studies simultaneously in the five cities of the multicentre study (Turku, Tampere, Helsinki, Kuopio and Oulu). Carotid artery intima-media thickness was measured approximately 10 mm proximal to the bifurcation on the left common carotid artery focusing the image on the posterior wall and recording images from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. At least four measurements were taken at each scan of the common carotid artery incident with the R-wave of the continuously monitored ECG to derive mean carotid IMT. The scans were analyzed by one reader (same reader in 2001 and 2007) blinded to participants' details. To assess intra-individual reproducibility of IMT measurements, 57 subjects were re-examined 3 months after the initial visit in 2001 (2.5% random sample). These scans were measured twice by the same reader to assess intra-observer reproducibility. The between visit coefficient of variation (CV) of IMT measurements was 6.4% and the intra-observer CV was 3.4%.In this study, high-risk carotid IMT was defined as age- and sex-specific ≥90 percentile.

4.5.2. Carotid artery elasticity

The elasticity of an artery can be estimated by measuring its distensibility. To assess carotid artery distensibility, the best quality cardiac cycle was selected from 5-second clip images. From B-mode images, the common carotid diameter was measured 10 mm proximal to the carotid bifurcation at least twice at end-diastole and end-systole. Ultrasound and concomitant brachial blood pressure measurements were used to calculate carotid artery distensibility = $[(D_s - D_d) / D_d] / (P_s - P_d)$. In the distensibility formula, Ds stands for systolic diameter, Dd for diastolic diameter, Ps for systolic blood pressure and Pd for diastolic blood pressure. The between-visit CV for carotid distensibility was 16.3% and intra-observer CV was 13.6%.In this study, high-risk distensibility was defined as age- and sex-specific ≤10 percentile.

4.5.3. Coronary artery calcification

In 2008, a cardiac CT study to measure CAC was conducted for a subsample of oldest three age cohorts in the Young Finns Study, then 40 to 46 years of age.

CT scans were carried out at 3 study locations: Turku, Tampere and Kuopio. The scans were performed with a GE Discovery VCT 64-slice CT/PET device (Turku), a Philips Brilliance 64-slice CT device (Tampere) and a Siemens Somaton Sensation 16-slice CT device (Kuopio). The field of view included the coronary vessels and was determined after lateral and/or frontal scout images. The acquisition time was 6-8 sec and the scan was performed during breath hold using prospective ECG triggering. The images were analyzed by one reader blinded to subjects' details using the CareStream software (Rochester, NY, USA). CAC scores were calculated using the Agatston method for each coronary artery (Agatston et al. 1990). The intra-observer CV was 4.0%. Absence of CAC was defined as an Agatston score of 0 and presence of CAC as an Agatston score of 1 or greater (Loria et al. 2007). Since different CT devices were used in different study sites, a phantom with deposits of known calcium concentration was also scanned twice using 3 projections at all of the study centres and the calcium scores from these scans were compared. The CV between all of the phantom scans was 3.9%.

4.6. Data acquisition in other cohorts

The adult measures of CVH metrics were in all cohorts similar to those performed in the Young Finns Study (Table 4). CDAH and PFS cohorts also had childhood risk factor data that were used in this thesis (Study III). Data on adult carotid IMT was available from Minnesota, CDAH, and Bogalusa cohorts (Study II).

In CDAH, childhood blood pressure measurements were obtained using a standard mercury sphygmomanometer. Data on diet, physical activity, participant's own smoking, parental smoking and family socioeconomic status were acquired through questionnaires. Parental education and occupation were considered as indicators of socioeconomic status in childhood. Participants retrospectively (at follow-up) reported the highest level of education completed by their parents when participants were aged 12 years. Participants also retrospectively reported the main occupation of their parents until participants turned 12 years. Participants own occupation and education were considered as indicators of socioeconomic status in adulthood.

In PFS, blood pressure was measured with a standard sphygmomanometer. Data on physical activity, diet, smoking and family socioeconomic status were acquired through questionnaires. Physical activity, diet and parental smoking status were not assessed in this cohort in childhood. Children who reported that they have never smoked or had quit smoking were classified as non-smokers and children who reported current smoking were classified as smokers. Educational and occupational classes (range 1 to 7) of the head of the household were considered as indicators of family socioeconomic status. For education, completion of less than the seventh grade was coded "1" and completing a graduate or professional degree was coded "7". For occupation, the code "1" represented unskilled labor while code "7" represented a higher executive, major professional, or proprietor of a large concern.

In Minnesota, the measurement of carotid IMT was performed with Acuson Sequoia 512 ultrasound scanners (Siemens Medical Solutions USA Inc., Mountain View, CA, USA). An 8.0 MHz linear array transducer was used, and carotid IMT was measured in the common carotid artery approximately 5–11 mm proximal to the carotid bulb. In CDAH, carotid IMT was measured using a portable Acuson Cypress ultrasound scanner with a 7.0 MHz linear array transducer following the standardized imaging protocols used in the Young Finns Study. Six measurements of the common carotid far wall were taken approximately 10 mm before the border of the carotid bulb to derive mean carotid IMT. In the BHS, carotid IMT was measured with a Toshiba Ultrasound instrument (Power Vision Toshiba SSH-380 Digital Ultrasound System, Toshiba America Medical Systems, Carrollton, Texas, USA), using a 7.5 MHz linear array transducer in the far wall of the left common carotid artery.

Table 4. Definitions used to assess ideal cardiovascular health metrics in adulthood for each of the study cohorts.

Metric	AHA criterion	Young Finns Study	Minnesota	PFS	BHS	CDAH
Ideal health factors						
Blood pressure	120/80 mmHg	120/80 mmHg	120/80 mmHg	120/80 mmHg	120/80 mmHg	120/80 mmHg
Total cholesterol	≤5.17 mmol/l	≤5.17 mmol/l	≤5.17 mmol/l	≤5.17 mmol/l	≤5.17 mmol/l	≤5.17 mmol/l
Glucose	<5.6 mmol/l	<5.6 mmol/l	<5.6 mmol/l	<5.6 mmol/l	<5.6 mmol/l	<5.6 mmol/l
Ideal health behaviors						
BMI	<25 kg/m^2	<25 kg/m^2	<25 kg/m^2	<25 kg/m^2	<25 kg/m^2	<25 kg/m^2
Non-smoking	never smoked or quit >1 year ago	never smoked or quit >1 year ago	never smokers	never smoked or quit >1 year ago	currently not smoking	never smoked or quit >1 year ago
Physical activity	≥150 min/wk moderate or ≥75 min/wk vigorous or combination	≥120 min/wk moderate or combination or ≥60 min/wk vigorous	≥150 min/wk combination or ≥75 min/wk vigorous	≥150 min/wk combination or ≥75 min/wk vigorous	≥150 min/wk combination	≥150 min/wk moderate or combination or ≥75 min/wk vigorous
Diet	4/5 components expressed for a 2000-kcal diet	4/5 components scaled for caloric intake	2/3 components scaled for caloric intake	4/5 components scaled for caloric intake	4/5 components scaled for caloric intake	3/4 components
Fruits and vegetables	≥4.5 cups per day	≥450 g/day	not available	≥4.5 servings/day	≥450 g/day	≥4.5 servings/day
Fish	≥two 3.5-oz servings/wk	≥two servings (100 g)/wk	saturated fat intake <7 E%	saturated fat intake <7 E%	saturated fat intake <7 E%	≥two fin fish servings/wk
Whole grains	≥three 1-oz servings/day	≥three servings (30 g)/day of whole grain rye bread	≥3 servings (30 g)/day	≥3 servings (30 g)/day	≥3 servings (30 g)/day of cooked breakfast cereals, dark bread, 1/3 cornbread, 1/3 pasta	≥3 servings/day
Sodium	<1500 mg/day		<1500 mg/day	<1500 mg/day	<1500 mg/day	not available
Sugared drinks	≤450 kcal/wk		not available	sugar from sweets ≤12.8 E%/day	≤450 kcal/wk	≤4 servings/wk

AHA = American Heart Association; Young Finns Study = the Cardiovascular Risk in Young Finns Study; Minnesota = Minneapolis Childhood Cohort Studies; PFS = Princeton Follow-up Study; BHS = Bogalusa Heart Study; CDAH = Childhood Determinants of Adult Health Study; BMI = body mass index.

4.7. Statistical methods

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as percentages unless stated otherwise. The normality assumptions were assessed by examining histograms and normal probability plots. The statistical tests were performed with SAS versions 9.2 and 9.3 (SAS institute, Inc, Cary, NC). Statistical significance was inferred at a 2-tailed P-value <0.05.

Study I

Differences between characteristics of participants and those lost to follow-up in the Young Finns Study were studied using unadjusted and age- and sex-adjusted linear and logistic regression models. To study the associations of the ideal CVH index in childhood with cardiometabolic outcomes in adulthood, age- and sex-adjusted odds ratios for the ideal CVH index using logistic regression were examined. To study associations of ideal CVH index in childhood with carotid IMT, age- and sex-adjusted linear regression was used to calculate p-value for trend.

Study II

Demographic and clinical adult characteristics across cohorts were compared with analysis of variance. Associations between ideal health factors and behaviors were studied with Spearman's correlation. To test the independent cross-sectional effects of the ideal CVH metrics on carotid IMT, multivariable linear regression models that adjusted for age, sex, race and cohort, for each metric was first tested separately and then in a mutually adjusted model including all seven ideal CVH metrics. To examine differences in the effect of ideal CVH on carotid IMT between cohorts, an interaction term of ideal CV health*cohort was used in the pooled analysis and interactions between the individual metrics in cohort-stratified models. An interaction between ideal health factors and behaviors on carotid IMT was examined by including an interaction term of health factors*health behaviors.

Study III

Associations between individual baseline metrics and ideal CVH index in adulthood were examined using age- and sex-adjusted linear regression.

The significant determinants were then entered into an age- and sex-adjusted multivariable linear regression model constructed to determine the independent childhood predictors of ideal CVH index. This model was additionally adjusted for race in the PFS cohort.

Study IV

The calculated CVH indices were first standardized for age and sex to ensure the data were comparative between children (childhood criteria) and young adults (adult criteria). To study the associations of average lifetime CVH index and continuous change in CVH index with T2DM and markers of subclinical atherosclerosis, relative risks for the average lifetime CVH index and continuous change in CVH index respectively were calculated using Poisson regression with robust standard errors. Participants were then classified into 4 groups according to their CVH status at baseline and follow-up: "Persistently high group" (high CVH at baseline and at follow-up); "resolution group" (low CVH at baseline but high CVH at follow-up); "incident group" (low CVH at follow-up but not at baseline); and "persistently low group" (low CVH both at baseline and follow-up). Poisson regressions with robust standard errors were used to study the relative risks of T2DM and markers of subclinical atherosclerosis according to these CVH groups.

5. RESULTS

5.1. Characteristics of the participants

Table 5 shows characteristics of the Young Finns Study participants 12-24 years of age in 1986, which is baseline in this study because it was the first follow-up at which glucose values were measured. Descriptive adult characteristic of all five study populations are shown in Table 6.

Table 5. Characteristics of the Cardiovascular Risk in Young Finns Study participants in 1986. Data are mean ± SD or %.

	Female	Male
N	822	643
Age, years	17.5±4.2	17.5±4.2
Caucasian, %	100	100
BMI, kg/m²	20.7 ± 3.0	20.9±3.3
Systolic blood pressure, mmHg	113.8±10.7	120.3±13.4
Diastolic blood pressure, mmHg	66.4±9.3	67.0 ±10.8
Total cholesterol, mmol/l	5.0±0.9	4.8±0.9
Glucose, mmol/l	4.6±0.7	4.8±0.6
Non-smokers, age 21-24 yr, % (N=504)	66.6	54.3
Never smoked whole cigarette, age 12-18 yr, % (N=961)	24.8	18.8

BMI=Body mass index.

Table 6. Descriptive adult characteristics of the study populations.

Variable	Young Finns Study	Minnesota	PFS	BHS	CDAH	All
N	1,893	335	723	981	1,848	5,785
Age, years	37.8 ± 5.0	39.2 ± 1.5	38.5 ± 3.6	29.5 ± 5.1	31.0 ± 2.7	34.4 ± 5.6
Men, %	44	50	45	37	48	45
Caucasian, %	100	65	71	77	100	90
BMI, kg/m²	25.9 ± 4.7	29.3 ± 7.4	28.7 ± 6.9	27.2 ±6.8	25.6 ±4.8	26.6 ± 5.8
Systolic blood pressure, mmHg	120 ± 14	125 ± 16	121 ± 15	110 ± 11	118 ± 13	118 ± 14
Diastolic blood pressure, mmHg	75 ± 11	72 ± 10	80 ± 11	73 ± 9	72 ± 9	74 ± 10
Total cholesterol, mmol/l	5.0 ± 0.9	4.8 ± 0.8	5.0 ± 1.0	4.9 ± 1.0	4.9 ± 1.0	5.0 ± 1.0
Glucose, mmol/l	5.3 ± 0.9	5.9 ± 1.9	5.0 ± 1.5	4.5 ± 0.6	5.0 ± 0.5	5.1 ± 1.0
Non-smokers, %	72.3		71.4	66.9	76.9	71.6
Never smoking, %		38.2*				

Differences across cohorts p<0.0001 (except for % of men p=0.04).
BMI=Body mass index, SD=Standard deviation, Young Finns Study = Cardiovascular Risk in Young Finns Study, Minnesota = Minneapolis Childhood Cohort Studies, PFS = Princeton Follow-up Study. BHS = Bogalusa Heart Study, CDAH = Childhood Determinants of Adult Health Study. *Daily smoking was not available for Minnesota.

5.2. Ideal cardiovascular health in childhood and adulthood

5.2.1. Childhood prevalence of ideal cardiovascular health

In this thesis, the number of ideal CVH metrics and the ideal CVH index as their sum are used to describe CVH. Children 12-18 years of age, studied in 1986 in the Young Finns Study, met on average 3.5 ± 1.0 of all 7 ideal CVH metrics. None of the participants met 0 or all 7 metrics of the ideal CVH index. Thus, none of the participants had ideal CVH. Individual ideal CVH metrics were met by 85.6% of the children for BMI, 6.9% for physical activity, 24.3% for diet, 22.4% for smoking status, 82.2% for blood pressure, 97.4% for glucose level and 33.2% for total cholesterol (Figure 8).

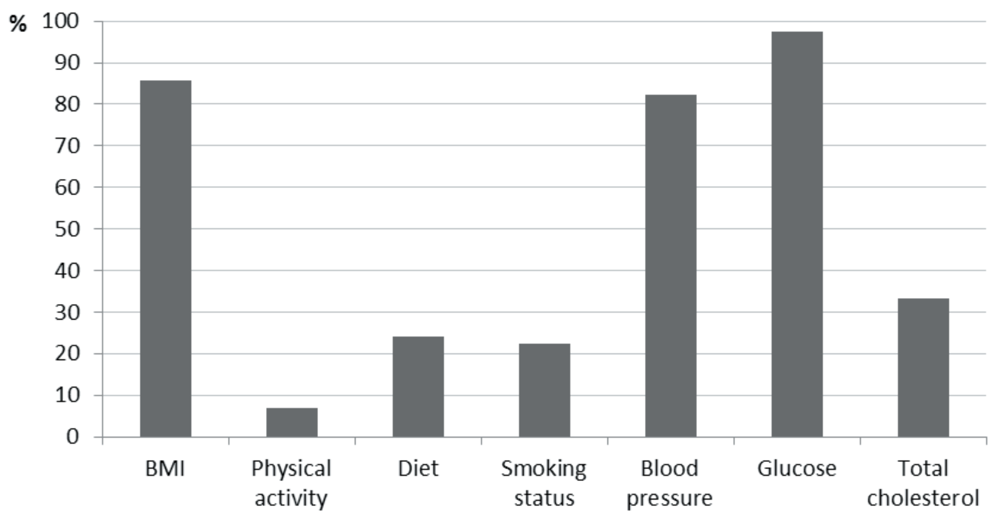

Figure 8. Children 12-18 years of age meeting individual ideal cardiovascular health metrics.

5.2.2. Adulthood prevalence of ideal cardiovascular health

Ideal CVH in adulthood was rare in all cohorts studied (Figure 9). Only 1.0% of the participants from the combined cohorts had all 7 ideal health metrics (range across cohorts 0-2.0%).

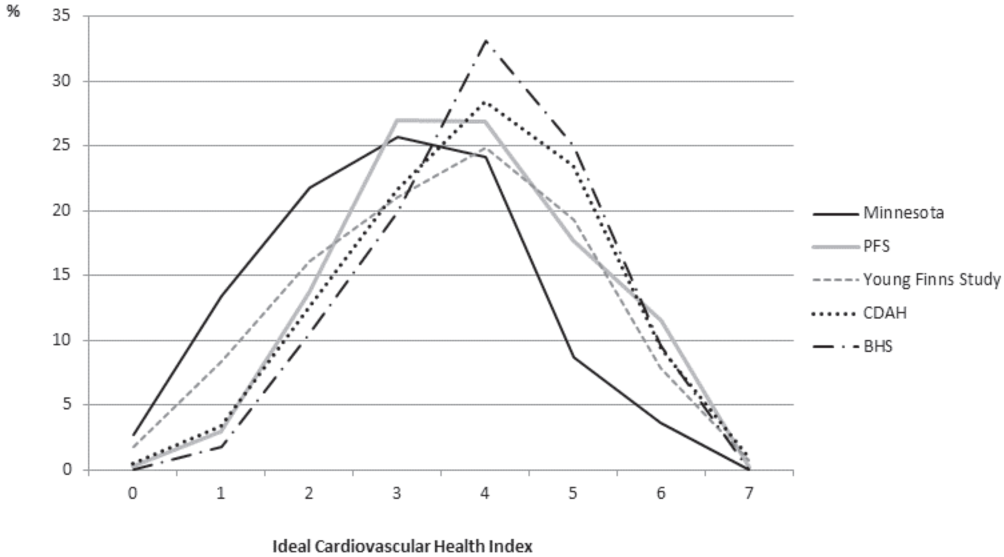

Figure 9. Number of ideal cardiovascular health metrics met by participants. Young Finns Study = Cardiovascular Risk in Young Finns Study, Minnesota = Minneapolis Childhood Cohort Studies; PFS = Princeton Follow-up Study; BHS = Bogalusa Heart Study; CDAH = Childhood Determinants of Adult Health Study.

Ideal fasting plasma glucose (82%, range across cohorts 47-96%), ideal smoking status (70%, range across cohorts 38-77%) and ideal total cholesterol (62%, range across cohorts 57-72%) were met most commonly while ideal diet (7%, range across cohorts 0-15%) and ideal BMI (46%, range across cohorts 30-52%) were least commonly found among the participants (Figure 10). Proportions of participants with the ideal diet components are shown in Figure 11. The number of ideal health behaviors (BMI, physical activity, smoking and diet) was directly correlated with the number of ideal health factors (blood pressure, glucose and cholesterol) in each of the cohorts (Spearman's $r=0.20$, $p=0.0002$ in Minnesota; $r=0.26$, $p<0.0001$ in PFS; $r=0.23$, $p<0.0001$ in Young Finns Study; $r=0.15$, $p<0.0001$ in the BHS; $r=0.23$, $p<0.0001$ in CDAH).

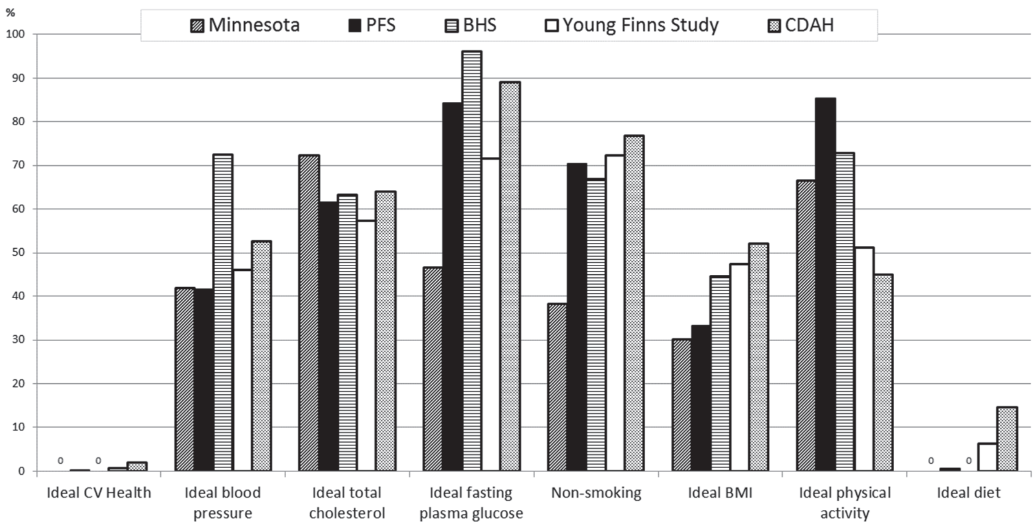

Figure 10. Proportions of participants with ideal CVH and individual ideal CVH metrics. Young Finns Study = Cardiovascular Risk in Young Finns Study, Minnesota = Minneapolis Childhood Cohort Studies; PFS = Princeton Follow-up Study; BHS = Bogalusa Heart Study; CDAH = Childhood Determinants of Adult Health Study.

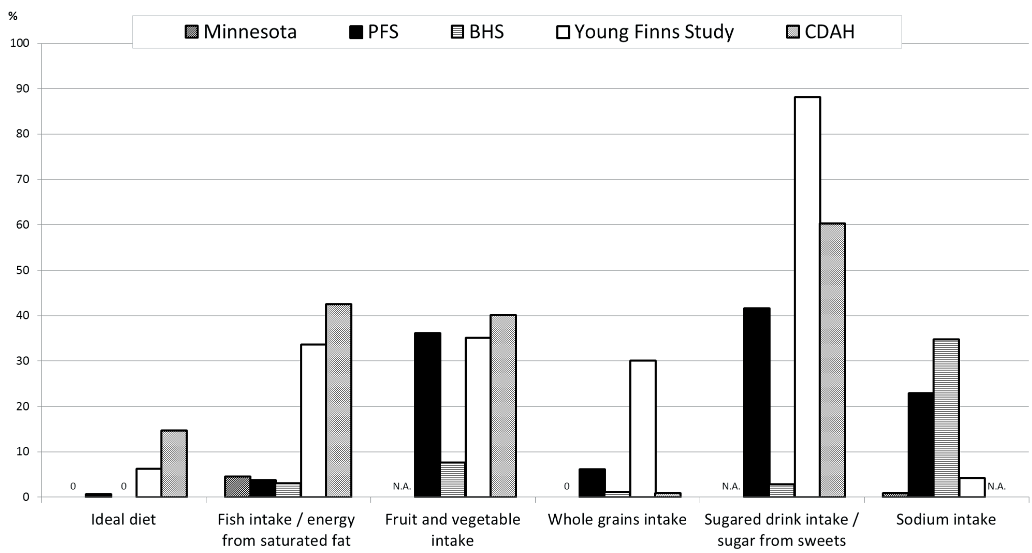

Figure 11. Proportions of participants with ideal diet and the ideal diet components. Young Finns Study = Cardiovascular Risk in Young Finns Study, Minnesota = Minneapolis Childhood Cohort Studies; PFS = Princeton Follow-up Study; BHS = Bogalusa Heart Study; CDAH = Childhood Determinants of Adult Health Study.

5.2.3. *Stability of cardiovascular health*

Ideal CVH index in childhood was associated with the ideal CVH index 21 years later in adulthood (β±SE 0.37±0.05, $p<0.001$, adjusted for age at baseline and sex). 54% of children (12-18 years of age, childhood CVH criteria) and 63% of young adults (21-24 years of age, adult CVH criteria) with high scores of ideal CVH index (≥5 metrics present) lost the high CVH status before middle age (Table 7). On the contrary, from those participants with ≥5 metrics present in middle age, 78% of the younger and 39% of the older participants had gained the high CVH status as they aged. Altogether, 41% of the participants reduced, 34% improved, and 25% maintained ideal CVH status from childhood or young adulthood to middle age.

Table 7. Prevalence (N) of Cardiovascular Risk in Young Finns Study participants according to number of ideal cardiovascular health (CVH) metrics in childhood or young adulthood (1986) and in middle age (2007).

	CVH metrics in middle age		
CVH metrics at baseline (12-18 years of age)	0-2 (N=228)	3-4 (N=435)	5-7 (N=298)
0-2 (N=133)	57	52	24
3-4 (N=685)	153	324	208
5-7 (N=143)	18	59	66
CVH metrics at baseline (21-24 years of age)	0-2 (N=147)	3-4 (N=230)	5-7 (N=127)
0-2 (N=40)	26	11	3
3-4 (N=258)	87	124	47
5-7 (N=206)	34	95	77

5.3. Childhood lifestyle and clinical factors in predicting cardiovascular health in adulthood

Independent predictors of adult ideal CVH in the Young Finns Study included parental smoking and childhood BMI, systolic blood pressure, and LDL-cholesterol (inverse association) as well as family socioeconomic status (direct association). In CDAH, independent predictors of ideal CVH in adulthood included participant's own smoking in childhood, childhood BMI (inverse association) and family socioeconomic status (direct association).

In the CDAH subset that had data on lipids and blood pressure (N=366), parental education (direct association) and childhood measures of BMI and LDL-cholesterol (inverse association) were independent predictors of future ideal CVH. In PFS, independent predictors of ideal CVH included family socioeconomic status (direct association) and childhood BMI (inverse association) (Table 8).

Table 8. Multivariable age- and sex-adjusted associations between individual childhood metrics and ideal cardiovascular health index in adulthood.

	Young Finns Study (N=1,668)		**CDAH (N=1,365)**		**PFS (N=659)**	
Childhood regressor variable	β(SE)	p-value	β(SE)	p-value	β(SE)	p-value
Family socioeconomic status	0.21(0.05)	<0.0001	0.13(0.04)	0.002	0.12(0.04)	0.001
Parental smoking (no/yes)	-0.26(0.07)	0.0006	-0.10(0.07)	0.12	-	-
Own smoking (no/yes)	-	-	-0.38(0.11)	0.001	-	-
Vegetable consumption (times/week)	0.01(0.01)	0.27	-	-	N.A.	
Fruit consumption (times/week)	0.01(0.01)	0.42	-	-	N.A.	
BMI (kg/m^2)	-0.08(0.02)	<0.0001	-0.10(0.01)	<0.001	-0.07(0.01)	<0.0001
Systolic blood pressure (10 mmHg)	-0.09(0.03)	0.007	-	-	N.A.‡	
LDL-cholesterol (mmol/l)	-0.25(0.05)	<0.0001	N.A.‡		-0.10(0.06)	0.09
HDL-cholesterol (mmol/l)	-	-	N.A.‡		0.27(0.16)	0.09
Triglycerides (mmol/l)	-0.17(0.12)	0.16	N.A.‡		-0.09(0.12)	0.45
Race (white vs.black)	-†	-	-†	-	-0.16(0.11)†	0.18
Sex(female vs. male)	-1.06(0.07)	<0.0001	-0.99(0.06)	<0.001	-0.83(0.09)	<0.0001
Age (years)	-0.004 (0.010)	0.67	0.06(0.02)	0.002	0.03(0.01)	0.09

Young Finns Study = Cardiovascular Risk in Young Finns Study, CDAH = Childhood Determinants of Adult Health Study, PFS = Princeton Follow-up Study. Regression coefficients and standard errors are for a 1-unit change in the covariate.*Indicators of family socioeconomic status were family income (Young Finns Study, 1 to 3) or parental education (CDAH, 1 to 3 and PFS,1 to 7). †Race = 33% black in Princeton, 0% Young Finns Study and 0% in CDAH. - Nonsignificant variables from age- and sex-adjusted univariate analyses were not included in the analysis. N.A.= Not Available. N.A. ‡=Available only from a subcohort, hence not included in this analysis.

Because family environmental factors were observed to predict future ideal CVH, these associations were further explored. In the Young Finns Study, a parental risk score that assigned a value of 1 for low family income and a value of 1 for parental smoking was created (possible score range 0-2). The parental risk score was inversely associated with the child's ideal CVH index in adulthood ($P<0.001$). The association between parental risk score and the number of ideal CVH metrics in adulthood was graded (Figure 12). Participants who had none of the parental risk factors met on average 3.8 ± 0.07 ideal metrics in adulthood while those with 2 risk factors met 3.2 ± 0.08 adult ideal metrics. The parental risk score was created also for the CDAH cohort where the parental risk score was assigned a value of 1 for parental smoking and a value of 1 for school-only parental education. Also in CDAH, the parental risk score was associated in an inverse, graded manner with ideal CVH index in adulthood (Figure 13).

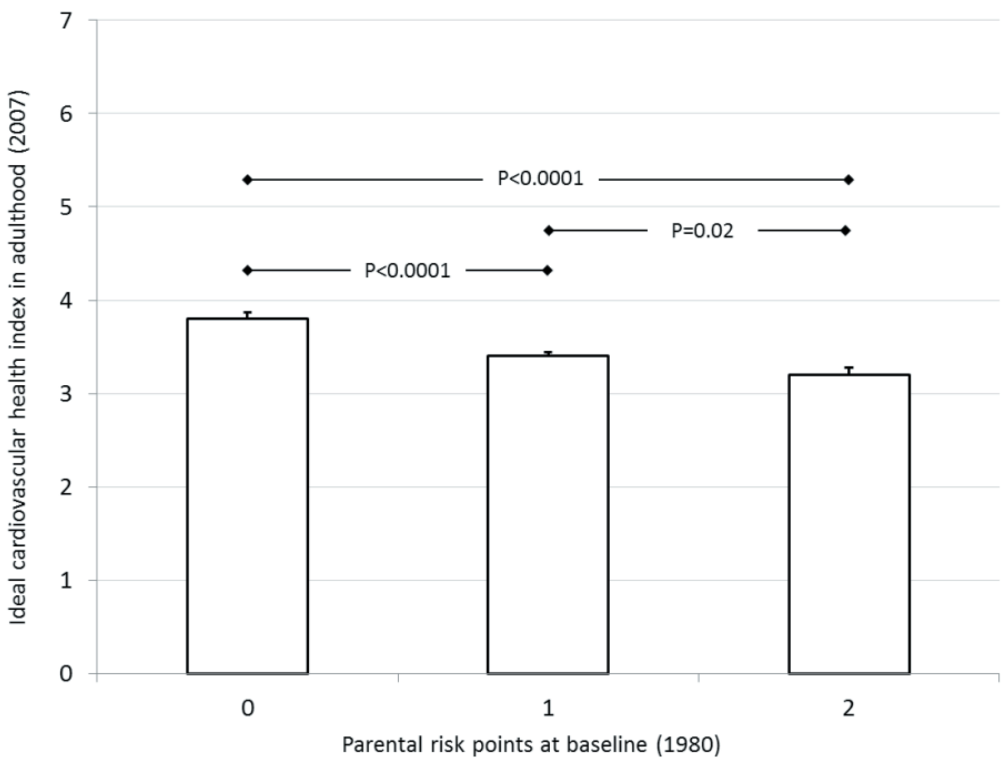

Figure 12. Number of ideal CVH metrics in adulthood according to parental risk points in childhood in the Cardiovascular Risk in Young Finns Study.

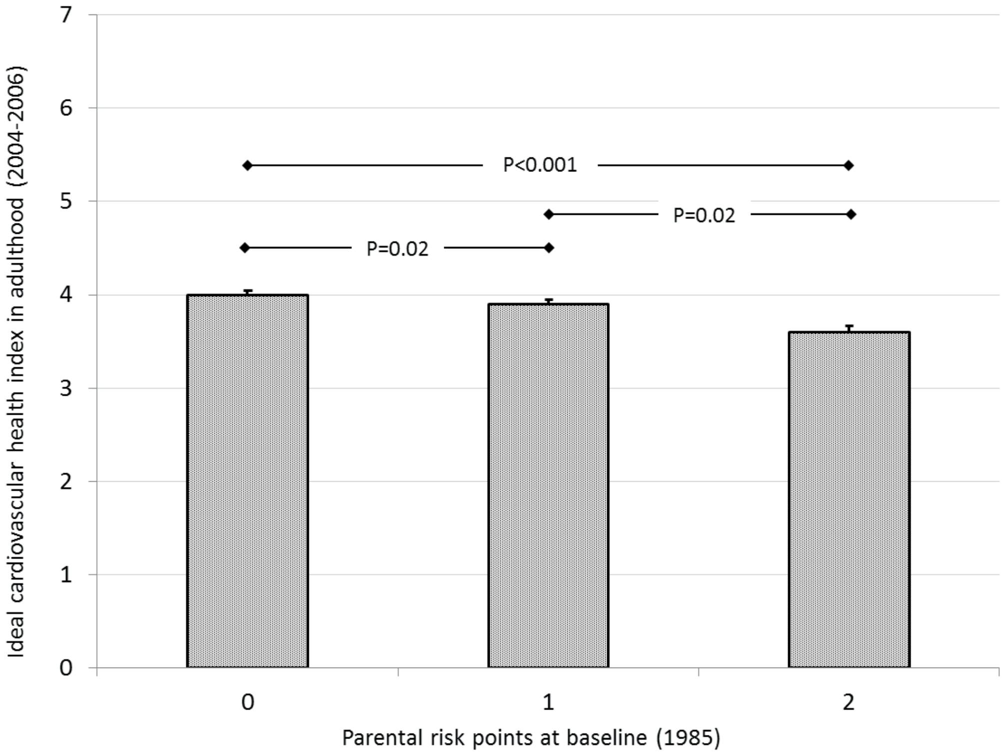

Figure 13. Number of ideal CVH metrics in adulthood according to parental risk points in childhood in the Childhood Determinants of Adult Health Study.

5.4. Association of cardiovascular health status with cardiometabolic outcomes

5.4.1. Cardiovascular health in childhood in predicting adult cardiometabolic outcomes

Using data from the Young Finns Study, the associations of ideal CVH index in childhood and cardiometabolic outcomes in adulthood with a follow-up time of 21 years are shown in Table 9. Higher ideal CVH index in childhood was associated with reduced odds of hypertension, MetS, high LDL-cholesterol, high triglycerides and high-risk IMT.

Table 9. Ideal CVH index in childhood in predicting incident cardiometabolic outcomes 21 years later in adulthood.

	OR	95% CI	p-value
Hypertension	0.66	0.54−0.80	<0.001
Metabolic syndrome	0.63	0.52−0.77	<0.001
Type 2 diabetes	0.70	0.32−1.52	0.37
High LDL cholesterol	0.66	0.52−0.85	0.001
Low HDL cholesterol	0.94	0.79−1.13	0.54
High triglycerides	0.80	0.65-0.99	0.04
High-risk IMT	0.75	0.60−0.94	0.01

Odds ratios (OR) for a 1 unit increase in ideal CVH index. Analyses are adjusted for age at baseline and sex. LDL= low-density lipoprotein, HDL=high-density lipoprotein IMT= carotid intima-media thickness

Mean adult carotid IMT according to the number of childhood ideal CVH metrics is shown in Figure 14. The ideal CVH index in childhood was inversely associated with adult carotid IMT. Children with 6 (highest) ideal CVH metrics had 67 μm lower carotid IMT in adulthood compared to those who met 1 (lowest) ideal CVH metric in childhood. The effect of the ideal CVH index on adult carotid IMT remained significant after adjusting for change in the ideal CVH index between childhood and adulthood (β±SE −11±3 μm, P=0.001). In addition, change in CVH index was associated with IMT in this analysis (β±SE −9±2 μm, P<0.001).

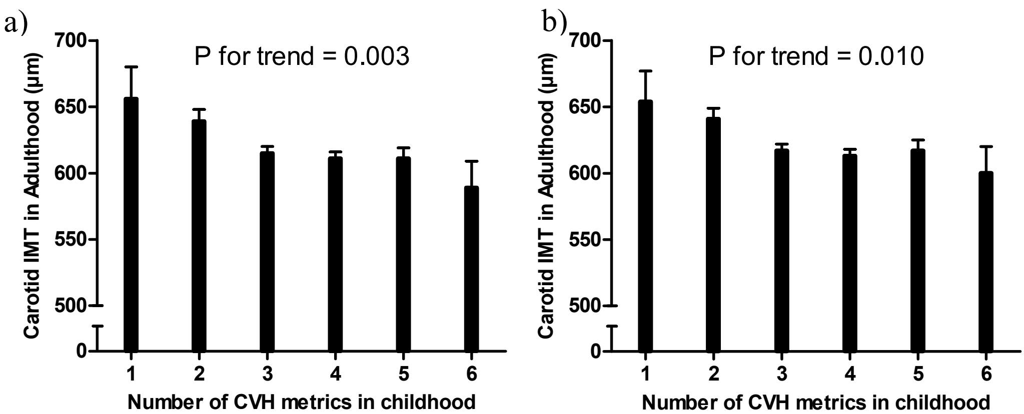

Figure 14. Mean values (Standard error of the mean) of unadjusted (a) and age- and sex-adjusted (b) adult carotid IMT according to the number of ideal cardiovascular health metrics in childhood

5.4.2. Association of cardiovascular health in adulthood with carotid IMT and distensibility

The cross-sectional association of number of ideal CVH metrics in adulthood with carotid IMT was studied in the Young Finns Study, Minnesota, BHS, and CDAH cohorts. Figure 15 shows mean carotid IMT according to the number of ideal CVH metrics for each of the individual cohorts and for the combined cohorts. There was a similar pattern of differences in carotid IMT over the number of ideal CVH metrics, and the main difference was in the level of carotid IMT across cohorts. For each additional ideal CVH metric, carotid IMT was 10.4 µm thinner in the Young Finns Study ($p<0.0001$), 12.7 µm thinner in Minnesota ($p=0.0002$), 9.1 µm thinner in BHS ($p=0.05$), and 3.4 µm ($p=0.03$) thinner in CDAH. In the pooled data, carotid IMT was 6.6 µm thinner for each additional ideal CVH metric ($p<0.0001$).

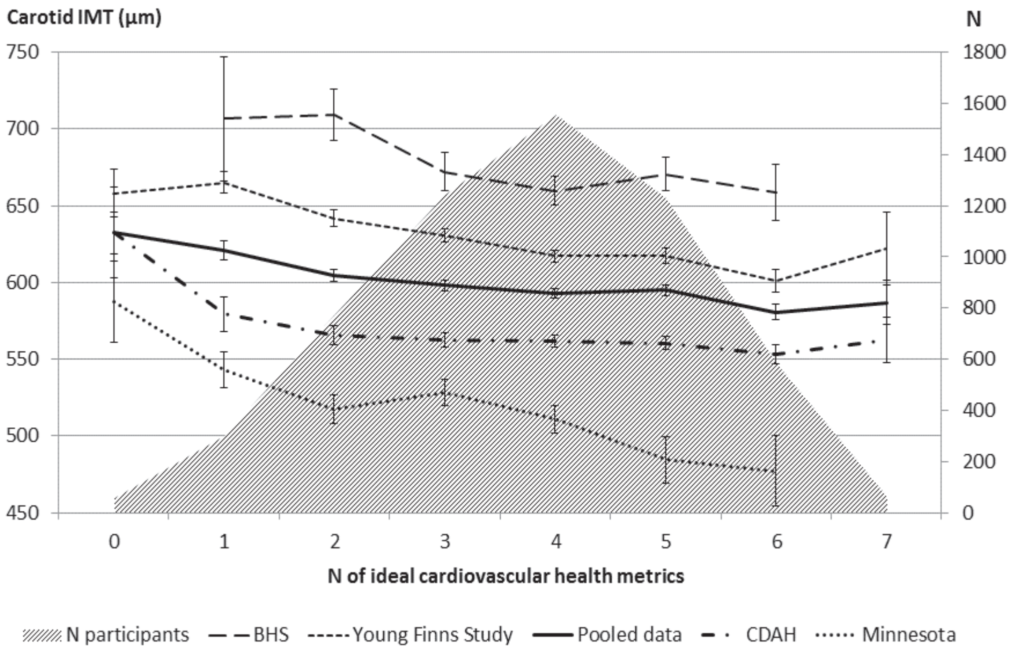

Figure 15. Age- and sex-adjusted mean±SE carotid intima-media thickness (carotid IMT, µm) according to the number of ideal cardiovascular health metrics in pooled data (N=4,144) and in the Cardiovascular Risk in Young Finns Study (Young Finns Study, N=1,893), Minneapolis Childhood Cohort Studies (Minnesota, N=335), Bogalusa Heart Study (BHS, N=322), and Childhood Determinants of Adult Health Study (CDAH, N=1,584) cohorts.

In addition, in the Young Finns Study, the association of ideal CVH and carotid distensibility was studied. The number of CVH metrics present in adulthood was directly associated with carotid distensibility (β±SE 0.08±0.01 %/10mmHg, P<0.0001). Carotid distensibility stratified by the number of ideal health factors and health behaviors is presented in Figure 16.

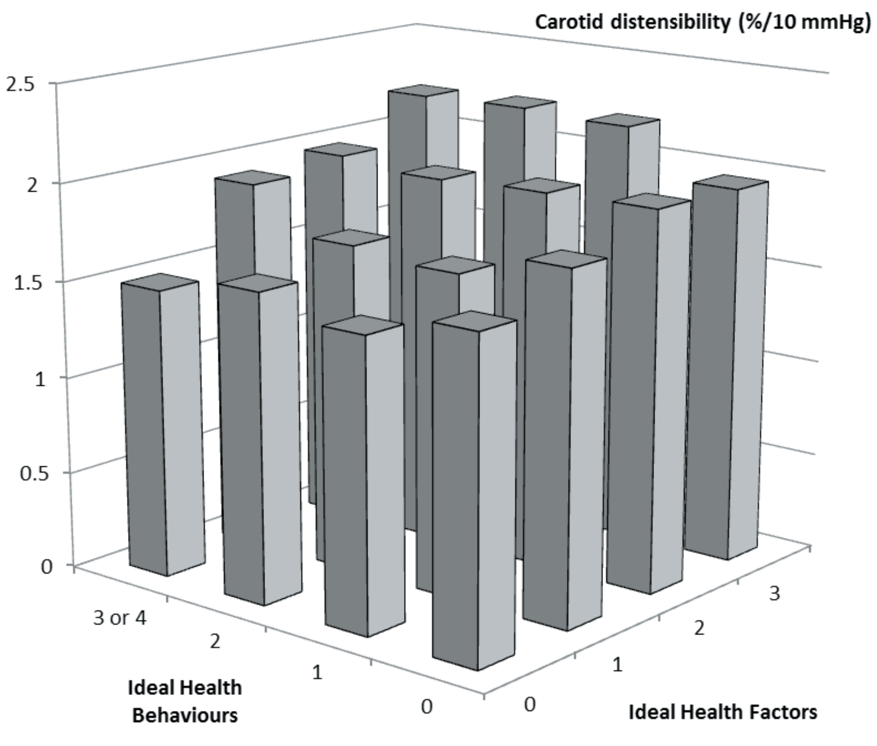

Figure 16. Carotid distensibility according to the number of ideal health behaviors (P=0.16) and health factors (P<0.0001) in the Cardiovascular Risk in Young Finns Study.

5.4.3. Lifetime cardiovascular health and change in cardiovascular health in predicting markers of subclinical atherosclerosis and type 2 diabetes

Higher average lifetime CVH index (mean of ideal CVH indices in childhood or young adulthood and middle age) was associated with reduced risk of CAC, high-risk carotid IMT, high-risk distensibility, and T2DM in middle age (Table 10). Increase in ideal CVH index was also associated with reduced risk of CAC, high-risk IMT, high-risk distensibility and T2DM in middle age. In addition, increase in the health behavior index (sum of ideal health behaviors) was associated with reduced risk for high-risk IMT [RR (95%CI) = 0.84 (0.72-0.98), P=0.02] and high-risk distensibility [0.81 (0.70-0.93), P=0.004]. The association with CAC was borderline significant [0.80 (0.66-1.03), P=0.09]. Favorable change in health factor index (sum of ideal health factors) was associated with reduced risk of CAC [0.80 (0.64-0.99), P=0.04], high-risk IMT [0.81 (0.69-0.95), P=0.008], high-risk distensibility [0.69 (0.58-0.81), P<0.0001] and T2DM [0.46 (0.34-0.64), P<0.0001].

Table 10. Average lifetime cardiovascular health (Average lifetime CVH) and change in ideal cardiovascular health index (CVH change) in predicting cardiometabolic outcomes in middle age.

	n/N	RR (95%CI)	p-value
Average lifetime CVH			
Coronary artery calcification	70/370	0.66 (0.53-0.83)	0.0004
High-risk IMT	154/1457	0.71 (0.59-0.86)	0.0005
High-risk distensibility	155/1453	0.60 (0.50-0.72)	<0.0001
T2DM	40/1450	0.54 (0.38-0.78)	0.001
CVH change			
Coronary artery calcification	70/370	0.71 (0.56-0.89)	0.003
High-risk carotid IMT	154/1457	0.75 (0.63-0.88)	0.0004
High-risk carotid distensibility	155/1453	0.66 (0.56-0.78)	<0.0001
T2DM	40/1450	0.58 (0.41-0.80)	0.001

Relative risks (RR) and 95% confidence intervals (95% CI) for a 1 SD increase in age- and sex-standardized lifetime CVH and CVH change. Adjusted for age and sex. For CVH change analyses, adjustment was also made for baseline CVH

Compared to individuals with high ideal CVH index both in childhood or young adulthood and middle age (persistently high group), those with persistently low ideal CVH index had higher risk for CAC [RR (95%CI) = 1.90 (1.12-3.24), P=0.02], high-risk IMT [1.66 (1.10-2.50), P= 0.02], high-risk distensibility [2.25 (1.50-3.36), P<0.0001] and T2DM [3.38 (1.34-8.50), P=0.01] (Figures 17 a-d). In addition, those who impaired their ideal CVH index (incident group) had higher risk of high-risk IMT [1.81 (1.16-2.81), P=0.008], high-risk distensibility [1.80 (1.13-2.85), P=0.01] and T2DM [3.89 (1.50-10.10), P=0.005] compared to the persistently high group. Risk of those who improved their ideal CVH index (resolution group) to develop CAC [1.04 (0.53-2.05), P=0.90], high-risk IMT [1.31 (0.83-2.07), P=0.25], high-risk distensibility [1.07 (0.64-1.79), P=0.80] or T2DM [0.98 (0.28-3.48), P=0.98] was not different from the risk of persistently high group.

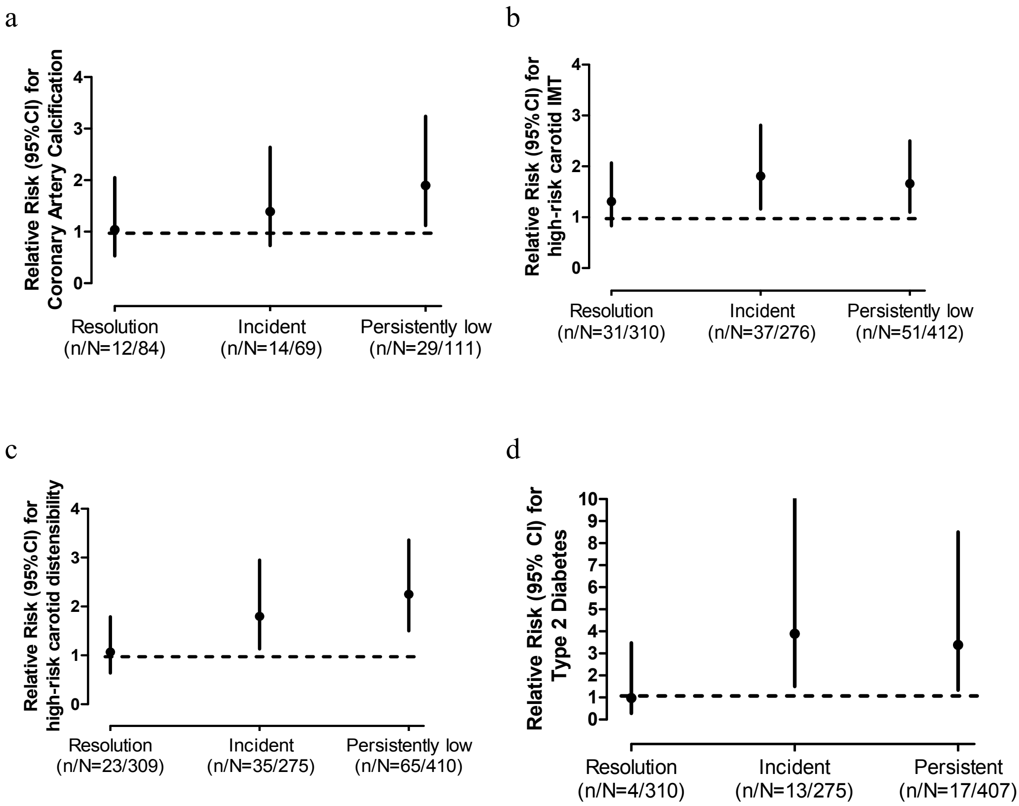

Figure 17. Relative risks and 95% confidence intervals of a) coronary artery calcification, b) high-risk carotid IMT (>90th percentile) c) high-risk carotid distensibility (<10th percentile) and d) type 2 diabetes according to cardiovascular health (CVH) status in childhood or young adulthood and in middle age. Dotted line - Persistently high group: high CVH (above median) in childhood or young adulthood and high CVH in middle age (n/N=15/106 for coronary artery calcification, 35/459 for high-risk carotid IMT, 32/459 for high-risk carotid distensibility, and 6/458 for type 2 diabetes); Resolution: low CVH (below median) in childhood or young adulthood but high CVH in middle age; Incident: high CVH in childhood or young adulthood, but low CVH in middle age; and Persistently low: low ICH in childhood or young adulthood and in middle age.

6. DISCUSSION

The present study showed that the prevalence of ideal CVH is very low in Finnish children and young adults, and is also low in a large international cohort of young adults. Of the childhood lifestyle and clinical indicators studied, parental smoking and family socioeconomic status were independent predictors of CVH in adulthood. The number of ideal CVH metrics present in childhood is an independent predictor of adult cardiometabolic outcomes. In addition, adult subclinical atherosclerosis is determined by the number of ideal CVH metrics in childhood as well as adulthood. On the other hand, it seems that individuals who improve their CVH status between childhood and adulthood do not have a different risk of cardiometabolic outcomes compared to those who always have had high CVH status. Figure 18 highlights main findings of the study.

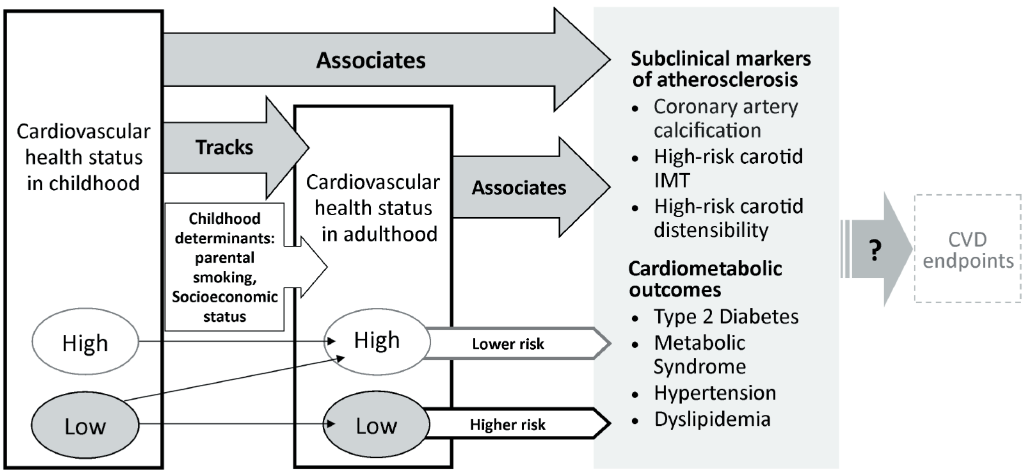

Figure 18. Main findings of the study.

6.1. Participants

The participants in this study were from the Cardiovascular Risk in Young Finns Study; an on-going epidemiological study of CVD risk factors in children and young adults. The initial sampling in 1980 consisted of 4,320 participants aged 3, 6, 9, 12, 15 and 18 years that were invited to a cross-sectional survey. Participants were randomly selected from different parts of the country, equally from both genders, and from urban and rural areas to represent Finnish children and adolescents as closely as possible. A total of 3,596 subjects (83.2% of those invited) participated in the study in 1980 and were considered to be representative of the total random sample (Åkerblom et al. 1985).

In a longitudinal study, it is inevitable that some participants are lost to follow-up. Of the original study cohort from 1980, a total of 2,283 individuals (63.5%) in 2001 and 2,204 individuals (61.3%) in 2007 participated. Analyses performed earlier have shown that those lost to follow-up tend to be more often male and younger than participants (Juonala et al. 2011). However, childhood risk factors were similar between participants and non-participants. In addition, in this study no differences were observed in childhood ideal CVH metrics between participants and those lost to follow-up (Study I). Therefore, this study cohort seems to be representative of the original study population. However, it is not possible to compare whether current CVH is similar between participants and dropouts.

In this thesis, additional data from other cohorts were included in Studies II and III: 1,848 participants from CDAH, 981 participants from the BHS, 723 from the PFS, and 335 from Minnesota. Attrition analyses indicate that those who participated as adults within these cohorts were very similar to non-participants for the major CVD risk factors measured at baseline (Dwyer et al. 2013). Since the study participants in all cohorts were predominantly white, the results of this study may not be generalizable to other races or ethnic groups.

Altogether, the sample size of this study provided sufficient power for the statistical analyses undertaken, and the loss to follow-up does not seem to have been differential and therefore affect the representativeness of the original study population. Therefore, the results in this study may be generalized in populations consisting of white, apparently healthy individuals.

6.2. Methods

6.2.1. Assessing cardiovascular health metrics

The methods for measuring health factors: total cholesterol, plasma glucose and blood pressure, as well as measurement of BMI, are well standardized and therefore generalizable from study to study. Although self-reported questionnaire measures of diet, physical activity and smoking may constitute a potential limitation, they remain feasible and affordable instruments for monitoring health behaviors. In the Young Finns Study, a non-quantitative FFQ was used in childhood. Regarding the ideal diet definition, the quantitative amounts of fruits and vegetables, fish and soft drinks consumed could not be derived, nor was it possible to measure the intakes of sodium and fibre-rich whole grain. However, the questionnaire provided an approximation of ideal diet in childhood. In adulthood, a more detailed FFQ, providing an estimate of food consumption in grams per day was used. In studies II and III, due to the differing questionnaire measures between cohorts, there was a need to use modified definitions for ideal health behaviors across the cohorts. Additionally there was absence of data on some of the components in some cohorts. However, these limitations are offset by the strength of being able to construct most of the ideal CVH metrics according to the definitions.

6.2.2. Carotid intima-media thickness

Carotid IMT provides a measure of preclinical atherosclerosis that predicts CVD risk in population studies. It is non-invasive and reproducible, and correlates well with cardiovascular risk factors and the extent of atherosclerosis elsewhere in the arterial system (Allan et al. 1997; Raitakari et al. 2003). Importantly, it is independently associated with future CVD events in asymptomatic adults (O'Leary et al. 1999).

Carotid IMT was measured in the far wall of the left common carotid artery. Measurement of IMT in the common carotid artery is more reliable than measurement of IMT in the internal carotid artery or carotid bifurcation, but it is also less sensitive to local atherosclerosis (Kanters et al. 1997). Therefore the present study may underestimate the associations of CVH metrics and carotid atherosclerosis. The ultrasound scans were analyzed by one reader blinded to participants details (Raitakari et al. 2003) and the reproducibility of IMT measurements were acceptable (CV 6.4%) and comparable with other studies (Johnson et al. 2007). In study II, when several cohorts were assessed, carotid IMT was measured using ultrasonographic transducers of various manufacturers and with different frequencies, ranging between 7 and 13 MHz. Differences in image quality may explain part of the observed differences in carotid IMT levels across cohorts. However, the direction of effect on carotid IMT of the number of ideal CVH metrics was the same in all cohorts.

6.2.3. Carotid distensibility

Decreased carotid distensibility is considered an independent CVD risk factor and predicts cardiovascular events (Haluska et al. 2010). CVD risk factors are associated with increased arterial stiffness already in childhood (Aggoun et al. 2000; Tounian et al. 2001). Carotid distensibility measures the ability of the arteries to expand as a response to pulse pressure caused by cardiac contraction and relaxation. In this study, pulse pressure was measured from the brachial artery in order to calculate carotid artery distensibility. Because pulse pressure measured from the brachial artery can overestimate the pulse pressure in central arteries, it would have been ideal to measure pulse pressure from the carotid artery (Karamanoglu et al. 1993). However, invasive blood pressure from the ascending aorta has been shown to correlate strongly with noninvasive blood pressure from the brachial artery (Borow et al. 1982), supporting the assumption that brachial pulse pressure can be used in deriving carotid distensibility. The long term variation for carotid distensibility was 16.4% which is comparable with other studies (Lorenz et al. 2007). Small variation (CV 2.7%) in the carotid artery end diastolic diameter suggests that much of the long term variation of carotid distensibility is due to physiological fluctuation and not to measurement error (Juonala et al. 2005).

6.2.4. Coronary artery calcification

Measurement of CAC has consistently shown to be the best subclinical CVD measure for improving CHD risk prediction (Yeboah et al. 2012). The standard methodology for scoring the amount of CAC from CT scans is the Agatston method (Agatston et al. 1990). The CAC score is correlated with overall atherosclerotic burden and is highly reproducible (Detrano et al. 2008). In this study, CAC scores were calculated using the Agatston method for each coronary artery. The images were analyzed by one reader blinded to subjects' details. The CV for intraobserver measurements was 4.0%. Different CT devices were used in different study cities. Therefore, a phantom with deposits of known calcium concentration was also scanned twice using 3 projections at all study centres and the calcium scores from these scans were compared. The CV between all phantom scans was 3.9%. Recent data suggest that the Agatston area or volume scores alone are not optimal measures to use in CVD risk prediction because there is an inverse association between the density of the plaque and CVD risk, indicating that the role of CAC density should also be considered when evaluating current CAC scoring systems (Criqui et al. 2014).

6.3. Results

6.3.1. Prevalence of ideal cardiovascular health in childhood

None of the 856 children examined in 1986 (aged 12–18 years) met all seven ideal CVH metrics and thus had ideal CVH (Study I). This is in line with two other studies conducted in the USA and Finland, where no child met all sevenmetrics for ideal CVH (Pahkala et al. 2013; Shay et al. 2013). In the present study, children met on average 3.5±1.0 of all 7 ideal metrics, and there were no differences between girls and boys exhibiting the ideal metrics. A clear majority of the children met the ideal goals for BMI, blood pressure and fasting glucose, while the goals for total cholesterol (33.4%), physical activity (6.9%), diet (24.3%) and smoking (22.4%) were more rarely met. The level of ideal physical activity appeared to be the most difficult to achieve in this sample with less than 10% of participants meeting an ideal physical activity level. Similar results for meeting the childhood goal of ≥60 minutes of moderate-to-vigorous physical activity per day have been reported using accelerometers. (Troiano et al. 2008). Recently, it was reported that children accumulate on average 30 minutes per day in moderate-to-vigorous physical activity (Ekelund et al. 2012). In the STRIP study, the prevalence of ideal physical activity was 50% in 15-year-olds but this decreased to 40% in 19-year-olds (Pahkala et al. 2013). In this study, the very low prevalence of ideal physical activity may be partly related to the criteria used to define ideal physical activity. The questionnaire assessed leisure-time, not total, physical activity and the highest option in the multiple choice questionnaire was needed to achieve ideal physical activity. Lack of physical activity in children is worrisome, as there is abundant evidence of the wide-ranging health benefits of physical activity in early life. Accordingly, recent guidelines concerning CVH in children and adolescents encourage adolescents to aim for at least 60 min per day of moderate-to-vigorous activity, with vigorous intensity physical activity on at least 3 days per week (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents and National Heart, Lung, and Blood Institute 2011).

The arbitrary criteria for the health behaviors and, to a lesser degree, the health factors have been criticized. The quality and availability of data in NHANES datasets have strongly influenced the definitions of ideal metrics (Lloyd-Jones et al. 2010). In addition, there are challenges in the measurement and follow-up of CVH metrics especially in children, which affects how data in nationally representative studies are collected and reported. This has led to limitations in how the metrics for CVH can be constructed, with somewhat different age groups being available or appropriate for inclusion in the CVH metrics (Lloyd-Jones et al. 2010). The low percentage of children (22.4%) categorized as having ideal smoking status in this study is probably due to the strict criteria – never tried/never smoked a whole cigarette – required for meeting the goal. In this study, ideal diet was also alarmingly rare (24.3%), which may partly explain the relatively low prevalence of ideal cholesterol– only 33% meeting the ideal level – observed in this study.

6.3.2. Prevalence of ideal cardiovascular health in adulthood

Study II showed that ideal CVH is rare also among young adult populations in Finland, the United States, and Australia. In fact, it was observed for only 1% of the 5785 young adults participating in the international cohorts. Many of the participants had ideal glucose (73%), cholesterol (64%), and were not currently smoking (64%). Ideal diet (7%) was the least common metric for participants from any of the cohorts.

The goal of the CVH concept has been to emphasize prevention of CVD by promoting healthy behaviors. The very low prevalence of ideal CVH in this and other studies suggests that the behavior changes required for compliance with the ideal health behaviors are difficult targets to achieve (Bambs et al. 2011; Del Brutto et al. 2013; Wu et al. 2012; Yang et al. 2012). The low prevalence of ideal CVH may also reflect an imbalance in the thresholds for each ideal health metric. In this study, four of the five dietary criteria in adults were required for an ideal diet, which was a more stringent requirement than compliance with the other components having just one threshold (or two in the case of blood pressure). Although widely applied in population studies, the FFQ method used here is not ideally suitable for precise measurement of nutrient intakes, in part needed to form ideal diet (Willett 2012). For example, sodium intake might be incorrectly estimated because of the assumptions made in the composition of the food and nutrient database. Therefore, it is possible that some participants did consume diets with lower or higher sodium content than estimated here, leading to an under- or over-estimation of diet compliance.

6.3.3. Stability of cardiovascular health

Ideal CVH metrics are modifiable and as study IV showed, evidently change during the life course. There are two ways to increase the prevalence of ideal CVH in adulthood: either to maintain it from youth through middle age, or to improve the status through lifestyle modification. A worrisome finding in this study is that most of the children and young adults who had ≥5 ideal CVH metrics lost this high CVH status before middle age. This finding suggests that children with good health behaviors and high CVH should not be forgotten in lifestyle interventions that aim to improve future CVH. On the contrary, from those participants with ≥5 CVH metrics present in middle age, 78% of younger and 39% of older participants had gained high CVH status as they aged. The relatively large difference in the proportion of younger and older participants who improve CVH suggests that the childhood CVH criteria applied to younger participants may be more difficult to meet than the adult CVH criteria applied to older participants.

6.3.4. Childhood factors in predicting adult cardiovascular health

In study III, a comprehensive set of childhood predictors of adult CVH was examined. Among several clinical and lifestyle indicators studied, parental non-smoking and higher socioeconomic status was independently associated with better CVH two to three decades later.

Already in childhood, exposure to environmental tobacco smoke has been shown to associate with unfavorable lipid profiles (Neufeld et al. 1997), increase in platelet aggregation (Glantz et al. 1995), and carotid and aortic IMT (Kallio et al. 2010). It has been previously reported in the Young Finns and CDAH studies that parental smoking status in childhood is associated with reduced endothelium-dependent vasodilatation and greater carotid IMT measured over 20 years later (Gall et al. 2014; Juonala et al. 2012). However, there are no previous studies concerning the association between parental smoking in childhood and clustered CVH factors and behaviors in adulthood. This study showed that children whose parents did not smoke met a greater number of ideal CVH metrics in adulthood suggesting that interventions should be targeted to families with smoking parents. Because of their partially developed or compromised cardiovascular, endocrine, and immune systems, the physiologically immature children may be more susceptible to damage from the toxic effects of passive smoking, particularly given the fact that the effects of passive smoking may occur at very low levels of exposure. (Barnoya et al. 2005; Metsios et al. 2010) This may be one reason why the effect of parental smoking found in our study seems to remain long-term, and independent of potential confounders (socioeconomic status) or other mediators such as traditional CVD risk factors. Although other parental health habits were not studied, parental smoking may be considered a marker of parental health-related behaviors in a broader sense and it is possible that these unhealthy habits are then adopted by their offspring.

In previous studies, childhood socioeconomic disadvantage has also been shown to associate with individual cardiovascular risk factor levels in adulthood (Poulton et al. 2002). In addition, childhood socioeconomic circumstance and intergenerational education mobility is associated with health-related behaviors in adulthood (Cleland et al. 2009; Gall et al. 2010). In line with these studies, this study reported novel data using as an endpoint a cluster of ideal CVH factors and behaviors associated with CVD morbidity and mortality. Importantly, it was observed that children with higher family socioeconomic status exhibited a greater number of ideal CVH metrics in adulthood independent of several other childhood risk factors. Thus, children with higher parental socioeconomic status may have adopted a healthier lifestyle than those with lower socioeconomic background. These data support recent recommendations (Pearson et al. 2013) that encourage implementation of community-wide interventions that are socially and culturally appropriate to reduce disparities and inequities in the CVH of socioeconomically disadvantaged subgroups.

6.3.5. Ideal cardiovascular health in predicting cardiometabolic outcomes and subclinical atherosclerosis

Childhood

A higher number of ideal CVH metrics in childhood predicted reduced risk of hypertension, high LDL-cholesterol, high triglycerides, MetS and high-risk carotid IMT in adulthood. These results suggest a major impact of childhood CVH metrics on subsequent risk of CVD. Accordingly, in a recent report from the STRIP study, the number of ideal CVH metrics was favorably associated with carotid IMT and distensibility in adolescence (Pahkala et al. 2013). Previous reports have also shown associations between childhood risk factors and carotid IMT in adulthood (Davis et al. 2001; Li et al. 2003; Raitakari et al. 2003). In these studies, however, either fewer metrics were used or individual risk factors were studied. The uniqueness of the present analysis is applying the cluster of both ideal health factors and ideal health behaviors to a long-term prospective study of CVH in children. Cardiometabolic risk factors tend to occur together more frequently than expected by chance alone (Berenson et al. 1998; Raitakari et al. 1994) and clustering of risk factors is thought to be a better measure of CVH in children (Andersen et al. 2003). In the Young Finns Study, it has been previously documented that pediatric MetS and high BMI alone predict high carotid IMT and T2DM in adulthood (Magnussen et al. 2010). Few population-based studies have prospectively examined the utility of childhood lipid classifications in predicting adult high-risk levels (Friedman et al. 2006; Magnussen et al. 2009). Also, blood pressure is shown to track from childhood to adulthood (Juhola et al. 2011). In addition, health-related behaviors e.g. physical activity and food preferences are established early in life and may significantly track into adulthood (Mikkila et al. 2005; Telama et al. 2014).

A previous report from the Young Finns Study showed that carotid IMT increases 5.7±0.4 µm/year in healthy young adults (Juonala et al. 2008). In Study I, there was a difference of 67 µm in adult carotid IMT between those with childhood ideal CVH index groups of 1 (lowest) and 6 (highest). Using the vascular age concept (Stein et al. 2004), this corresponds to 11.8 years, meaning that participants with only 1 ideal health metric are almost 12 years older in vascular age than those with 6 metrics. These results indicate that interventions that target health behaviors and factors in childhood are needed to improve adult vascular health.

Adulthood

Study II demonstrated a significant cross-sectional association between the number of ideal CVH metrics and carotid IMT in young adults in Finland, the United States, and Australia. The cross-sectional association between ideal CVH and carotid IMT in young adults has not been shown previously. Two studies of middle-aged participants have recently shown an inverse association between the number of CVH metrics and carotid IMT (Kulshreshtha et al. 2014; Xanthakis et al. 2014). In this study, young adults with greater ideal CVH index had lower carotid IMT in all cohorts studied. In addition, many of the individual CVH metrics — ideal BMI, blood pressure, total cholesterol, and physical activity — were shown to have independent associations with carotid IMT. These results indicate a favorable effect of CVH status on vascular health already in young adulthood. Although there were differences in the CVH metrics and the mean carotid IMT in different populations, adherence to the components of ideal CVH in young adulthood was shown to be universally associated with a lower risk of subclinical atherosclerosis. Understanding the significant association between CVH status and subclinical atherosclerosis should further enhance prevention efforts to target people with low CVH.

From childhood to adulthood

In study IV it was observed that persons with persistently low CVH status in childhood and adulthood were at increased risk for developing CAC, high-risk distensibility, high-risk IMT and T2DM, but those who improved their CVH status from low to high had a similar risk compared to those who always had high scores of CVH. In addition, it was found that a greater number of lifetime CVH metrics and improvement in continuous CVH index independently predicted lower risk for CAC, high-risk distensibility, high-risk IMT and T2DM. These results are in line with previous reports from the Young Finns Study showing childhood overweight-related risks for T2DM, hypertension, high risk IMT and dyslipidemia to be reversible among those who become non-obese adults (Juonala et al. 2011) and that MetS in youth that resolves by adult life is associated with a normalization of risk for T2DM and high carotid IMT (Magnussen et al. 2012). In addition, it has been reported that change in CVH status was favorably associated with arterial pulse wave velocity (Aatola et al. 2014).

Limited data are available concerning associations between CVH metrics and CAC. In a recent report, a higher number of ideal CVH metrics was associated with decreased CAC prevalence and progression in adults with or without type 1 diabetes (mean age 37.0 and 39.0 years, respectively) (Alman et al. 2014a). Previously, it has been observed that early adulthood risk factors are associated with increased CAC in middle age independent of contemporary risk factors (Loria et al. 2007), and that elevated BMI in childhood associates with adult CAC (Mahoney et al. 1996). In the Young Finns Study, elevated levels of LDL-cholesterol and systolic blood pressure in adolescence were shown to predict CAC independent of longitudinal change in these risk factors (Hartiala et al. 2012). Recently, change in a continuous composite healthy lifestyle score (not overweight/obese, low alcohol intake, healthy diet, physically active, non-smoker) in young adults (mean age 25.1 years), was associated with CAC and also IMT 20 years later (Spring et al. 2014). In this study, the construct of ideal CVH was applied, the cohort was younger (aged 12-24 years at baseline), and the effect of change in CVH with the outcomes was specifically studied. In addition, Study IV showed that a favorable change in health behaviors independent of change in health factors to predict lower IMT and higher distensibility. These findings are important clinically because they emphasize the important role that health behaviors have in prevention of meaningful adult outcomes, independent of their role in controlling individual health factors.

6.4. Implications in cardiovascular health promotion in children and young adults

It is well accepted that atherosclerosis begins in childhood and is associated with the same CVD risk factors that are well established in adults. Since the roots of CVD are in early life, the need for appropriate CVD prevention strategies in children and adolescents is obvious (Ford 2012). Through preventive efforts, it should be possible to maintain low-risk status into adulthood. Indeed, low CVD-risk status maintained to 50 years of age is associated with a very low future risk of CVD (Lloyd-Jones et al. 2006). This is a fundamental principle behind the AHA's goals that are focused on achieving and monitoring CVH. The results of this study substantiate the AHA-defined CVH metrics in children and young adults by showing them to associate with lower risk of subclinical atherosclerosis and incidental cardiometabolic outcomes. This study also demonstrates that almost no children and young adults meet all 7 metrics for ideal CVH, highlighting the considerable amount of progress in improving CVH that is yet to be realized. Additionally, these results reinforce that substantial improvement in lowering CVD incidence remains feasible. Prevention of risk factor development (primordial prevention) and the development of atherosclerotic lesions (primary prevention) constitute the principal pathways to promoting CVH in children and young adults. Healthcare providers have a central role in reaching children and young adults and in identifying and controlling non-ideal levels of health factors. The prevention strategies are also applicable in well-baby clinics, daycare units, schools and non-profit organizations as well as in the general community. Furthermore, healthcare providers have an opportunity to educate parents and children themselves about the importance of an overall healthy lifestyle, including appropriate physical activity, not smoking and a healthy diet, already at an early age. Results from the STRIP study have shown that a family-based dietary intervention has beneficial long-term effects on lipids and vascular function among children (Niinikoski et al. 2012; Raitakari et al. 2005). In this study, parental smoking and socioeconomic disadvantage in childhood was shown to have a deleterious effect on future CVH, thus further emphasizing that approaches to prevention must be directed also at the family environment of the developing child. Moreover, this study showed evidence for tracking of CVH from childhood to adulthood. This finding confirms the wisdom of helping children to get a healthy start to life by guiding them to adopt healthy practices that will persist.

Prevention of atherosclerotic CVD is best achieved by maintaining high CVH status, but even when high CVH is lost, it can be regained by improving health behaviors. The results of the present study suggest that interventions should be targeted to those with low scores of CVH both in childhood and adulthood. In addition, the large number of children that reduced their CVH from high to low between childhood and adulthood is a reminder that children with ideal health behaviors may also need help in maintaining their CVH through middle and older ages.

6.5. Strengths and limitations

The strengths of this study include the longitudinal population-based design and the long follow-up of the participants, who were well phenotyped in childhood and adulthood. Physical, laboratory, ultrasound and CT examination data were determined with well-established methods and using a large number of participants. This study has limitations. Firstly, it is not currently possible to study the associations with the clinical outcome of cardiovascular events. Instead, carotid IMT, carotid distensibility, CAC and a series of cardiometabolic outcomes were used as surrogate markers of CVH. Secondly, subjective methods were used to assess diet, physical activity, smoking, and exposure to environmental tobacco smoke, and these methods differed between cohorts and have partly changed during the study years. Thirdly, because of the low number of black participants in the study cohorts, the generalizability of the results is limited to white Caucasian subjects. A potential limitation is loss to follow-up that was differential, discussed in more detail on page 75. Finally, an observational study design cannot conclusively differentiate whether the observed associations between childhood CVH metrics and adult outcomes are due to specific effects of youth behaviors and risk marker levels, or their life-long tracking to adulthood.

6.6. Future research prospectives

Although CAC, carotid IMT and distensibility are well established surrogate markers of CVD, the ability to study the associations with cardiovascular events as the outcome would lead to a better understanding of the implications of childhood CVH status on CVDs. Because CVD events will accumulate as the Young Finns Study participants age, the relationships between CVH in childhood and hard cardiovascular events will be able to be examined in the future. Studies with multiple follow-ups make it possible to study how changes in CVH status affect subsequent cardiovascular morbidity and mortality, highlighting that it may never be too late to change one's health-related behaviors. Studying the efficacy and effectiveness of different lifestyle interventions will be instrumental in promoting CVH. Moreover, examining the associations of the individual CVH metrics with cardiovascular outcomes are important to compare the relative importance of the individual metrics that are combined into a CVH index. It is possible that the weight of the individual metrics vary during the life course and also by the time frame used for risk projection. In addition, further data is needed concerning the clinical usefulness of noninvasive measurement of preclinical atherosclerosis in apparently healthy individuals. These methods may have implications in finding high-risk individuals and also in monitoring the success of primordial and primary prevention of CVD.

7. SUMMARY AND CONCLUSIONS

1. None of the children and very few of the young adults met all 7 ideal CVH metrics and thus had ideal CVH. These findings strengthen the need for early evaluation of CVH factors and behaviors, and for development of effective intervention strategies for behavioral change.

2. Among several lifestyle and clinical indicators examined, parental non-smoking and higher family socioeconomic status in childhood independently predict better CVH in adulthood. As atherosclerotic CVDs are rooted in childhood, these findings suggest that special attention be paid to children whose parents smoke and who are from low socioeconomic status families to promote future CVH and thus prevent disease.

3. A high number of CVH metrics in childhood and adulthood predicts lower risk of subclinical atherosclerosis and cardiometabolic outcomes in adulthood. Interventions should be targeted to those with low scores of CVH.

4. Those who improved CVH status from childhood to adulthood had a comparable risk of subclinical atherosclerosis to participants who had always had a high CVH status. These results emphasize that even when high CVH is lost, it can be regained by improving health behaviors.

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