HEIKKI AATOLA

Lifetime Risk Factors, Lifestyle, and Vascular Health in Adulthood

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ACADEMIC DISSERTATION
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University of Tampere, School of Medicine
Tampere University Hospital, Department of Pediatrics
Pirkanmaa Hospital District, Medical Imaging Center, Department of Clinical Physiology and Nuclear Medicine
Finland

Supervised by
Professor Mika Kähönen
University of Tampere
Finland
Docent Nina Hutri-Kähönen
University of Tampere
Finland

Reviewed by
Docent Juha Koskenvuo
University of Turku
Finland
Docent Matti Mäntysaari
University of Eastern Finland
Finland

Cover design by
Mikko Reinikka

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TIIVISTELMÄ

Tausta: Valtimokovettumataudin patofysiologia on tarkentunut merkittävästi viimeisten 20 vuoden aikana. Kyseessä on monitekijäinen prosessi, jossa molekyyli- ja solutason etenevät muutokset johtavat kliiniseen sairauteen. Muutokset käynnistyvät jo lapsuudessa, vaikka sairauden kliiniset esiintymismuodot, kuten sepelvaltimotauti, sydäninfarkti ja aivohalvaus, ilmaantuvat yleensä vuosikymmeniä myöhemmin keski-iässä tai vanhuusiässä. Useissa tutkimuksissa on osoitettu, että sairauden riskiä saadaan vähennettyä elämäntapamuutoksilla.

Primordiaalinen ennaltaehkäisy tarkoittaa riskitekijöiden kehittymisen ehkäisyä, ja sen tueksi Amerikan sydänyhdistys (American Heart Association) on julkaisut käsitteen ihanteellinen sydän- ja verisuoniterveys. Se tarkoittaa neljää yhtäaikaista terveellistä elämäntapatekijää (tupakoimattomuus, normaali painoindeksi, suositusten mukainen liikunta-aktiivisuus ja terveellinen ruokavalio) sekä kolmea yhtäaikaista terveystekijää (ihanteellinen kokonaiskolesteroli, verenpaine ja plasman paastosokeri). Yksittäisten komponenttien terveysvaikutukset on luotettavasti osoitettu, ja yhdessä ne ennustavat matalaa sydän- ja verisuonisairauksien riskiä sekä alentunutta kokonaiskuolleisuutta. Ihanteellisen sydän- ja verisuoniterveyden esiintyvyys on kuitenkin erittäin matala sekä lapsilla että aikuisilla.

Samanaikaisesti valtimokovettumataudin kanssa tapahtuu ikääntymisen aiheuttamaa elastisten valtimoiden ja erityisesti aortan jäykistymistä. Iän myötä jäykistyvä aortta ei pysty vaimentamaan riittävän tehokkaasti vasemman kammion aiheuttamaa sykintää, ja se välittyy kapillaareihin aiheuttaen mikrovaskulaarisia vaurioita aivoihin ja munuaisiin. Aortan jäykistyminen lisää myös systolista verenpainetta, joka aiheuttaa vasemman kammion kuormittumista ja valtimokovettumataudin etenemisen kiihtymistä. Valtimoiden ikääntyminen on itsenäinen prosessi, joka etenee ilman valtimokovettumatautia. Ikääntymisen aiheuttamien muutosten erottaminen valtimokovettumataudin aiheuttamista muutoksista on hyvin vaikeaa, ellei jopa mahdotonta. Valtimojäykkyys voidaan mitata määrittämällä pulssiaallon etenemisnopeus, joka ennustaa sydän- ja verisuonisairauden päätetapahtumia kuten sydäninfarktia ja sydänperäistä kuolemaa ja on lisäksi valtimoiden ikääntymisen mittari.

Tavoitteet: Tutkimuksen avulla selvitettiin lapsuudessa ja aikuisiällä määritettyjen perinteisten ja elämäntapaan liittyvien riskitekijöiden yhteyttä aikuisiän pulssiaallon etenemisnopeuteen. Riskitekijöitä käytettiin analyyseissä sekä jatkuvina muuttujina että luokiteltuina ihanteellisen sydän- ja verisuoniterveyden määritelmän mukaisesti. Lisäksi selvitettiin riskitekijöiden muutoksen yhteyttä pulssiaallon etenemisnopeuteen lapsuudesta aikuisikään ja nuoresta aikuisiästä keski-ikään. Kohonnut verenpaine määriteltiin lapsuudessa kolmen eri luokittelun mukaisesti, minkä perusteella tutkittiin näiden luokittelujen kykyä ennustaa korkeaa pulssiaallon etenemisnopeutta aikuisiällä.

Aineisto ja menetelmät: Tämä tutkimus on osa Lasten sepelvaltimotaudin riskitekijät -tutkimusta, joka on Suomen viidessä yliopistosairaalassa edelleen jatkuva prospektiivinen kohorttitutkimus. Tutkimus alkoi vuonna 1980. Ensimmäiseen poikkileikkaustutkimukseen osallistui 3596 3−18 -vuotiasta henkilöä. Seurantatutkimuksia on tehty vuosina 1983, 1986, 2001 ja 2007. Viimeisen seurantatutkimuksen yhteydessä määritettiin impedanssikardiografian avulla pulssiaallon etenemisnopeus 1872 30−45-vuotiaalta henkilöltä (52.1 % alkuperäisestä otoksesta).

Tulokset: Systolinen verenpaine ja verensokeri lapsuudessa sekä systolinen verenpaine, insuliini ja triglyseridit aikuisiällä ennustivat itsenäisinä tekijöinä aikuisiän pulssiaallon etenemisnopeutta. Kasvisten syönti sekä lapsuudessa että aikuisiällä oli käänteisesti verrannollinen pulssiaallon etenemisnopeuteen, ja tämä yhteys säilyi tilastollisesti merkitsevänä,

vaikka huomioitiin muut perinteiset ja elämäntapoihin liittyvät riskitekijät. Lapsuusiän kohonnut verenpaine ennusti kohonnutta aikuisiän pulssiaallon etenemisnopeutta. Ennuste oli yhtäpitävä, kun verrattiin yksinkertaistettuja luokitteluja hoitosuosituksen mukaiseen luokitteluun. Muutos ihanteellisessa sydän- ja verisuoniterveydessä oli suoraan verrannollinen aikuisiän pulssiaallon etenemisnopeuteen, eli muutos huonompaan oli yhteydessä lisääntyneeseen valtimoiden jäykkyyteen. Tämä muutos oli merkitsevä sekä lapsuudesta aikuisikään että nuoresta aikuisiästä keski-ikään ja säilyi merkitsevänä, kun huomioitiin lähtötilanteen riskiprofiili.

Johtopäätökset: Lapsuudessa ja aikuisiällä määritetyt, perinteiset ja elämäntapaan liittyvät valtimokovettumataudin riskitekijät ennustavat aikuisiän pulssiaallon etenemisnopeutta. Suotuisat riskiprofiilin muutokset sekä lapsuudesta aikuisikään että nuoresta aikuisiästä keski-ikään ovat yhteydessä matalampaan pulssiaallon etenemisnopeuteen ja siten alhaisempaan valtimoiden jäykkyyteen aikuisiällä. Kohonnut verenpaine on merkittävä valtimotaudin riskitekijä, ja yksinkertaistettuja lapsuusiän seulontaluokitteluja voidaan hyödyntää riskiyksilöiden tunnistamisessa. Tämän tutkimuksen tulokset kannustavat vähentämään valtimotaudin riskitekijöitä sekä lapsuudessa että aikuisiällä.

ABSTRACT

Background: Our understanding of the pathophysiology of atherosclerosis has expanded considerably during last two decades. A multifactorial pathophysiological process describes the progression at molecular and cellular levels, eventually manifesting itself as clinical disease. All these processes already begin in childhood, but clinical manifestations—e.g. coronary heart disease, myocardial infarction, or stroke—usually occur decades later in middle-age or in old age. Several reports have consistently shown the favorable effects of lifestyle changes.

To improve primordial prevention, i.e. to prevent the development of risk factors, the American Heart Association released in 2010 the concept of Ideal Cardiovascular Health: the simultaneous presence of 4 ideal health behaviors (non-smoking, normal body mass index, being physically active, and a healthy diet) and 3 ideal health factors (normal total cholesterol, blood pressure, and fasting glucose). The health-promoting benefits of each of the components have been well established. This concept has been shown to predict lower cardiovascular disease risk and mortality of all causes. However, the prevalence of Ideal Cardiovascular Health has been extremely low in adolescence and in adulthood.

Simultaneously with the atherosclerotic process, aging causes stiffening of elastic arteries, and especially of the aorta. When the aorta ages and stiffens, the pulsations created by the left ventricle cannot be cushioned and are transmitted into the capillaries especially in the brain and kidneys, causing microvascular damage. Arterial aging also increases pressure throughout the systole, which leads to left ventricle hypertrophy and an acceleration of the atherosclerotic process. Arterial aging is an independent process which could advance without atherosclerosis. It is not possible to study only the process of atherosclerosis without arterial stiffening, because it is difficult to separate age-related changes from disease-related changes. Arterial stiffness could be assessed by measuring pulse wave velocity, which is accepted as an independent predictor of cardiovascular events and as a biomarker of vascular aging.

Aims: The present study elucidates the associations of traditional and lifestyle risk factors measured in childhood and adulthood with pulse wave velocity assessed in adulthood. Risk factors were used as continuous variables and as defined in the concept of Ideal Cardiovascular Health. Additionally, the present study investigated the association between the change in Ideal Cardiovascular Health status (both from childhood to adulthood and from young adulthood to middle age) and pulse wave velocity in adulthood. Moreover, blood pressure in childhood was defined as normal or elevated according to the three different definitions to investigate whether elevated pediatric blood pressure could predict high pulse wave velocity in adulthood and whether there is a difference in predictive ability between the different definitions.

Subjects and Methods: The population studied in this thesis is from the Cardiovascular Risk in Young Finns Study. The first cross-sectional study was conducted in 1980, and 3,596 subjects aged 3−18 years attended. Follow-up studies with standard physical examinations and blood samplings were conducted in 1983, 1986, 2001, and 2007. Pulse wave velocity measurements by impedance cardiography were carried out in 2007, with 1,872 (52.1% of original cohort) participants (aged 30−45 years) attending.

Results: Systolic blood pressure and glucose in childhood, and systolic blood pressure, insulin, and triglycerides in adulthood were independent predictors of adult pulse wave velocity. Vegetable consumption both in childhood and in adulthood was inversely and

independently associated with adult pulse wave velocity, and the association remained significant when adjusted for lifestyle or traditional risk factors. Elevated pediatric blood pressure predicted high adult pulse wave velocity, and the predictions were equivalent for the simplified and complex definitions. The change in the ideal cardiovascular health index was inversely related to pulse wave velocity in adulthood. This relationship was significant for the younger (change from childhood to adulthood) and the older (change from young adulthood to middle-age) participants and remained significant after adjusting for the ideal cardiovascular health index at baseline.

Conclusions: Traditional and lifestyle risk factors in childhood and adulthood predict pulse wave velocity in adulthood. Favorable changes in risk factor status, both from childhood to adulthood and from young adulthood to middle-age, are associated with lower pulse wave velocity in adulthood. Elevated blood pressure is a major risk factor and the simplified blood pressure tables could be used to identify children at an increased risk of high arterial stiffness in adulthood. These results support the efforts to reduce risk factors both in childhood and adulthood in the primary prevention of atherosclerosis.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications. In the text, they are referred to by their Roman numerals I–IV.

I Aatola H, Hutri-Kähönen N, Juonala M, Viikari JSA, Hulkkonen J, Laitinen T, Taittonen L, Lehtimäki T, Raitakari OT, Kähönen M. Lifetime Risk Factors and Arterial Pulse Wave Velocity in Adulthood: The Cardiovascular Risk in Young Finns Study. Hypertension. 2010; 55: 806-811.

II Aatola H, Koivistoinen T, Hutri-Kähönen N, Juonala M, Mikkilä V, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation. 2010; 122: 2521-2528.

III Aatola H, Magnussen CG, Koivistoinen T, Hutri-Kähönen N, Juonala M, Viikari JS, Lehtimäki T, Raitakari OT, Kähönen M. Simplified Definitions of Elevated Pediatric Blood Pressure and High Adult Arterial Stiffness. Pediatrics. 2013; 132: 70-76.

IV Aatola H, Hutri-Kähönen N, Juonala M, Laitinen TT, Pahkala K, Mikkilä V, Telama R, Koivistoinen T, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Prospective Relationship of Change in Ideal Cardiovascular Health Status and Arterial Stiffness: The Cardiovascular Risk in Young Finns Study. Submitted.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
AGE	advanced glycation end-product
AHA	American Heart Association
AIx	augmentation index
ANOVA	analysis of variance
ARB	angiotensin receptor blocker
AUC	area under receiver-operating characteristic curve
BMI	body mass index
BP	blood pressure
CCB	calcium-channel blocker
CHD	coronary heart disease
CI	confidence interval
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiography
HDL	high-density lipoprotein
ICG	impedance cardiography
IPG	impedance plethysmogram
LDL	low-density lipoprotein
LV	left ventricle/ventricular
LVH	left ventricular hypertrophy
MRI	magnetic resonance imaging
NHBPEP	National High Blood Pressure Education Program
NO	nitric oxide
NPV	negative predictive value
NRI	net reclassification index
PKC	protein kinase C
PP	pulse pressure
PPV	positive predictive value
PWV	pulse wave velocity
ROS	reactive oxygen species
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SMC	smooth muscle cell

1. INTRODUCTION

Atherosclerosis, a progressive vascular pathophysiology, has its roots in childhood, and cardiovascular (CV) risk factors—i.e. elevated cholesterol, elevated blood pressure (BP), hyperglycemia, obesity, and cigarette smoking—are already related to atherosclerotic lesions in childhood and young adulthood (McGill et al. 1995, McGill et al. 1997, Berenson et al. 1998, McGill et al. 1998). These risk factors promote oxidative stress in the vascular wall and cause endothelial dysfunction, initiating a cascade of events, including alterations in vasoactive mediators, inflammatory responses, and vascular remodeling (Dzau et al. 2006a). This multifactorial process leads to clinical manifestations of atherosclerosis, e.g. coronary heart disease (CHD), myocardial infarction, or stroke, which occur decades later. Therefore, early modification of risk factors by lifestyle changes to prevent or even reverse the progression of atherosclerosis is one of the major contemporary challenges in the primary prevention of cardiovascular disease (CVD). This long delay also underlines the important role of biomarkers and surrogate markers in evaluating CVD risk and assessing the response to interventions. (Dzau et al. 2006a, Vlachopoulos 2012.)

Because of the epidemic of overweight and obesity in adolescence, the prevalence of hypertension is increasing (Wang and Beydoun 2007, McCrindle 2010). Previous studies have shown that BP tracks from childhood to adulthood, and individuals with elevated BP in childhood and adolescence are at an increased risk of developing hypertension in adulthood (Bao et al. 1995, Chen and Wang 2008, Juhola et al. 2011). These data indicate that elevated BP is established early in life; hence, prehypertension and hypertension are already identifiable in adolescence, underlying the potential to reduce risks and optimize health outcomes as they relate to hypertensive diseases.

Risk factor modifications have a remarkable impact on the atherosclerotic process. Several studies have consistently shown the protective effect of fruit and vegetable consumption against the risk of CVD (Ness and Powles 1997, Bazzano et al. 2003, Ignarro et al. 2007). Furthermore, regular physical activity and exercise training have important roles in preventing CVD and managing CVD risk factors both in children and adults (Thompson et al. 2003, Ruiz et al. 2009). Smoking cessation, and even smoke-free public places and workplaces, have been found to decrease acute myocardial infarctions, ischemic strokes, and CV deaths markedly (Sargent et al. 2004, The Health Consequences of Smoking: A Report of the Surgeon General. 2004, Lightwood and Glantz 2009, Meyers et al. 2009).

In January 2010, the American Heart Association (AHA) released its 2020 Impact Goals and changed the focus from primary prevention of CVD to primordial prevention, i.e. to preventing the development of risk factors (Lloyd-Jones et al. 2010). To improve the primordial prevention, AHA defined the concept of Ideal Cardiovascular Health: the simultaneous presence of 4 ideal health behaviors (non-smoking, normal body mass index [BMI], being physically active, and a healthy diet) and 3 ideal health factors (normal total cholesterol, BP, and fasting glucose) (Lloyd-Jones et al. 2010). This combination of risk factors, along with the health-promoting benefits of each of the components, has been well

established, highlighting the importance of evaluating a person's CVD risk profile rather than single risk factors alone (Lloyd-Jones et al. 2010).

Arterial stiffness is a surrogate marker for CVD and, assessed as pulse wave velocity (PWV), is generally accepted as an independent predictor of CV events and all-cause mortality (Cohn et al. 2004, Vlachopoulos et al. 2010b). The stiffness of elastic arteries increases steadily with age, reflecting true arterial wall damage and integrating the long-lasting effects of all identified and non-identified CV risk factors (Nichols et al. 2011). PWV has fulfilled the criteria for a biomarker of vascular aging, and it may prevent patients from being mistakenly classified as being at a low or moderate risk when they actually have an abnormally high vascular age, and vice versa (Vlachopoulos 2012). Increased elastic artery stiffness accelerates the atherosclerotic process (macrovascular disease) and increases the transmission of pulsatile energy into the microcirculation, leading to progressive damage (microvascular disease) (Nichols et al. 2011). Increased PWV was also added to the list of markers of subclinical organ damage and prognostic factors in the European guidelines for management of arterial hypertension (Mancia et al. 2007, Mancia et al. 2013).

Previous observations concerning the relationship between risk factors identified in childhood/adolescence and arterial PWV in adulthood have been controversial (Oren et al. 2003, Li et al. 2004). To the best of our knowledge, reports concerning associations between childhood lifestyle risk factors and PWV, or the Ideal Cardiovascular Health and PWV, are sparse. Therefore, the specific aims of this thesis were to study the associations of both traditional and lifestyle risk factors in childhood with PWV in adulthood. Risk factors were used as continuous variables and as defined for the concept of Ideal Cardiovascular Health. The effect of the change in the risk profile was also studied because all major risk factors are modifiable, particularly through lifestyle adjustments. Another major study aim was to evaluate and compare the utility of 3 different pediatric elevated BP definitions to predict high adult PWV because hypertension is one of the most significant risk factor for CVD and arterial stiffening. PWV was measured in 1,872 white adults aged 30−45 years. These individuals were participants of the prospective Cardiovascular Risk in Young Finns Study for whom risk factor data were available since childhood (aged 3−18 years).

2. REVIEW OF THE LITERATURE

2.1 The natural course of arterial aging

The human circulation, described in its simplest form, consists of a pump, the heart, which forces blood periodically and rhythmically into a branching system of elastic tubes, the arterial system. The pulsations generated by the heart travel centrifugally and are partially reflected at points of discontinuity or change in impedance to travel backwards again (pressure amplification). These pulsations themselves are normally damped down before they reach the smallest branches, the capillaries. The blood then returns in a more or less steady stream to the right side of the heart with secondary pulsations imposed in the veins by skeletal muscular activity and by the heart itself. The whole human circulation is, of course, much more complicated than this and the human arterial system markedly so, with varied geometric patterns of branching, non-uniform elasticity of arteries, and non-linear elastic wall properties. (Nichols et al. 2011.)

The human arterial system has two different functions. Firstly, the purpose is to deliver blood from the left ventricle (LV) to the capillaries of bodily organs and tissues according to their need. Secondly, the function is to cushion the pulsations of blood generated by LV so that capillary blood flow is continuous and steady. Hence, it is working simultaneously and efficiently as a conduit and as a cushion. The combination of these two functions leads to pressure waves travelling at a finite wave velocity and strong wave reflection. (Nichols et al. 2011.) The wave reflection occurs at the origin of the myriad of terminations of low resistance arteries into high resistance arterioles. The beautiful design of the CV system locates the resultant of all reflecting sites at such a distance from the heart that, with the usual ventricular rate and ejection period in adolescence, the reflected wave is able to boost coronary flow during diastole without adding to systolic load. (Figure 2.1) (O'Rourke and Hashimoto 2007, Nichols et al. 2011.)

The heart and the arterial system are tuned for optimal efficiency: greater distensibility of the proximal aorta than the distal aorta, dispersion of peripheral reflecting sites causing perfect timing of reflecting wave, the location of the heart in the upper thorax, and the inverse relationship between heart rate and body length (O'Rourke and Hashimoto 2007, Nichols et al. 2011). This optimal efficiency, however, is fragile. It can only be maintained for the first three decades. As the aorta ages and stiffens, the pulse wave travels faster in the stiffer tube and returns earlier. So, the reflected wave boosts the pressure in late systole and the favorable interaction between LV and the arterial tree is lost (Figure 2.1). (Lakatta and Levy 2003a, O'Rourke and Hashimoto 2007, Nichols et al. 2011.)

Aging causes two major physical changes in elastic arteries, dilatation and stiffening. These changes are most marked in the aorta and less so in the peripheral muscular arteries (Avolio et al. 1983, Avolio et al. 1985, Lakatta 2000, Nichols et al. 2011), which can be explained by the differences in the degree of stretch. In adolescence, the aorta dilates by approximately 10% with each beat of the heart, while the muscular arteries dilate by only 2%−3% (Boutouyrie et al. 1992, Nichols et al. 2011). Elastin, which is one of the most inert substances in the body, could be compared to natural rubber. In studies of cyclic

stress, for a 10% extension of natural rubber, fracture is calculated to occur at 8×10^8 cycles. This corresponds with approximately 25 years at a heart rate of 70 beats per minute. For a 3% extension, fracture is expected to occur at more than 3×10^9 cycles, corresponding with more than 100 years of life at the same heart rate. This conventional engineering theory supports the clinical and histological findings to the effect that arterial aging starts beyond the age of 30 years. (O'Rourke and Hashimoto 2007, Nichols et al. 2011.)

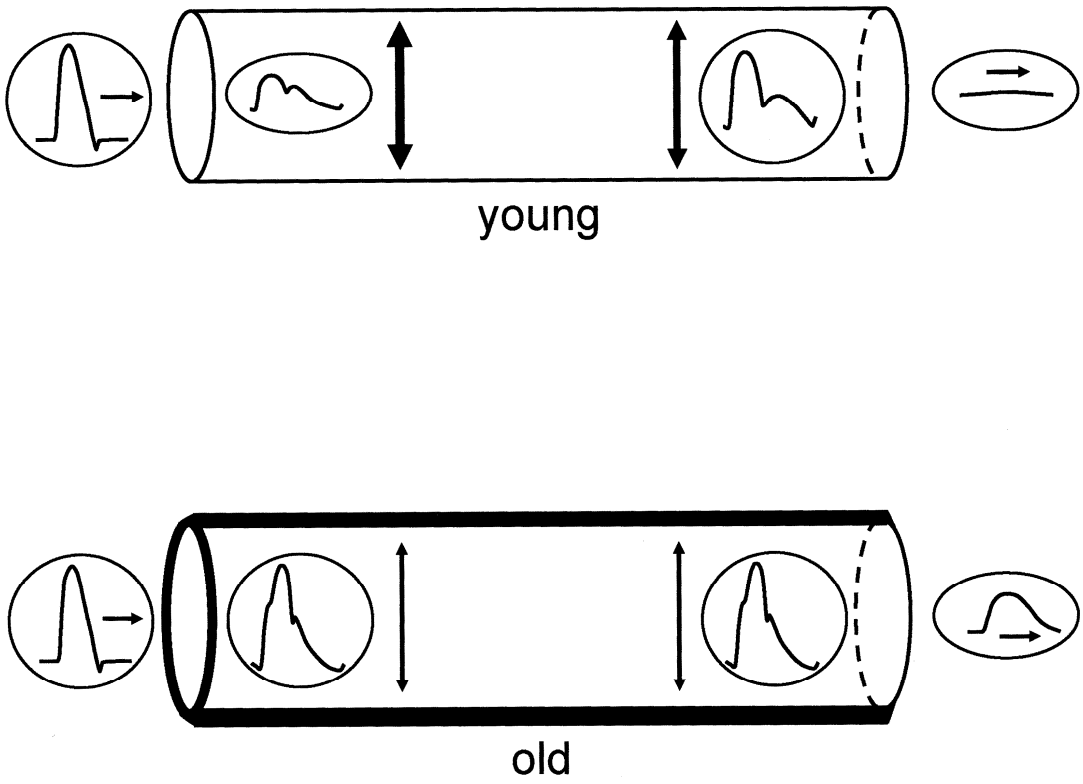

Figure 2.1 Distributed Models of the Arterial Tree

Simple tubular models of the arterial system, connecting the heart *(left)* to the peripheral circulation *(right)* in a young *(top)* and old *(bottom)* subject. In the young subject, the tube is distensible, whereas in the old subject it is stiff. The distal end of the tube constitutes a reflection site where the pressure wave travelling down the tube is reflected back to the heart. The wave travels slowly in the young distensible tube so that the reflected wave boosts the pressure in diastole when it returns to the proximal end. The wave travels faster in the old stiffer tube, returns earlier, and boosts pressure in late systole. Flow input from the heart is intermittent in both young and old subjects. In the young subject, pulsations are absorbed in the distensible tube so that outflow is steady or almost so. In the old subject with a stiff tube, pulsations cannot be absorbed, and so the output from the tube into the peripheral microvessels is pulsatile.

As cyclic stress fractures the elastic lamellae of the aorta, these fractures can account both for dilatation (after the fracture of load-bearing material) and for stiffening (through the transfer of stresses to the more rigid collagenous components of the arterial wall) (Nichols et al. 2011). Increased arterial stiffening could be seen in measures of PWV. A PWV value for a 20-year-old is typically 5 m/s and for 80-year-old 12 m/s, signifying a 2.4-fold increase over 60 years. (Avolio et al. 1983, Avolio et al. 1985.)

It is important to remember that this increase is not apparent in brachial pulse pressure (PP). While PP increases with age, the extent of change is lower since the brachial pulse in adolescence is markedly amplified, whereas the amplification is much lower at 80 years of age (Lakatta and Levy 2003a, Nichols et al. 2011). Systolic blood pressure (SBP) increases with age from roughly 120 to 145 mmHg, diastolic blood pressure (DBP) falls from 80 to 75 mmHg, and brachial PP increases from some 40 to 70 mmHg (i.e. by 75%) (Franklin et al. 1997, Lakatta and Levy 2003a). When comparing these differences, 240% in PWV and 75% in brachial PP, it is clear that the effects of aging have been underestimated in the past, on account of a reliance on the brachial cuff systolic pressure (O'Rourke and Hashimoto 2007).

Since aging causes dilation of proximal elastic arteries, it does not affect conduit function of the arterial tree (Nichols et al. 2011). However, the effect on the cushioning function is marked and progressive, and ineffective cushioning has a devastating effect on the heart and the microcirculation, especially in the brain and kidneys (O'Rourke and Hashimoto 2007, Nichols et al. 2011). Aortic stiffening increases pressure throughout systole (both from the stiffening of the proximal aorta and the early return of the reflected wave) and decreases aortic pressure throughout diastole (Lakatta and Levy 2003a, Nichols et al. 2011). Increased SBP increases LV load, leading to LV hypertrophy (LVH) and increased LV oxygen requirements (Katz 1990). All these predispose to the development of heart failure (Levy et al. 1996).

In addition to this, a hypertrophied heart contracts and relaxes more slowly, further increasing the duration of systole and reducing the duration of diastole at any given heart rate (Nichols et al. 2011). Because of the lengthened duration of systole, wave reflection causes further augmentation of late systolic pressure, and myocardial oxygen needs are thus boosted by increases in both tension and time (Nichols et al. 2011). All these changes increase coronary blood flow requirements but are, however, associated with a decreased ability to supply such blood (Lakatta and Levy 2003a, Nichols et al. 2011). This cascade develops quite independently of coronary narrowing, is worsened by any degree of atherosclerosis, and predisposes to myocardial ischemia (Ferro et al. 1995). Additionally, any degree of ischemia worsens the situation by causing further impairment of ventricular contraction (and also relaxation) and a prolongation of the ejection period (Lakatta and Levy 2003a, Nichols et al. 2011). Figure 2.2 illustrates the adverse effects of aging, from aortic stiffening to dyspnoea and angina.

This vicious cycle links LVH with ischemia (and with angina) even in the presence of what might ordinarily be considered hemodynamically insignificant coronary stenosis or no coronary stenosis (Nichols et al. 2011). This mechanism also becomes relevant in the development of "diastolic" heart failure (Katz 1990, Levy et al. 1996, Hundley et al. 2001). In this condition, which is probably the most common form of heart failure in the elderly, a chronically increased LV load results in an impaired ability of the heart to relax, with shortened diastole, slowed-down and incomplete LV filling, and increased left atrial and pulmonary pressure (Weber et al. 2006, Nichols et al. 2011).

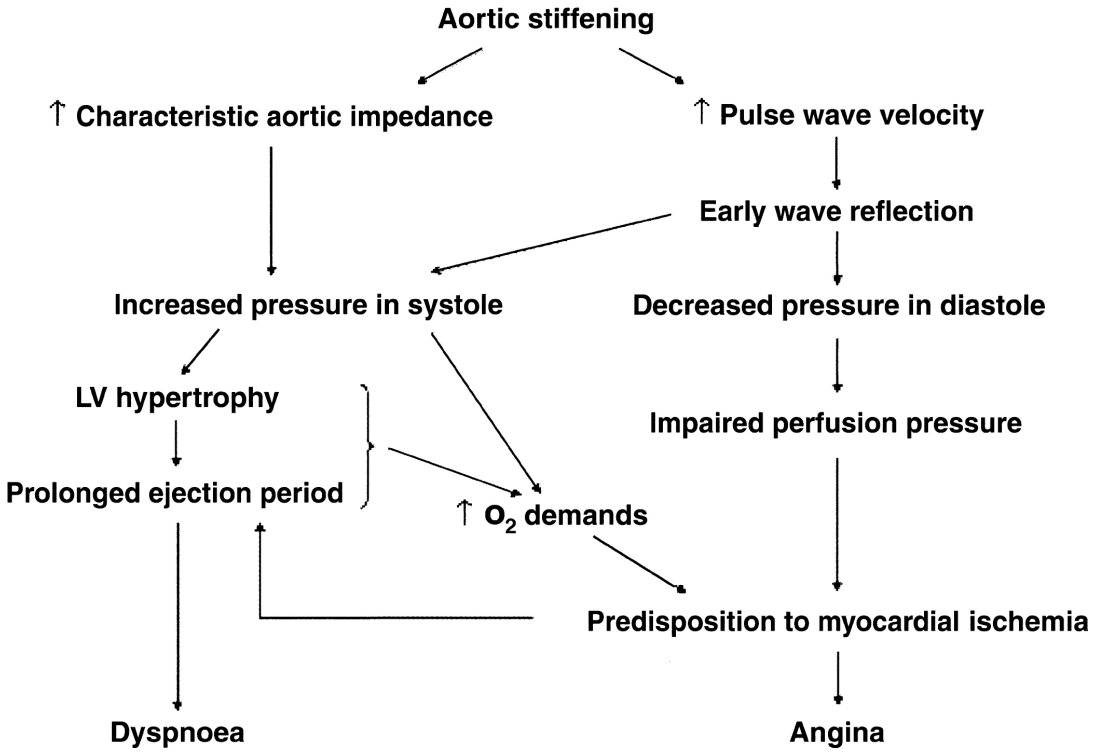

Figure 2.2 Ill Effects of Aging.

LV = left ventricle.

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As mentioned above, an ineffective cushion function has a devastating effect on microcirculation, i.e. small arteries, arterioles, and capillaries (Christensen and Mulvany 2001, Nichols et al. 2011). These vessels usually present the greatest resistance to blood flow, and they complete the change of pulsatile flow from the heart to steady flow in the capillaries by repelling the pulsations that enter from larger arteries (Nichols et al. 2011). This transition from pulsation to steady flow is complete in most organs and tissues, but in those with a high resting blood flow and the most dilated vessels, notably the brain and kidneys, pulsations may extend more deeply towards the capillaries (Christensen and Mulvany 2001, Schofield et al. 2002, Mitchell et al. 2004, O'Rourke and Safar 2005, Nichols et al. 2011). When the aorta ages and stiffens, the pulsations created by the LV cannot be cushioned and they are transmitted into the capillaries (especially in the brain and kidneys), causing a change from steady to pulsatile flow as shown in Figure 2.3 (O'Rourke and Hashimoto 2007, Nichols et al. 2011). As a result, the most severe lesions in older persons can be seen in the microcirculation of the brain and kidneys (Pantoni and Garcia 1997, Cullen et al. 2005, Greenberg 2006). These lesions are similar to the pulmonary microvascular lesions that develop over the years in congenital heart disease with the left-

to-right shunt causing high pulmonary flow pulsations (Edwards 1957). Typical microvasculature findings include damage to the endothelium with thrombosis, and to the media with edema, hemorrhage, and inflammation (Pantoni and Garcia 1997, Cullen et al. 2005, Greenberg 2006), which are similar to those found in medionecrosis caused by physical damage (Nichols et al. 2011). This links large artery stiffening and microvascular disease in the brain and kidneys, as well as neurology, nephrology, cardiology, and geriatrics with magnetic resonance imaging (MRI) and other imaging techniques (Bateman 2002, Vermeer et al. 2003, van Dijk et al. 2004, Henry Feugeas et al. 2005, O'Rourke and Safar 2005, Scuteri et al. 2005, Verhave et al. 2005). There are also studies showing a strong and causative association on the basis of the above-mentioned pathophysiological mechanisms (Mitchell et al. 2004, O'Rourke and Safar 2005).

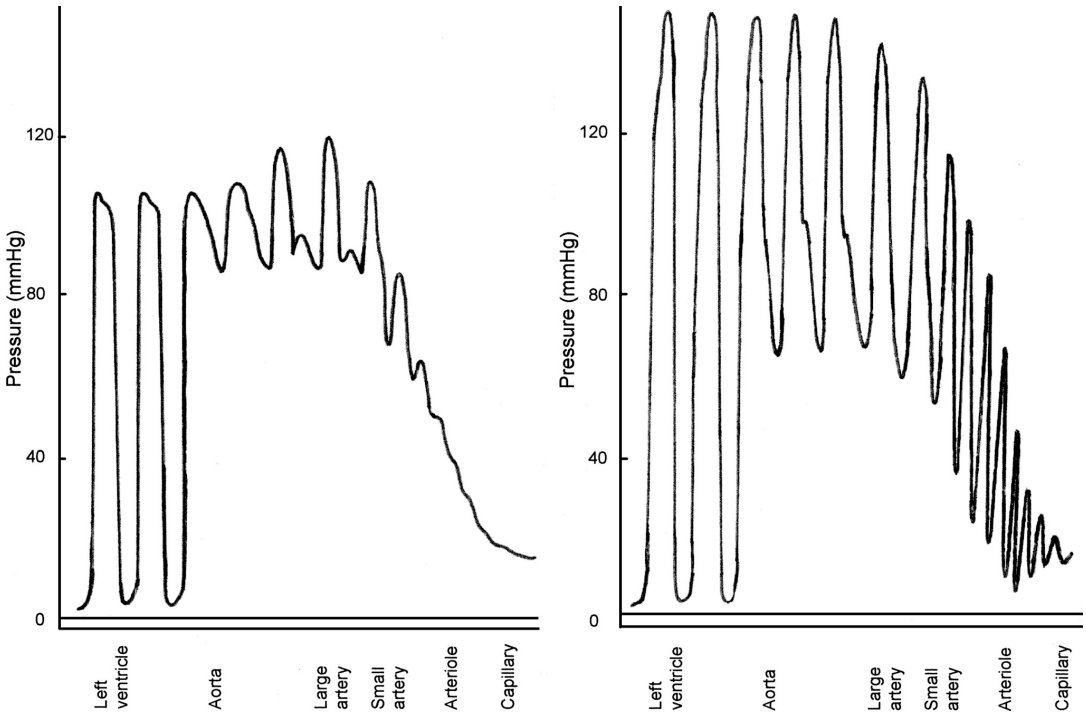

Figure 2.3 Pulsatile Pressure Changes in the Vascular Tree

Schematic representation of the pulsatile pressure change between the left ventricle and capillaries of a young subject *(left)* and an older human with arterial stiffening *(right).* In the older person, pulsations are not absorbed in the large arteries and they extend down into the microcirculation.

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2.2 Arterial stiffness and cardiovascular disease

William Osler (1898) stated over a century ago, "Longevity is a vascular question, which has been well expressed in the axiom that 'a man is only as old as his arteries.' To a majority of men death comes primarily or secondarily through this portal. The onset of what may be called physiological arterio-sclerosis depends, in the first place, upon the quality of arterial tissue (vital rubber) which the individual has inherited, and secondly upon the amount of wear and tear to which he has subjected it." Roy (1881) and Bramwell and Hill (1922) were also well aware of the progressive stiffening of arteries with age and of the adverse effects that such stiffening has on CV function.

These pioneers of vascular and cardiac physiology made their findings without BP measurements, only evaluating PWV and pulse waveform (Roy 1881, Osler 1898, Bramwell and Hill 1922). However, studies on arterial stiffening elapsed in the 1920s with the clinical acceptance of the cuff sphygmomanometer. DBP elevation was considered the only manifestation of atherosclerosis in its early stages, SBP elevation was regarded as a manifestation of cardiac strength, and arterial stiffness was dismissed as irrelevant (Nichols et al. 2011).

These views persisted for many decades and could at least partially explain the limited progress on aging, in addition to the fact that researchers have tended to promote other genetic, hormonal, and molecular tools to explain aging and its interaction with CVD (Lakatta and Levy 2003a, Lakatta and Levy 2003b, Najjar et al. 2005, Lakatta et al. 2009, North and Sinclair 2012). The "Cardiovascular Continuum", published in 2006, explained the development of coronary atherosclerosis from pre-existing risk factors to myocardial infarction, and summarized the advances made in CV medicine over three decades (Dzau et al. 2006a, Dzau et al. 2006b). The Continuum does not mention aging, not even as a risk factor for CVD (Dzau et al. 2006a, Dzau et al. 2006b).

Atherosclerosis has its predisposing risk factors, but arterial aging, i.e. arterial stiffening, is an independent process which could advance even without atherosclerosis (Avolio et al. 1985, Nichols et al. 2011). As mentioned earlier, arterial stiffening plays a much bigger role in the pathophysiology of CVD than the above-mentioned reports expected (Nichols et al. 2011). It is not possible to study only the process of atherosclerosis without arterial stiffening, because it is difficult to separate age-related changes from disease-related changes (Nichols et al. 2011). However, both atherosclerosis and arterial aging have their typical features which are contrasting. Atherosclerosis is primarily intimal, usually localized, typically causing problems by narrowing a muscular artery and limiting blood flow to the tissue or organ beyond, and it is very rare in some populations (Dzau et al. 2006a, Nichols et al. 2011). Aging-related changes are diffuse, initially and predominantly medial, dilating, causing ill effects both upstream (LV load) and downstream (microvascular damage in brain and kidney), and they are ubiquitous (Nichols et al. 2011).

The Cardiovascular Aging Continuum, introduced in 2010, showed an excellent combination of the coexistent progressions of arterial aging (as shown in Figure 2.2) and atherosclerosis (O'Rourke et al. 2010). It begins from both aging-related and CVD risk factors and finally manifests as both end-stage heart disease and end-stage microvascular diseases. It is more mechanically oriented than the Early Vascular Aging concept (Nilsson et al. 2008, Nilsson et al. 2009, Nilsson et al. 2013), and it also promotes measures of arterial stiffness (e.g. PWV) to be used as guides in CVD prognosis and therapy (O'Rourke et al. 2010, Nichols et al. 2011). With the Cardiovascular Aging Continuum concept, there is real potential to slow down the process of arterial aging and offset its inevitable adverse effects and the diseases it promotes, such as atherosclerosis (O'Rourke and Hashimoto 2007, O'Rourke et al. 2010, Nichols et al. 2011).

As a conclusion, increased arterial stiffness (and especially large artery stiffness caused by arterial aging) is not only a surrogate marker or a risk factor of atherosclerosis (Nichols et al. 2011). At the same time, atherosclerosis is a disease which may be superimposed on arterial aging (O'Rourke 2007, Nichols et al. 2011). Genetic, cellular, hormonal, and molecular mechanisms could explain much of the CVD variability among individuals of the same age (Lakatta and Levy 2003a, Lakatta and Levy 2003b), and, simultaneously, the mechanical consequences of aging apply to everyone (O'Rourke 2007, Nichols et al. 2011).

2.3 Cardiovascular risk factors and arterial stiffness

2.3.1 Elevated blood pressure

High BP increases the load on the heart and the stresses on arteries, hence accelerating CV degeneration (aging) and atherosclerosis (Benetos et al. 2002b, Lakatta and Levy 2003a, Lakatta and Levy 2003b, McEniery et al. 2005, Nichols et al. 2011). From the point of view of the large arteries, hypertension can be seen as an accelerated form of aging, and the separation of disease from aging is arbitrary, especially in the elderly (Nichols et al. 2011). There is also physical interaction between BP and arterial stiffness; elastic arteries are stiffer at higher pressures because of the increased arterial diameter (O'Rourke 1990, Laurent and Boutouyrie 2007, Nichols et al. 2011). Avolio et al. (1985) showed higher stiffness in a population with a high prevalence of hypertension compared with a population with a low prevalence of hypertension, and aortic stiffness has been demonstrated independently predict the progression to hypertension in non-hypertensive subjects (Dernellis and Panaretou 2005).

The increase in the LV external load, caused by increased aortic stiffness and elevated BP, results in decreased endothelial function and prominent neurohumoral activation with increased circulatory plasma catecholamines and renin-angiotensin-aldosterone concentrations. Through these mechanisms, a rise in arterial stiffness causes a further elevation in arterial BP, consequent on an increase in peripheral resistance and increased cardiac output from volume overload. (Safar and Benetos 2003, Zieman et al. 2005, Goldsmith et al. 2010, Kaess et al. 2012.) Arterial stiffening could also impair the activation of carotid and aortic baroreceptors because higher pressure thresholds and a more intense pressure change are required to distend the arterial wall (Mattace-Raso et al. 2007, Weisbrod et al. 2013), thus predisposing individuals to hypertension (Okada et al. 2012).

BP was the strongest independent predictor of PWV in the previously reported review (Cecelja and Chowienczyk 2009). Elevated BP is already directly associated with PWV in childhood (Avolio et al. 1983, Avolio et al. 1985, Im et al. 2007, Urbina et al. 2011), and pediatric BP predicts PWV in adulthood (Li et al. 2004). In the Atherosclerosis Risk in Young Adults Study, no association between adolescent BP and adult PWV was observed, but this controversial result could be explained by the BP measurement method (Oren et al. 2003).

As hypertension also causes the acceleration of the atherosclerotic process, it should be treated as one of the most significant risk factor for CVD (Chobanian and Alexander 1996, Wissler and Strong 1998, Smith et al. 2006, Lloyd-Jones 2010). Treatment of hypertension leads to a decrease in stiffness, since the reduction of BP unloads the stiff components of the arterial wall, leading to a passive decrease in stiffness. However, because of the greater arterial medial degeneration in hypertensive subjects, the arteries may remain stiffer than those of age-matched controls (Asmar et al. 2001, Ait-Oufella et al. 2010, Nichols et al.

2011). In the high-risk renal failure group, reduced stiffness has been associated with a better outcome than in patients without stiffness reduction (Guerin et al. 2001), but this finding remains to be established in other populations (Laurent et al. 2006). The Guidelines of the European Society of Hypertension and European Society of Cardiology for the management of arterial hypertension have accepted high PWV as evidence of asymptomatic target organ damage in the arterial circulation and as integral to the treatment of hypertension (Mancia et al. 2007, Mancia et al. 2013).

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium-channel blockers (CCBs) are recommended as anti-hypertensive agents, because by dilating muscular conduit arteries, they reduce wave reflection and thus the LV load (Nichols et al. 2008, Nichols et al. 2011). This beneficial effect has been shown in recent reports, also independently of brachial BP reduction, so it may not manifest fully in conventional recording of the pressure in the brachial artery (Williams et al. 2006, Karalliedde et al. 2008, Matsui et al. 2009, Ong et al. 2011, Shahin et al. 2012). Improved ventricular-vascular interaction could also be the mechanism explaining the improved prognosis when using these medications (Nichols et al. 2011, Mancia et al. 2013).

2.3.2 Diabetes and insulin resistance

Hyperglycemia, caused by impaired insulin secretion or insulin resistance, is now recognized as a key player in the development of atherosclerosis and its complications (Paneni et al. 2013). Prolonged exposure to hyperglycemia alters vascular homeostasis due to endothelial and smooth muscle cell (SMC) dysfunction, and favors a pro-inflammatory/thrombotic state which ultimately leads to atherothrombosis (Paneni et al. 2013). Importantly, the unfavorable effects of glucose already occur at glycemic levels below the threshold for the diagnosis of diabetes mellitus (DM) (Coutinho et al. 1999), and Sung et al. (2009) have reported a linear relationship between fasting glucose levels and CV outcomes.

A higher-than-optimum glucose concentration reduces the bioavailability of nitric oxide (NO), causes an overproduction of reactive oxygen species (ROS), and activates unfavorable biochemical pathways, e.g. the production of advanced glycation end products (AGEs) and protein kinase C (PKC) (Creager et al. 2003, Paneni et al. 2013). AGEs further increase the oxidative stress and form cross-linking of proteins to matrix components, leading to decreased elasticity (Schmidt et al. 1999, Libby and Plutzky 2002, Zieman et al. 2005, Yan et al. 2010). PKC is responsible for increased cellular permeability, inflammation, increased ROS production, angiogenesis, extracellular matrix expansion, and apoptosis (Inoguchi et al. 2000, Quagliaro et al. 2003, Geraldes and King 2010). Increased synthesis of vasoconstrictors and prostanoids further impairs endothelial function (Hink et al. 2001). Interestingly, endothelial, mesangial, and retinal cells are equipped to handle high sugar levels, further increasing the oxidative stress in these cells (Naudi et al. 2012).

All functional and structural alterations of the vessel wall, caused by disglycemia, involve both the muscular and elastic arteries (Megnien et al. 1992, Cruickshank et al. 2002, Haller et al. 2004, Urbina et al. 2010a). They predispose diabetic blood vessels to hypertensive injury (Williams 1999), and the impaired myogenic response (Schofield et al. 2002) allows pulsatile flow to extend into the smaller vessels downstream. This can cause the microvascular disease of diabetes and typical damages to the retina, brain and kidneys (Safar et al. 2003). These damages are comparable to those seen in microvascular changes caused by arterial aging (Nichols et al. 2011) and underline the importance of efficient BP reduction. Large studies have shown that a reduction of BP is the most important for

diabetic patients (Hansson et al. 1998, Yusuf et al. 2000, Dahlof et al. 2002) and even more important than improved glycemic control (Adler et al. 2000, Libby and Plutzky 2002, Gæde et al. 2003). This finding has been added on the latest published pediatric (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004) and adult (Mancia et al. 2007, Mancia et al. 2013) BP guidelines.

DM and insulin resistance are also directly linked with hypertension and arterial stiffness (Nichols et al. 2011). Hypertension appears to predispose individuals to insulin resistance and DM (Barzilay et al. 2006, Conen et al. 2007), and a major part of the complications and deaths in diabetic patients are due to arterial events (Sowers et al. 2001, Mancia 2010, Riddle 2010). The CV risk in diabetic subjects has been found to be similar to non-diabetic people of the same age who had already suffered a myocardial infarct (Haffner et al. 1998, Schramm et al. 2008). Interestingly, it has also been estimated that DM confers an equivalent risk to aging 8−15 years (Brooks et al. 1999, Ravikumar et al. 2002, Booth et al. 2006).

Many studies have shown that arterial stiffness is increased in pediatric and adult patients with either type 1 or type 2 diabetes (Woolam et al. 1962, Megnien et al. 1992, Salomaa et al. 1995, De Angelis et al. 2004, Gungor et al. 2005, Urbina et al. 2010b, Urbina et al. 2010a, Wadwa et al. 2010) and those with insulin resistance or metabolic syndrome (Lee et al. 2007, Sipilä et al. 2007, Stehouwer et al. 2008, Urbina et al. 2012, Kangas et al. 2013). Even a positive parental history of DM is associated with stiffer arteries in childhood (Riley et al. 1986) and in adulthood (Hopkins et al. 1996). Arterial stiffness, measured as aortic PWV, has been shown to be a more powerful predictor of CV risk than SBP in patients with type 2 diabetes or glucose intolerance, pointing to its value as an integrated index of vascular status (Cruickshank et al. 2002).

2.3.3 Obesity

Obesity is not just a cosmetic matter but a serious health problem and a growing epidemic. Increasing evidence indicates that obesity is a heterogeneous condition in which the accumulation of visceral (intra-abdominal) fat is closely associated with hypertension, hypercholesterolemia, hypercoagulability, platelet dysfunction, metabolic syndrome, insulin resistance, and type 2 diabetes,—and therefore with CVD risk (Sowers 2003, Berg and Scherer 2005, Mathieu et al. 2009). Visceral adipose tissue produces and secretes cytokines and factors that promote oxidative stress, systemic inflammation, vasoconstriction and thrombosis, i.e. similar metabolic disturbances as those seen in disglycemia (Berg and Scherer 2005, Perrini et al. 2008, Sowers 2013). In line with all this are the findings that weight loss and calorie restriction improve the CV risk profile (Mathieu et al. 2009, Weiss and Fontana 2011).

The strong negative impact of obesity on arterial stiffness has been investigated both in children and adolescents (Tounian et al. 2001, Miyai et al. 2009, Sakuragi et al. 2009, Urbina et al. 2010a, Harris et al. 2012, Dangardt et al. 2013) and in adults (Wildman et al. 2005, Ferreira et al. 2004, Zebekakis et al. 2005, Orr et al. 2008). Importantly, weight loss and calorie restriction were associated with favorable change in arterial stiffness (Wildman et al. 2005, Blumenthal et al. 2010, Gregory et al. 2011, Weiss and Fontana 2011), and a similar effect has been reported in patients who underwent bariatric surgery (Ikonomidis et al. 2007). Those favorable effects were not associated with the type of diet used (Keogh et al. 2008, Wycherley et al. 2010), and the reduction in arterial stiffness could be independent of BP changes (Wildman et al. 2005).

2.3.4 Lipid risk factors

Dyslipidemias—i.e. high total cholesterol levels, high low-density lipoprotein (LDL) cholesterol levels, high triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels—are the key players in the atherosclerotic process. They promote inflammation, oxidative stress, endothelial dysfunction, and plaque formation. Statin therapy has reduced LDL cholesterol levels efficiently, every 1.0 mmol/L reduction in LDL cholesterol associating with a corresponding 22% reduction in CVD mortality and morbidity. However, low HDL and high triglyceride levels have been recognized as remarkable risk factors, especially when associated with visceral obesity and insulin resistance. (Dzau et al. 2006a, Douglas and Channon 2010, Blankstein et al. 2011, Reiner et al. 2011, Welty 2013.)

Patients with familial hypercholesterolemia have been demonstrated to have significantly increased aortic stiffness when compared to age-matched normolipidemic siblings despite similar aortic dimensions (Pitsavos et al. 1998). Aortic PWV has also been found to be higher in patients with hypercholesterolemia than age-matched controls, despite similar peripheral BP levels (Wilkinson et al. 2002). Low HDL cholesterol has been related with increased arterial stiffness in childhood (Li et al. 2004) and in adulthood (Li et al. 2004, Wang et al. 2011, van den Bogaard et al. 2012, Zhao et al. 2012), and high LDL and triglyceride levels have been reported to predict increased arterial stiffness both in childhood and in adulthood (Li et al. 2004, Wang et al. 2011, Protopsaltis et al. 2012, Urbina et al. 2013). Additionally, statin therapy has been reported to lower elastic artery stiffness (Muramatsu et al. 1997, Ferrier et al. 2002).

2.3.5 Smoking

Smoking is an independent major risk factor for CVD, and the evidence infers a causal relationship between smoking and CVD. Smoking leads to endothelial injury and dysfunction, inflammation, platelet activation, sympathetic activation, a modification of the lipid profile, and a reduction in the ability of the blood to carry oxygen (The Health Consequences of Smoking: A Report of the Surgeon General. 2004, Ambrose and Barua 2004). Passive smoking is as dangerous as active smoking (Barnoya and Glantz 2005, Raupach et al. 2006), so smoke-free environments are important. This is supported by the reductions in CVD outcomes after both short-term and long-term banning of smoking in public places and workplaces (Sargent et al. 2004, Lightwood and Glantz 2009, Meyers et al. 2009).

Smoking has acute and chronic unfavorable effects on arterial stiffness in habitual smokers (Stefanadis et al. 1997, Mahmud and Feely 2003, Vlachopoulos et al. 2004), non-smokers, and passive smokers (Stefanadis et al. 1998, Mahmud and Feely 2003, Barnoya and Glantz 2005, Raupach et al. 2006). Similar effects have also been reported for hypertensive subjects (Rhee et al. 2007). The acute increase, 0.8 $\pm$ 0.3 m/s (mean$\pm$SD), in arterial stiffness lasts roughly one hour after smoking one cigarette, and, interestingly, smoking and coffee consumption have a synergistic unfavorable effect (Vlachopoulos et al. 2004). Smoking increases arterial stiffness chronically and even small quantities of smoking are able to produce deleterious effects (Vlachopoulos et al. 2004, Rehill et al. 2006, Jatoi et al. 2007).

Smoking is also associated with an elevated risk of developing hypertension (Primatesta et al. 2001, Bowman et al. 2007) and even increased BP after smoking cessation (Lee et al. 2001, Janzon et al. 2004). Smoking increases BP directly and thus affects arterial stiffness,

but nicotine-dependent impairment of microvascular function and reduced bioavailability of NO have also been reported (Stefanadis et al. 1997, Argacha et al. 2008, Adamopoulos et al. 2009). Smoking cessation is associated with a significant improvement in arterial stiffness parameters, although PWV may take even a decade to normalize (Rehill et al. 2006, Jatoi et al. 2007, Takami and Saito 2011, Yu-Jie et al. 2013).

2.3.6 Physical inactivity

A sedentary lifestyle is one of the major risk factors for CVD (Apullan et al. 2008, Warren et al. 2010). Regular physical activity and aerobic exercise training are related to a reduced risk of CV events in healthy individuals and cardiac patients over a wide age range (Piepoli et al. 2004, Richardson et al. 2004, Taylor et al. 2004, Nocon et al. 2008, Samitz et al. 2011). Hence, they are suggested by guidelines as very important non-pharmacological tools for CV prevention (Balady et al. 2007, Perk et al. 2012). The beneficial vascular effects of regular physical activity could be explained by improved endothelial function, increased smooth muscle relaxation, reduced arterial pressure, reduced wave reflection, and improved ventricular-vascular interaction (DeSouza et al. 2000, Tanaka et al. 2000, McGuire et al. 2001a, McGuire et al. 2001b).

Previous reports have also clearly shown a beneficial relationship between regular physical activity and arterial stiffness. This relationship has been demonstrated to apply to both sexes, both children and adults, and both the general population and subjects with CVD risk factors or even CVD itself (Vaitkevicius et al. 1993, Tanaka et al. 1998, Ferreira et al. 2002, Mackey et al. 2002, Tall 2002, Boreham et al. 2004, Ferreira et al. 2006, Kozakova et al. 2007, Farpour-Lambert et al. 2009, Ruiz et al. 2009, Sakuragi et al. 2009, Yamamoto et al. 2009, Gando et al. 2010, Edwards et al. 2012). There are also reports showing dose-dependent effects: the more exercise, the less stiff arteries (Tanaka et al. 2000, Otsuki et al. 2007). It should also be kept in mind that subjects whose arteries are compliant and elastic to begin with can exercise more easily, which could underestimate the relationship between exercise and arterial stiffness in large cohorts (Nichols et al. 2011).

Aerobic training has been shown to reduce both arterial stiffness and wave reflection (Vaitkevicius et al. 1993, Tanaka et al. 1998, Tanaka et al. 2000, Kingwell 2002), while resistance training increases stiffness, BP, and LV load (Miyachi et al. 2004, DeVan et al. 2005). However, recent studies have demonstrated that progressive and low-intensity resistance training (Okamoto et al. 2008), or a combination of aerobic and resistance training (Stewart et al. 2005, Loimaala et al. 2009), seems to have no adverse effect on arterial stiffness.

Exercise capacity declines with age, and arterial stiffening (aging) accelerates it by increasing the LV load (Hundley et al. 2001, Nichols et al. 2011). However, it is possible to achieve improvements in exercise capacity and ventricular-vascular interaction in older age (Chen et al. 1999, McGuire et al. 2001a, McGuire et al. 2001b, Ferrier et al. 2001, Gando et al. 2010). Regular exercise is also often a marker of better control of other CVD risk factors (Nichols et al. 2011), but not even a marathon runner could be completely safe from CVD (Möhlenkamp et al. 2008, Kroger et al. 2011).

2.3.7 Dietary habits

Overwhelming evidence suggests that dietary factors have a significant impact on CVD risk independently or through an effect on risk factors such as lipids, BP, body weight, and DM

(Ness and Powles 1997, Bazzano et al. 2003, Knoops et al. 2004, Ignarro et al. 2007, Bamia et al. 2007, Trichopoulou et al. 2007). Recent published articles have been focusing on dietary patterns instead of single nutrients, similarly to than the shift from evaluating single risk factors to evaluating a person's overall total risk profile. Dietary patterns could better show the full preventive potential of diet (Perk et al. 2012). As an example of this, a meta-analysis has demonstrated the protective effect of the Mediterranean diet, i.e. high intake of fruits, vegetables, legumes, wholegrain products, fish, and unsaturated fatty acids (especially olive oil), a moderate consumption of alcohol (mostly wine, preferably consumed with meals), and a low consumption of (red) meat, dairy products, and saturated fatty acids (Sofi et al. 2010).

Studies concerning the relations between arterial stiffness and dietary habits are scarce. However, increasing evidence shows that a high intake of plant-derived isoflavones, phytoestrogens, and polyphenols reduces arterial stiffness (van der Schouw et al. 2002, Teede et al. 2003, Corti et al. 2009, Pase et al. 2011, Curtis et al. 2013). Habitual cocoa consumption has also been shown to be inversely associated with arterial stiffness and this effect could not be observed when only peripheral BP was measured (Vlachopoulos et al. 2007). Avolio et al. (1985) reported that PWV was clearly lower in the population with a lower salt intake. Sodium restriction is also associated with lower arterial stiffness both in diabetic (Lambert et al. 1997) and hypertensive subjects (Seals et al. 2001, Gates et al. 2004). In addition, the Dietary Approaches to Stop Hypertension diet (rich in fruits, vegetables, whole grains, and low-fat dairy foods; includes meat, fish, poultry, nuts and beans; and is limited in sugar-sweetened foods and beverages, red meat, and added fats) has been shown to decrease PWV (Blumenthal et al. 2010). Moderate alcohol consumption has been associated with lower PWV in both sexes (Mahmud and Feely 2002, Sierksma et al. 2004b, Sierksma et al. 2004a), but higher daily alcohol consumption has been associated with increased PWV (Nakanishi et al. 2001, Mahmud and Feely 2002).

2.3.8 Other risk factors

The associations between elevated c-reactive protein (CRP), as a marker of inflammation, and CVD are slightly controversial (De Buyzere and Rietzschel 2006), but elevated CRP has been reported to be associated with arterial stiffness in a general population (Nagano et al. 2005) and in hypertensive subjects (Kim et al. 2007). However, arterial aging (increasing stiffness) causes microvascular damage in the brain and kidneys. It could be possible that elevated CRP is a marker of ongoing damage and repair of the microcirculation, and not a marker of inflammation in atherosclerotic lesions (Hashimoto and O'Rourke 2006).

Sex-related differences in all ethnicities have been observed for many CV parameters, which could at least partly be explained on the basis of bodily habitus (females as a group are shorter than males and weigh less) (Skurnick et al. 2010, Nichols et al. 2011). Sex also affects PWV. Female subjects have slightly higher PWV values in the prepubertal years when female sex steroids are low (Ahimastos et al. 2003). During the reproductive years, no correlation has been reported between PWV and sex hormone concentrations, PWV and the menstrual cycle, or even PWV and pregnancy (Williams et al. 2001, Robb et al. 2009). In menopause, PWV increases sharply in females compared to males in respective years (Staessen et al. 2001, Koivistoinen et al. 2007), but large population studies have shown no clear difference between the sexes in this respect (The Reference Values for Arterial Stiffness' Collaboration 2010).

2.4 The concept of Ideal Cardiovascular Health

In January 2010, the AHA defined its 2020 Impact Goals as follows: "By 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%" (Lloyd-Jones et al. 2010). These Impact Goals changed the focus from primary prevention of CVD to primordial prevention, i.e. to preventing whole societies from experiencing epidemics of the risk factors (Lloyd-Jones et al. 2010). The two other key concepts of this prevention were the evidence that CVD and its risk factors often develop in childhood, and that there should be an appropriate balance between population-level health promotion and individualized high-risk approaches (Lloyd-Jones et al. 2010). It is no longer effective enough to focus the efforts on individuals at risk, but we must rather seek to prevent the development of risk factors at the population level (Lloyd-Jones et al. 2010).

To improve the primordial prevention of CVD, the AHA defined the concept of Ideal Cardiovascular Health and the metrics needed to monitor it over time: the simultaneous presence of 4 ideal health behaviors (never smoked or quit >12 months ago in adults and never tried or never smoked a whole cigarette in children; BMI <25 kg/m2 in adults and <85th percentile in children; physical activity at goal levels; and diet consistent with current guideline recommendations) and 3 ideal health factors (untreated total cholesterol <5.17 mmol/l in adults and <4.40 mmol/l in children; untreated BP <120/80 mm Hg in adults and <90th percentile in children; and untreated fasting plasma glucose <5.6 mmol/l both in adults and in children). (Lloyd-Jones et al. 2010.)

This concept has been shown to predict lower CVD risk and mortality of all causes (Folsom et al. 2011, Ford et al. 2012, Liu et al. 2012), also among different ethnic groups (Dong et al. 2012). However, the prevalence of Ideal Cardiovascular Health has been extremely low in adolescence (Laitinen et al. 2012, Pahkala et al. 2013, Shay et al. 2013) and in adulthood (Bambs et al. 2011, Folsom et al. 2011, Shay et al. 2012). Moreover, Huffman et al. (2012) reported that the changes in health behaviors and factors were quite far from the AHA 2020 Impact Goals.

The prevalence of Ideal Cardiovascular Health appears to be low in adolescence and adulthood, as mentioned above, so a large proportion of individuals would likely benefit from changing their profile towards the ideal. However, reports concerning the relationship between a change in Ideal Cardiovascular Health and CV outcomes are sparse. The effect of the change is interesting because all components of Ideal Cardiovascular Health are modifiable, particularly through lifestyle adjustments.

2.5 Measurement of arterial stiffness

The elastic properties of conduit arteries vary along the arterial tree: proximal arteries are more elastic and distal arteries stiffer, because of differences in the molecular, cellular, and histological structure of the arterial wall (Latham et al. 1985, Laurent et al. 2005, Nichols et al. 2011). No single arterial segment has identical viscoelastic properties, so it is not possible to extrapolate segmental arterial properties to the whole arterial tree (Nichols et al. 2011). Notably, the thoracic and abdominal aorta make the largest contribution to the arterial cushioning function (Latham et al. 1985, Nichols et al. 2011), and as mentioned in section 2.1, age-related changes are most marked in the aorta and clearly less marked in the peripheral muscular arteries (Avolio et al. 1983, Avolio et al. 1985, Lakatta 2000, Nichols et al. 2011). Therefore, arterial stiffness measured along the aortic and aorto-iliac pathway is the most clinically relevant, and increased stiffness in this pathway is responsible for most

of the pathophysiological effects (Laurent et al. 2006, Nichols et al. 2011). However, all arterial sites have their own potential interest: the forearm circulation because of the standard BP measurement techniques, the lower limb arteries because they are specifically altered by atherosclerosis, and the carotid artery as a frequent site of atheroma formation (Laurent et al. 2006).

2.5.1 Pulse wave velocity

The LV ejection generates pressure and flow waves, which travel along the wall of the arterial tree. Since fluid in the arteries is incompressible, energy propagation occurs predominantly along the arterial wall, and arterial wall stiffness is the major determinant of the velocity of the wave. This velocity is also related to direct measurements of arterial elastic modulus—the stiffer the artery, the higher the velocity (Nichols et al. 2011). There are different ways to measure PWV, but the gold standard PWV is measured using waveforms obtained at the right common carotid artery and at the right femoral artery (i.e. carotid-femoral PWV) (Laurent et al. 2006). Between these two sites, the pulse wave has to travel through the aorta, which is the clinically most relevant, as mentioned earlier (Laurent et al. 2006, Nichols et al. 2011, Van Bortel et al. 2012).

The distance (D) between the two recording sites is usually measured over the body and should be measured precisely, because even small inaccuracies may influence the absolute value of PWV (Laurent et al. 2006). It is well known that a measured distance is not the same as the real traveled distance due to, for example, abdominal obesity particularly in men, large bust size in women, and age-dependent aortic elongation (Laurent et al. 2006, Nichols et al. 2011). The last published expert consensus advises the use of the simple 80% of the direct carotid−femoral (common carotid artery−common femoral artery×0.8) tape or caliper measure distance as standard for daily practice, because age adjustment did not perform better in the elderly, the adjusted formula is difficult to use in daily practice, and the age-dependent elongation of the aortic path length is limited (Sugawara et al. 2008, Van Bortel et al. 2012). This recommended measurement allows the use of previously published normal and reference values directly without any conversion (The Reference Values for Arterial Stiffness' Collaboration 2010).

The most commonly used method for estimating pulse wave transit time between two recording sites is the foot-to-foot method. The foot of the pulse wave is defined at the end of diastole, when the steep rise of the wavefront begins. The pulse wave is obtained either by simultaneous measurement, or by gating to the peak of the R-wave of the electrocardiography (ECG). The time delay (Δt) is measured between the arrival of the foot at these two recording sites. (Laurent et al. 2006, Van Bortel et al. 2012) PWV is then calculated as,

$$PWV = D\ (\text{meters}) / \Delta t\ (\text{seconds}).$$

PWV could be assessed by using different methods including pressure measurements (Kelly et al. 1989, Asmar et al. 1995), distension measurements (van der Heijden-Spek et al. 2000), Doppler ultrasound (Cruickshank et al. 2002), and electrical impedance (Kööbi et al. 2003), but also with the aid of MRI (Nelson et al. 2009, Redheuil et al. 2010). MRI has the potential advantage of a more accurate determination of path length, but the poor availability and relatively high cost per measurement restrict its use in clinical studies (Nelson et al. 2009, Redheuil et al. 2010, Nichols et al. 2011). Japanese researchers, especially, have used brachial−ankle PWV and showed that it provides qualitatively similar

information as carotid–femoral PWV (Yamashina et al. 2002, Sugawara et al. 2005). When comparing two populations or pooling data for meta-analyses, differences in the methods used to assess the path length are critically important, but in intervention studies with repeated measures, differences are unimportant (Laurent et al. 2006).

PWV measurement is influenced by all factors influencing BP, and several recommendations on user procedures have been given to get CV function and vasomotor tone as close to basal resting conditions as possible (Van Bortel et al. 2002, Laurent et al. 2006, Ahuja et al. 2009, Papaioannou et al. 2012). Measurements should be performed in a quiet room with a stable room temperature and in the supine position after at least 10 min of rest. Repeated measurements should be taken at the same time of the day because of diurnal variations. No meal, caffeine, or smoking is allowed within 3 hours before measurement, and speaking or sleeping is not allowed during measurements. The recorded data should be the mean of registrations during at least one respiratory cycle, i.e. approximately 5–6 s. A white coat effect is possible and should be born in mind. The distance between the recording points should be measured in a straight line with a tape measure or a caliper. At least two repeated measurements should be taken, and if the difference is more than 0.5 m/s, it is recommended to take a third measurement and then use the median value. Subjects having arrhythmia, an unstable clinical situation, or high-grade stenosis of the carotid artery should be excluded.

Aortic PWV is an independent predictor of CVD outcomes in a large variety of populations (Blacher et al. 1999a, Blacher et al. 1999b, Asmar et al. 2001, Laurent et al. 2001, Meaume et al. 2001, Shoji et al. 2001, Boutouyrie et al. 2002, Cruickshank et al. 2002, Lebrun et al. 2002, Laurent et al. 2003, Pannier et al. 2005, Shokawa et al. 2005, Sutton-Tyrrell et al. 2005, Mattace-Raso et al. 2006, Willum Hansen et al. 2006, DeLoach and Townsend 2008, Yu et al. 2008, Mitchell 2009a, Mitchell 2009b, McEniery et al. 2010a, McEniery et al. 2010b, Mitchell et al. 2010, Tsuchikura et al. 2010a, Vlachopoulos et al. 2010b). CVD risk stratification using aortic PWV is also better than traditional risk factors, including SCORE and the Framingham risk score, and patients at an intermediate risk could be reclassified into higher or lower CV risk when PWV is measured (Mitchell et al. 2010, Sehestedt et al. 2010, Sehestedt et al. 2012). PWV can be easily measured in childhood and adolescence, and the PWV in adolescence is also associated with CVD risk factors (Niboshi et al. 2006, Im et al. 2007, Collins et al. 2008).

2.5.2 Other measurements

Aortic stiffness could also be estimated using central pulse wave analysis by applanation tonometry, directly recorded at the carotid artery or computed from the radial artery waveform using a transfer function (Chen et al. 1996, Chen et al. 1997). The pulse wave should be analyzed through three major parameters: augmentation index (AIx: defined as the difference between the second and first systolic pulse wave peaks and expressed as a percentage of the PP), central PP, and central SBP (Laurent et al. 2006). AIx is a relative measurement and can be calculated without calibration, but central PP and central SBP are absolute values and require calibration according to methods reported previously (Kelly and Fitchett 1992, Van Bortel et al. 2001, Van Bortel et al. 2002), which is why they require clearly more technical expertise than PWV measurements (Laurent et al. 2006).

There is also a clear sex-related difference in wave reflection indices, women having higher indices. These could be explained by shorter body stature (closer reflecting site) (McEniery et al. 2005, Lieber et al. 2010), and differences in the magnitude of the reflected wave depending on vasomotor tone influenced by sex hormones (Smulyan et al. 2001) and

aortic tapering (Cecelja et al. 2009). The faster heart rate in women could partly compensate for these factors and the reflected wave return closer to diastole (Nichols et al. 2011), but significant sex-related differences remain after adjustment for heart rate (Lieber et al. 2010).

Central PP and AIx have demonstrated their predictive value for future clinical events in different patient groups (London et al. 2001, Safar et al. 2002, Weber et al. 2005, Williams et al. 2006, Vlachopoulos et al. 2010a), therefore having the potential to be implemented in clinical practice. Williams et al. (2006) also reported that a higher treatment-related decrease in central PP that was not evident in brachial BP was independently associated with a decreased risk of CV events. However, further evidence is needed before any implementation in clinical practice can occur (Vlachopoulos 2012).

Local, especially carotid artery, stiffness may be of particular interest, since in that artery, atheroma formation is frequent. Local arterial stiffness (and also thickness) could be measured by ultrasound and calculated as the ratio of PP to the relative change in artery diameter, i.e. carotid artery distensibility, carotid artery compliance, and carotid Young's elastic modulus (Laurent et al. 2006). However, this measurement could be overestimated if brachial PP is used in the calculations instead of central PP due to PP amplification between central and peripheral arteries, and it is recommended to calculate local arterial stiffness from (preferentially simultaneous) measurements of stroke changes in diameter and local PP (Laurent et al. 2006, Nichols et al. 2011). Local measurements of arterial stiffness are suitable for analyses in pathophysiology, pharmacology, and therapeutics, rather than for epidemiological studies (Laurent et al. 2006) because the aorta stiffens more than the carotid artery in patients with CV risk factors such as hypertension or DM (Paini et al. 2006).

3. AIMS OF THE STUDY

Aortic stiffening is the principal cause of CVD and exposure to risk factors accelerates it. Arterial stiffness assessed as PWV is generally accepted as an independent predictor of CV events and all-cause mortality. The importance of maintaining a favorable risk profile from childhood to adulthood, and preventing, if possible, the development of risk factors, is well known. In 2010, the AHA defined the concept of Ideal Cardiovascular Health to improve the primordial prevention of CVD. This concept has been shown to predict lower CVD risk and mortality of all causes, although the prevalence of Ideal Cardiovascular Health has been extremely low in adolescence and adulthood. In addition to this, there are only few reports concerning the relationship between lifetime traditional or lifestyle CVD risk factors and PWV. Reports concerning the relationship between a change in Ideal Cardiovascular Health and CV outcomes are also sparse

The present study elucidated the associations of traditional and lifestyle risk factors measured in childhood and adulthood with PWV assessed in adulthood. Risk factors were used as continuous variables and as classified according to the concept of Ideal Cardiovascular Health defined by the AHA. Moreover, BP in childhood was defined as normal or elevated according to the three different definitions. The specific aims of the present thesis are as follows:

1. To evaluate the associations of lifetime traditional CVD risk factors (HDL cholesterol, LDL cholesterol, triglycerides, SBP, BMI, skinfold thickness in childhood, glucose, insulin, CRP, and smoking) with PWV in adulthood (original publication I).
2. To study whether elevated pediatric BP could predict high PWV in adulthood and if there is a difference in the predictive ability between the standard BP definition endorsed by the National High Blood Pressure Education Program (NHBPEP) and the recently proposed two simplified definitions (original publication III).
3. To evaluate the associations of lifetime lifestyle CVD risk factors (vegetable consumption, fruit consumption, butter use in childhood, alcohol consumption in adulthood, smoking, and physical activity) with PWV in adulthood (original publication II).
4. To investigate the relationship of the Ideal Cardiovascular Health index defined by the AHA and PWV—and the change in the index (both from childhood to adulthood and from young adulthood to middle age) and PWV in particular (original publication IV).

4. SUBJECTS AND METHODS

4.1 Subjects

The population studied in this thesis is from the Cardiovascular Risk in Young Finns Study. It is one of the largest follow-up studies of CV risk from childhood to adulthood. At the beginning of the study, a total of 4,320 children and adolescents aged 3, 6, 9, 12, 15, and 18 years were randomly chosen from the Finnish national population register to get a sample which would represent Finnish children and adolescents reasonably well. (Åkerblom et al. 1985) In practice, boys and girls of each age cohort in each study community (5 university cities in Finland with medical schools and 12 rural communities in their vicinity) were placed separately in random order on the basis of their unique personal identification number. Every *k*th girl and every *k*th boy in each community was selected so that the sample consisted of the required number of boys and girls. The varying *k* factors were determined on the basis of sample size and the total number of boys and girls in the different age cohorts in each community. Out of those invited, 3,596 participated in the first cross-sectional study in 1980 (Figure 4.1). Follow-up studies with a physical examination and blood sampling were conducted in 1983, 1986, 2001, and 2007, with 2,991 (83.2%), 2,779 (77.3%), 2,283 (63.5%), and 2,204 (61.3%) participants, respectively. PWV measurements were carried out in 2007, and 1,872 (52.1%) participants (aged 30−45 years) attended. During the follow-up, 76 participants have died; 2 of these deaths were due to atherosclerotic disease.

The subjects with incomplete risk factor data, those with type 1 or type 2 diabetes, and those female subjects who were pregnant were excluded. In studies I and II, subjects using antihypertensive or cholesterol-lowering medication were also excluded. In Study III, subjects aged 3 years in 1980 (n=577) were not included in the analyses because BP measures were collected using an ultrasound method, and adolescents aged 18 years in 1980 (n=537) were not included because the BP cut-off points are identical for all three BP definitions and equate to those used in adults. Therefore, a total of 1,241 subjects aged 6−15 years in 1980 were included in Study III. In Study IV, we chose the year 1986 as the baseline because it was the first follow-up at which fasting plasma glucose values were measured. We also divided the study cohort into two subgroups: younger subjects (aged 9–18 years in 1986, n=803) to study the change in risk factor status from childhood to young adulthood, and older subjects (aged 21–24 years in 1986, n=340) to study the change in risk factor status from young adulthood to middle age. All participants gave a written informed consent, and the study was approved by the local ethics committees.

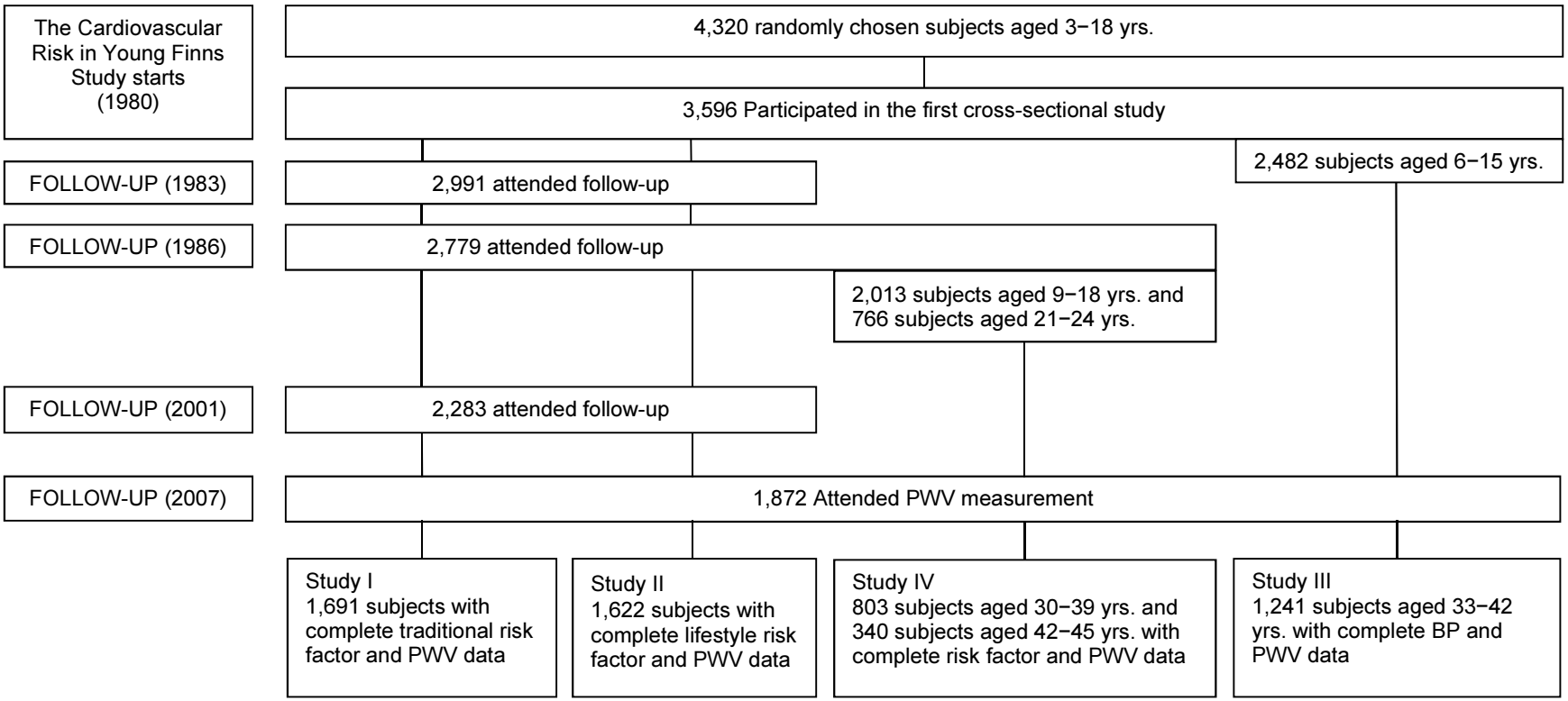

Figure 4.1 Flow Chart of Studies I−IV.

PWV = pulse wave velocity, BP = blood pressure.

4.2 Methods

4.2.1 Physical examination and questionnaires

At the baseline and follow-ups, weight was measured in light clothing without shoes with an accuracy of 0.1 kg, and height was measured with the accuracy of 0.5 cm. BMI was calculated from the measured weight and height using the formula, BMI=weight (kg)/[height (m)]^2. Skinfold thickness (in 1980, 1983, and 1986) was measured by Harpenden calipers (Holtain and Bull-British Indicators instruments) to the accuracy of 0.2 mm readings. The combined thickness of 3 skinfold measurements (subscapular, triceps, and biceps) was used in the analysis.

BP was measured from the right brachial artery after the participant had been seated for 5 minutes. The cuff size was chosen according to arm circumference. In 1980, BP was measured with a standard mercury sphygmomanometer. In 3-years-olds, BP was measured with an ultrasound device. At the follow-ups, BP measurements were taken with a random zero sphygmomanometer (Hawksley & Sons Ltd, Lansing, United Kingdom). SBP was recorded for Korotkoff's first phase. DBP was recorded at both Korotkoff's fourth and fifth phases. Korotkoff's fifth phase results have been used in the analyses because in 1980, DBP was better achieved with Korotkoff's fifth phase (no missing values in this study population) than with Korotkoff's fourth phase (absent in 2.5% of subjects). This was consistent with results reported previously (Uhari et al. 1991). Readings to the nearest integer of millimeters of mercury were performed 3 times on each participant. The mean of these 3 measurements was used in the analyses.

Questionnaires using self-reports were completed to collect data on smoking, physical activity, dietary habits, and alcohol consumption (in adulthood). For subjects aged 3−9 years, the information was requested from the parents. At the age of 12−18 years, study subjects answered the questions themselves, assisted by their parents when necessary.

In childhood, smoking was assessed in subjects aged ≥12 years. Smoking data were collected in connection with the medical examination in a secluded room where participants could respond confidentially and undisturbed. Smoking was modeled as a dichotomous variable (smoking or non-smoking). Smoking was defined as regular cigarette smoking on a weekly basis or more often (Study I) or on a daily basis (Study II) in adolescence and in adulthood.

Physical activity was assessed by a self-report questionnaire. In childhood, these data were gathered at the age of 9−18 years so that study subjects answered the questions themselves, with the parents' assistance as necessary. The questions concerned the frequency and intensity of leisure time physical activity, participation in sports club training, participation in sports competitions, and habitual ways of spending leisure time. In adulthood, the physical activity questionnaire consisted of the following variables: intensity of physical activity, frequency of vigorous physical activity, hours spent on vigorous physical activity, average duration of a physical activity session, and participation in organized physical activity. A physical activity index (range, 5−15) was calculated by summing these variables. The lowest scores indicate passive subjects, and the highest scores indicate active subjects (Telama et al. 2005).

Information on dietary habits was obtained with a non-quantitative food frequency questionnaire. To examine the frequency of fruit and vegetable consumption, 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. In Study II, the response categories were converted into times of consumption per month (1→35; 2→25; 3→10; 4→4; 5→2; 6→0). In 2007, a more detailed quantitative food frequency questionnaire providing an estimate of food consumption in grams per day was introduced. Subjects were also asked whether they use butter or butter-based spreads on bread. Habitual use of butter or butter-based spread on bread was defined as a risk factor. The dietary variables chosen for this analysis are indicators of 2 major dietary patterns, health-conscious and traditional, identified in this study population (Mikkilä et al. 2005). The health-conscious pattern correlated positively with fruit and vegetable consumption, and this pattern was more predominant among female subjects (Mikkilä et al. 2005). Dietary patterns remained stable from childhood to adulthood (Spearman correlation, r=0.32 for traditional and r=0.38 for health conscious) and especially among older subjects (Mikkilä et al. 2005). These patterns were also associated with CV risk factors (Mikkilä et al. 2007).

In 2001 and 2007, participants were asked to report their consumption of 0.33 l cans or bottles of beer, glasses (12 cl) of wine, and 4 cl shots of liquor or spirits during the past week. These doses are comparable to ≈14 g of alcohol (=1 U). The values of different beverages consumed during the past week were summed to determine the total alcohol consumption. The distribution of the continuous alcohol consumption variable was strongly skewed and could not be normalized with logarithmic transformation. Therefore, the variable was categorized. The categorization of the participants according to daily ethanol consumption (average amount through the week) was performed as follows: (1) no alcohol consumption during the last week, (2) >0 to <2 U of alcohol per day, (3) 2 to <4 U of alcohol per day, and (4) ≥4 U of alcohol per day.

4.2.2 Blood collection and analyses

Venous blood samples were drawn from the right antecubital vein of recumbent subjects after a 12-hour fast. If the sampling from the right arm failed the left antecubital vein was used alternatively. All assays were done in the same laboratory.

Serum total cholesterol concentrations were measured using an enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) in 1980, 1983, and 1986, and the enzymatic cholesterol esterase–cholesterol oxidase method (Olympus Diagnostica GmbH, Hamburg, Germany) in 2001 and 2007. Serum HDL cholesterol concentrations were measured from the supernatant after the precipitation of very low density lipoprotein cholesterol and LDL cholesterol (Kostner 1976). Serum triglycerides were determined enzymatically both in 1980, 1983, and 1986 (Boehringer Mannheim) and in 2001 and 2007 (Olympus Diagnostica GmbH). The concentration of LDL cholesterol was calculated by using the Friedewald formula (Friedewald et al. 1972).

Fasting plasma glucose concentrations (only in 1986, 2001, and 2007) were analyzed enzymatically (Olympus Diagnostica GmbH). Serum insulin was measured with a modification of the immunoassay method (Herbert et al. 1965, Juonala et al. 2005) in 1980, 1983, and 1986, and with a microparticle enzyme immunoassay kit (Abbott Laboratories, Abbott Park, USA) in 2001 and 2007.

Childhood (only in 1980) CRP was analyzed by a latex turbidimetric immunoassay (Wako Chemicals GmbH, Neuss, Germany) in 2005 from serum samples that were taken in 1980 and stored at −20°C. During the storage, the samples were not thawed or refrozen. Adulthood CRP concentrations were analyzed by the same method (Wako Chemicals GmbH) in 2001 and 2007. The lower detection limit reported for the assay was 0.06 mg/l.

Due to changes in the determination methods and reagents during the study years, specific quality control and correction factor equations for total cholesterol, HDL cholesterol, triglycerides, glucose, and insulin have been published previously (Porkka et al. 1997, Juonala et al. 2004, Juonala et al. 2006, Raiko et al. 2009).

4.2.3 Definition of elevated blood pressure levels in childhood

In Study III, participants aged 6−15 years in 1980 were classified to have normal or elevated BP according to three different definitions.

Simple 1 definition: Participants were defined according to age-specific (increments of 3 years) cut-off points proposed by Mitchell et al. (2011). The cut-off points are near the lowest pre-hypertensive (≥90th percentile) BP value in the NHBPEP tables and are set to end in 0 or 5.

Simple 2 definition: Participants were defined according to age- and sex-specific BP cut-off points proposed by Kaelber and Pickett (2009). The cut-off points correspond to the lower limit of height (5th percentile) in the pre-hypertensive BP range (≥90th percentile) for a given age and sex in the NHBPEP tables.

Complex definition: Participants were defined according to age, sex, and height percentiles for pre-hypertensive youth BP issued by the NHBPEP (2004).

4.2.4 Definition of Cardiovascular Health Status

In Study IV (baseline 1986), the AHA definition (Lloyd-Jones et al. 2010) for health behaviors and factors were followed as closely as possible.

Subjects aged 12–18 years in 1986 who reported having never smoked a whole cigarette were categorized as having an ideal childhood smoking status and those who had smoked 1 or more cigarettes as having a poor smoking status. Subjects aged <12 years were categorized as having an ideal child smoking status. Subjects aged 21–24 years in 1986 and all subjects in 2007 were classified as current smokers (poor), former smokers <12 months (intermediate), and never smokers or as having quit smoking >12 months ago (ideal).

BMI was classified as ideal (<85th percentile in children and <25 kg/m^2 in adults), intermediate (85th−90th percentile in children and 25−29.9 kg/m^2 in adults), or poor (>90th percentile in children and ≥30 kg/m^2 in adults).

The ideal physical activity for subjects aged 9−18 years was approximated as ≥7 hours of moderate or vigorous activity per week, and for adults as ≥1 h/wk vigorous intensity, ≥2−3 h/wk moderate intensity, or ≥2−3 h/wk moderate plus vigorous activity. Intermediate physical activity was classified as falling below these limits but exceeding none (poor).

In 1986, information on dietary habits was obtained with a non-quantitative food frequency questionnaire. Subjects answered the questions themselves, assisted by their parents when necessary. To examine the frequency of the 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 the following 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. We classified the subjects as having an ideal fruit and vegetable consumption profile 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 an ideal fish consumption profile. Subjects

who consumed soft drinks a couple of times per week or less frequently were classified as having an ideal soft drink consumption profile. Subjects who had 2−3 of these 3 ideal diet components were categorized as having an ideal healthy diet score, subjects with 1 component as an intermediate, and subjects with 0 components as having a poor healthy diet score in 1986. Although the quantitative amounts of fruits and vegetables, fish, and soft drinks consumed could not be inferred nor the AHA-recommended intakes of sodium and fiber-rich whole grain measured, the questionnaire provided approximations of a healthy diet score. In 2007, a more detailed quantitative food frequency questionnaire providing an estimate of food consumption in grams per day was introduced. Intake goals defined by the AHA are expressed for a 2000-kcal diet (Lloyd-Jones et al. 2010), so we first scaled the intake goals according to the subjects' total energy intake. We then categorized the achievement of the 5 AHA ideal dietary goals: ≥4.5 cups per day of fruits and vegetables (approximated as 450 g/d), ≥two 3.5-oz servings per week of fish (approximated as 28.4 g/d), ≥three 1-oz servings per day of whole grains (approximated as 85.0 g/d), <1500 mg/d of sodium, and ≤450 kcal of sugar-sweetened beverages per week (approximated as 141.8 g/d). Subjects who scored 4 or 5 out of these 5 ideal diet components were categorized as having an ideal healthy diet score, subjects who scored 2 or 3 as having an intermediate, and those with 0 or 1 component as having a poor healthy diet score in 2007.

Total cholesterol was classified as ideal (<4.40 mmol/l in children and <5.17 mmol/l in adults), intermediate (4.40−5.16 mmol/l in children, and 5.17−6.20 mmol/l or treated to goal in adults), and poor (≥5.17 mmol/l in children and ≥6.21 mmol/l in adults).

BP was classified as ideal (<90th percentile in children, and <120/<80 mmHg in adults), intermediate (90th−95th percentile in children, and SBP 120−139 or DBP 80−89 mmHg or treated to goal in adults), or poor (>95th percentile in children, and SBP ≥140 or DBP ≥90 mmHg in adults).

Fasting plasma glucose was classified as ideal (<5.6 mmol/l both in children and adults), intermediate (5.6-6.9 mmol/l in children, and 5.6-6.9 mmol/l or treated to goal in adults), and poor (≥7.0 mmol/l both in children and adults).

Based on the individual health factors and behaviors, we generated corresponding AHA indices. The Ideal Cardiovascular Health index corresponds to the number of ideal health factors and behaviors present at the baseline survey (Index86) and at the 2007 survey (Index07). In analyses, we used the Ideal Cardiovascular Health indices as continuous variables. Change in the Ideal Cardiovascular Health index was calculated by subtracting Index86 from Index07.

4.2.5 Pulse wave velocity measurements

We used a commercially available circulation monitoring device CircMon™ (JR Medical Ltd., Saku Vald, Estonia) to determine arterial PWV. CircMon™ includes a whole-body impedance cardiography (ICG) channel, a distal impedance plethysmogram (IPG) channel, and an ECG channel (Figure 4.2A), and it records the continuous heart-synchronous changes in the body's electrical impedance (Kööbi et al. 2003). A pair of electrically connected current electrodes (Medicotest A/S, Ölstykke, Denmark) was placed on the distal part of the extremities just proximal to the wrists and ankles. Voltage sensing electrodes were placed proximal to the current electrodes, with the distance between the centers of the electrodes being 5 cm. The whole-body ICG was recorded with this electrode configuration, and it reflects the weighted sum of the pulsatile plethysmograms of the vessels between the electrodes, i.e. almost the whole vascular system. The distal IPG

was recorded from a popliteal artery at knee-joint level. The active electrode was placed on the lateral side of the knee joint and the reference electrode on the calf, the distance between the electrodes being approximately 20 cm.

When the PP wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases, making it possible to estimate the beginning of the pulse wave transmission. The CircMon™ software measures the time difference between the onset of the decrease in impedance in the whole-body impedance (ICG) signal and, later, the popliteal artery (IPG) signal (Figure 4.2B). The impedance tracing was recorded continuously, and software-based detection of R waves of the ECG and feet of the impedance tracings was used. An average of time intervals measured from five consecutive heart cycles was used to calculate the time difference. The time resolution of the recordings was 5 ms. PWV was then calculated using the standard equation:

$$PWV_{impedance} = D\ (\text{meters}) / \Delta t\ (\text{seconds})$$

where D is the distance between the measurement sites and Δt is the time difference between the onsets of the proximal and distal impedance plethysmograms. This aorta−popliteal PWV differs slightly from the gold-standard carotid−femoral PWV. However, it includes the aorto-iliac pathway, which is the most clinically relevant (Laurent et al. 2006, Nichols et al. 2011), and even brachial−ankle PWV has been showed to provide qualitatively similar information to carotid−femoral PWV (Yamashina et al. 2002, Sugawara et al. 2005).

The validation study has been reported previously (Kööbi et al. 2003). Comparison between whole-body impedance cardiography- and Doppler-derived PWV values showed moderate variation—2 SD between two measurements was 2.42 m/s and 2.17 m/s, respectively—but these changes were concordant and represented the true physiological variability of PWV (Kööbi et al. 2003). The whole-body impedance cardiography could not reflect the beginning of pulse transition in the aortic arch precisely enough because ICG is the sum of the arterial plethysmograms of the whole body. Due to this, the $PWV_{impedance}$ was slightly overestimated, and this small bias can be corrected using a validated equation:

$$PWV = PWV_{impedance} \times 0.696 + 0.864 \text{ (Kööbi et al. 2003)}$$

Corrected values were used in all studies.

The repeatability index for the impedance method, reflecting the variation between two consecutive PWV measurements, and the reproducibility index, describing the variation in the PWV measurements performed on four separate days, was 99% and 87%, respectively (Tahvanainen et al. 2009). In addition to this, PWV measured by the impedance method represents the mean of recordings during 30 s, which is clearly longer than the 5−6 s recommended for tonometric devices (Laurent et al. 2006). This longer period could further increase the reliability of PWV values measured by the impedance method. The reference values for subjects aged 25 to 76 years has been reported previously (Koivistoinen et al. 2007), but the predictive value of PWV measured by whole-body impedance cardiography is still lacking.

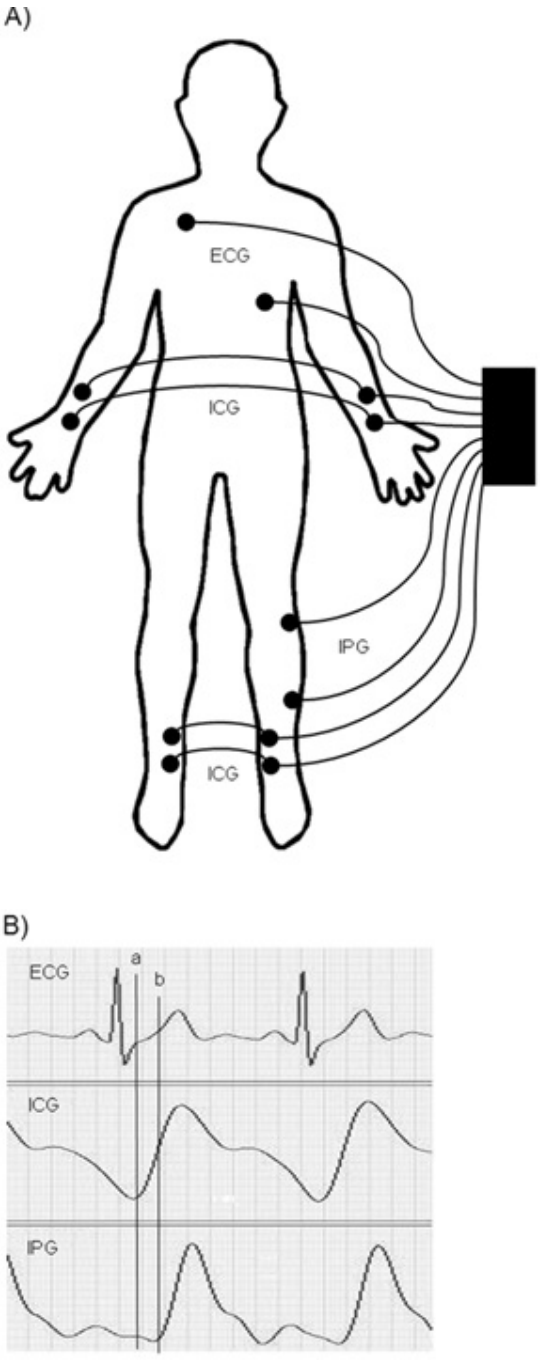

Figure 4.2 A, Placement of electrodes in whole-body impedance cardiography with an additional voltage-sensing channel on the left calf for pulse wave velocity measurement.
B, Synchronous recording of ECG, ICG, and IPG. The time difference between the feet of the ICG (a) and IPG (b) indicates the pulse transit time from aortic arch to popliteal artery.

ECG = electrocardiography, ICG = whole-body impedance cardiography, IPG = distal impedance plethysmogram.

4.2.6 Statistical methods

Values for triglycerides, insulin, glucose, and CRP were log-transformed before analyses due to skewed distributions. The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed using age- and sex-adjusted linear and logistic regression analysis, and the *t* test to examine differences in age.

To study the effects of risk variables on PWV, we calculated age- and sex-specific z scores for each risk variable in each study year. The z score values were used to account for the possible biases caused by age, sex, and secular trends in risk factors. Childhood risk variable load was assessed by calculating the average of z scores from the years 1980, 1983, and 1986, except for CRP (measured childhood only in 1980) and glucose (measured childhood only in 1986). In these analyses, only measurements conducted at ages 3 to 18 years were used. Smoking was modeled as a dichotomous variable (yes or no) if subjects had been smoking at the time of at least 1 of the follow-ups. Adulthood risk variable load was assessed by calculating the average of z scores in 2001 and 2007. The univariate relationships between load variables and PWV in childhood and adulthood were examined by linear regression analysis. To examine whether sex or age modifies the associations between risk variables and PWV, we included sex×risk variable and age×risk variable interaction terms in the regression models. To evaluate which childhood or adulthood risk variables were independently associated with PWV, we used stepwise multivariable regression analysis. In regression analysis we used a heart-rate-specific z score for PWV because heart rate may be a confounding factor (Lantelme et al. 2002, Cecelja and Chowienczyk 2009). In Study IV, we used age-, sex-, and heart-rate-adjusted linear regression to study the associations between the indices and PWV, and between the change in Ideal Cardiovascular Health index and PWV.

To examine the effect of multiple risk factors on PWV (in studies I and II), we calculated a risk score, determined as the number of risk factors. Risk factors were defined in Study I as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, SBP, and BMI; at or below the 20th percentile for HDL cholesterol; and smoking (assessed in subjects ≥12 years of age). In Study II, lifestyle risk factors were defined as values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity index, and smoking. One-way analysis of variance (ANOVA) (Study I) and linear regression analysis (Study II) was used to test the associations between the number of risk factors and the linear trend in PWV.

In Study I, we investigated whether changes in the risk factor score and obesity status between childhood and adulthood were associated with PWV. In these analyses, the presence of ≥1 risk factor was considered an unfavorable risk factor status, and a cut-off point of the age- and sex-specific 80th percentile for BMI was used in determining favorable or unfavorable obesity status. We used t tests to assess whether subjects with unfavorable status in childhood and favorable in adulthood, favorable status in childhood and unfavorable in adulthood, and favorable status both in childhood and adulthood differed from those having an unfavorable status in childhood and in adulthood.

We calculated quintiles of fruit and vegetable consumption to study whether an increase in fruit and vegetable consumption in childhood and adulthood is associated with PWV in adulthood (Study II). We used linear regression to test for trend in PWV across quintiles of fruit and vegetable consumption. In addition, as subgroup analyses, we used *t* tests to assess whether subjects persistently in the lowest quintile of fruit and vegetable consumption in childhood and adulthood differed from those persistently in the highest quintile of fruit and vegetable consumption.

In Study III, age- and sex-adjusted logistic regression was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) of adult high PWV according to the 3 definitions for elevated pediatric BP. High PWV was defined as values at or above the age-, sex- and heart-rate-specific 80th percentile. The ability of each definition to predict high adult PWV was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under receiver operating characteristic curves (AUC), and estimates of risk reclassification; statistics that are in line with criteria put forward by the AHA (Hlatky et al. 2009). Sensitivity was calculated as true-positives/ (true-positives + false-negatives) ×100; specificity as true-negatives/ (true-negatives + false-positives) ×100; NPV as true-negatives/ (true-negatives + false-negatives) ×100; and PPV as true-positives/ (true-positives + false-positives) ×100. AUC was determined from the logistic model and represents an estimate of the probability of the model assigning a higher risk to those who have the outcome (high PWV) compared with those who do not have the outcome. Differences in AUC between the simplified and complex definitions were estimated using the DeLong algorithm (1988). Net reclassification improvement (NRI) was also calculated to determine the extent to which the Complex (vs. Simple 1 or Simple 2) definition reassigned participants to a risk status that better reflected their final outcome (case or control) (Pencina et al. 2008, Cook and Ridker 2009). The proportions of participants reclassified to either higher- or lower-risk categories are presented. Risk classification is improved if an individual with the outcome in adulthood (case) is placed in a higher risk category in youth or if an individual without the outcome in adulthood (control) is moved to a lower risk category in youth. The NRI is the sum of improvements in the reclassification of both case and control participants.

Statistical analyses were performed with the SPSS for Windows (releases 16.0.1, 16.0.2, 20.0.0 SPSS Inc, IBM Corporation, Armonk, NY, USA). In AUC and NRI analyses (Study III), Stata (Release 10, StataCorp LP, College Station, TX, USA) was employed. Statistical significance was inferred at a 2-tailed P value of <0.05.

5. RESULTS

5.1 Characteristics of the population

In all studies, the representativeness of the study cohort was examined by comparing the baseline characteristics between the participants and nonparticipants (subjects missed follow-up or excluded). There were more males among nonparticipants and they had somewhat higher SBP, DBP, BMI, and skinfold thickness than participants. There were no statistically significant differences in the levels of other variables (Table 5.1).

In Study III, only subjects aged 6−15 years in 1980 were included, and the baseline characteristics are shown in Table 5.2. In these age groups, there were more females among participants and they were slightly older. There was no difference in height, SBP, or DBP. Additionally, the prevalence of elevated BP in childhood was the same in both groups according to the Simple 1, Simple 2, and Complex definitions.

In Study IV, the baseline comparisons were made in 1986 because it was the first follow-up at which fasting plasma glucose values were measured (Table 5.3). Participants aged 9−18 years were more often female and were more likely to have an ideal physical activity profile and ideal smoking status than nonparticipants. The older (aged 21–24 years) participants more often had an ideal physical activity status, an ideal healthy diet score, an ideal smoking status, and lower SBP than nonparticipants. There was no difference in age, BMI, or glucose and total cholesterol levels between participants and nonparticipants.

Table 5.1 Baseline characteristics of study participants and nonparticipants (subjects lost to follow-up or excluded) in 1980

Variable	Participants	Nonparticipants	p
No. of subjects*	1622-1691	1905-1974	
Sex, female, %	54.5	47.8	<0.001
Age, years	10.5 (5.0)	10.4 (5.0)	0.31
Total cholesterol, mmol/l	5.3 (0.9)	5.3 (1.0)	0.09
High-density lipoprotein cholesterol, mmol/l	1.6 (0.3)	1.6 (0.3)	0.84
Low-density lipoprotein cholesterol, mmol/l	3.4 (0.8)	3.5 (0.9)	0.12
Triglycerides, mmol/l	0.7 (0.3)	0.7 (0.3)	0.39
Systolic blood pressure, mmHg	112 (12)	113 (13)	<0.001
Diastolic blood pressure, mmHg	68 (10)	69 (10)	0.001
Body mass index, kg/m^2	17.8 (2.9)	17.9 (3.3)	0.04
Skinfold thickness, mm†	25.9 (11.3)	26.1 (12.2)	0.049
Insulin, IU/l	7.7 (5.0−13.0)	7.8 (5.0−12.5)	0.40
C-reactive protein, mg/l	0.29 (0.11−0.56)	0.29 (0.11−0.60)	0.86
Smoking prevalence, %‡	10.8	13.8	0.11
Vegetables, consumption frequency per month	6.2 (2.9)	6.4 (2.8)	0.18
Fruits, consumption frequency per month	6.9 (2.8)	6.9 (2.8)	0.65
Users of butter or butter-based spreads, %	19.8	11.3	0.50
Physical activity index, points§	9.0 (1.8)	9.1 (1.8)	0.99

Values are mean (SD), geometric mean (25−75 percentiles), or prevalence rates expressed as %.

Comparisons between participants and nonparticipants were performed using age- and sex-adjusted linear and logistic regression analysis as well as the *t* test to examine differences in age.

*Some variables have missing data.

†Combined thickness of 3 skinfold measurements (subscapular, triceps, and biceps).

‡Smoking data was gathered on subjects aged 12−18 years defined as regular cigarette smoking on a daily basis.

(participants, n=825; nonparticipants, n=965).

§Index range 5−15, the lowest scores indicate passive and the highest scores indicate active.

Table 5.2 Baseline characteristics of study participants and nonparticipants (subjects lost to follow-up or excluded) aged 6−15 years in 1980 (Study III)

Variable	Participants	Nonparticipants	p
No. of subjects	1241	1241	
Sex, female, %	55.4	47.0	<0.001
Age, years	10.7 (3.3)	10.4 (3.2)	0.01
Height, cm	145 (19)	143 (19)	0.59
Systolic blood pressure, mmHg	112 (10)	112 (11)	0.07
Diastolic blood pressure, mmHg	68 (9)	68 (9)	0.07
Prevalence of elevated BP, *Simple 1 definition*, (age-specific), %	53.9	57.2	0.10
Prevalence of elevated BP, *Simple 2 definition*, (age- and sex-specific), %	57.8	60.9	0.11
Prevalence of elevated BP, *Complex definition*, (age-, sex-, and height percentile-specific), %	43.2	45.1	0.33

Values are mean (SD) or prevalence rates expressed as %.

Comparison between participants and nonparticipants were performed using age- and sex adjusted regression analysis for continuous variables, $\chi 2$ tests for categorical variables and t test to examine differences in age.

Table 5.3 Characteristics of study participants and nonparticipants (subjects lost to follow-up or excluded) in 1986 (Study IV)

Variable	Participants	Nonparticipants	p
Children 9−18 years of age			
No. of subjects	803	1210	
Sex, female, %	56.4	48.0	<0.001
Age, years	13.6 (3.4)	13.3 (3.3)	0.06
Body mass index, kg/m^2	19.4 (3.1)	19.1 (3.4)	0.43
Ideal physical activity, %	6.5	4.6	0.03
Ideal healthy diet score, %	23.8	21.2	0.19
Never smoked whole cigarette, %*	22.8	18.3	0.01
Systolic blood pressure, mmHg	112 (12)	111 (12)	0.22
Diastolic blood pressure, mmHg	63 (9)	62 (10)	0.58
Glucose, mmol/l	4.7 (0.4)	4.8 (1.1)	0.13
Total cholesterol, mmol/l	4.9 (0.9)	5.0 (1.0)	0.28
Adults 21−24 years of age			
No. of subjects	340	426	
Sex, female, %	56.5	51.2	0.15
Age, years	22.5 (1.5)	22.4 (1.5)	0.41
Body mass index, kg/m^2	22.3 (2.9)	22.5 (2.8)	0.42
Ideal physical activity, %	49.4	31.2	<0.001
Ideal healthy diet score, %	22.9	16.4	0.03
Ideal smoking status, %	60.9	39.2	<0.001
Systolic blood pressure, mmHg	121 (12)	123 (12)	0.02
Diastolic blood pressure, mmHg	71 (9)	71 (11)	0.27
Glucose, mmol/l	4.6 (0.4)	4.6 (0.5)	0.88
Total cholesterol, mmol/l	5.1 (0.9)	5.1 (1.0)	0.99

Values are mean (SD) or prevalence rates expressed as %.

Comparison between participants and nonparticipants were performed using age- and sex-adjusted linear and logistic regression analysis as well as the *t* test to examine differences in age.

* Smoking data were gathered on subjects aged 12−18 years (participants, n=609; nonparticipants, n=900)

5.2 Associations of traditional risk factors and pulse wave velocity (original publications I and III)

We used risk factor load variables, i.e. the average of age- and sex-specific z scores for each traditional risk variable (HDL cholesterol, LDL cholesterol, triglycerides, SBP, BMI, skinfold thickness in childhood, glucose, insulin, CRP, and smoking), in childhood (ages 3−18 years) and in adulthood (ages 24−45 years) to study univariate associations between traditional risk factors and adult PWV (Table 5.4). In childhood, SBP and glucose were directly associated with PWV ($p<0.001$ and $p=0.04$, respectively). In adulthood, all of the risk factor load variables except smoking were associated with PWV. The magnitude of the association was the highest for SBP ($\beta=0.34$; $p<0.001$). Sex modified the associations between HDL cholesterol and PWV, and triglycerides and PWV. HDL cholesterol was significantly ($\beta=-0.18$; $p<0.001$) related to PWV in males but not in females ($\beta=0.01$; $p=0.89$). Triglycerides were directly related to PWV in both males and females ($\beta=0.25$; $p<0.001$ and $\beta=0.15$; $p<0.001$, respectively), but in females the magnitude of the association was lower. There were no interactions with age, except between SBP and PWV in adulthood. The association between SBP and PWV was statistically significant ($p<0.001$) in all age groups, but older subjects had higher β values (0.244 to 0.479).

Table 5.4 Univariate relations between childhood (ages 3−18 years) and adulthood (ages 24−45 years) risk factor load and pulse wave velocity (n=1691).

	Risk factor load in childhood (in 1980, 1983, 1986)			Risk factor load in adulthood (in 2001, 2007)		
Risk variable	β	(SE)	p	β	(SE)	p
HDL cholesterol	-0.05	(0.03)	0.051	-0.09	(0.03)	<0.001
LDL cholesterol	0.01	(0.03)	0.59	0.08	(0.03)	0.001
Triglycerides	0.03	(0.03)	0.29	0.19	(0.03)	<0.001
SBP	0.11	(0.03)	<0.001	0.34	(0.02)	<0.001
BMI	-0.03	(0.03)	0.23	0.13	(0.02)	<0.001
Skinfold thickness	0.01	(0.03)	0.85			
Glucose (childhood only 1986)	0.06	(0.03)	0.04	0.14	(0.03)	<0.001
Insulin	0.02	(0.03)	0.47	0.19	(0.03)	<0.001
CRP (childhood only 1980)	-0.01	(0.03)	0.69	0.13	(0.03)	<0.001
Smoking*	0.02	(0.06)	0.51	-0.01	(0.05)	0.53

* Smoking: no=0, yes=1 (only over 12 years, n=849).

HDL = high-density lipoprotein, LDL = low-density lipoprotein, SBP = systolic blood pressure, BMI = body mass index, CRP = C-reactive protein.

In sex- and age-adjusted stepwise multivariable regression analysis (final model including HDL cholesterol, LDL cholesterol, triglycerides, SBP, BMI, skinfold thickness [childhood only], glucose, insulin, and CRP) childhood SBP and glucose (measured only in 1986) were independent predictors of adult PWV. SBP was an independent predictor of PWV in adulthood as well. The other independent predictors in adulthood were insulin and triglycerides (Table 5.5).

Table 5.5 Sex- and age-adjusted multivariable (final model for stepwise linear regression analysis initially including high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, body mass index, skinfold thickness [childhood only], glucose, insulin, and C-reactive protein) relations between childhood (ages 3−18 years) and adulthood (ages 24−45 years) risk factor load and pulse wave velocity (n=1691).

	Risk factor load in childhood (in 1980, 1983, 1986)			Risk factor load in adulthood (in 2001, 2007)		
Risk variable	β	(SE)	p	β	(SE)	p
SBP	0.08	(0.03)	0.002	0.30	(0.02)	<0.001
Glucose (childhood only 1986)	0.06	(0.03)	0.02	-		
Insulin	-			0.08	(0.03)	<0.001
Triglycerides	-			0.07	(0.03)	0.003

SPB = systolic blood pressure.

The association between childhood elevated BP and high adult PWV was evaluated in Study III. Subjects having elevated BP in childhood were at an increased risk of high PWV in adulthood (Table 5.6). The magnitude of the risk was quite similar according to the Simple 1 (age-specific cut-points), Simple 2 (age- and sex-specific cut-points), or Complex (age-, sex-, and height percentile-specific cut-points) definition for elevated pediatric BP (50%, p=0.007, 60%, p=0.001, and 70%, p=0.001, respectively).

Table 5.6 The prediction of high pulse wave velocity in adulthood according to the three different definitions for elevated pediatric blood pressure (n=1241).

Outcome		Simple 1 definition (age)	Simple 2 definition (age and sex)	Complex definition (age, sex, and height percentile)
High PWV	RR	1.5	1.6	1.7
	(95%CI)	1.1−2.0	1.2−2.2	1.2−2.2
	p	0.007	0.001	0.001

High PWV was defined as values at or above the age-, sex-, and heart-rate-specific 80th percentile.
All estimates adjusted for age and sex.

PWV = pulse wave velocity, RR = relative risk, CI = confidence interval.

The prediction of high adult PWV by the simplified definitions was equal to the prediction provided by the Complex definition. Neither AUC nor NRI were significantly different between the Simple 1 and Complex definition (AUC: 0.548 vs. 0.561; p=0.25 and NRI: -2.8%; p=0.13) or between the Simple 2 and Complex definition (AUC: 0.556 vs. 0.561; p=0.68 and NRI: -1.0; p=0.35). The Simple 1 and Simple 2 definitions had higher sensitivity than the Complex definition (61.5, 66.8, and 53.0, respectively) but lower specificity (48.0, 44.5, and 59.3, respectively). All definitions had high NPV (83.4, 84.4, and 83.5, respectively).

An increasing number of childhood traditional risk factors (values at or above the age- and sex-specific 80th percentile for LDL cholesterol, SBP, and BMI; at or below the 20th

percentile for HDL cholesterol; and smoking) was directly associated with adult PWV (p=0.005; Figure 5.1A). An even clearer trend could be seen between an increasing number of adulthood risk factors and PWV (p<0.0001; Figure 5.1B).

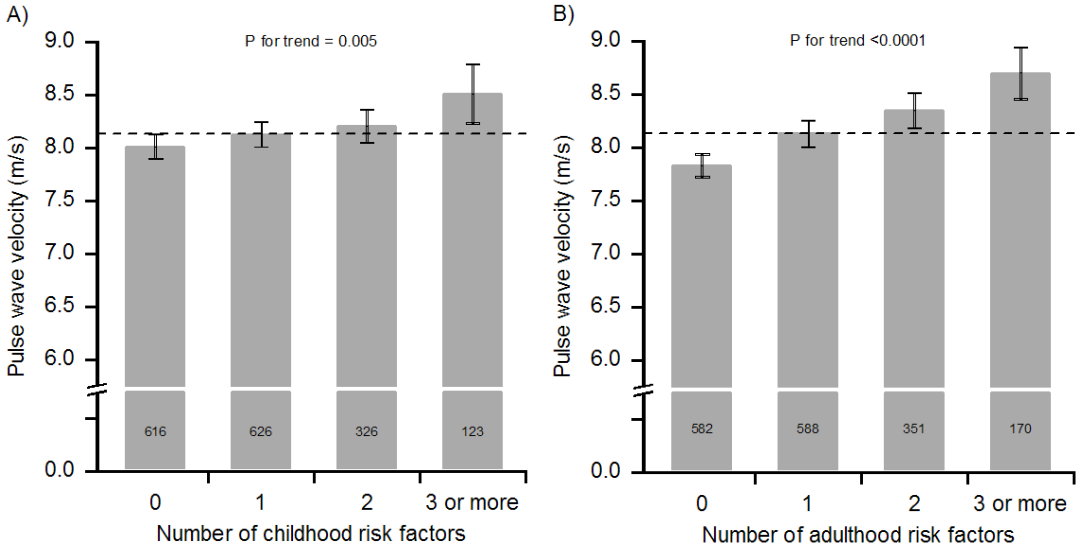

Figure 5.1 Pulse wave velocity by number of risk factors in childhood (ages 3−18 years, in 1980, 1983, and 1986; A) and in adulthood (ages 24−45 years, in 2001 and 2007; B). Risk factors were defined as values at or above the age- and sex-specific 80th percentile for low-density lipoprotein cholesterol, systolic blood pressure, and body mass index; at or below the 20th percentile for high-density lipoprotein cholesterol; and smoking (in childhood assessed in subjects ≥12 years old). P values from one-way ANOVA. Bars represent mean±95% confidence interval. Dashed line represents population mean. Values inside columns indicate the number of subjects in each group.

Subjects with one or more traditional risk factors in both childhood and adulthood had increased PWV in adulthood compared to those with no risk factors in adulthood (p<0.0001; Figure 5.2A). In addition to this, subjects having one or more risk factors in childhood but no risk factors in adulthood had clearly slower PWV than those having risk factors in both childhood and adulthood (p<0.0001) Similarly, a favorable change in BMI between childhood and adulthood was associated with slower adult PWV (p=0.0002; Figure 5.2B). Moreover, subjects having a normal BMI from childhood to adulthood had slower PWV than those with a high lifetime BMI (p=0.002).

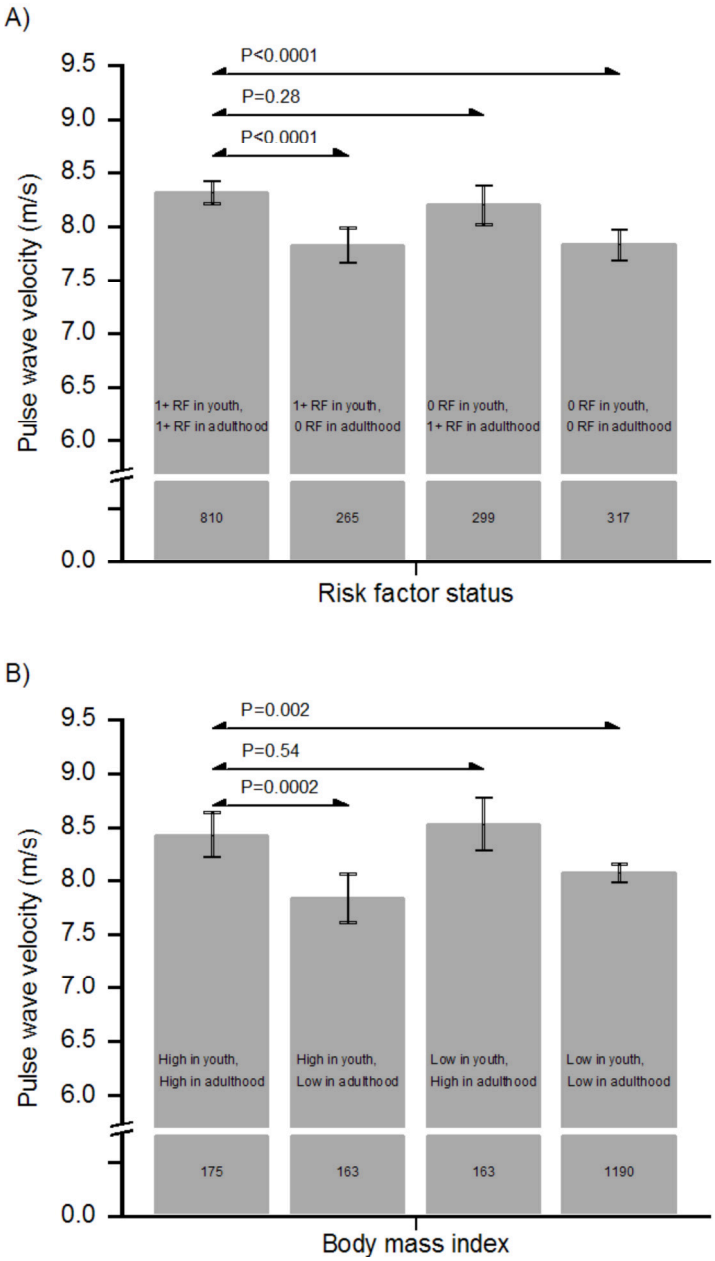

Figure 5.2 A) Relationships of risk score in childhood (ages 3−18 years) and adulthood (ages 24−45 years) with pulse wave velocity (PWV) in adulthood (2007). Subjects having 0 risk factors (RF) were considered to have favorable status and those with ≥1 RFs an unfavorable status. RFs were defined as values at or above the age- and sex-specific 80th percentile for low-density lipoprotein cholesterol, systolic blood pressure, and body mass index (BMI); at or below the 20th percentile for high-density lipoprotein cholesterol; and smoking (in childhood assessed in subjects ≥12 years old).
B) Relationships of BMI in childhood (ages 3−18 years) and adulthood (ages 24−45 years) with PWV in adulthood (2007). A cut-off point of the 80th percentile was used classifying BMI as favorable or unfavorable status. P values from *t* tests. Bars represent mean±95% confidence interval. Values inside columns indicate the number of subjects in each group.

5.3 Associations of lifestyle risk factors and pulse wave velocity (original publication II)

The relationships between lifestyle risk factors (vegetable consumption, fruit consumption, butter use in childhood, alcohol consumption in adulthood, smoking, and physical activity) and PWV were evaluated using risk load variables (the average of age- and sex-specific z scores for each risk variable) in childhood (ages 3−18 years) and in adulthood (ages 24−45 years). Vegetable consumption in childhood was inversely related to PWV in both males and females, but in females the association was lower and not statistically significant (β=-0.12, p=0.002 and β=-0.02, p=0.58, respectively). There was no sex×risk variable interaction with other lifestyle risk factors. Fruit consumption (β=-0.04, p=0.08), butter use (β=0.04, p=0.09), smoking (β=0.003, p=0.89), and physical activity index (β=-0.03, p=0.26) were not associated with PWV in childhood. In adulthood vegetable consumption and fruit consumption were statistically significantly related to PWV (β=-0.09, p=0.001 and β=-0.06, p=0.03, respectively). The association of alcohol consumption, smoking, and physical activity index with PWV in adulthood was not statistically significant (β=0.03, p=0.20, β=-0.03, p=0.22, and β=-0.05, p=0.07, respectively).

Sex- and age-adjusted multivariable relationships between childhood risk factor load and PWV is demonstrated in Table 5.7. Vegetable consumption in childhood was the only independent lifestyle predictor of adult PWV, and this association remained significant after adjustment for the traditional risk factors.

Table 5.7 Age- and sex-adjusted multivariable relationships between childhood (ages 3−18 years) lifestyle and traditional risk factors and pulse wave velocity (n=1622).

	Risk factor load in childhood (in 1980, 1983, and 1986)		
Risk variable	β	(SE)	p
Multivariable relations			
Vegetable consumption	-0.06	(0.03)	0.02
Fruit consumption	-0.01	(0.03)	0.57
Butter use*	0.05	(0.05)	0.07
Smoking†	-0.005	(0.07)	0.84
Physical activity index	-0.02	(0.03)	0.43
Multivariable relations with traditional risk factors			
Vegetable consumption	-0.07	(0.03)	0.004
High-density lipoprotein cholesterol	-0.04	(0.03)	0.07
Low-density lipoprotein cholesterol	0.002	(0.03)	0.94
Triglycerides	0.02	(0.03)	0.53
Systolic blood pressure	0.13	(0.03)	<0.001
Body mass index	-0.08	(0.03)	0.001

Multivariable relations with traditional risk factors only included the significant lifestyle risk factors.

*Butter use: no=0, yes=1

†Smoking: no=0, yes=1 (only over 12 years, n=1375)

In adulthood (Table 5.8), vegetable consumption was also the only lifestyle risk factor that was an independent predictor of PWV when adjusted with lifestyle or traditional risk factors. In the model of lifestyle risk factors, smoking had a significant association with PWV. However, this association became non-significant when the traditional risk factors were taken into account (Table 5.18). The age- and sex-adjusted association between childhood vegetable consumption and PWV was borderline significant (β=-0.05, p=0.05) in the multivariable model when adjusted with adulthood vegetable consumption.

Table 5.8 Age- and sex-adjusted multivariable relationships between adulthood (ages 24−45 years) lifestyle and traditional risk factors and pulse wave velocity (n=1622).

	Risk factor load in adulthood (in 2001 and 2007)		
Risk variable	β	(SE)	p
Multivariable relations			
Vegetable consumption	-0.08	(0.03)	0.002
Fruit consumption	-0.02	(0.03)	0.44
Alcohol consumption	0.04	(0.03)	0.13
Smoking*	-0.05	(0.06)	0.03
Physical activity index	-0.03	(0.03)	0.23
Multivariable relations with traditional risk factors			
Vegetable consumption	-0.07	(0.03)	0.0007
Smoking*	-0.04	(0.05)	0.08
High-density lipoprotein cholesterol	-0.03	(0.03)	0.20
Low-density lipoprotein cholesterol	0.01	(0.02)	0.55
Triglycerides	0.09	(0.03)	0.0002
Body mass index	-0.02	(0.03)	0.44
Systolic blood pressure	0.32	(0.02)	<0.0001

Multivariable relations with traditional risk factors only included the significant lifestyle risk factors.
*Smoking: no=0, yes=1

The mean number of lifestyle risk factors (values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity, and smoking [in childhood assessed in subjects ≥12 years old] was 0.7 (range 0−4) in childhood and 0.8 in adulthood. An increasing trend in adult PWV was observed across the groups with increasing number of childhood lifestyle risk factors (p=0.001; Figure 5.3A). This association remained significant when adjusted for the number of lifestyle risk factors in adulthood (p=0.003; Figure 5.3B).

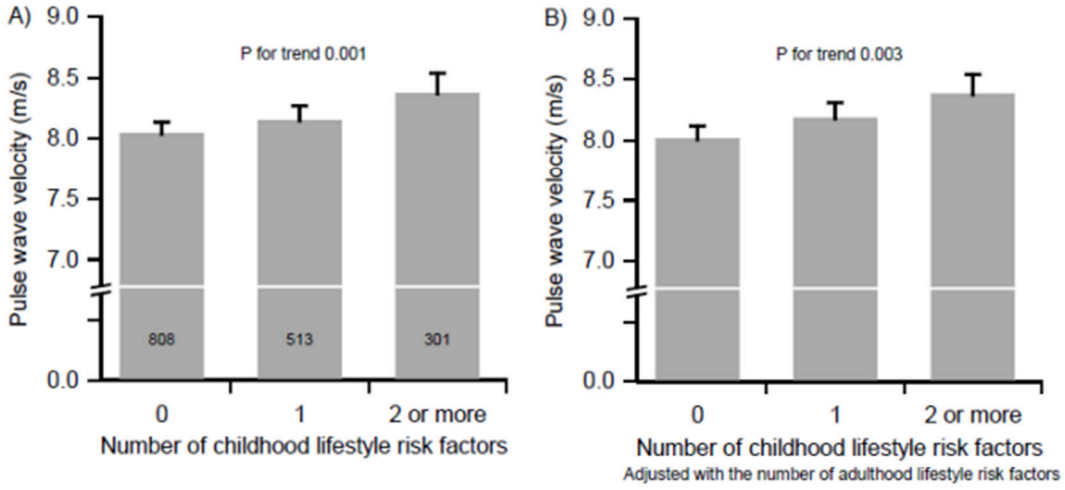

Figure 5.3 Pulse wave velocity by number of lifestyle risk factors in childhood (ages 3−18 years, in 1980, 1983, and 1986; A) and adjusted with the number of adulthood lifestyle risk factors (B). Lifestyle risk factors were defined as values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity, and smoking. P values from linear regression analysis. Bars represent mean plus 95% confidence interval. Values inside columns indicate the number of subjects in each group.

Reprinted from Circulation, 122, Aatola H, Koivistoinen T, Hutri-Kähönen N, Juonala M, Mikkilä V, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study, 2521-2528, Copyright (2010), with permission from Wolters Kluwer Health.

An increase in fruit consumption, both in childhood and adulthood, had an inverse association with PWV (p for trend across quintiles of fruit consumption 0.04 and 0.03, respectively). An even clearer association could be seen between an increase in vegetable consumption and PWV in both childhood and adulthood (p for trend across quintiles of vegetable consumption 0.005 and 0.003, respectively). There was also a significant difference (0.47 m/s, p=0.03) when those in the lowest quintile of vegetable consumption in both childhood and adulthood were compared with those persistently in the highest quintile (Figure 5.4A). Subjects in the highest quintile of fruit consumption in both childhood and adulthood had significantly lower adult PWV than those persistently in the lowest quintile (difference in PWV 0.46 m/s, p=0.03; Figure 5.4B).

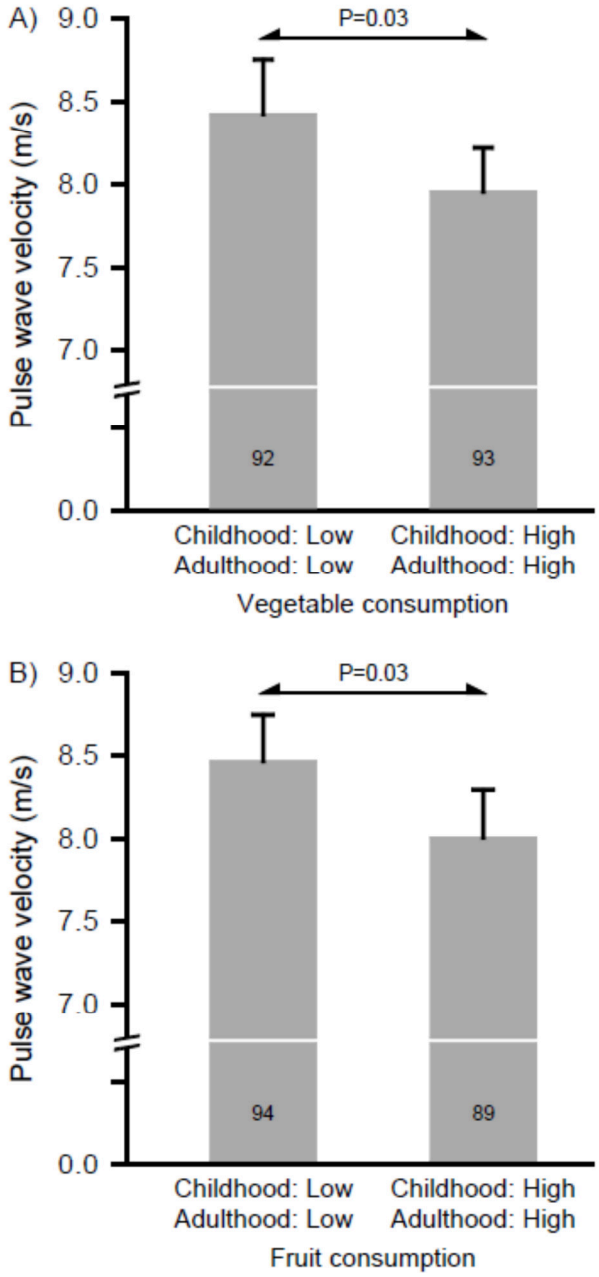

Figure 5.4 Pulse wave velocity in subjects persistently in the lowest or highest quintiles of vegetable consumption (A) and fruit consumption (B) in childhood (ages 3−18 years) and adulthood (ages 24−45 years). *P* values from *t* tests. Bars represent mean plus 95% confidence interval. Values inside columns indicate the number of subjects in each group.

Reprinted from Circulation, 122, Aatola H, Koivistoinen T, Hutri-Kähönen N, Juonala M, Mikkilä V, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Lifetime fruit and vegetable consumption and arterial pulse wave velocity in adulthood: the Cardiovascular Risk in Young Finns Study, 2521-2528, Copyright (2010), with permission from Wolters Kluwer Health.

5.4 Association of ideal cardiovascular health status and pulse wave velocity (original publication IV)

The Ideal Cardiovascular Health status was first defined starting from the 1986 survey because it was the first follow-up at which fasting plasma glucose values were measured. The Ideal Cardiovascular Health index corresponds to the number of ideal health factors and behaviors (range 0−7). In 1986, the mean Ideal Cardiovascular Health index of the younger participants (aged 9−18 years) was 3.7 (SD 1.0; Table 5.9). Ideal glucose levels and BMI levels were the most common. Ideal status in physical activity and smoking was the most difficult to achieve for younger participants, and none of them scored 0 or a full 7 out of 7 ideal health components in Index86.

Table 5.9 Prevalence of ideal cardiovascular health behaviors and factors in 1986 and 2007, participants aged 9−18 years in 1986, n=803

Variable	1986	2007
Sex, female, %	56.4	56.4
Age, years	13.6 (3.4)	34.6 (3.4)
Ideal smoking status, %*	22.8	71.0
Ideal body mass index, %†	85.4	48.2
Ideal physical activity level, %‡	6.5	49.4
Ideal healthy diet score, %§	23.8	13.1
Ideal total cholesterol level, %‖	29.3	65.3
Ideal blood pressure level, %#	81.9	50.3
Ideal fasting plasma glucose level, %**	98.4	81.6
Ideal cardiovascular health index, points††	3.7 (1.0)	3.8 (1.5)
Pulse wave velocity, m/s‡‡		7.9 (0.6)

Values are mean (SD) or prevalence rates expressed as %.

* Smoking data were gathered on subjects aged 12−18 years in 1986, n=609.

Childhood: never tried or never smoked a whole cigarette; Adulthood: never smoked or quit >12 months ago.

† Childhood: <85th age- and sex-specific percentile; Adulthood: <25 kg/m^2

‡ Childhood: ≥7 hours of moderate or vigorous activity per week; Adulthood: ≥1 h/wk vigorous intensity or ≥2−3 h/wk moderate intensity or ≥2−3 h/wk moderate plus vigorous.

§ Healthy diet components in 1986 (ideal=2−3 components): fruits and vegetables = consumption of both fruits and vegetables daily; fish = consumption of fish or fish products a couple of times per week or more frequently; soft drinks = consumption of soft drinks a couple of times per week or less frequently. Components in 2007 (ideal=4−5 components): fruits and vegetables ≥450 g/d; fish: ≥28 g/d; whole grains ≥85 g/d; sodium <1500 mg/d; sugar-sweetened beverages ≤142 g/d.

‖ Childhood: <4.40 mmol/l; Adulthood: <5.17 mmol/l

Childhood: <90th age- and sex-specific percentile; Adulthood: <120/<80 mmHg

** Childhood and Adulthood: <5.6 mmol/l

†† Corresponds to the number of ideal health factors and behaviors

‡‡ Adjusted for sex, age, and heart-rate

In older participants (aged 21−24 years), the mean Index86 was 4.3 (SD 1.2; Table 5.10). Only 7 (2.1%) of them scored 7 out of 7 ideal health components in 1986, but none scored 0. Ideal status in terms of healthy diet, physical activity, and BP was the most difficult to achieve, and ideal glucose and BMI levels were the most common.

Table 5.10 Prevalence of ideal cardiovascular health behaviors and factors in 1986 and 2007, participants aged 21−24 years in 1986, n=340

Variable	1986	2007
Sex, female, %	56.5	56.5
Age, years	22.5 (1.5)	43.5 (1.5)
Ideal smoking status, %*	60.9	77.6
Ideal body mass index, %†	84.7	43.8
Ideal physical activity level, %‡	49.4	50.9
Ideal healthy diet score, %§	22.9	13.5
Ideal total cholesterol level, %‖	59.4	50.6
Ideal blood pressure level, %#	49.4	41.5
Ideal fasting plasma glucose level, %**	98.8	74.4
Ideal cardiovascular health index, points††	4.3 (1.2)	3.5 (1.5)
Pulse wave velocity, m/s‡‡		8.7 (0.5)

Values are mean (SD) or prevalence rates expressed as %.

* Never smoked or quit >12 months ago

† <25 kg/m^2

‡ ≥1 h/wk vigorous intensity or ≥2–3 h/wk moderate intensity or ≥2−3 h/wk moderate plus vigorous

§ Healthy diet components in 1986 (ideal=2–3 components: fruits and vegetables = consumption of both fruits and vegetables daily; fish = consumption of fish or fish products a couple of times per week or more frequently; soft drinks = consumption of soft drinks a couple of times per week or less frequently. Components in 2007 (ideal=4–5 components): fruits and vegetables ≥450 g/d; fish: ≥28 g/d; whole grains ≥85 g/d; sodium <1500 mg/d; sugar-sweetened beverages ≤142 g/d.

‖ <5.17 mmol/l

<120/<80 mmHg

** <5.6 mmol/l

†† Corresponds to the number of ideal health factors and behaviors

‡‡ Adjusted for sex, age, and heart-rate

Remarkable changes could be seen in the levels of individual ideal health components between 1986 and 2007 in both groups (Table 5.9 and 5.10). Younger participants reached ideal smoking status, ideal physical activity, and ideal level of total cholesterol clearly more often in 2007 than in 1986. However, ideal status in BMI, healthy diet, or BP was more difficult to reach. Only 16 (2.0%) younger subjects were able to score a full 7 out of 7 ideal health components in Index07. Ideal smoking status (increase from 60.9% to 77.6%) and ideal physical activity (increase from 49.4% to 50.9%) were the only components which were more common in 2007 than in 1986 for older participants. In addition to this, they reached ideal status in BMI, healthy diet, and fasting plasma glucose less often in 2007 than in 1986. None of them were able to maintain the ideal 7 out of 7 score from baseline to follow-up, and only 7 (2.1%) subjects were able to achieve this status at follow-up.

Index86 was associated with Index07 in both groups (β=0.21, $p<0.001$ for younger and β=0.36, $p<0.001$ for older participants). This association remained significant (β=0.22, $p<0.001$ and β=0.31, $p<0.001$, respectively) after adjustment for age and sex. Index86 was inversely related to PWV in both groups, but the relationship was significant only for older participants (β=-0.05, p=0.16 and β=-0.16, p=0.004, respectively). Index07 was significantly related to PWV in both groups (β=-0.30, $p<0.001$ and β=-0.37, $p<0.001$, respectively) and remained significant (β=-0.30, $p<0.001$ and β=-0.36, $p<0.001$, respectively) after adjustment for Index86.

There was wide variation in the change in Ideal Cardiovascular Health index—from -4 to +5 points for the younger and from -5 to +4 points for the older participants. The average change was 0.1 (SD 1.6) and -0.7 (SD 1.5), respectively. Female subjects had slightly higher means than males in both groups (0.6 vs. -0.5, $p<0.001$, and -0.4 vs. -1.1, $p<0.001$, respectively). 41.6% of younger and 20.3% of older participants could improve their Ideal Cardiovascular Health status. Changes in the Ideal Cardiovascular Health index according to the Index86 scores are shown in Tables 5.11 and 5.12.

Table 5.11 Change in the ideal cardiovascular health index according to the index in 1986, participants aged 9−18 years

		Ideal Cardiovascular Health Index in 1986, Points							
	All	0	1	2	3	4	5	6	7
n	803		8	83	254	306	133	19	
Change									
2 or more	19.4		37.5	49.4	28.3	11.8	3.0		
1	22.2		37.5	18.1	21.3	28.8	12.8	5.3	
0	24.5		25.0	24.1	24.8	23.2	27.1	26.3	
-1	17.4			8.4	16.5	17.3	24.1	31.6	
-2 or less	16.4				9.1	19.0	33.3	36.8	

Values are prevalence rates expressed as %.

Table 5.12 Change in the ideal cardiovascular health index according to the index in 1986, participants aged 21−24 years

		Ideal Cardiovascular Health Index in 1986, Points							
	All	0	1	2	3	4	5	6	7
n	340		4	19	63	105	105	37	7
Change									
1 or more	20.3		50.0	26.3	39.7	16.2	18.1	2.7	
0	25.3		50.0	52.6	31.7	27.6	19.0	13.5	
-1	23.5			21.1	17.5	23.8	26.7	27.0	28.6
-2	18.8				7.9	26.7	17.1	27.0	42.9
-3 or less	12.1				3.2	5.7	19.0	29.7	28.6

Values are prevalence rates expressed as %.

The change in Ideal Cardiovascular Health index was inversely related to PWV (adjusted for age, sex, and heart-rate) in younger (β=-0.25, p<0.001) and in older (β=-0.23, p<0.001) participants (Figure 5.5). The effect was even stronger after adjustment for Index86 (β=-0.32, p<0.001, and β=-0.37, p<0.001, respectively). In this model, Index86 also had an independent, significant inverse effect on PWV in both groups (β=-0.19, p<0.001, and β=-0.32, p<0.001, respectively).

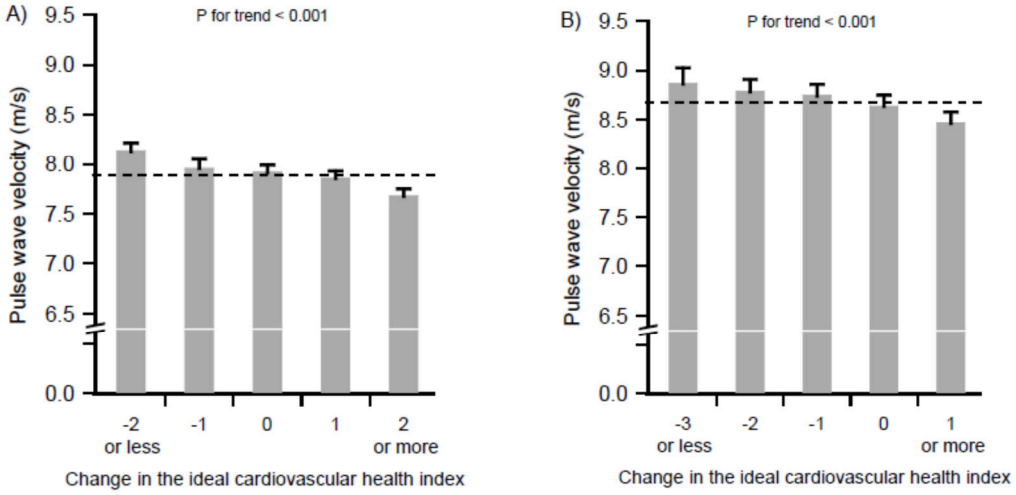

Figure 5.5 Pulse wave velocity in 2007 by the change in the ideal cardiovascular health index for participants aged 30−39 years (A) and for participants aged 42−45 years (B). Change was calculated by subtracting the ideal cardiovascular health index in 1986 from the index in 2007. Bars represent sex-, age-, and heart-rate-specific mean plus 95% confidence interval. Dashed line represents population mean.

5.5 Sensitivity analyses

Because smoking was only evaluated in children aged 12 years or older, we repeated all analyses using the number of risk factors that did not include smoking as a risk variable and obtained essentially similar results as in studies I and II.

In Study III, we tested the robustness of our findings performing analyses using other standardized cut-off points corresponding to the 70th, 75th, 85th, and 90th percentiles of PWV with essentially similar results (Tables 5.13 and 5.14).

Table 5.13 The prediction of high pulse wave velocity (values at or above the standardized cut-off points corresponding to the 90th, 85th, 80th, 75th and 70th percentiles) in adulthood according to the Simple 1 (age-specific), Simple 2 (age- and sex-specific), and Complex (age-, sex-, and height percentile-specific) definition for elevated pediatric blood pressure

Outcome	Simple 1 definition			Simple 2 definition			Complex definition		
	RR	(95%CI)	p	RR	(95%CI)	p	RR	(95%CI)	p
PWV90th	1.2	0.8−1.8	0.29	1.4	0.9−2.1	0.11	1.6	1.1−2.3	0.02
PWV85th	1.5	1.1−2.1	0.009	1.7	1.2−2.3	0.003	1.8	1.3−2.4	0.001
PWV80th	1.5	1.1−2.0	0.007	1.6	1.2−2.2	0.001	1.7	1.2−2.2	0.001
PWV75th	1.3	1.0−1.7	0.05	1.4	1.1−1.9	0.01	1.4	1.1−1.8	0.01
PWV70th	1.4	1.1−1.8	0.006	1.5	1.2−1.9	0.002	1.5	1.2−1.9	0.002

All estimates adjusted for age and sex

PWV = pulse wave velocity, RR = relative risk, CI = confidence interval.

Table 5.14 Sensitivity, specificity, positive predictive value, negative predictive value, and area under receiver-operating characteristic curve with 95% confidence interval of the Simple 1 (age-specific), Simple 2 (age- and sex-specific), and Complex (age-, sex-, and height percentile-specific) definition for elevated pediatric blood pressure to predict high pulse wave velocity (values at or above the standardized cut-off points corresponding to the 90th, 85th, 80th, 75th and 70th percentiles)

Adult outcome	Definition	Sens, %	Spec, %	PPV, %	NPV, %	AUC	(95% CI)
PWV 90th	Simple 1	58.6	46.6	10.2	91.6	0.526	(0.471−0.581)
	Simple 2	64.7	42.9	10.5	92.2	0.538	(0.484−0.592)
	Complex	53.4	57.8	11.6	92.3	0.557	(0.502−0.612)
PWV 85th	Simple 1	62.8	47.6	16.9	88.3	0.552	(0.507−0.597)
	Simple 2	67.8	43.9	17.0	88.9	0.558	(0.514−0.603)
	Complex	55.0	58.8	18.5	88.5	0.569	(0.524−0.614)
PWV 80th	Simple 1	61.5	48.0	22.7	83.4	0.548	(0.508−0.587)
	Simple 2	66.8	44.5	23.0	84.4	0.556	(0.517−0.596)
	Complex	53.0	59.3	24.4	83.5	0.561	(0.521−0.602)
PWV 75th	Simple 1	58.6	47.6	26.9	77.8	0.531	(0.494−0.568)
	Simple 2	63.8	44.2	27.3	78.8	0.540	(0.503−0.577)
	Complex	49.2	58.8	28.2	77.9	0.540	(0.503−0.577)
PWV 70th	Simple 1	59.8	48.6	33.2	74.0	0.542	(0.507−0.577)
	Simple 2	64.4	45.1	33.3	74.8	0.547	(0.513−0.582)
	Complex	49.9	59.7	34.5	73.6	0.548	(0.513−0.583)

PWV = pulse wave velocity, Sens=sensitivity, Spec=specificity, PPV = positive predictive value, NPV = negative predictive value, AUC = area under receiver operating characteristic curve, CI = confidence interval.

In Study III, we also performed two additional subgroup analyses. First, we studied age- and sex-related differences in two age groups and used 9 years of age as a cut-off point. This cut-off point was chosen because Juonala et al. have reported previously that risk factor measurements obtained at or after 9 years of age are predictive of subclinical atherosclerosis in adulthood in this cohort (Juonala et al. 2010). All three definitions produced equal predictions for high PWV for older boys and girls, except for the Simple 1 definition for boys (Table 5.15). Predictions for younger subjects were not statistically significant, which can at least partly be explained by small group sizes (114 boys and 170 girls).

Table 5.15 The prediction of high pulse wave velocity in adulthood according to the Simple 1 (age-specific), Simple 2 (age- and sex-specific), and Complex (age-, sex-, and height percentile-specific) definition for elevated pediatric blood pressure, stratified by sex and age

			< 9 years of age			9−15 years of age		
Sex	Outcome	Definition	RR	(95%CI)	p	RR	(95%CI)	p
Girls	High PWV	Simple 1	0.9	0.4−1.9	0.8	2.0	1.2−3.1	0.003
		Simple 2	1.0	0.5−2.3	0.9	1.9	1.2−3.0	0.006
		Complex	1.3	0.6−2.8	0.5	1.9	1.2−3.0	0.003
Boys	High PWV	Simple 1	0.8	0.3−2.2	0.7	1.5	0.9−2.4	0.1
		Simple 2	0.8	0.3−2.1	0.6	1.9	1.1−3.1	0.01
		Complex	0.9	0.3−2.4	0.9	1.7	1.1−2.7	0.02

High pulse wave velocity was defined as values at or above the age-, sex- and heart rate-specific 80th percentile.

PWV = pulse wave velocity, RR = relative risk, CI = confidence interval.

Secondly, we used the age- and sex-specific 85th percentile for BMI in 1980 as a cut-off point to define subjects as normal-weight or overweight. All three definitions yielded equal predictions of high PWV (1.8−2.1) for overweight subjects (Table 5.16). These predictions were not statistically significant, possibly due to small group size (n=185).

Table 5.16 The prediction of high pulse wave velocity in adulthood according to the three different definitions of elevated pediatric blood pressure by body mass index status in childhood

		Normal weight			Overweight		
Outcome	Definition	RR	(95%CI)	p	RR	(95%CI)	p
High PWV	Simple 1	1.4	1.0−1.9	0.03	1.8	0.8−4.2	0.15
	Simple 2	1.5	1.1−2.1	0.008	2.1	0.8−5.2	0.12
	Complex	1.6	1.2−2.2	0.004	1.8	0.9−3.8	0.09

All estimates adjusted for age and sex.

High pulse wave velocity was defined as values at or above the age-, sex- and heart rate-specific 80th percentile.

Overweight was defined as body mass index values at or above the age- and sex-specific 85th percentile.

PWV = pulse wave velocity, RR = relative risk, CI = confidence interval.

In Study IV, we performed two sensitivity analyses. First, because smoking was only evaluated in subjects aged 12 years or older, we repeated all analyses without subjects aged less than 12 years. Secondly, we repeated the analyses excluding the subjects using antihypertensive or cholesterol-lowering medication. The results of all these additional analyses were similar to those shown.

6. DISCUSSION

6.1 Study population and dropout analysis

The strength of this study is the large randomly selected cohort of participants followed up for 27 years for whom risk factor data were available since their childhood and adolescence (aged 3−18 years). However, bias due to nonparticipation in the long follow-up study needs to be considered. Nonparticipants were more often male in studies I–III. Baseline characteristics in 1980 were mainly similar among participants and nonparticipants, with the exception of SBP, DBP, BMI, and combined skinfold thickness in studies I and II as well as age in Study III. These statistically significant differences could at least partly be explained by the large number of participants, because the absolute differences were small (e.g. mean SBP difference 1 mmHg) and not clinically meaningful. Therefore, the study cohort appears to be fairly representative of the original study population.

In Study IV, the baseline comparison was made in 1986 because it was the first follow-up at which fasting plasma glucose values were measured. There was no difference in age, BMI, or plasma glucose and total cholesterol levels between participants and nonparticipants. Participants aged 9–18 years were more often female and were more likely to have an ideal physical activity profile and ideal smoking status than nonparticipants. The older (aged 21–24 years) participants more often had an ideal physical activity status, an ideal healthy diet score, an ideal smoking status, and lower SBP than nonparticipants. These differences may lead to an underestimation of associations.

In 2007, PWV measurements were carried out with 1,872 (52.1% of the original study population) participants aged 30−45 years attending. As arterial aging starts beyond the age of 30 years (O'Rourke and Hashimoto 2007, Nichols et al. 2011), absolute differences in PWV values could be limited in this population and may thus underestimate associations. Notably, many reports have shown cross-sectional association between CVD risk factors and PWV as early as in childhood and adolescence (Avolio et al. 1985, Li et al. 2004, Im et al. 2007, Lee et al. 2007, Urbina et al. 2010a, Urbina et al. 2012). Finally, the ethnic homogeneity of our study cohort limits the generalizability of our results to white European subjects only.

6.2 Methodological considerations

6.2.1 Assessment and definition of risk factors

The measurement of major risk factors is well standardized and therefore reasonably generalizable from one study to the next, but the measurement of diet and physical activity is not. At baseline, information on dietary habits was obtained with a non-quantitative food frequency questionnaire, which has some limitations. Firstly, the food frequency questionnaire used provides the fruit and vegetable consumption frequency only as times per month and is therefore possibly an imprecise estimate (leading to an underestimation

of associations) because current dietary recommendations are ≥4−5 servings per day (Lichtenstein et al. 2006). Secondly, soft drinks included not only sugar-sweetened beverages but also diet drinks; the category of fruits included fruit juices; and fish was assessed as "fish foods," which included fish and all fish products. In addition, the intakes of sodium and fiber-rich whole grain, which the AHA (Lloyd-Jones et al. 2010) also include in their estimates, could not be inferred at baseline. In 2007, a more detailed quantitative food frequency questionnaire that provided an estimate of food consumption in grams per day was adopted. Physical activity was assessed with a subjective method both at baseline and follow-up. Self-reported data on diet, physical activity, and smoking are subject to known biases. However, as reported previously, validation studies showed significant correlations between the information obtained by the food frequency questionnaire and the 48-hour recall (Mikkilä et al. 2005), between the physical activity questionnaire and the maximal cycle ergometer test (Telama et al. 2005), and between the self-reported smoking (a measure similar to that used in our study) and biochemical measurements (Kentala et al. 2004). These findings support the validity of the self-reports.

The approach evaluating the association between the number of traditional or lifestyle risk factors and PWV in this study has not been validated. This limits the interpretation of the results and warrants validation in separate cohorts in future studies. Taking an average of Z scores over ages might oversimplify these data, although age did not modify the associations between risk factors and PWV in childhood. It is also important to remember that both the impact of baseline values and the impact of follow-up changes in risk factors could have been underestimated or overestimated due to possible regression dilution bias. Finally, observational studies cannot establish causality between CV risk factors and arterial stiffness.

6.2.2 Pulse wave velocity measurement

A potential limitation of this study is the PWV measurement method, which is not yet widely used in epidemiological settings, obviously limiting the comparability of the present findings with the observations from other cohorts. However, PWV values measured with the impedance method are highly comparable to those measured with a Doppler ultrasound method—2 SD between two measurements was 2.42 m/s for PWV measured with the impedance method and 2.17 m/s for PWV measured with Doppler ultrasound (Kööbi et al. 2003), indicating the generalizability of the present findings. In addition, the impedance method derives PWV values directly from the region of the aortic arch to the popliteal artery (Kööbi et al. 2003), which is, physiologically speaking, a more "real" pathway than the gold standard carotid−femoral PWV (pulse wave travels up the carotid artery and down the aorta at the same time) (Laurent et al. 2006).

In the arterial tree, there is a steep gradient of increasing arterial stiffness moving from the heart to the periphery, but aging decreases this gradient because stiffening is most marked in the aorta (Avolio et al. 1983, Paini et al. 2006, Mitchell 2009b, Nichols et al. 2011). Measuring PWV over arteries with different properties should always be considered as a methodological limitation, especially when assessing the distance between two recording sites (Laurent et al. 2006, Weber et al. 2011, Van Bortel et al. 2012). PWV values measured with the impedance method (aorta−popliteal) could be somewhat higher (mean values 0.3 m/s higher, no difference in SD values) than those measured by the gold standard (carotid−femoral) PWV for subjects aged <60 years, but at the same level for subjects >60 years. (Koivistoinen et al. 2007, The Reference Values for Arterial Stiffness' Collaboration 2010). These differences are clinically small because the accepted difference

between repeated measurements is <0.5 m/s (Laurent et al. 2006, Van Bortel et al. 2012). The observed variability of the PWV measured by means of the impedance method is mainly physiological (Kööbi et al. 2003, Tahvanainen et al. 2009).

The impedance method setting has been especially planned for epidemiological studies: the electrodes are easily applied, the knee level is easy to locate between subjects, the longer arterial pathway (aorta-popliteal) provides a more global index of vascular health (measurement of changes caused by aging in the aorta and atherosclerosis in lower limb arteries), and the measurement does not require active participation by a technician (e.g. no positioning of the transducers) (Kööbi et al. 2003, Koivistoinen et al. 2007). PWV measured with the impedance method could also be used in clinical management of patients because of previously reported reference values (Koivistoinen et al. 2007).

We have used heart-rate-adjusted PWV in statistical analyses because Li et al. (2004) have also used it in their study. The same adjustment eases comparison between studies on the same topic. Heart rate may also be a confounding factor for arterial stiffness (Cecelja and Chowienczyk 2009). The correlation between heart rate and arterial stiffness has been reported in animals (Mangoni et al. 1996, Mircoli et al. 1999) and in humans (Sa Cunha et al. 1997, Lantelme et al. 2002, Millasseau et al. 2005). Fatigue and fracture of elastic fibers in the wall of large arteries are clearly related to the number of cycles of strain and stroke volume (Nichols et al. 2011). Heart rate is also a known risk factor and predictor of CVD outcomes (Greenland et al. 1999, Bangalore et al. 2010).

Japanese researchers have also shown that PWV measured over an even longer pathway, i.e. brachial−ankle PWV, may provide a qualitatively similar association with CV risks and clinical outcomes as carotid−femoral PWV (Yamashina et al. 2002, Sugawara et al. 2005, Tsuchikura et al. 2010b, Tsuchikura et al. 2010a). Nevertheless, comparison between aorta−popliteal PWV and carotid−femoral PWV, and hard end-point data concerning the prognostic influence of PWV measured with the impedance method are still lacking. It is also a limitation that PWV has been measured only once in this study population.

6.3 Traditional risk factors and pulse wave velocity

The results of the present thesis show that SBP in childhood is an independent predictor of adult PWV. This finding is consistent with previous reports demonstrating a cross-sectional association between elevated BP and PWV as early as in childhood and adolescence (Avolio et al. 1985, Im et al. 2007, Urbina et al. 2011) as well as a longitudinal association between SBP and PWV (Li et al. 2004). These associations between elevated BP and arterial stiffness correlate perfectly with the mechanical stress hypothesis (Nichols et al. 2011). Elevated BP, caused initially by increased peripheral resistance or cardiac output, causes a direct increase in the diameter and stiffness of elastic arteries because elastic arteries are stiffer at higher rather than lower pressures (Nichols et al. 2011). These changes increase the amplitude of the pressure wave generated by LV ejection and the earlier return of the reflected wave from peripheral sites, thus increasing pressure in systole and decreasing pressure in diastole (Nichols et al. 2011). From the point of view of the large elastic arteries, elevated BP or hypertension can be looked upon as an accelerated form of aging (O'Rourke and Hashimoto 2007, Nichols et al. 2011).

The present thesis also shows that elevated pediatric BP predicts a risk for increased PWV in adulthood. We also observed that two simplified definitions (Kaelber and Pickett 2009, Mitchell et al. 2011) for elevated pediatric BP predict high adult PWV equivalent to the more complex definition currently endorsed by the NHBPEP (2004). This finding is

clinically meaningful because as both simplified tables could be more easily implemented as a screening tool in pediatric health care settings and outside a physician's office when the height percentile required for the Complex definition may not be obtainable. To the best of our knowledge, this is the first study to demonstrate that all these definitions are able to differentiate adolescents at an increased risk of high PWV in adulthood.

We also found that subjects having high PWV in adulthood had higher BP values in childhood. Moreover, they had a higher prevalence of elevated BP in childhood regardless of the BP definition. In adulthood, differences between these groups were markedly greater (e.g., the prevalence of elevated BP was more than twofold in the high-PWV group). Overall, all these observations suggest that early exposure to elevated BP plays an important role in the development of arterial stiffness and CVD. Previous studies have reported clear tracking of BP, and especially elevated BP, from childhood to adulthood (Bao et al. 1995, Chen and Wang 2008, Juhola et al. 2011). Additionally, SBP in childhood predicts hypertension (Sun et al. 2007, Juhola et al. 2011, Juhola et al. 2012), arterial stiffness (Li et al. 2004, Juonala et al. 2005), and coronary artery calcium (Hartiala et al. 2012) in adulthood. Our findings are in agreement with these reports showing that subjects having elevated BP in childhood are at a higher risk of having increased PWV in adulthood. The risk is increased if elevated BP in childhood is defined according to either the NHBPEP definition or the simple 1 version of the two simplified definitions.

As mentioned earlier, elevated BP tracks from childhood to adulthood (Bao et al. 1995, Chen and Wang 2008, Juhola et al. 2011), thus having a long-term influence on the stiffening process. To slow down this process, it is necessary to identify subjects whose high BP needs adequate intervention and treatment. It is especially important to make an early diagnosis of hypertension in childhood because hypertension is a major modifiable risk factor. However, hypertension and prehypertension in children and adolescents are mostly undiagnosed (Hansen et al. 2007, Mitchell et al. 2011). This is a major clinical problem, which prompted Kaelber and Pickett (2009) and Mitchell et al. (2011) to propose the new BP definition tables to aid in decision-making between normal and abnormal pediatric BP. Extremely clear improvement, from 15% to 77%, has been reported in the recognition of hypertensive pressures when using their simplified table instead of the NHBPEP table (Mitchell et al. 2011). This user-friendly screening tool could lead to wider screenings and diagnosis of prehypertension and hypertension in children and adolescents, allowing effective lifestyle interventions and medication to be optimized for health outcomes.

Because the clinical screening of elevated BP is more efficient with the simplified tables, it is important to know how well the simplified tables identified subjects at an increased CVD risk. The findings of the present thesis show that the simplified definitions made almost identical predictions of high PWV to the Complex definition. In addition, AUC and NRI analyses showed no difference between the simplified and complex definitions. The Complex definition had lower sensitivity (53.0%) for high PWV than the Simple 1 and Simple 2 (61.5%–66.8%, respectively) definitions, and all definitions had satisfactory (83.4%–84.4%) NPV. These findings further support the usability of both simplified tables in identifying children and adolescents in need of an additional evaluation of BP. It is also worth mentioning that the RRs of high PWV for overweight subjects were equal (1.8–2.1) according to all 3 definitions. These predictions were not statistically significant, but this may be due to the small group size.

The present thesis shows that, in addition to SBP, fasting plasma glucose level in childhood and adolescence (measured only once in 1986) is also an independent predictor of adult PWV. This is in line with previous findings that impaired fasting glucose or DM are already strongly associated with PVW in youth (Urbina et al. 2010a, Urbina et al. 2010b,

Wadwa et al. 2010, Urbina et al. 2012) and that unfavorable effects of glucose already occur at glycemic levels below the threshold for the diagnosis of DM (Coutinho et al. 1999). Hyperglycemia reduces the bioavailability of NO and causes the overproduction of ROS leading to the activation of an unfavorable production of AGEs and PKC (Creager et al. 2003, Paneni et al. 2013). AGEs decrease elasticity by forming cross-linking of proteins to matrix components (Schmidt et al. 1999, Libby and Plutzky 2002, Zieman et al. 2005, Yan et al. 2010) and PKC is responsible for increased cellular permeability, inflammation, increased ROS production, angiogenesis, extracellular matrix expansion, and apoptosis (Inoguchi et al. 2000, Quagliaro et al. 2003, Geraldes and King 2010). All these changes involve both the muscular and the elastic arteries and predispose these vessels to hypertensive injury (Megnien et al. 1992, Williams 1999, Cruickshank et al. 2002, Haller et al. 2004, Urbina et al. 2010a).

The results of the present thesis also show that SBP, insulin, and triglycerides in adulthood are independent predictors of PWV. As mentioned earlier, there is clear interaction between SBP and arterial stiffness, and increased mechanical stress caused by elevated SBP accelerates the fracture and fatigue of elastic fibers in the arterial wall (Nichols et al. 2011). High insulin and triglyceride levels are well-known markers of metabolic disturbances, and these risk factors have been shown to be directly associated with PWV in previous studies (Benetos et al. 2002a, Mackey et al. 2002, Li et al. 2004, Stehouwer et al. 2008). High insulin levels cause similar AGE synthesis, PKC activation and endothelial dysfunction as high glucose levels (Paneni et al. 2013). Hypertriglyceridemia activates the formation of small, dense LDL, which promotes oxidative stress, further impairs endothelial dysfunction, and accelerates the atherosclerotic process (Welty 2013). These aforementioned metabolic disturbances also lead to impaired myogenic response, allowing pulsatile flow to extend into the smaller vessels downstream causing microvascular damage (Safar et al. 2003, Paneni et al. 2013, Welty 2013).

Different risk factors may have a cumulative effect on the stiffening process because the present thesis shows direct correlation between a number of traditional risk factors (values at or above the age- and sex-specific 80th percentile for LDL cholesterol, SBP, and BMI; at or below the 20th percentile for HDL cholesterol; and smoking [assessed in subjects >12 years of age]) and PWV both in childhood and in adulthood (Figure 5.1). Although this index is not validated, it shows similar findings that have been reported previously between increasing risk load and different intermediary CV outcomes (Berenson et al. 1998, Urbina et al. 2002a, Juonala et al. 2005, Kis et al. 2008). Notably, the difference in adult PWV between subjects with no risk factors and subjects with three risk factors was 0.87 m/s in adulthood. This difference is worthy of mention as Blacher et al. (1999b) observed an all-cause mortality-adjusted odds ratio of 1.39 for each PWV increase of 1 m/s in patients with end-stage renal failure and Vlachopoulos et al. (2010b) demonstrated the all-cause mortality risk to increase by >10% in low- and high-risk patients for each PWV increase of 1 m/s. All these findings strengthen the notion that PWV could be a useful integrated index of vascular status (Cruickshank et al. 2002).

Moreover, observations from the present thesis suggest that early-life vascular effects can be modified by low risk factor levels in adulthood. High risk factor levels in childhood were related to significantly decreased PWV in adulthood if combined with low risk factor levels in adulthood. Additionally, obese youths who became lean adults had slower PWV than persistently obese subjects. These observations support the concept that the vascular changes may be improved over time with appropriate intervention (Wildman et al. 2005, Gregory et al. 2011).

6.4 Lifestyle risk factors and pulse wave velocity

The findings of the present thesis show that vegetable consumption in childhood is an independent predictor of adult PWV, and this inverse association remained significant after adjustment for traditional risk factors in childhood. High fruit and vegetable consumption is associated with lower adult PWV, especially if the consumption is persistently high from childhood to adulthood. To the best of our knowledge, other reports concerning childhood diet and adult PWV are lacking. Vegetable consumption in adulthood was also an independent predictor of PWV. These independent associations strengthen the hypothesis that vegetable consumption has a favorable influence on the process of arterial stiffening.

The univariate inverse association between fruit consumption and PWV was relatively weak in adulthood, and this statistically significant finding may possibly be due, at least in part, to the large number of participants. However, the magnitude of the association was quite similar to that between traditional risk factors and PWV. Frequent fruit consumption can be considered to represent a conscious intention toward healthy food choices, particularly in the 1980s, when not all fruits were available throughout the year in Finland. Therefore, the associations observed with frequent fruit consumption may reflect the effect of an overall healthier diet, and the effect of fruit consumption may be diluted by other lifestyle changes. This highlights the relevance of the present findings.

The present thesis shows that adulthood fruit and vegetable consumption is inversely associated with adult PWV, and these findings are in agreement with the previous studies (van der Schouw et al. 2002, Teede et al. 2003, Vlachopoulos et al. 2007, Corti et al. 2009). Subjects consuming high quantities of fruits and vegetables had slower PWV than those with low consumption. The difference in PWV was more evident if subjects had a high fruit and vegetable consumption from childhood to adulthood compared with those who had a persistently low consumption. The impact of fruit and vegetable consumption (and thus of nutrients and phytochemicals such as potassium, flavonoids, folate, vitamins, and dietary fiber) on the complex pathophysiological process of arterial stiffening is largely unknown. Nevertheless, the antioxidative and anti-inflammatory effects, the reduction of triglycerides and very low-density lipoprotein, as well as enhanced glucose tolerance, reduced insulin resistance, and reversed endothelial dysfunction are possible underlying pathophysiological mechanisms (Bazzano et al. 2003, Zieman et al. 2005, Ignarro et al. 2007, Nichols et al. 2011). Functional aspects of fruits and vegetables, such as low glycemic load, low energy density, and high water content, may also play a role in this process (Bazzano et al. 2003, Teede et al. 2003).

The results of the present thesis show only a borderline significant inverse univariable association between adult physical activity and adult PWV. However, when adjusted for other risk factors, physical activity did not associate independently with PWV in our cohort. The dilution of the association between physical activity and PWV in the multivariable model may be explained by the fact that physical activity modulates traditional risk factors (e.g. HDL cholesterol and triglycerides) in this cohort (Raitakari et al. 1997). The possible favorable influence of physical activity on PWV may therefore not be direct but rather mediated through a modification of traditional risk factors. It is also important to keep in mind that other lifestyle risk factors could be confounders in these analyses.

The number of lifestyle risk factors (defined as values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity index, and smoking) identified in childhood correlated directly with adulthood PWV. This correlation remained significant after adjustment for a number of risk factors in adulthood.

This is in line with the previously mentioned relationship between a number of traditional risk factors and PWV and underlines the deleterious effect of a cumulative risk load. This approach of risk index has not been validated and warrants validation in separate cohorts in future studies.

6.5 Ideal cardiovascular health status and pulse wave velocity

As mentioned earlier, single risk factors could not explain all the differences in the process of arterial stiffening, and an increasing number of risk factors (both traditional and lifestyle) were associated with higher PWV. This is in line with the shift from evaluating single risk factors to evaluating a person's total CVD risk profile (Lloyd-Jones 2010, Perk et al. 2012). So, the concept of Ideal Cardiovascular Health, including four favorable health behaviors (non-smoking, ideal BMI, physical activity at goal, and dietary pattern that promotes CV health) and three favorable health factors (ideal levels of total cholesterol, BP, and fasting plasma glucose) is a promising index for analyses. The health-promoting benefits of each of the index components have also been well established (Lloyd-Jones et al. 2010).

Index86 was inversely associated with PWV in younger (aged 9−18 years in 1986) and in older participants (aged 21−24 years in 1986), but the relationship was statistically significant only for older participants. This could at least partially be explained by the methodological differences: assessments of diet, physical activity, and smoking are subject to the most uncertainty in childhood. Index07 was significantly and inversely related to PWV in both groups and remained significant after adjustment for Index86. This is in line with previously mentioned findings on a number of (traditional or lifestyle) risk factors, and with reports concerning the ability of ideal health index to predict CV outcomes (Folsom et al. 2011, Liu et al. 2012, Ford et al. 2012).

However, the prevalence of Ideal Cardiovascular Health has been reported to be extremely low in adolescence (Laitinen et al. 2012, Shay et al. 2013) and in adulthood. (Bambs et al. 2011, Folsom et al. 2011, Shay et al. 2012). To improve the outcomes of the primordial prevention of CVD and to reach the AHA 2020 Impact Goals, there should be a clear change towards Ideal Cardiovascular Health status. At the same time, it should be known how the changes in Ideal Cardiovascular Health status affect CV outcomes.

The results of the present thesis show that the change in the Ideal Cardiovascular Health index is inversely and linearly related to PWV in adulthood. This relationship was significant for the younger (change from childhood to adulthood) and the older (change from young adulthood to middle age) participants. The association was even stronger when adjusted for the index at baseline, supporting the hypothesis that a change in an individual's Ideal Cardiovascular Health index has an independent favorable effect on the process of arterial stiffening. The present findings also support the previous studies demonstrating the tracking of risk factors from childhood to adulthood (Chen and Wang 2008, Juhola et al. 2011), as the average change in the index for the younger participants was 0.1 points. Remarkably, the older participants showed an average change in index of -0.7 points, and only 20.3% demonstrated an increase of +1 or more points. None of them were able to maintain the ideal 7 out of 7 score from baseline to follow-up, and only 16 (2.0 %) younger (aged 30−39 years in 2007) and 7 (2.1 %) older (aged 42−45 years in 2007) subjects were able to achieve this status at follow-up. This corroborates the fact that lifestyle changes towards Ideal Cardiovascular Health are difficult to reach.

Cecelja and Chowienczyk (2009) reported the dissociation of aortic PWV with traditional CVD risk factors other than hypertension. However, few reports concerning physical activity and PWV and none concerning a healthy diet and PWV were included in

their systematic review—the review therefore included no reports concerning all 7 Ideal Cardiovascular Health components and PWV (Cecelja and Chowienczyk 2009). It is also known that smoking, low physical activity, and an unhealthy diet form an important combination of risk factors when assessing the risk load for CVD (Lloyd-Jones et al. 2010). Our present findings support the hypothesis that arterial stiffness measured by PWV reflects the ongoing multifactor pathologic process which could be assessed by means of the Ideal Cardiovascular Health index, with the change in the index in particular.

6.6 Clinical implications and future perspectives

Attention to CVD risk factors, especially smoking, cholesterols, hypertension, and diet, and improved treatments, both medical and surgical, has decreased acute CHD events and CV mortality among the middle-aged and the elderly in developed countries. These advances, with rapid aging, have resulted in a growing population of elderly patients with chronic CV conditions (Reitsma et al. 1999, Tunstall-Pedoe et al. 1999, Kattainen et al. 2006, Kesteloot et al. 2006). Although improvements in risk factors have efficiently slowed down the atherosclerotic process, they have only delayed the effects of arterial aging (increasing stiffness of elastic arteries). Arterial aging is ubiquitous and causes hypertrophy, ischemia, and failure of the LV upstream and microvascular disease in the brain and kidneys downstream (O'Rourke and Hashimoto 2008, O'Rourke et al. 2010). These changes lead to an exponential increase in disability and death as age advances, independently of atherosclerosis (Kirkwood 1997, O'Rourke 2007).

The stiffening of elastic arteries can now be better monitored by PWV measurements (Laurent et al. 2006, Van Bortel et al. 2012), its development can be slowed, and its manifestations as disease deferred by lifestyle changes and modern therapy (Najjar et al. 2005, O'Rourke and Hashimoto 2008, Nilsson et al. 2009, Brandt et al. 2012a, Brandt et al. 2012b, Mancia et al. 2013, Nilsson et al. 2013). However, the relationship between a reduction in arterial stiffness and reduced incidence of CV events has been reported in only one study (Guerin et al. 2001). This finding strengthens the fact that aortic stiffening with age is a consequence of fracture and fatigue of elastin lamellae and is largely irreversible. Hence, increased aortic stiffness is not a treatment target but may be useful for risk prediction, the screening of risk subjects, and assessing responses to treatment (O'Rourke 2007, Nichols et al. 2011, Sehestedt et al. 2012).

Increasing evidence shows that atherosclerosis has its origin in childhood and is associated with early risk factor levels (Urbina et al. 2002b, Li et al. 2003, Raitakari et al. 2003, Loria et al. 2007). In addition, it is clear that behaviors related to health (e.g. smoking, dietary patterns, physical activity) or the risk of CVD frequently begin in childhood or adolescence (The Health Consequences of Smoking: A Report of the Surgeon General. 2004, Mikkilä et al. 2005, Telama et al. 2005, Chen and Wang 2008, Lloyd-Jones et al. 2010, Juhola et al. 2011). The present results are in line with these findings, showing an association between childhood risk factors and adult PWV. However, lifestyle changes over the past 20 years have resulted in an epidemic of overweight and obesity, the emergence of type 2 diabetes in adolescents, and an increase in the prevalence of hypertension among children and adolescents (Wang and Beydoun 2007, Lloyd-Jones et al. 2009, McCrindle 2010). Therefore, the primordial and primary prevention of CVD should be sufficiently effective; otherwise, the current generations may have a shorter expected lifespan than their parents or grandparents (Olshansky et al. 2005). Moreover, the increased CHD mortality has already been reported among young adults (Ford and Capewell 2007, Allender et al. 2008, O'Flaherty et al. 2012). These findings highlight the importance of the

concept of Ideal Cardiovascular Health (Lloyd-Jones et al. 2010) as a tool for improving primordial prevention and managing a person's total CVD risk profile.

The results of the present thesis show remarkable associations between multiple (both traditional and lifestyle) risk factors and PWV, and especially between a change in the risk profile and PWV. PWV was measured only once in young adulthood and middle age, so more evident associations could be seen with repeated PWV measurement for older subjects. Although aging is inevitable, by maintaining a favorable risk profile from childhood to adulthood, or by changing the risk profile towards favorable in adulthood, it is possible to delay the pathologic processes. The management of vascular health and CV risk prediction could possibly be improved by implementing PWV measurements in clinical practice.

7. SUMMARY AND CONCLUSIONS

The relationship between lifetime risk factors (both traditional and lifestyle) and PWV was investigated among participants of the Cardiovascular Risk in Young Finns Study. The traditional risk factors studied in this thesis were HDL cholesterol, LDL cholesterol, triglycerides, SBP, BMI, skinfold thickness in childhood, plasma glucose, insulin, CRP, and smoking, and the lifestyle risk factors were vegetable consumption, fruit consumption, butter use, smoking, and physical activity. These risk factors were used both as continuous variables and as classified according to the concept of Ideal Cardiovascular Health defined by AHA. The ability of elevated pediatric BP to predict high adult PWV and the difference between the NHBPEP table and two simplified screening tables were also studied. The principal conclusions of the present study are as follows:

I The number of traditional CVD risk factors (extreme quintiles for LDL cholesterol, HDL cholesterol, SBP, BMI, and smoking) in childhood and in young adulthood were associated with adult PWV. SBP and plasma glucose in childhood and SBP, insulin, and triglycerides in young adulthood were independent predictors of adult PWV. Favorable changes in risk factor and obesity status from childhood to young adulthood were associated with lower PWV in adulthood. These results provide support for the reduction of traditional risk factors both in childhood and adulthood in the primary prevention of CVD.

II Elevated pediatric BP predicted high PWV in young adulthood. Additionally, it is possible to use the simplified pediatric BP tables to identify children and adolescents at increased CVD risk as the predictions using these tables were equivalent to the more complex NHBPEP table. These simplified tables could easily be implemented in clinical practice, aiding the screening of elevated pediatric BP and hence improving the primary prevention of CVD and hypertension-related diseases.

III Lifetime lifestyle CVD risk factors, most specifically vegetable consumption, were associated with adult PWV. Vegetable consumption in childhood independently predicted adult PWV when adjusted for traditional risk factors (HDL cholesterol, LDL cholesterol, triglycerides, SBP, BMI, and smoking). Adult vegetable consumption was also an independent predictor of PWV when adjusted for other lifestyle or traditional risk factors. The association appeared to be more pronounced if dietary habits remained favorable from childhood to adulthood or even changed from unfavorable to favorable. These findings highlight the importance of emphasizing dietary habits as early as in childhood in the primary prevention of CVD.

IV The Ideal Cardiovascular Health index, corresponding to the number of favorable health behaviors (non-smoking, ideal BMI, physical activity at goal, and dietary

pattern that promotes CV health) and favorable health factors (ideal levels of total cholesterol, BP, and fasting plasma glucose), was significantly associated with PWV in adulthood. Importantly, the change in the Ideal Cardiovascular Health index was directly associated with PWV for younger (change from childhood to adulthood) and older (change from young adulthood to middle age) participants. This association remained significant after adjustment for the baseline index. These findings suggest that it is always worthwhile to change one's lifestyle from unfavorable to favorable. The present results also support the concept of the Ideal Cardiovascular Health as a useful tool for primordial prevention of CVD.

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Heikki Aatola

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Lifetime Risk Factors and Arterial Pulse Wave Velocity in Adulthood

The Cardiovascular Risk in Young Finns Study

Heikki Aatola, Nina Hutri-Kähönen, Markus Juonala, Jorma S.A. Viikari, Janne Hulkkonen, Tomi Laitinen, Leena Taittonen, Terho Lehtimäki, Olli T. Raitakari, Mika Kähönen

***Abstract*—Limited and partly controversial data are available regarding the relationship of arterial pulse wave velocity and childhood cardiovascular risk factors. We studied how risk factors identified in childhood and adulthood predict pulse wave velocity assessed in adulthood. The study cohort consisted of 1691 white adults aged 30 to 45 years who had risk factor data available since childhood. Pulse wave velocity was assessed noninvasively by whole-body impedance cardiography. The number of conventional childhood and adulthood risk factors (extreme quintiles for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, body mass index, and smoking) was directly associated with pulse wave velocity in adulthood ($P=0.005$ and $P<0.0001$, respectively). In multivariable regression analysis, independent predictors of pulse wave velocity were sex ($P<0.0001$), age ($P<0.0001$), childhood systolic blood pressure ($P=0.002$) and glucose ($P=0.02$), and adulthood systolic blood pressure ($P<0.0001$), insulin ($P=0.0009$), and triglycerides ($P=0.003$). Reduction in the number of risk factors ($P<0.0001$) and a favorable change in obesity status ($P=0.0002$) from childhood to adulthood were associated with lower pulse wave velocity in adulthood. Conventional risk factors in childhood and adulthood predict pulse wave velocity in adulthood. Favorable changes in risk factor and obesity status from childhood to adulthood are associated with lower pulse wave velocity in adulthood. These results support efforts for a reduction of conventional risk factors both in childhood and adulthood in the primary prevention of atherosclerosis. (*Hypertension*. 2010;55:806-811.)**

Key Words: cardiovascular health ■ risk factors ■ elasticity ■ epidemiology ■ pulse wave velocity

It is well recognized that atherosclerosis has its roots in childhood. Risk factors identified in childhood predict the occurrence of preclinical carotid atherosclerosis in adulthood.[1–3] Risk factors have also been associated with decreased arterial elasticity in cross-sectional studies.[4–6] We have demonstrated previously a link between youth risk factor exposure and decreased carotid elasticity in adulthood.[7] Arterial pulse wave velocity (PWV) is commonly used as a marker of arterial stiffness. In various patient categories, including patients with hypertension,[8] end-stage renal failure,[9] and diabetes mellitus,[10] PWV is an independent predictor of all-cause and cardiovascular mortality. Furthermore, aortic PWV is associated with higher cardiovascular mortality, coronary heart disease, and stroke among generally healthy older adults.[11]

Previous observations concerning the relationship between risk factors identified in childhood/adolescence and arterial PWV in adulthood have been controversial. Li et al[12] (835 participants, aged 24 to 44 years) reported a direct correlation between childhood blood pressure and PWV in adulthood, whereas Oren et al[13] (524 participants, aged 27 to 30 years) did not find an association between adolescent blood pressure and adult PWV. To gain more insight on determinants of arterial PWV in adulthood, we measured PWV in 1691 white adults aged 30 to 45 years. These individuals were participants of the prospective Cardiovascular Risk in Young Finns Study for whom risk factor data were available since their childhood. In the present study, we have analyzed the associations of risk factors measured in childhood and adulthood with PWV assessed in adulthood.

Methods

Subjects

The first cross-sectional survey was conducted in 1980 for 3596 subjects aged 3 to 18 years.[14] They were randomly selected from the national register. Four follow-up studies were conducted in 1983,

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From the Departments of Clinical Physiology (H.A., J.H., M.K.), Pediatrics (N.H.-K.), and Clinical Chemistry (T.Le.), University of Tampere and Tampere University Hospital, Tampere, Finland; Departments of Medicine (M.J., J.S.A.V.) and Clinical Physiology (O.T.R.) and the Research Centre of Applied and Preventive Cardiovascular Medicine (M.J., O.T.R.), University of Turku and Turku University Hospital, Turku, Finland; Department of Clinical Physiology and Nuclear Medicine (T.La.), Kuopio University Hospital, Kuopio, Finland; Department of Pediatrics (L.T.), University of Oulu, Oulu, Finland; Vaasa Central Hospital (L.T.), Vaasa, Finland.

Correspondence to Mika Kähönen, Tampere University Hospital, Department of Clinical Physiology, PO Box 2000, FI-33521 Tampere, Finland. E-mail mika.kahonen@uta.fi

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1986, 2001, and 2007, with 2991, 2779, 2283, and 2204 participants, respectively. The study cohort for the present analysis included those 1691 nonpregnant subjects with available PWV data who were not using antihypertensive or cholesterol-lowering medication. Subjects with type 1 or 2 diabetes mellitus were also excluded. All of the subjects gave written, informed consent, and the study was approved by the local ethics committees.

Clinical Characteristics

Height and weight were measured, and body mass index (BMI) was calculated. Skinfold thicknesses (in 1980, 1983, and 1986) were measured as described previously.[7] Blood pressure was measured from the brachial artery with standard methods, as described previously.[7] The mean of 3 measurements was used in the analysis. Smoking habits were ascertained with a questionnaire in subjects aged ≥12 years. Smoking was modeled as a dichotomous variable (smoking or nonsmoking). Smoking was defined as regular cigarette smoking on a weekly basis or more often in adolescents and in adults.

Biochemical Analyses

Venous blood samples were taken after fasting for 12 hours. Standard methods were used for serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, insulin, and glucose concentrations (glucose only in 1986, 2001, and 2007). Low-density lipoprotein (LDL) cholesterol concentration was calculated by the Friedewald formula. Childhood C-reactive protein (CRP) was analyzed in 2005 from serum samples that were taken in 1980 and stored at −20°C. Details of all of the methods and analytic procedures have been reported previously.[7,15–17]

Arterial PWV Studies

We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd) to determine PWV. CircMon includes whole-body impedance cardiography channel (ICG), distal impedance plethysmogram channel (IPG), and an ECG channel (Figure 1A). When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal and, later, the popliteal artery signal. The PWV can be determined from the distance and the time difference between the 2 recording sites (Figure 1B). The repeatability index and the reproducibility index were good (99% and 87%, respectively).[18] A detailed description of the method and the validation study has been reported previously.[19]

Statistical Methods

Values for triglycerides, insulin, glucose, and CRP were log-transformed before analyses, because of skewed distributions. The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed using regression analysis adjusted with age for continuous variables and with the χ^2 test for categorical variables.

To study the effects of risk variables on PWV, we calculated age- and sex-specific z scores for each risk variable in each study year. Childhood risk variable load was assessed by calculating the average of z scores from years the 1980, 1983, and 1986. In these analyses, only measurements conducted at ages 3 to 18 years were used. Adulthood risk variable load was assessed by calculating the average of z scores in 2001 and 2007.

The univariate relationships between load variables and PWV in childhood and adulthood were examined by regression analysis. To examine whether sex modifies the associations between risk variables and PWV, we included sex×risk variable interaction terms in the regression models. To evaluate which childhood or adulthood risk variables were independently associated with PWV, we used stepwise multivariable regression analysis. In regression analysis we used a heart rate–specific z score for PWV.[20]

To examine the effect of multiple risk factors on PWV, we calculated a risk score, determined as the number of risk factors. Risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, systolic blood pressure (SBP), and BMI; at or below the 20th percentile for HDL cholesterol; and smoking (assessed in subjects ≥12 years of age). One-way ANOVA was used to compare the PWV values in the various groups.

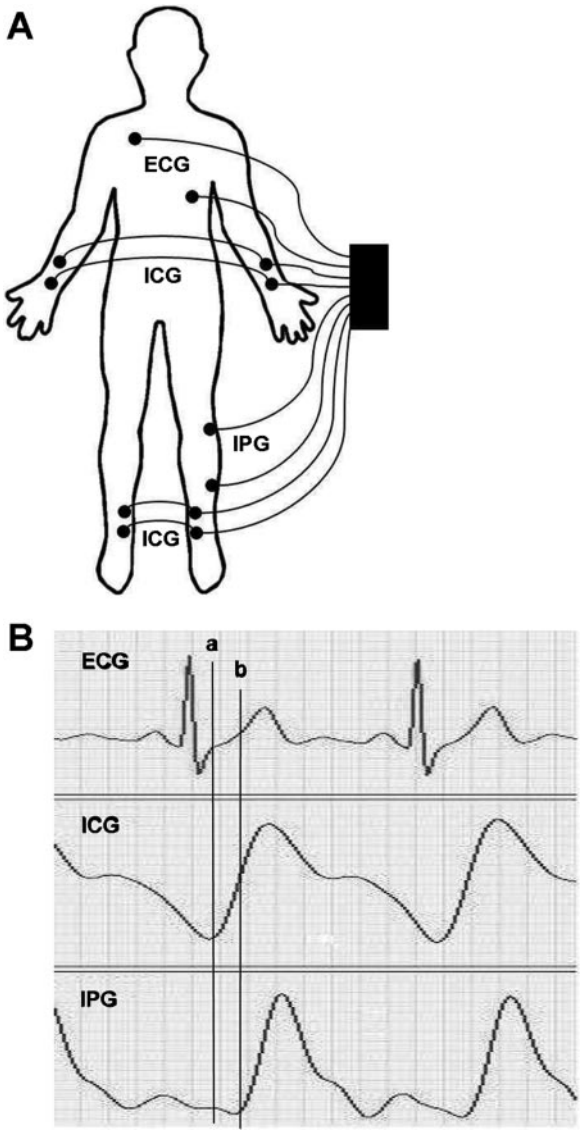

Figure 1. A, Placement of electrodes in whole-body impedance cardiography with an additional voltage-sensing channel on the left calf for PWV measurement. B, Synchronous recording of ECG, whole-body ICG, and IPG. Time difference between the feet of the ICG (a) and IPG (b) indicates the pulse transit time from aortic arch to popliteal artery.

In addition, we studied whether changes in the risk factor score and obesity status between childhood and adulthood were associated with PWV. In these analyses, the presence of ≥1 risk factor was considered an unfavorable risk factor status, and a cutpoint of age- and sex-specific 80th percentile for BMI was used in determining favorable or unfavorable obesity status. We used t tests to assess whether subjects with unfavorable status in childhood and favorable in adulthood, favorable status in childhood and unfavorable in adulthood, and favorable status both in childhood and adulthood differed from those having an unfavorable status in childhood and in adulthood.

All of the analyses were performed with the SPSS for Windows (release 16.0.1, SPSS Inc). Statistical significance was inferred at a 2-tailed P value <0.05.

Table 1. Baseline Characteristics in 1980 of Study Participants and Nonparticipants (Subjects Lost or Excluded)

Variable	Participants	Nonparticipants
No. of subjects	1691	1905
Sex, women, %*	54.5	47.8
Age, y†	10.5	10.4
Total cholesterol, mmol/L	5.28	5.31
HDL cholesterol, mmol/L	1.56	1.56
LDL cholesterol, mmol/L	3.42	3.45
SBP, mm Hg‡	112	113
BMI, kg/m^2§	17.8	17.9
Skinfold thickness, mm‖	25.9	26.1
Triglycerides, mmol/L¶	0.60	0.60
Insulin, IU/L¶	7.74	7.79
CRP, mg/L¶	0.29	0.29
Smoking prevalence,%#	17.7	15.0

Comparisons between participants and nonparticipants were performed using regression analysis adjusted with age and sex. *P* value was >0.05 unless informed otherwise.

*The sex differences between the participants and nonparticipants were examined with a χ^2 test ($P<0.0001$).

†The *t* test was applied between participants and nonparticipants to examine differences in age ($P=0.87$).

‡$P=0.0001$ vs participants.

§$P=0.04$ vs participants.

‖Data show combined thickness of 3 skinfold measurements (subscapular, triceps, and biceps; $P=0.049$).

¶Results are geometric mean values.

#Smoking data were gathered on subjects aged 12 to 18 years defined as regular cigarette smoking on a weekly basis or more often. The differences between the participants and nonparticipants were examined with a χ^2 test ($P=0.11$).

Results

The representativeness of the present study cohort was studied by comparing the characteristics at the original baseline study (1980) between the participants of the present study (n=1691) and nonparticipants (n=1905). There were more males than females among nonparticipants ($P<0.0001$) and they had higher SBP, BMI, and combined skinfold thickness than participants ($P=0.0001$, $P=0.04$, and $P=0.049$, respectively). There were no statistically significant differences in the levels of total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, insulin, CRP, or smoking prevalence between participants and nonparticipants (Table 1). The characteristics of the study subjects in 1980 and in 2007 are shown in Table 2.

Table 2. Baseline (1980) and Current (2007) Characteristics of Study Subjects

Variable	1980	2007
Age, y	10.5±5.0	37.5±5.0
Total cholesterol, mmol/L	5.28±0.87	5.01±0.9
HDL cholesterol, mmol/L	1.56±0.30	1.20±0.43
LDL cholesterol, mmol/L	3.42±0.79	3.22±0.85
SBP, mm Hg	112±12	120±14
BMI, kg/m^2	17.8±2.9	25.7±4.5
Triglycerides, mmol/L	0.60 (0.45 to 0.79)	1.32 (0.85 to 1.56)
Insulin, IU/L	7.74 (5.00 to 13.00)	6.46 (4.20 to 10.40)
CRP, mg/L	0.29 (0.11 to 0.56)	0.87 (0.39 to 1.77)
Smoking prevalence, %*	17.7	23.0
PWV, m/s		8.13±1.5

Values are mean±SD or geometric mean (25th to 75th percentiles) or percentages of subjects.

*In 1980, smoking data were gathered on subjects aged 12 to 18 years defined as regular cigarette smoking on a weekly basis or more often. In 2007, smoking was defined as smoking on a weekly basis or more often.

Table 3. Univariate and Multivariable (Final Model for Stepwise Linear Regression Analysis Initially Including Age, Sex, HDL Cholesterol, LDL Cholesterol, Triglycerides, SBP, Skinfold Thickness [Childhood Only], BMI, Glucose, Insulin, and CRP) Relations Between Childhood (Ages 3 to 18 Years) and Adulthood (Ages 24 to 45 Years) Risk Factor Load and PWV

	Risk Factor Load in Childhood (in 1980, 1983, and 1986)		Risk Factor Load in Adulthood (in 2001 and 2007)	
Risk Variable	β (SE)	*P*	β (SE)	*P*
Univariate relations				
HDL cholesterol	−0.05 (0.03)	0.051	−0.09 (0.03)	0.0005
LDL cholesterol	0.01 (0.03)	0.59	0.08 (0.03)	0.001
Triglycerides	0.03 (0.03)	0.29	0.19 (0.03)	<0.0001
SBP	0.11 (0.03)	<0.0001	0.34 (0.02)	<0.0001
BMI	−0.03 (0.03)	0.23	0.13 (0.02)	<0.0001
Skinfold thickness	0.01 (0.03)	0.85		
Glucose (childhood only 1986)	0.06 (0.03)	0.04	0.14 (0.03)	<0.0001
Insulin	0.02 (0.03)	0.47	0.19 (0.03)	<0.0001
CRP (childhood only 1980)	−0.01 (0.03)	0.69	0.13 (0.03)	<0.0001
Smoking (only over 12 y)	0.02 (0.06)	0.51	−0.01 (0.05)	0.53
Multivariable relations				
Sex	0.31 (0.05)	<0.0001	0.31 (0.04)	<0.0001
Age	0.30 (0.01)	<0.0001	0.28 (0.004)	<0.0001
SBP	0.08 (0.03)	0.002	0.30 (0.02)	<0.0001
Glucose (childhood only 1986)	0.06 (0.03)	0.02	…	…
Insulin	…	…	0.08 (0.03)	0.0009
Triglycerides	…	…	0.07 (0.03)	0.003

Table 3 shows the results of the regression of PWV on risk factor load variables measured since childhood. In univariate analysis, childhood SBP and glucose were directly associated with PWV in adulthood ($P<0.0001$ and $P=0.04$, respectively). In adulthood, all of the risk factor load variables except smoking were associated with PWV in adulthood. The magnitude of association was the highest for SBP. In adulthood, sex modified the associations between HDL cholesterol and PWV and triglycerides and PWV. HDL cholesterol was significantly ($\beta=-0.18$; $P<0.0001$) related to PWV in males but not in females ($\beta=0.01$; $P=0.89$). Triglycerides was directly related to PWV both in males and females ($\beta=0.25$,

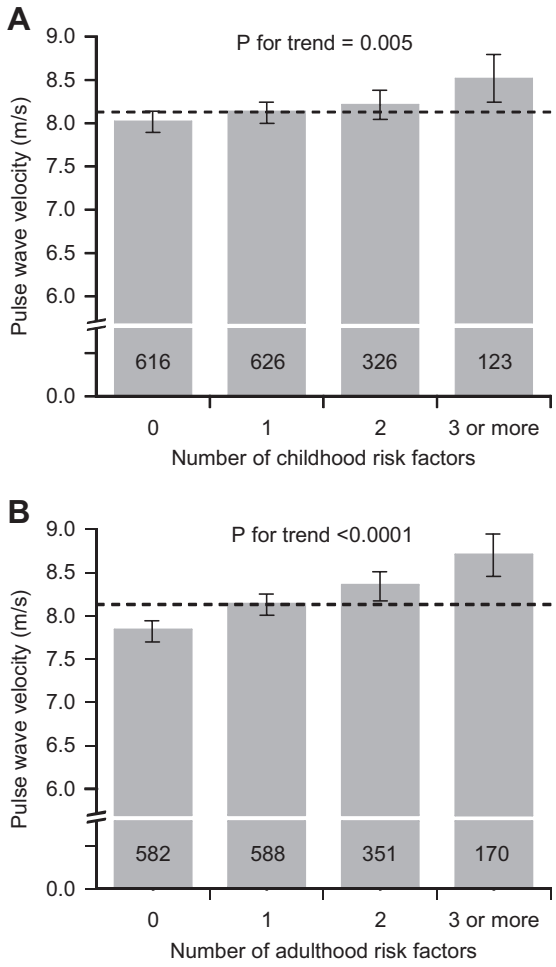

Figure 2. PWV by number of risk factors in childhood (ages 3 to 18 years, in 1980, 1983, and 1986; A) and in adulthood (ages 24 to 45 years, in 2001 and 2007; B). Risk factors were defined as values at or above the age- and sex-specific 80th percentile for LDL cholesterol, SBP, and BMI; at or below the 20th percentile for HDL cholesterol; and smoking (in childhood assessed in subjects ≥12 years old). *P* values from 1-way ANOVA. Bars represent mean±95%CI. Dashed line represents population mean. Values inside columns indicate the number of subjects in each group.

$P<0.0001$ and $\beta=0.15$, $P<0.0001$, respectively), but in females the magnitude of association was lower. In the multivariable model, the independent predictors of PWV were age, sex, SBP, and glucose in childhood and SBP, insulin, and triglycerides in adulthood.

An increasing trend in adulthood PWV was observed across the groups with an increasing number of childhood risk factors ($P=0.005$; Figure 2A). PWV also correlated strongly with an increasing number of adulthood risk factors ($P<0.0001$; Figure 2B). Subjects with ≥1 risk factor both in childhood and adulthood had increased PWV in adulthood compared with those with no risk factors in adulthood ($P<0.0001$; Figure 3A). Similarly, a favorable change in BMI between childhood and adulthood was associated with slower PWV in adulthood ($P=0.0002$; Figure 3B).

Discussion

The present study shows that age and sex, SBP, and glucose in childhood, as well as SBP, insulin, and triglycerides in adulthood, are independent predictors of PWV in adulthood. We also demonstrated that the number of risk factors identified in childhood and adulthood correlated directly with adult PWV. Moreover, we found that favorable changes in risk factor status and obesity status in adulthood were associated with lower PWV in adulthood.

Previous studies concerning the relationship between conventional risk factors in childhood/adolescence and PWV have been limited, and the results were partly controversial. In the Bogalusa Heart Study, Li et al[12] reported that SBP, BMI, and HDL cholesterol (inverse correlation) in childhood correlated with PWV in adulthood. They also showed that SBP, HDL cholesterol (inverse association), triglycerides, and smoking were cross-sectionally associated with PWV in young adulthood. In another cross-sectional study, Im et al[21] showed that mean blood pressure, BMI, sex, and total homocysteine levels were independently associated with PWV. In the Atherosclerosis Risk in Young Adults Study,[13] no association between adolescent blood pressure and adult PWV was observed. This controversial result could be at least partly explained by differences in blood pressure measurement methods. Oren et al[13] used only single measurement from school health records, whereas Li et al[12] and Im et al[21] measured blood pressure using the same protocol in the entire cohort.

In the present study, SBP load in childhood was an independent predictor of PWV in adulthood. This is consistent with reports mentioned earlier showing an association between arterial stiffness and cumulative burden of SBP since childhood.[7,12] The acceleration of atherosclerosis, vascular smooth muscle hyperplasia, and hypertrophy, as well as the induction of oxidative stress in the arterial wall caused by elevated blood pressure, are probable underlying pathophysiological mechanisms behind this association.[22] In addition to SBP, glucose in childhood was an independent predictor of PWV. This is in line with a previous finding that impaired fasting glucose had a strong association with high intima-media thickness, a marker of early atherosclerosis, in overweight children.[23] In adulthood, SBP, insulin, and triglyceride levels were independent predictors of PWV. These risk factors have been shown to be directly associated with arterial PWV and elasticity in adults[7,20] and are independent risk factors for ischemic heart disease.[22,24,25]

Our findings show that the number of risk factors identified in childhood was significantly associated with increased PWV in adulthood. The present results are in line with earlier observations showing that the presence of multiple risk factors may lead to the acceleration of atherosclerosis in young people.[7,26] In this study, we also demonstrated that the number of risk factors identified in adulthood correlated directly with adult PWV. Notably, the difference of adult PWV between subjects with no risk factors and subjects with ≥3 risk factors was 0.87 m/s. This difference is worthy of mention because Blacher et al[9] observed an all-cause mortality-adjusted odds ratio of 1.39 for each PWV increase of 1 m/s in patients with end-stage renal failure.

Observations from this analysis suggest that early life atherosclerotic effects can be modified by low risk factor levels in adulthood. In this study, high risk factor levels in

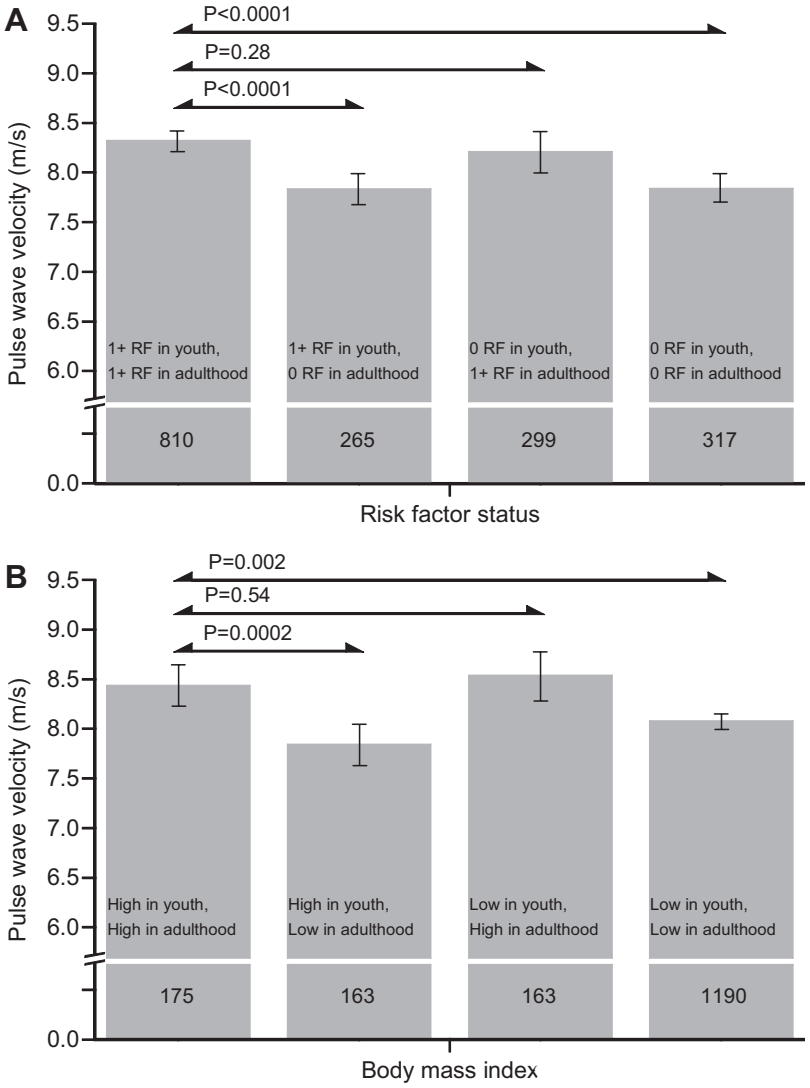

Figure 3. A, Relations between risk score in childhood (ages 3 to 18 years) and adulthood (ages 24 to 45 years) with PWV in adulthood (2007). Subjects having 0 risk factors were considered to have favorable status and those with ≥1 risk factors unfavorable status. B, Relations between BMI in childhood (ages 3 to 18 years) and adulthood (ages 24 to 45 years) with PWV in adulthood (2007). A cutpoint of the 80th percentile was used, classifying BMI as favorable or unfavorable status. *P* values from *t* tests. Bars represent mean±95%CI. Values inside columns indicate the number of subjects in each group.

childhood were related to significantly decreased PWV in adulthood if combined with low risk factor levels in adulthood. Moreover, obese youths who became lean adults had slower PWV compared with persistently obese subjects. These observations support the concept that the vascular changes in childhood may improve over time with appropriate intervention.

A limitation of this study is the PWV measurement method, which is not yet widely used in epidemiological settings, apparently limiting comparability of the present finding with the observations from other cohorts. However, PWV values measured by CircMon are highly comparable to those measured by Doppler ultrasound method,[19] indicating the generalizability of the present findings. In addition, ICG is very useful in epidemiological studies, because the method is easy, fast, operator independent and highly repeatable and reproducible, and the observed variability of the measured parameters is mainly physiological.[18,19] Reference values for PWV measured with this method have also been published previously.[27] Another potential limitation is the nonparticipation in the follow-up study. However, baseline risk factors in 1980 were mainly similar among participants and nonparticipants, with the exception of SBP, BMI, and combined skinfold thickness, which were slightly higher in nonparticipants. Thus, the present study cohort appears to be fairly representative of the original study population. Because our study cohort was racially homogenous, the generalizability of our results is limited to white European subjects. It is also important to remember that both the impact of baseline values and the impact of follow-up changes in risk factors could have been underestimated or overestimated because of possible regression dilution bias. Finally, observational studies cannot establish causality between cardiovascular risk factors and arterial stiffness.

Perspectives

There is accumulating and consistent evidence showing that conventional risk factors are predictive of cardiovascular risk later in life. However, favorable changes in risk factor status from childhood to adulthood may decrease the cardiovascular risk. These results provide support for the reduction of conventional risk factors both in childhood and adulthood.

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Disclosures

None.

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Lifetime Fruit and Vegetable Consumption and Arterial Pulse Wave Velocity in Adulthood

The Cardiovascular Risk in Young Finns Study

Heikki Aatola, MD; Teemu Koivistoinen, MD, MSc; Nina Hutri-Kähönen, MD, PhD; Markus Juonala, MD, PhD; Vera Mikkilä, PhD; Terho Lehtimäki, MD, PhD; Jorma S.A. Viikari, MD, PhD; Olli T. Raitakari, MD, PhD; Mika Kähönen, MD, PhD

Background—The relationships between childhood lifestyle risk factors and adulthood pulse wave velocity (PWV) have not been reported. We studied whether childhood and adulthood lifestyle risk factors are associated with PWV assessed in adulthood.

Methods and Results—The study cohort comprised 1622 subjects of the Cardiovascular Risk in Young Finns Study followed up for 27 years since baseline (1980; aged 3 to 18 years) with lifestyle risk factor data available since childhood. Arterial PWV was measured in 2007 by whole-body impedance cardiography device. Vegetable consumption in childhood was inversely associated with adulthood PWV ($\beta=-0.06$, $P=0.02$), and this association remained significant ($\beta=-0.07$, $P=0.004$) when adjusted for traditional risk factors (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, systolic blood pressure, body mass index, and smoking). Vegetable consumption was also an independent predictor of PWV in adulthood when adjusted for lifestyle or traditional risk factors ($\beta=-0.08$, $P=0.002$ and $\beta=-0.07$, $P=0.0007$, respectively). Persistently high consumption of both fruits and vegetables from childhood to adulthood was associated with lower PWV compared with persistently low consumption ($P=0.03$ for both). The number of lifestyle risk factors (the lowest quintile for vegetable consumption, fruit consumption, physical activity, and smoking) in childhood was directly associated with PWV in adulthood ($P=0.001$). This association remained significant when adjusted for the number of lifestyle risk factors in adulthood ($P=0.003$).

Conclusions—These findings suggest that lifetime lifestyle risk factors, with low consumption of fruits and vegetables in particular, are related to arterial stiffness in young adulthood. **(*Circulation*. 2010;122:2521-2528.)**

Key Words: epidemiology ■ lifestyle ■ atherosclerosis ■ risk factors

The atherosclerotic process begins in youth, but clinical manifestations may occur even decades later.[1] This long delay allows a number of risk factors to affect the process. In accord with this, we and others have shown that traditional childhood risk factors predict the occurrence of preclinical carotid atherosclerosis in adulthood.[2–4] Therefore, early modification of risk factors by lifestyle changes to prevent or even reverse the progression of atherosclerosis is one of the major contemporary challenges in the primary prevention of cardiovascular diseases (CVD). Indeed, several studies have consistently shown the protective effect of fruit and vegetable consumption against the risk of CVD.[5–7] Moderate alcohol consumption is also associated with lower risk of coronary heart disease.[8,9] Furthermore, regular physical activity and exercise training have important roles in preventing CVD and managing CVD risk factors.[7,10]

Clinical Perspective on p 2528

Arterial pulse wave velocity (PWV), a marker of central arterial stiffness, is generally accepted as an independent predictor of cardiovascular events and all-cause mortality.[11] In the prevention of CVD, it may be possible to identify subjects at a high CVD risk by measuring PWV. We and others have demonstrated that traditional cardiovascular risk factors from childhood to adulthood are associated with PWV in young adulthood.[12,13] Dietary habits and physical activity may also have an impact on the process of arterial stiffening. It has been shown that high intake of isoflavones or phytoestrogens may reduce arterial stiffness in middle-aged and elderly people.[14,15] Moderate alcohol consumption has cross-sectionally been associated with lower PWV in both sexes.[16,17] PWV has also been shown to be associated inversely with

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From the Departments of Clinical Physiology (H.A., T.K., M.K.), Pediatrics (N.H.-K.), and Clinical Chemistry (T.L.), University of Tampere and Tampere University Hospital, Tampere, Finland; Departments of Medicine (M.J., J.S.A.V.) and Clinical Physiology (O.T.R.) and Research Centre of Applied and Preventive Cardiovascular Medicine (M.J., O.T.R.), University of Turku and Turku University Hospital, Turku, Finland; and Division of Nutrition, University of Helsinki, Helsinki, Finland (V.M.).

Correspondence to Mika Kähönen, MD, PhD, Department of Clinical Physiology, Tampere University Hospital, PO Box 2000, FI-33521 Tampere, Finland. E-mail mika.kahonen@uta.fi

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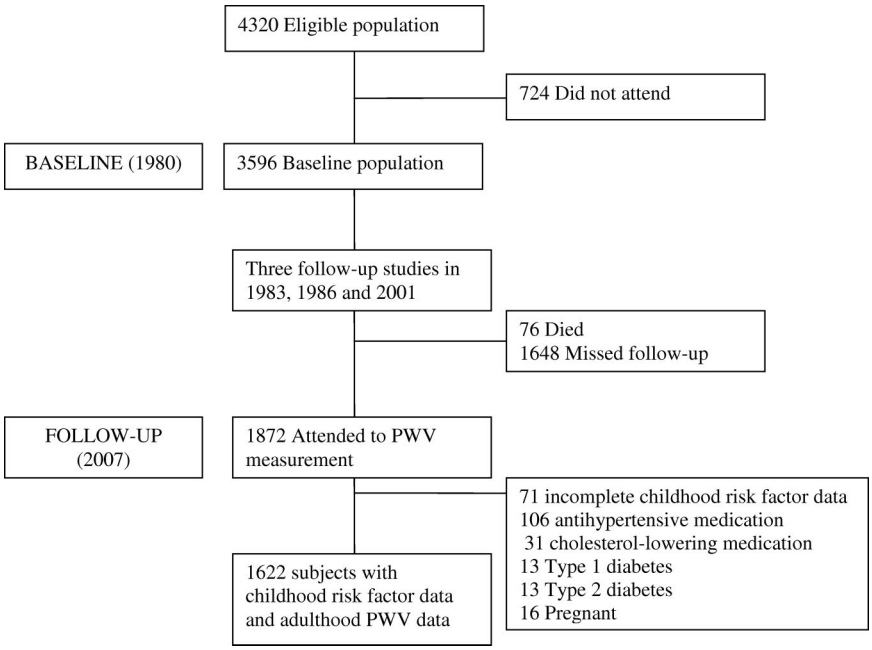

Figure 1. Study flow chart.

cardiorespiratory fitness in young adults,[18] and moderate aerobic exercise may reduce large-artery stiffness.[19]

To the best of our knowledge, no information has been published about the associations between childhood lifestyle risk factors and PWV in young adulthood. Therefore, the aim of the present study was to evaluate the relationship of lifestyle risk factors (vegetable consumption, fruit consumption, butter use, alcohol consumption, smoking, and physical activity) measured in childhood and adulthood with PWV in young adulthood. We measured PWV in 1622 white adults aged 30 to 45 years. These individuals were participants of the prospective Cardiovascular Risk in Young Finns Study followed up for 27 years since 1980, for whom risk factor data were available since their childhood (aged 3 to 18 years).

Methods

Subjects

In 1980, a total of 4320 children and adolescents aged 3, 6, 9, 12, 15, and 18 years were randomly chosen from the Finnish national population register to obtain a sample that would represent Finnish children and adolescents reasonably well.[20] In practice, girls and boys of each age cohort in each study community (5 university cities in Finland with medical schools and 12 rural communities in their vicinity) were separately placed in random order on the basis of the unique personal identification number. Every kth girl and every kth boy in each community was selected so that the sample consisted of the required number of boys and girls. The varying k factors were determined on the basis of sample size and the total number of boys and girls in the different age cohorts in each community. A total of 3596 (83.1%) of those invited participated in the first cross-sectional study. During the follow-up, 76 subjects have died; 2 of these deaths were due to atherosclerotic disease. The study flow chart is shown in Figure 1. All subjects provided written informed consent, and the study was approved by the local ethics committees.

Clinical Characteristics and Risk Variables

Height and weight were measured, and body mass index was calculated. Blood pressure was measured from the brachial artery with standard methods as described previously.[21] The mean of 3 measurements was used in the analysis. For the determination of serum lipoprotein levels, venous blood samples were drawn after an overnight fast. All determinations were performed with the use of standard methods reported previously.[22,23]

Questionnaires using self-reports were completed to collect data on dietary habits, alcohol consumption, smoking, and physical activity. Information on dietary habits was obtained with a nonquantitative food frequency questionnaire. For subjects aged 3 to 9 years, the data were requested from the parents. At the age of 12 to 18 years, study subjects answered the questions themselves, assisted by their parents when necessary. To examine the frequency of fruit and vegetable consumption, 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. The response categories were converted into times of consumption per month (1→35; 2→25; 3→10; 4→4; 5→2; 6→0). In 2007, a more detailed quantitative food frequency questionnaire providing an estimate of food consumption in grams per day was introduced. Subjects were also asked whether they use butter or butter-based spreads on bread. Habitual use of butter or butter-based spread on bread was defined as a risk factor. The dietary variables chosen for this analysis are indicators of 2 major dietary patterns, health conscious and traditional, identified in this study population.[24] The health-conscious pattern was positively correlated with fruit and vegetable consumption, and this pattern was more predominant among female subjects.[24] Dietary patterns remained stable from childhood to adulthood (Spearman correlation, $r=0.32$ for traditional and $r=0.38$ for health conscious) and especially among older subjects.[24] These patterns were also associated with cardiovascular risk factors.[25]

In 2001 and 2007, participants were asked to report their consumption of 0.33-L cans or bottles of beer, glasses (12 cL) of wine, and 4-cL shots of liquor or spirits during the past week. These doses are comparable to ≈14 g of alcohol (=1 U). The values of different beverages consumed during the past week were summed to determine the total alcohol consumption. The distribution of the continuous alcohol consumption variable was strongly skewed and could not be normalized with logarithmic transformation. Therefore, the variable was categorized. The categorization of the participants according to daily ethanol consumption (average amount through the week) was performed as follows: (1) no alcohol consumption during the last week, (2)

>0 to <2 U of alcohol per day, (3) 2 to <4 U of alcohol per day, and (4) ≥4 U of alcohol per day.

In childhood, smoking was assessed in subjects aged ≥12 years. Smoking data were collected in connection with the medical examination in a solitary room where the participants could respond confidentially and undisturbed. Smoking was defined as regular cigarette smoking on a daily basis in adolescence and in adulthood. Physical activity was assessed by a self-report questionnaire. In childhood, these data were gathered at the age of 9 to 18 years so that study subjects answered the questions themselves, with the parents' assistance as necessary. The questions concerned the frequency and intensity of leisure time physical activity, participation in sports club training, participation in sports competitions, and habitual ways of spending leisure time. In adulthood, the physical activity questionnaire consisted of the following variables: intensity of physical activity, frequency of vigorous physical activity, hours spent on vigorous physical activity, average duration of a physical activity session, and participation in organized physical activity. A physical activity index (range, 5 to 15) was calculated by summing these variables. The lowest scores indicate passive, and the highest scores indicate active.[23]

Arterial PWV Studies

We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd) to determine PWV. CircMon includes a whole-body impedance cardiography channel, a distal impedance plethysmogram channel, and an ECG channel. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in the whole-body impedance signal and subsequently in the distal plethysmogram signal from a popliteal artery at knee joint level. The measurement is triggered by the R wave of the ECG. The PWV can be determined from the distance and the time difference between the 2 recording sites. The repeatability index and the reproducibility index were good (99% and 87%, respectively).[26] A detailed description of the method[12,27] and the validation study[27] has been reported previously.

Statistical Methods

The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed with the use of age- and sex-adjusted regression analysis for continuous variables and the χ^2 test for categorical variables.

To study the effects of risk variables on PWV, we calculated age- and sex-specific Z scores for fruit consumption, vegetable consumption, physical activity, and alcohol consumption at each study year. The Z score values were used to account for the possible biases caused by age, sex, and secular trends in risk factors. Childhood risk variable load was assessed by calculating the average of Z scores from the years 1980, 1983, and 1986. In these analyses, only measurements conducted at the ages of 3 to 18 years were included. Smoking was modeled as a dichotomous variable (no or yes) if subjects have smoked in at least 1 of the follow-ups. Adulthood risk variable load was assessed by calculating the average of measurements in 2001 and 2007.

The univariable relationships between load variables and PWV in childhood and adulthood were examined by regression analysis. To investigate whether sex or age modifies the associations between risk variables and PWV, we included sex×risk variable and age×risk variable interaction terms in the regression models. We have previously shown with this cohort that traditional risk factors in childhood (systolic blood pressure [SBP] and glucose) and adulthood (SBP, triglycerides, and insulin) were independent predictors of PWV in adulthood.[12] Therefore, to study whether the effects of lifestyle risk factors are independent of traditional risk factors, we fitted a multivariable model also including data on those traditional risk factors. To study whether the effects of childhood lifestyle risk factors are independent of current risk factors, we fitted a multivariable model also including adulthood data on those risk factors with significant effects in the childhood multivariable model. In regression analysis, we used a heart rate–specific Z score for PWV because heart rate may be a confounding factor.[28]

Table 1. Baseline Characteristics of Study Participants and Nonparticipants (Subjects Lost or Excluded) in 1980

Variable	Participants	Nonparticipants	*P*
No. of subjects	1622	1974	
Sex, women, n (%)	884 (54.5)	948 (48.0)	0.0001
Age, y	10.5±5.0	10.4±5.0	0.31
HDL cholesterol, mmol/L	1.56±0.30	1.56±0.31	0.84
LDL cholesterol, mmol/L	3.41±0.79	3.45±0.87	0.12
Triglycerides, mmol/L	0.66±0.30	0.67±0.33	0.39
SBP, mm Hg	112±12	113±13	0.0003
Body mass index, kg/m^2	17.8±2.9	17.9±3.3	0.03
Vegetables, consumption frequency per month	6.3±2.9	6.4±2.8	0.18
Fruits, consumption frequency per month	6.9±2.8	6.9±2.8	0.65
Users of butter or butter-based spreads, n (%)	321 (19.8)	223 (11.3)	0.26
Smoking prevalence, n (%)*	89 (10.8)	133 (13.8)	0.06
Physical activity index†	9.0±1.8	9.1±1.8	0.99

Values are mean±SD or n (%). HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Comparisons between participants and nonparticipants were performed with the use of age- and sex-adjusted regression analysis for continuous variables and χ^2 tests for categorical variables.

*Smoking data were gathered on subjects aged 12 to 18 years (participants, n=825; nonparticipants, n=965).

†Physical activity data were gathered on subjects aged 9 to 18 years (participants, n=1072; nonparticipants, n=1237).

To examine the effect of multiple lifestyle risk factors on PWV, we calculated the number of lifestyle risk factors. Lifestyle risk factors were defined as values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity index, and smoking. The mean number of risk factors was 0.7 (range, 0 to 4) in childhood and 0.8 (range, 0 to 4) in adulthood. Because smoking was only evaluated in children aged 12 years or older, we repeated all analyses using the number of risk factors that did not include smoking as a risk variable and obtained essentially similar results. Linear regression analysis was used to test the associations between the number of risk factors and the linear trend in PWV.

We calculated quintiles of fruit and vegetable consumption to study whether increase in fruit and vegetable consumption in childhood and adulthood is associated with PWV in adulthood. We used linear regression to test for trend in PWV across quintiles of fruit and vegetable consumption. In addition, as subgroup analyses, we used t tests to assess whether subjects persistently in the lowest quintile of fruit and vegetable consumption in childhood and adulthood differed from those persistently in the highest quintile of fruit and vegetable consumption.

All analyses were performed with SPSS for Windows (release 16.0.2, SPSS Inc). Statistical significance was inferred at a 2-tailed P value <0.05.

Results

The characteristics of study participants (n=1622) and nonparticipants (n=1974) are shown in Table 1. A comparison of baseline (1980) values showed that nonparticipants were

Table 2. Multivariable Relationships Between Childhood (Ages 3 to 18 Years) Risk Factor Load and PWV

	Risk Factor Load in Childhood (in 1980, 1983, and 1986)	
Risk Variable	β (SE)	P
Multivariable relations		
Sex	0.32 (0.05)	<0.0001
Age	0.30 (0.01)	<0.0001
Vegetable consumption	−0.06 (0.03)	0.02
Fruit consumption	−0.01 (0.03)	0.57
Butter use*	0.05 (0.05)	0.07
Smoking†	−0.005 (0.07)	0.84
Physical activity index	−0.02 (0.03)	0.43
Multivariable relations with traditional risk factors		
Sex	0.32 (0.04)	<0.0001
Age	0.28 (0.01)	<0.0001
Vegetable consumption	−0.07 (0.03)	0.004
HDL cholesterol	−0.04 (0.03)	0.07
LDL cholesterol	0.002 (0.03)	0.94
Triglycerides	0.02 (0.03)	0.53
SBP	0.13 (0.03)	<0.0001
Body mass index	−0.08 (0.03)	0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Sex- and age-specific *Z* scores were used for risk factor variables. Heart rate–specific *Z* scores were used for PWV. Multivariable relations with traditional risk factors only included the significant lifestyle risk factors.

*Butter use: no=0, yes=1.

†Smoking: no=0, yes=1; n=1375.

Table 3. Multivariable Relationships Between Adulthood (Ages 24 to 45 Years) Risk Factor Load and PWV

	Risk Factor Load in Adulthood (in 2001 and 2007)	
Risk Variable	β (SE)	P
Multivariable relations		
Sex	0.32 (0.05)	<0.0001
Age	0.27 (0.01)	<0.0001
Vegetable consumption	−0.08 (0.03)	0.002
Fruit consumption	−0.02 (0.03)	0.44
Alcohol consumption	0.04 (0.03)	0.13
Smoking*	−0.05 (0.06)	0.03
Physical activity index	−0.03 (0.03)	0.23
Multivariable relations with traditional risk factors		
Sex	0.32 (0.04)	<0.0001
Age	0.28 (0.01)	<0.0001
Vegetable consumption	−0.07 (0.03)	0.0007
Smoking*	−0.04 (0.05)	0.08
HDL cholesterol	−0.03 (0.03)	0.20
LDL cholesterol	0.01 (0.02)	0.55
Triglycerides	0.09 (0.03)	0.0002
Body mass index	−0.02 (0.03)	0.44
SBP	0.32 (0.02)	<0.0001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Sex- and age-specific *Z* scores were used for risk factor variables. Heart rate–specific *Z* scores were used for PWV. Multivariable relations with traditional risk factors only included the significant lifestyle risk factors.

*Smoking: no=0, yes=1.

more often male and had higher SBP and body mass index than participants.

There were no interactions with age, except between SBP and PWV in adulthood. The association between SBP and PWV was statistically significant ($P<0.0001$) in all age groups, but older subjects had higher β values (0.244 to 0.479). Sex did not modify the associations between risk variables and PWV, except for vegetable consumption in childhood. Vegetable consumption in childhood was inversely related to PWV in both males and females, but in females the association was lower and not statistically significant ($\beta=-0.12$, $P=0.002$ and $\beta=-0.02$, $P=0.58$, respectively). Fruit consumption ($\beta=-0.04$, $P=0.08$), butter use ($\beta=0.04$, $P=0.09$), smoking ($\beta=0.003$, $P=0.89$), and physical activity index ($\beta=-0.03$, $P=0.26$) were not associated with PWV in childhood. In adulthood, vegetable consumption and fruit consumption were statistically significantly related to PWV ($\beta=-0.09$, $P=0.001$ and $\beta=-0.06$, $P=0.03$, respectively). The association of alcohol consumption, smoking, and physical activity index with PWV in adulthood was not statistically significant ($\beta=0.03$, $P=0.20$; $\beta=-0.03$, $P=0.22$; and $\beta=-0.05$, $P=0.07$, respectively). Table 2 shows the results of the multivariable regression models in childhood. Vegetable consumption was an independent predictor of PWV in childhood as adjusted with lifestyle risk factors or traditional risk factors ($\beta=-0.06$, $P=0.02$ and $\beta=-0.07$, $P=0.004$, respectively). In adulthood (Table 3), vegetable consumption was also the only lifestyle risk factor that was an independent predictor of PWV when adjusted for lifestyle or traditional risk factors. The association with smoking in adulthood became nonsignificant when the associations of traditional risk factors were taken into account (Table 3). The association between childhood vegetable consumption and PWV was borderline significant ($\beta=-0.05$, $P=0.05$) in the multivariable model when adjusted for adulthood vegetable consumption ($\beta=-0.07$, $P=0.002$), age ($\beta=0.28$, $P<0.0001$), and sex ($\beta=0.32$, $P<0.0001$).

An increasing trend in adulthood PWV was observed across the groups with increasing number of childhood lifestyle risk factors ($P=0.001$; Figure 2A). This association remained significant when adjusted for the number of lifestyle risk factors in adulthood ($P=0.003$; Figure 2B).

Increase in fruit and vegetable consumption had an inverse association with PWV in childhood (P for trend across quintiles of fruit and vegetable consumption=0.04 and 0.005, respectively) and in adulthood (P for trend=0.03 and 0.003, respectively). There was also a significant difference (0.47 m/s; $P=0.03$) when those in the lowest quintile of vegetable consumption in both childhood and adulthood were compared with those persistently in the highest quintile (Figure 3A). Subjects in the highest quintile of fruit

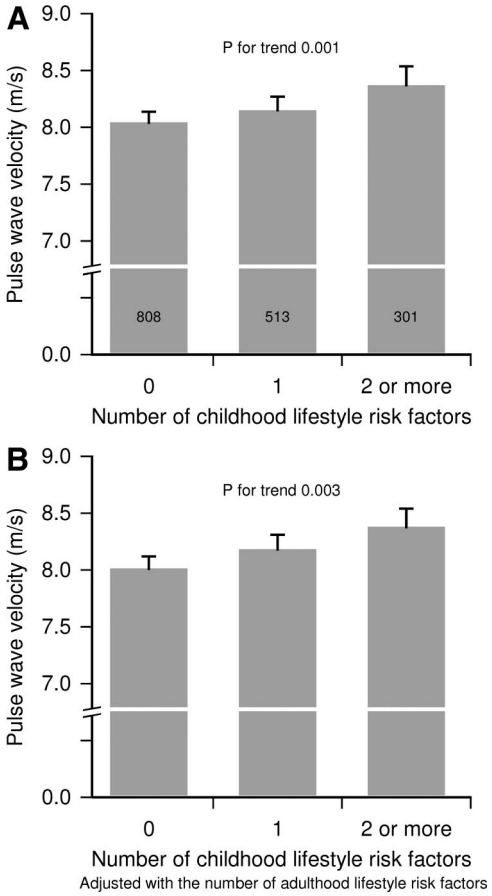

Figure 2. PWV by number of lifestyle risk factors in childhood (ages 3 to 18 years, in 1980, 1983, and 1986; A) and adjusted with the number of adulthood lifestyle risk factors (B). Lifestyle risk factors were defined as values at or below the age- and sex-specific 20th percentile for vegetable consumption, fruit consumption, physical activity, and smoking. *P* values are from linear regression analysis. Bars represent mean plus 95% confidence interval. Values inside columns indicate the number of subjects in each group.

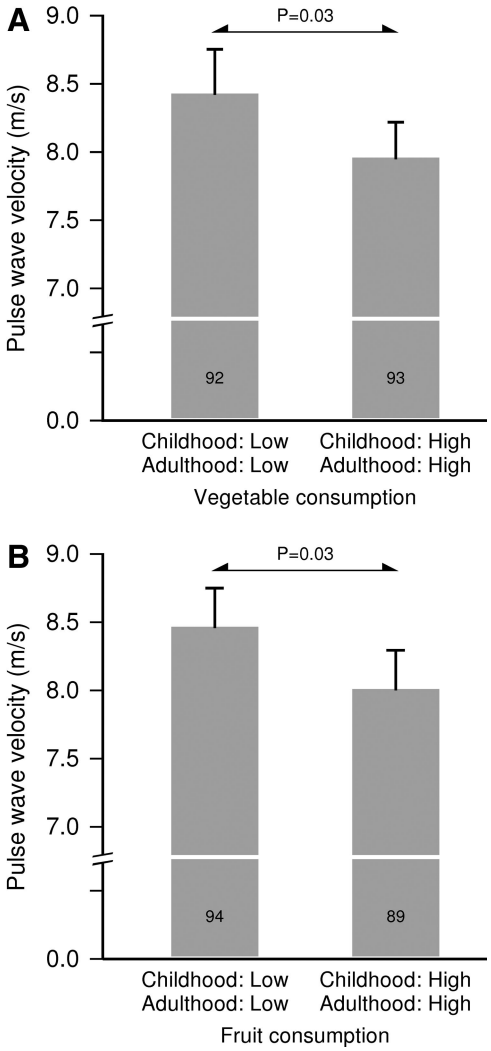

Figure 3. PWV in subjects persistently in the lowest or highest quintiles of vegetable consumption (A) and fruit consumption (B) in childhood (ages 3 to 18 years) and adulthood (ages 24 to 35 years). *P* values are from *t* tests. Bars represent mean plus 95% confidence interval. Values inside columns indicate the number of subjects in each group.

consumption in both childhood and adulthood had significantly lower PWV in adulthood than those persistently in the lowest quintile (difference in PWV of 0.46 m/s; $P=0.03$; Figure 3B).

Discussion

We found that the number of lifestyle risk factors identified in childhood correlated directly with adulthood PWV. We observed that high fruit and vegetable consumption is associated with lower adulthood PWV, especially if the consumption is persistently high from childhood to adulthood. We also found that vegetable consumption in both childhood and adulthood is an independent predictor of adulthood PWV.

To the best of our knowledge, this is the first study to demonstrate the associations between childhood lifestyle risk factors and adulthood PWV. Traditional childhood CVD risk factors have previously been shown to predict PWV in adulthood.[12,13] With regard to childhood lifestyle factors and PWV, current knowledge is limited to cross-sectional data. Sakuragi et al[29] have reported a cross-sectional association between childhood adiposity and physical activity and PWV.

Previous studies have reported inverse associations between plant-derived compounds and arterial stiffness in middle-aged and older adults.[14,15] High fruit and vegetable consumption has also been related to reduced CVD risk in prospective settings with middle-aged and elderly subjects.[5–7] Our present findings are in agreement with the previous studies and suggest that fruit and vegetable consumption is associated with the process of arterial stiffening in young adulthood. Subjects consuming high quantities of fruits and vegetables had slower PWV than those with low consumption. The difference in PWV was more evident if subjects had a high fruit and vegetable consumption from childhood to adulthood compared with those who had a persistently low consumption. The differences in PWV between the highest and the lowest quintile were 0.47 m/s for vegetable consumption and 0.46 m/s for fruit consumption. These

differences may be clinically meaningful because Blacher et al[30] reported an all-cause mortality adjusted odds ratio of 1.39 in patients with end-stage renal failure, and Vlachopoulos et al[11] demonstrated the all-cause mortality risk to increase by >10% in low- and high-risk patients for each PWV increase of 1 m/s.

We showed in our previous study that age, sex, SBP, childhood glucose, adulthood triglycerides, and adulthood insulin levels were independent predictors of adulthood PWV.[12] The pathophysiology related to these traditional risk factors has been discussed in the earlier report. To evaluate whether lifestyle risk factors have an independent effect on PWV, we used multivariate regression models including traditional and lifestyle risk factors. Notably, vegetable consumption was an independent predictor of adulthood PWV. This independent association strengthens the hypothesis that vegetable consumption has a favorable influence on the process of arterial stiffening.

The association between fruit consumption and PWV was relatively weak in adulthood, and this statistically significant finding may possibly be due, at least in part, to the large number of participants. However, the magnitude of the association was quite similar to that previously reported between traditional risk factors and PWV (for example, β values for triglycerides of 0.065 to 0.07).[12,13] Frequent fruit consumption can be considered to represent a conscious intention toward healthy food choices, particularly in the 1980s, when not all fruits were available throughout the year in Finland. Therefore, the associations observed with frequent fruit consumption may reflect the effect of an overall healthier diet, and the effect of fruit consumption may be diluted by other lifestyle changes. This highlights the relevance of the present findings.

We found a borderline significant inverse univariable association between adulthood physical activity and adulthood PWV. However, when adjusted for other risk factors, physical activity did not associate independently with PWV in our cohort. The dilution of the association between physical activity and PWV in the multivariable model may be explained by the fact that physical activity modulates traditional risk factors (eg, high-density lipoprotein cholesterol and triglycerides) in this cohort.[31] The possible favorable influence of physical activity on PWV may therefore not be direct but rather mediated through a modification of traditional risk factors. It is also important to keep in mind that other lifestyle risk factors could be confounders in these analyses.

The stiffness of large arteries increases with age. The mechanism of the stiffening process is complex,[32,33] including structural changes of the vascular wall as well as elastocalcinosis, overproduction of collagen, and degradation and remodeling of normal elastin, as caused by repeated mechanical load and inflammation. Structural stiffening may alter endothelial function and thereby further worsen the stiffening. Endothelial dysfunction reduces the expression of nitric oxide, thus increasing vascular smooth muscle cell tone and arterial stiffness.[32,33] Furthermore, increased local activity of the renin-angiotensin-aldosterone system enhances vascular hypertrophy, reduces elastin synthesis, and increases oxidative stress and fibrosis.[32] The impact of fruit and vegetable consumption (and thus of nutrients and phytochemicals such as potassium, flavonoids, folate, vitamins, and dietary fiber) on this complex pathophysiological process is largely unknown. Nevertheless, the antioxidative and anti-inflammatory effects, reduction of triglycerides and very-low-density lipoprotein, as well as enhanced glucose tolerance, reduced insulin resistance, and reversed endothelial dysfunction are possible underlying pathophysiological mechanisms.[6,7,32] Functional aspects of fruits and vegetables, such as low glycemic load, low energy density, and high water content, may also play a role in this process.[6,14]

Our study has some limitations. First, the food frequency questionnaire used provides the fruit and vegetable consumption frequency only as times per month and is therefore possibly an imprecise estimate (leading to underestimation of associations) because current dietary recommendations are ≥4 to 5 servings per day.[34] Another potential limitation is the nonparticipation in the follow-up study. However, baseline lifestyle risk factors in 1980 were mainly similar among participants and nonparticipants, with the exception of SBP and body mass index, which were slightly higher in nonparticipants. This significant difference can be explained at least in part by the large number of participants because the absolute difference was quite small. Therefore, the present study cohort appears to be fairly representative of the original study population. It is also a limitation that taking an average of Z scores over ages might oversimplify these data, although age did not modify the associations between risk factors and PWV in childhood. The approach evaluating the association between the number of risk factors and PWV in this study has not been validated. This limits the interpretation of the results and warrants validation in separate cohorts in future studies. Self-reported retrospective data on diet, alcohol, smoking, and physical activity will have bias. However, as reported previously, validation studies showed significant correlations between information obtained by the food frequency questionnaire and the 48-hour recall[24] and between physical activity index and maximal cycle ergometer test.[35] Kentala et al[36] showed a significant association between self-reports of smoking (a measure similar to that used in our study) and biochemical measurements. These findings support the validity of the self-reports. Because our study cohort was ethnically homogeneous, the generalizability of our results is limited to white European subjects. It is also important to remember that observational studies cannot establish causality, and the impact of both baseline values and the changes in risk factors during follow-up may have been underestimated or overestimated because of possible regression dilution bias.

In conclusion, lifetime lifestyle risk factors, most specifically vegetable consumption, are associated with arterial stiffness measured by PWV. The decrease in PWV appears to be more pronounced if dietary habits remain favorable from childhood to adulthood. These findings highlight the importance of emphasizing dietary habits as early as in childhood in the primary prevention of CVD.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The primary prevention of cardiovascular diseases should be started in childhood because the atherosclerotic process develops silently for decades before clinical events such as myocardial infarction or stroke occur. Epidemiological studies have shown that it may be possible to modify cardiovascular disease risk by favorable lifestyle changes (eg, healthy diet, adequate physical activity, smoking restriction). However, a limited amount of information is available on childhood lifestyle risk factors and cardiovascular disease risk in adulthood. The Cardiovascular Risk in Young Finns Study is an ongoing 5-center follow-up study of atherosclerosis risk factors in Finnish children and adolescents. Participants were followed up since 1980 and had lifestyle risk factor data since childhood (3 to 18 years). Arterial pulse wave velocity was determined in young adulthood (aged 30 to 45 years) because it is a marker of arterial stiffness and an independent predictor of cardiovascular events and all-cause mortality. We showed that high fruit and vegetable consumption was associated with lower pulse wave velocity. The decrease in pulse wave velocity was more evident if the consumption of fruits and vegetables remained high from childhood to adulthood. It is also important to modify all lifestyle risk factors (low fruit consumption, low vegetable consumption, low physical activity, and smoking) in childhood because multiple risk factors led to increased arterial stiffness in this study. These findings highlight the importance of emphasizing lifestyle as early as in childhood in the primary prevention of cardiovascular disease.

Simplified Definitions of Elevated Pediatric Blood Pressure and High Adult Arterial Stiffness

WHAT'S KNOWN ON THIS SUBJECT: Elevated blood pressure (BP) has long-term influence on the atherosclerotic process. The relative predictive ability of the standard BP definition endorsed by the National High Blood Pressure Education Program and the recently proposed 2 simplified definitions has not been studied.

WHAT THIS STUDY ADDS: Simplified pediatric BP tables predict risk of high adult arterial stiffness as well as the complex table does. These simple screening tools could be used for identifying pediatric subjects at risk and for intervening to improve adult cardiovascular outcomes.

abstract

OBJECTIVE: The ability of childhood elevated blood pressure (BP) to predict high pulse wave velocity (PWV), a surrogate marker for cardiovascular disease, in adulthood has not been reported. We studied whether elevated pediatric BP could predict high PWV in adulthood and if there is a difference in the predictive ability between the standard BP definition endorsed by the National High Blood Pressure Education Program and the recently proposed 2 simplified definitions.

METHODS: The sample comprised 1241 subjects from the Cardiovascular Risk in Young Finns Study followed-up 27 years since baseline (1980, aged 6–15 years). Arterial PWV was measured in 2007 by whole-body impedance cardiography.

RESULTS: The relative risk for high PWV was 1.5 using the simple 1 (age-specific) definition, 1.6 using the simple 2 (age- and gender-specific) definition, and 1.7 using the complex (age-, gender-, and height-specific) definition (95% confidence interval: 1.1–2.0, $P = .007$; 1.2–2.2, $P = .001$; and 1.2–2.2, $P = .001$, respectively). Predictions of high PWV were equivalent for the simple 1 or simple 2 versus complex definition ($P = .25$ and $P = .68$ for area under the curve comparisons, $P = .13$ and $P = .35$ for net reclassification indexes, respectively).

CONCLUSIONS: Our results support the previous finding that elevated BP tracks from childhood to adulthood and accelerates the atherosclerotic process. The simplified BP tables could be used to identify pediatric patients at increased risk of high arterial stiffness in adulthood and hence to improve the primary prevention of cardiovascular diseases. *Pediatrics* 2013;132:e70–e76

AUTHORS: Heikki Aatola, MD,[a] Costan G. Magnussen, PhD,[b,c] Teemu Koivistoinen, MD, MSc,[a] Nina Hutri-Kähönen, MD, PhD,[d] Markus Juonala, MD, PhD,[b,e] Jorma S.A. Viikari, MD, PhD,[e] Terho Lehtimäki, MD, PhD,[f] Olli T. Raitakari, MD, PhD,[b,g] and Mika Kähönen, MD, PhD[a]

Departments of [a]Clinical Physiology, [d]Pediatrics, and [f]Clinical Chemistry, Fimlab Laboratories, University of Tampere and Tampere University Hospital, Tampere, Finland; Departments of [e]Medicine, and [g]Clinical Physiology and Nuclear Medicine, and the [b]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and Turku University Hospital, Turku, Finland; and [c]Menzies Research Institute Tasmania, University of Tasmania, Tasmania, Australia

KEY WORDS

blood pressure, pediatrics, prehypertension, screening, stiffness

ABBREVIATIONS

AUC—area under receiver-operating characteristic curve
BP—blood pressure
CVD—cardiovascular diseases
NHBPEP—National High Blood Pressure Education Program
NPV—negative predictive value
NRI—net reclassification improvement
PPV—positive predictive value
PWV—pulse wave velocity

Dr Aatola analyzed and interpreted the data, performed statistical analysis, and drafted the initial manuscript; Dr Magnussen analyzed and interpreted the data, performed statistical analysis, and critically reviewed and revised the manuscript; Dr Koivistoinen analyzed and interpreted the data, and reviewed and revised the manuscript; Drs Hutri-Kähönen, Viikari, and Lehtimäki acquired the data, handled funding and supervision, and reviewed and revised the manuscript; Dr Juonala acquired the data, analyzed and interpreted the data, and critically reviewed and revised the manuscript; Dr Raitakari conceived and designed the research, acquired the data, handled funding and supervision, and critically reviewed and revised the manuscrip; Dr Kähönen conceived and designed the research, acquired the data, analyzed and interpreted the data, handled funding and supervision, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Mika Kähönen, MD, PhD, Tampere University Hospital, Department of Clinical Physiology, PO Box 2000, FI-33521 Tampere, Finland. E-mail: mika.kahonen@uta.fi

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Previous reports have shown that the atherosclerotic process begins in youth, and elevated blood pressure (BP) accelerates it.[1–4] Because of the epidemic of overweight and obesity in youth, the prevalence of hypertension is increasing.[5,6] Early modification of risk factors, especially elevated BP and obesity, to prevent the progression of atherosclerosis is among the major contemporary challenges in the primary prevention of cardiovascular diseases (CVD).

Previous studies have shown that BP tracks from childhood to adulthood, and subjects having elevated BP in childhood and adolescence are at increased risk of developing hypertension in adulthood.[7–9] These data indicate that elevated BP is established early in life, hence the prehypertension and hypertension are able to be identified already in youth, underlying the potential to reduce risks and optimize health outcomes as they relate to hypertensive diseases.

In the most recent guidelines issued by the National High Blood Pressure Education Program (NHBPEP), BP screening was recommended at all pediatric visits for health care from age 3 years.[10] The NHBPEP guidelines provide decision-based cut-points to allow clinicians and pediatric health providers to define youth as normal, prehypertensive (formerly high normal, >90th percentile) and hypertensive (>95th percentile), according to age, gender, and height percentiles. Considering there are 7 height percentiles, 2 measures (systolic and diastolic BP), and 17 age groups (1–17 years) for boys and girls, the NHBPEP tables contain 476 threshold values for the definition of pediatric prehypertension alone, the same amount for definition of pediatric hypertension. This complex definition could at least partly explain the poor diagnosis of prehypertension and hypertension in children and adolescents reported previously.[11,12] As a solution for this problem, Kaelber and Pickett[13] and Mitchell et al[12] recently proposed new screening tables. Kaelber and Pickett reduced the number of threshold values to 64 (2 measures and 16 age groups for boys and girls) by omitting height percentiles and separate cut-points to denote hypertension.[13] Mitchell et al introduced a table with only 10 threshold values (2 measures and 5 age groups in increments of 3 years).[12] Those values were near the lowest prehypertensive BP value in the NHBPEP table and were set to end in either 0 or 5. Both these simplified tables are proposed to use as a screening tool, which can more quickly and easily be used to identify pediatric patients whose BP levels need additional evaluation.

Arterial stiffness is a surrogate marker for CVD and, assessed as pulse wave velocity (PWV), is generally accepted as an independent predictor of cardiovascular events and all-cause mortality.[14,15] Increased PWV was also added to the list of markers of subclinical organ damage and prognostic factors in the European guidelines for management of arterial hypertension.[16] We and others have shown that childhood systolic BP is an independent predictor of PWV in adulthood.[17–19]

These previously mentioned findings strengthen the hypothesis that elevated pediatric BP accelerates the arterial stiffening and atherosclerotic process. However, to the best of our knowledge, no information has been published concerning the ability of the childhood elevated BP definitions to predict arterial stiffness in adulthood. Therefore, the aim of the current study was to evaluate and compare the utility of these 3 definitions to predict high adult PWV using participants of the prospective Cardiovascular Risk in Young Finns Study.

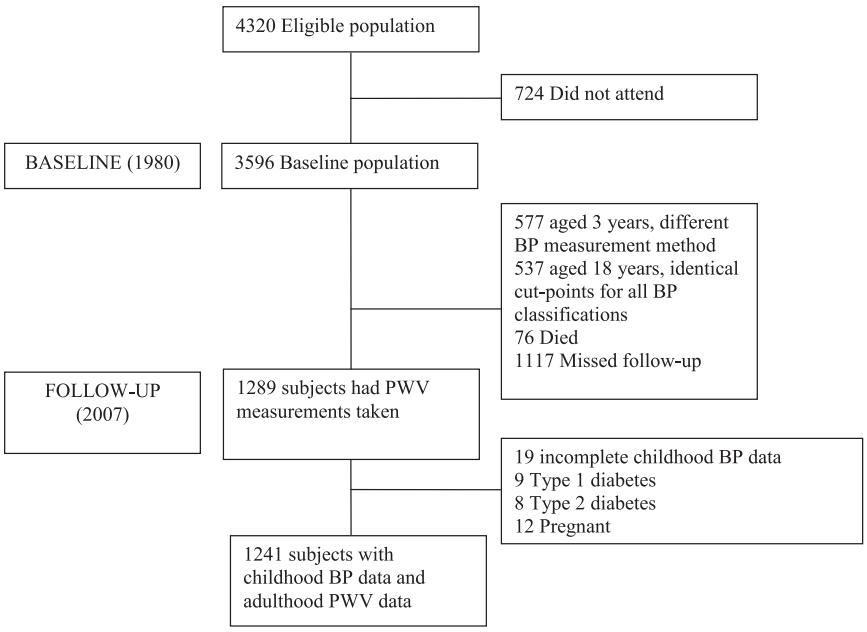
METHODS

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter follow-up study of atherosclerosis precursors in Finnish children and adolescents. The first cross-sectional study was conducted in 1980 for 3596 subjects aged 3 to 18 years.[20] They were randomly selected from the Finnish national population register. Although data were available for participants aged 3 years in 1980 (n = 577), they were not included in the analyses because BP measures were collected using an ultrasound device. Measures from youth aged 18 years (n = 537) were not included in the analyses because the cut-points are identical for all 3 definitions. In 2007, 1289 subjects had PWV measurements taken. The subjects with incomplete childhood data (n = 19), subjects with type 1 (n = 9) or type 2 (n = 8) diabetes, and female patients who were pregnant (n = 12) were excluded. Therefore, 1241 subjects were included in the analysis. Study flowchart is shown in Fig 1. We repeated the analysis after excluding participants taking lipid-lowering (n = 24) or antihypertensive medications (n = 76), with essentially similar results. All subjects gave written informed consent, and the study was approved by local ethics committees.

Clinical Measurements

At baseline and follow-up, height was measured using a Seca stadiometer with 0.5 cm accuracy. BP was measured with a standard mercury sphygmomanometer in 1980 and a random zero sphygmomanometer (Hawksley & Sons Ltd, Lansing, United Kingdom) in 2007. All measurements were taken on the right arm after the participant had been seated for 5 minutes. Cuff size was chosen according to arm circumference. Systolic BP was recorded for Korotkoff's first phase. Diastolic BP was recorded at both Korotkoff's fourth and fifth phases. Korotkoff's fifth phase results have been



BP – blood pressure
PWV – pulse wave velocity

FIGURE 1
Study Flowchart.

used in the analyses because in 1980 in all age groups, diastolic BP was better achieved with Korotkoff's fifth phase (no missing values in this study population) than Korotkoff's fourth phase (absent in 2.5% of subjects). This was consistent with results reported previously by Uhari et al[21] Readings to the nearest integer of millimeters of mercury were performed 3 times on each participant. The mean of these 3 measurements was used in the analyses.

Definition of Elevated BP Levels in Childhood

Simple 1 Definition

Participants were defined according to age-specific (increments of 3 years) cut-points proposed by Mitchell et al.[12] The cut-points are near the lowest prehypertensive (≥90th percentile) BP value in the NHBPEP tables and are set to end in 0 or 5.

Simple 2 Definition

Participants were defined according to age- and gender-specific BP cut-points proposed by Kaelber and Pickett.[13] The cut-points correspond to the lower limit of height (5th percentile) in the prehypertensive BP range (≥90th percentile) for a given age and gender in the NHBPEP tables.

Complex Definition

Participants were defined according to age, gender, and height percentiles for prehypertensive youth BP issued by the NHBPEP.[10]

Arterial PWV Studies

We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd, Saku Vald, Estonia) to determine PWV. CircMon includes a whole-body impedance cardiography channel, distal impedance plethysmogram channel, and an electrocardiogram channel. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in the whole-body impedance signal and, subsequently, in the distal plethysmogram signal from a popliteal artery at knee joint level. The measurement is triggered by the R wave of the electrocardiogram. The PWV can be determined from the distance and the time difference between the 2 recording sites. The repeatability index and the reproducibility index were good (99% and 87%, respectively).[22] A detailed description of the method,[17,23] the validation study,[23] and reference values[24] have been reported previously. High PWV was defined as values at or above the age-, gender-, and heart-rate-specific 80th percentile.

Statistical Methods

The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed with the use of age- and gender-adjusted regression analysis for continuous variables, the χ^2 test for categorical variables and the *t* test to examine differences in age. Age- and gender-adjusted logistic regression was used to estimate relative risks and 95% confidence intervals of adult high PWV according to the 3 definitions for elevated pediatric BP.

The ability of each definition to predict high adult PWV was assessed using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under receiver-operating characteristic curves (AUC), and estimates of risk reclassification; statistics that are in line with criteria put forward by the American Heart Association.[25] Sensitivity was calculated as true-positives/(true-positives + false-negatives) × 100; specificity as true-negatives/(true-negatives + false-positives) × 100; NPV as true-negatives/(true-negatives + false-negatives) × 100; and PPV as true-positives/(true-positives + false-positives) × 100. AUC was determined

from the logistic model and represents an estimate of the probability that the model assigns a higher risk to those who have the outcome (high PWV) compared with those who do not have the outcome. Differences in AUC between the simplified and complex definitions were estimated using the DeLong algorithm.[26] Net reclassification improvement (NRI) was also calculated to determine the extent to which the complex (vs simple 1 or simple 2) definition reassigned participants to a risk status that better reflected their final outcome (case or control).[27,28] The proportions of participants reclassified to either higher- or lower-risk categories are presented. Risk classification is improved if an individual with the outcome in adulthood (case) is placed in a higher risk category in youth or if an individual without the outcome in adulthood (control) is moved to a lower risk category in youth. The NRI is the sum of improvements in the reclassification of both case and control participants.

Analyses were performed with the SPSS for Windows (Release 20.0.0, SPSS Inc, IBM Corporation, Armonk, NY) and Stata (Release 10, StataCorp LP, College Station, TX). Statistical significance was inferred at a 2-tailed P value $<.05$.

RESULTS

The baseline (1980) characteristics of study participants (n = 1241) and nonparticipants (n = 1241) are shown in Table 1. There were more boys among nonparticipants ($P < .0001$), and they were slightly younger (P = .01). There was no difference in height, systolic BP, or diastolic BP. The prevalence of elevated BP in childhood was the same in the both groups according to the simple 1, simple 2, and complex definition (P = .10, P = .11, and P = .33, respectively).

Table 2 shows the characteristics of study participants in baseline and follow-up by PWV status in adulthood.

TABLE 1 Baseline Characteristics of Study Participants and Nonparticipants (Subjects Missed Follow-up or Excluded) in 1980

Variable	Participants	Nonparticipants	*P* Value
No. of subjects	1241	1241	
Gender, female, *n*	687 (55.4)	583 (47.0)	<.0001
Age, y	10.7 ± 3.3	10.4 ± 3.2	.01
Height, cm	145 ± 19	143 ± 19	.59
Systolic BP, mm Hg	112 ± 10	112 ± 11	.07
Diastolic BP, mm Hg	68 ± 9	68 ± 9	.07
Prevalence of elevated BP, simple 1 definition (age), *n*	669 (53.9)	710 (57.2)	.10
Prevalence of elevated BP, simple 2 definition (age and gender), *n*	717 (57.8)	756 (60.9)	.11
Prevalence of elevated BP, complex definition (age, gender, and height percentile), *n*	536 (43.2)	560 (45.1)	.33

Values are mean ± SD or *n* (%). Comparison between participants and nonparticipants were performed using age- and gender-adjusted regression analysis for continuous variables, χ^2 tests for categorical variables, and *t* test to examine differences in age

There was no difference in gender, age, or height between low- and high-PWV groups in the baseline. Those having high adult PWV had higher systolic and diastolic BP values (P = .02 and P = .004, respectively) and higher prevalence of elevated BP in childhood according to the simple 1, simple 2, and complex BP definition (P = .007, P = .001, and P = .0005, respectively). In the follow-up the BP differences were more evident, and the absolute differences in the prevalence of elevated BP (23.1% vs 48.6%, $P <$ .0001) and in PWV (7.7 m/s vs 9.9 m/s, $P <$ .0001) were remarkable.

Subjects having elevated BP in childhood were at increased risk of high PWV in adulthood (Table 3). The magnitude of risk was similar according to the simple 1, simple 2, or complex BP definition (50%, P = .007, 60%, P = .001, and 70%, P = .001, respectively).

Prediction of high adult PWV by the simplified definitions was equal with the

TABLE 2 Baseline (1980) and Follow-up (2007) Characteristics of Study Subjects by PWV Status in Adulthood

Variable	Low PWV	High PWV	*P* Value
No of subjects	994	247	
Gender, female, *n*	554 (55.3)	137 (55.5)	.97
1980			
Age, y	10.7 ± 3.3	10.7 ± 3.3	.87
Height, cm	145 ± 19	145 ± 19	.55
Systolic BP, mm Hg	112 ± 10	113 ± 11	.02
Diastolic BP, mm Hg	67 ± 9	69 ± 10	.004
Prevalence of elevated BP, simple 1 definition (age), *n*	517 (52.0)	152 (61.5)	.007
Prevalence of elevated BP, simple 2 definition (age and gender), *n*	552 (55.5)	165 (66.8)	.001
Prevalence of elevated BP, complex definition (age, sex and height percentile), n	405 (40.7)	131 (53.0)	.0005
2007			
Age, y	37.7 ± 3.3	37.7 ± 3.3	.87
Height, cm	172 ± 19	172 ± 9	.37
Systolic BP, mm Hg	118 ± 13	128 ± 14	<.0001
Diastolic BP, mm Hg	74 ± 11	81 ± 11	<.0001
Prevalence of elevated BP, *n*[a]	230 (23.1)	120 (48.6)	<.0001
PWV, m/s	7.7 ± 1.1	9.9 ± 1.4	<.0001

Low PWV was defined as values below the age-, gender-, and heart-rate-specific 80th percentile. High PWV was defined as values at or above the age-, gender-, and heart-rate-specific 80th percentile. Values are mean ± SD or *n* (%). Comparison between groups were performed using age- and gender-adjusted regression analysis for continuous variables, χ^2 tests for categorical variables, and *t* test to examine differences in age

[a] Classified as systolic BP ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg

prediction provided by the complex definition (Table 4). Neither AUC nor NRI were significantly different between the simple 1 and complex definition ($P = .25$ and $P = .13$, respectively) or between the simple 2 and complex definition ($P = .68$ and $P = .35$, respectively). The simple 1 and simple 2 definitions had higher sensitivity than complex definition (61.5, 66.8, and 53.0, respectively) but lower specificity (48.0, 44.5, and 59.3, respectively). All definitions had high NPV (83.4, 84.4, and 83.5, respectively).

Sensitivity Analyses

To test the robustness of our findings, we performed analyses using other standardized cut-points corresponding to the 70th, 75th, 85th, and 90th percentiles of PWV with essentially similar results (Supplemental Tables 5 and 6). We made also 2 additional subgroup analyses. First, we studied age and gender differences in 2 age groups and used 9 years of age as a cut-point. This cut-point was chosen because Juonala et al reported that risk factor measurements obtained at or after 9 years of age were predictive of subclinical atherosclerosis in adulthood in this cohort.[29] All 3 definitions made equal predictions for high PWV for older girls and boys, except the simple 1 definition for boys (Supplemental Table 7). Predictions for younger subjects were not statistically significant which at least partly can be explained by small group sizes (170 girls and 114 boys). Second, we used age- and gender-specific 85th percentile for BMI in 1980 as a cut-point to define subjects as normal weight or overweight. All 3 definitions made equal predictions for high PWV (1.8–2.1) for overweight subjects (Supplemental Table 8). These predictions were not statistically significant, possibly because of small group size ($N = 185$).

DISCUSSION

This study shows that elevated pediatric BP predicts increased PWV in adulthood. We also observed that 2 simplified definitions[12,13] for elevated pediatric BP predict high adult PWV equivalent to the more complex definition currently endorsed by the NHBPEP.[10] This finding is clinically meaningful because both these simplified tables could be more easily implemented as a screening tool in pediatric health care settings and outside of a physician's office when the height percentile required for the complex definition may not be obtainable.

We found also that subjects having high PWV in adulthood had higher BP values in childhood. Moreover, they have higher prevalence of elevated BP in childhood regardless the BP definition. In adulthood, differences between these groups were markedly greater (eg, the prevalence of elevated BP was more than twofold in the high-PWV group). Overall, all these observations suggest that early exposure to elevated BP plays an important role in the development of arterial stiffness and CVD.

Previous studies have reported clear tracking of BP, and especially elevated BP, from childhood to adulthood.[7–9] Additionally, systolic BP in childhood predicts hypertension,[9,30,31] arterial stiffness,[17–19,32] and coronary artery calcium[4] in adulthood. Our findings are in agreement with these reports showing that subjects having elevated BP in childhood are at higher risk of having increased PWV in adulthood. The risk is increased if elevated BP in childhood is defined according to either the NHBPEP table or 1 of the 2 simplified tables. To the best of our knowledge, this is the first study to demonstrate that all these definitions are able to differentiate youth at increased risk of high PWV in adulthood.

The stiffening process of large arteries is complex.[33,34] It is suggested that elevated blood BP causes mechanical load that leads to overproduction of collagen and degradation and remodeling of normal elastin.[33,34] As mentioned earlier, elevated BP tracks from childhood to adulthood[7–9] thus having long-term influence on the stiffening process. To slow down this process, it is necessary to identify subjects whose

TABLE 3 RR and 95% CI of High PWV in Adulthood According to the 3 Definitions for Elevated Pediatric BP

	Simple 1 Definition (Age)	Simple 2 Definition (Age and Gender)	Complex Definition (Age, Gender, and Height Percentile)
RR	1.5	1.6	1.7
(95% CI)	1.1–2.0	1.2–2.2	1.2–2.2
P value	.007	.001	.001

High PWV was defined as values at or above the age-, gender, and heart-rate-specific 80th percentile. All estimates adjusted for age and gender. CI, confidence interval; RR, relative risk.

TABLE 4 Sensitivity, Specificity, PPV, NPV, AUC With 95% CIs, and NRI Values of the 3 Definitions for Elevated Pediatric BP to Predict High PWV in Adulthood

Definition	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC	95% CI	*P* value	NRI, %	*P* value
Simple 1 definition (age)	61.5	48.0	22.7	83.4	0.548	0.508–0.587	0.25[a]	−2.8	0.13[a]
Simple 2 definition (age and gender)	66.8	44.5	23.0	84.4	0.556	0.517–0.596	0.68[b]	−1.0	0.35[b]
Complex definition (age, gender, and height percentile)	53.0	59.3	24.4	83.5	0.561	0.521–0.602			

High PWV was defined as values at or above the age-, gender- and heart rate-specific 80th percentile. CI, confidence interval.

[a] Simple 1 vs complex.

[b] Simple 2 vs complex.

high BP needs adequate intervention and treatment. It is especially important to make early diagnosis of hypertension in childhood because hypertension is a major modifiable risk factor. However, hypertension and prehypertension in children and adolescents are mostly undiagnosed.[11,12] This is a major clinical problem, and every effort should be made to help physicians in the screening process. Before it is possible to make correct diagnosis of hypertension, it is first necessary to identify elevated BP measurements. Because of that, Kaelber and Pickett[13] and Mitchell et al[12] proposed the new BP tables to aid in decision-making between normal and abnormal pediatric BP. Mitchell et al reported sixfold improvement, from 15% to 77%, in recognition of hypertensive pressures when using their simplified table than NHBPEP table.[12] This user-friendly screening tool could lead to wider screenings and diagnosis of prehypertension and hypertension in children and adolescents such that effective lifestyle interventions and medication could be optimized for health outcomes.

Because the clinical screening of elevated BP is more efficient with the simplified tables, it is important to know how well the simplified tables identified subjects at increased CVD risk. In this study, we found that the simplified definitions made almost identical predictions for high PWV as the complex definition. In addition, AUC and NRI analyses showed no difference between the simplified and complex definitions. The complex definition had lower sensitivity (53.0%) for high PWV than simple 1 and simple 2 (61.5%–66.8%, respectively) definitions, and all definitions had satisfactory (83.4%–84.4%) NPV. These findings further support the usability of both simplified tables to identify children and adolescents needing additional evaluation of BP. It is also worth mentioning that relative risks of high PWV for overweight subjects were equal (1.8–2.1) according to all 3 definitions. These predictions were not statistically significant, but this may be due to small group size.

The strength of this study is the large randomly selected cohort of young adults followed for 27 years since childhood. However, our study has some limitations that need to be considered in the interpretation of our findings. First, the CircMon-based PWV measurement method is not yet widely used in epidemiologic settings, apparently limiting comparability of our findings with observations from other cohorts. However, PWV values measured by CircMon are highly comparable to those measured by Doppler ultrasound method.[23] Also reference values for PWV measured with CircMon method[24] are similar to those observed in other studies in which varying methods of measurement have been used, indicating the generalizability of our findings. Second, bias due to nonparticipation in the follow-up study needs to be considered. Baseline characteristics in 1980 were mainly similar among participants and nonparticipants, with the exception of age. This statistically significant difference can be explained by the large number of participants because the absolute difference was small and not clinically meaningful. Therefore, the current study cohort appears to be fairly representative of the original study population. Third, as shown in Supplemental Tables 7 and 8, these results should be interpreted with caution for children aged <9 years and overweight subjects. Finally, the ethnic homogeneity of our study cohort limits the generalizability of our results to white European subjects.

CONCLUSIONS

Our results suggest that elevated BP in childhood predicts high PWV in adulthood. Additionally, it is possible to use the simplified BP tables to identify children and adolescents at increased risk of high adult PWV because the predictions using these tables are equivalent to the more complex NHBPEP table. This could aid the screening of elevated pediatric BP and hence improve the primary prevention of CVD and hypertension-related diseases.

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Simplified Definitions of Elevated Pediatric Blood Pressure and High Adult Arterial Stiffness

Heikki Aatola, Costan G. Magnussen, Teemu Koivistoinen, Nina Hutri-Kähönen, Markus Juonala, Jorma S.A. Viikari, Terho Lehtimäki, Olli T. Raitakari and Mika Kähönen

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Prospective Relationship of Change in Ideal Cardiovascular Health Status and Arterial Stiffness: The Cardiovascular Risk in Young Finns Study

Heikki Aatola, MD; Nina Hutri-Kähönen, MD, PhD; Markus Juonala, MD, PhD; Tomi T. Laitinen, BM; Katja Pahkala, PhD; Vera Mikkilä, PhD; Risto Telama, PhD; Teemu Koivistoinen, MD, MSc; Terho Lehtimäki, MD, PhD; Jorma S.A. Viikari, MD, PhD; Olli T. Raitakari, MD, PhD; Mika Kähönen, MD, PhD

From the Departments of Clinical Physiology (H.A., T.K., M.K.), Pediatrics (N.H.-K.), and Clinical Chemistry, Fimlab Laboratories (T.L.), University of Tampere and Tampere University Hospital, Tampere, Finland; School of Medicine (T.L., M.K.), University of Tampere, Tampere, Finland; Departments of Medicine (M.J., J.S.A.V.) and Clinical Physiology and Nuclear Medicine (O.T.R.), Research Centre of Applied and Preventive Cardiovascular Medicine (M.J., T.T.L, K.P., O.T.R.) and Paavo Nurmi Center, Sports and Exercise Medicine Unit (K.P.), University of Turku, Turku, Finland; Division of Nutrition (V.M.), University of Helsinki, Helsinki, Finland and Department of Sport Sciences (R.T.), University of Jyväskylä, Jyväskylä, Finland.

Address for correspondence: Mika Kähönen, MD, PhD, Tampere University Hospital, Department of Clinical Physiology, P.O. Box 2000, FI-33521 Tampere, FINLAND; Email: mika.kahonen@uta.fi, Tel: +358 3 3116 5394; fax: +358 3 3116 5511

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Abstract

Background—In 2010, the American Heart Association (AHA) defined ideal cardiovascular health as the simultaneous presence of 4 favorable health behaviors (non-smoking, ideal body mass index, physical activity at goal, and dietary pattern that promotes cardiovascular health) and 3 favorable health factors (ideal levels of total cholesterol, blood pressure, and fasting glucose). The association between a change in ideal cardiovascular health status and pulse wave velocity (PWV), a surrogate marker of cardiovascular disease (CVD), has not been reported.

Methods and Results—The study cohort consisted of 1143 Caucasian adults from the Cardiovascular Risk in Young Finns Study who were followed up for 21 years since baseline (1986). This cohort was divided in two subgroups; 803 participants (aged 9 to 18 years at baseline) to study the health status change from childhood to adulthood, and 340 participants (aged 21 to 24 years at baseline) to study health status change from young adulthood to middle age. The change in the ideal cardiovascular health index was inversely associated with PWV (adjusted for age, sex, and heart-rate) in younger (β=-0.25. $p<0.001$) and in older (β=-0.23, $p<0.001$) participants. The effect was even stronger (β=-0.32, $p<0.001$ and β=-0.37, $p<0.001$, respectively) after adjustment for the baseline ideal cardiovascular health index.

Conclusions—The change in ideal cardiovascular health status, both from childhood to adulthood and from young adulthood to middle age, was an independent predictor of adult PWV. Our results support the concept of ideal cardiovascular health as a useful tool for primordial prevention of CVD.

Key Words: ideal cardiovascular health, epidemiology, pulse wave velocity

Introduction

In January 2010, the American Heart Association (AHA) released its 2020 Impact Goals and changed the focus from primary prevention of cardiovascular disease (CVD) to primordial prevention.[1] It is no longer effective enough to focus the efforts on subjects at risk, but we must rather seek to prevent the development of risk factors.[1] To improve the primordial prevention of CVD AHA defined the concept of Ideal Cardiovascular Health: the simultaneous presence of 4 ideal health behaviors (non-smoking, normal body mass index [BMI], being physically active, and a healthy diet) and 3 ideal health factors (normal total cholesterol, blood pressure [BP], and fasting glucose).[1] This concept has been shown to predict lower CVD risk and mortality of all causes,[2-4] also among different ethnic groups[5]. However, the prevalence of ideal cardiovascular health has been extremely low in adolescence[6-8] and in adulthood.[2, 9, 10] Moreover, Huffman et al[11] reported that the changes in health behaviors and factors were quite far from the AHA 2020 Impact Goals.

Ideal cardiovascular health should be achieved early in life, as atherosclerosis has its origin in childhood[12] and childhood risk factors predict the occurrence of preclinical carotid atherosclerosis in adulthood.[13-15] There are two ways to reach ideal cardiovascular health in adulthood: to maintain favorable status from childhood or to change the profile from unfavorable to favorable. As the prevalence of ideal cardiovascular health appears to be low in adolescence and adulthood, as mentioned above, a large proportion of individuals would likely benefit from changing their profile towards the ideal.

However, reports concerning the relationship between a change in ideal cardiovascular health and cardiovascular outcomes are sparse. The effect of the change is interesting because all components of ideal cardiovascular health are modifiable, particularly through lifestyle

adjustments. We reported previously that a change in the ideal cardiovascular health index was independently associated with subclinical atherosclerosis.[6] We have also reported that favorable change in risk profile was inversely associated with the progression of carotid artery intima-media thickness[16] and arterial stiffness.[17]

To the best of our knowledge no data has been published about the associations between the ideal cardiovascular health index and pulse wave velocity (PWV) which is generally accepted as an intermediary cardiovascular outcome and an independent predictor of cardiovascular events and all-cause mortality.[18] The aim of the present report was to evaluate the relationship of the ideal cardiovascular health index and PWV—and the change in the index and PWV in particular. We used two subgroups: younger subjects (n=803, aged 9–18 years at baseline) to study the 21-year change from childhood to adulthood, and older subjects (n=340, aged 21–24 years at baseline) to study the 21-year change from young adulthood to middle age.

Methods

Subjects

The Cardiovascular Risk in Young Finns Study is an ongoing multicenter follow-up study of atherosclerosis precursors in Finnish children and adolescents. In 1980, a total of 4320 children and adolescents aged 3–18 years were randomly selected from the Finnish national population register.[19] For the present study, we chose the year 1986 as the baseline because it was the first follow-up at which fasting glucose values were measured. The follow-up survey was performed in 2007, when 1872 (aged 30–45 years) of the original participants attended PWV measurement. The subjects with incomplete risk factor data (n=687), those with type 1 (n=13) or type 2 (n=13) diabetes, and female subjects who were pregnant (n = 16) were

excluded. The present sample therefore comprised 1143 participants aged 30–45 years for whom complete risk factor data were available from baseline and who had undergone PWV and laboratory measurements during the 2007 survey. The study flow chart is shown in Figure 1. All subjects gave written informed consent, and the study was approved by local ethics committees.

Assessment and Definition of Health Behaviors

For all variables, the AHA definition[1] for health behaviors were followed as closely as possible.

In 1986, smoking was assessed in subjects aged ≥12 years. Smoking data were collected in connection with the medical examination in a secluded room where participants could respond confidentially and undisturbed. Subjects aged 12–18 years who reported having never smoked a whole cigarette were categorized as having an ideal childhood smoking status and those who had smoked 1 or more cigarettes as having a poor smoking status. Subjects aged <12 years were categorized as having an ideal child smoking status. Subjects aged 21–24 years in 1986 and all subjects in 2007 were classified as current smokers (poor), former smokers <12 months (intermediate), and never smokers or as having quit smoking >12 months ago (ideal).

Height and weight were measured and the BMI calculated as BMI=weight (kg)/(height (m))^2. BMI was classified according to the AHA criteria.[1]

Physical activity was assessed with a self-report questionnaire. Subjects answered the questions themselves, with their parents' assistance as necessary. The physical activity questionnaire consisted of the following variables: intensity of physical activity, frequency of moderate or vigorous activity, and hours spent on moderate or vigorous activity per week. The ideal physical activity for subjects aged 9–18 was approximated as ≥7 hours of moderate

or vigorous activity per week, and for adults as ≥1 h/wk vigorous intensity, ≥2–3 h/wk moderate intensity, or ≥2–3 h/wk moderate plus vigorous activity. Intermediate physical activity was classified as falling below these limits but exceeding none (poor).

In 1986, information on dietary habits was obtained with a nonquantitative food frequency questionnaire. Subjects answered the questions themselves, assisted by their parents when necessary. 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 the following 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. We classified the subjects as having an ideal fruit and vegetable consumption profile 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 profile. Subjects who consumed soft drinks a couple of times per week or less frequently were classified as having ideal soft drink consumption profile. Subjects who had 2–3 of these 3 ideal diet components were categorized as having an ideal healthy diet score, subjects with 1 component as an intermediate, and subjects with 0 components as having a poor healthy diet score in 1986. Although the quantitative amounts of fruits and vegetables, fish, and soft drinks consumed could not be inferred nor the AHA-recommended intakes of sodium and fiber-rich whole grain measured the questionnaire provided approximations of healthy diet score. In 2007, a more detailed quantitative food frequency questionnaire providing an estimate of food consumption in grams per day was introduced. Intake goals defined by the AHA are expressed for a 2000-kcal diet,[1] so we first scaled the intake goals according to the subjects' total energy intake. We then categorized achievement of the 5 AHA ideal dietary goals: ≥450 g/d per day of fruits and vegetables, ≥1 oz/d of fish, ≥3 oz/d of whole grains, <1500 mg/d of sodium, and ≤5 oz/d

of sugar-sweetened beverages. Subjects who scored 4 or 5 out of these 5 ideal diet components were categorized as having an ideal healthy diet score, subjects who scored 2 or 3 as having an intermediate, and those with 0 or 1 component as having a poor healthy diet score in 2007.

Assessment and Definition of Health Factors

For the determination of serum lipoprotein levels and plasma glucose concentrations, venous blood samples were drawn after an overnight fast. All determinations were performed with standard methods reported previously.[16, 20] BP was measured from the brachial artery with a random zero sphygmomanometer. All measurements were taken from the right arm after the participant had been seated for five minutes. Cuff size was chosen according to arm circumference. The average of 3 readings was used in the analysis. The total cholesterol status, the BP status, and the fasting plasma glucose status were classified as ideal, intermediate, and poor according to the AHA criteria.[1]

Indices of the Ideal Cardiovascular Health

Based on the individual health factors and behaviors, we generated corresponding AHA indices. The ideal cardiovascular health index corresponds to the number of ideal health factors and behaviors present at the baseline survey (Index86) and at the 2007 survey (Index07). In analyses, we used the ideal cardiovascular health indices as continuous variables.

Arterial Pulse Wave Velocity Studies

We used a whole-body impedance cardiography device (CircMon, JR Medical Ltd) to determine PWV. CircMon includes a whole-body impedance cardiography channel, distal

impedance plethysmogram channel, and an ECG channel. When the pulse pressure wave enters the aortic arch and the diameter of the aorta changes, the whole-body impedance decreases. The CircMon software measures the time difference between the onset of the decrease in the whole-body impedance signal and, subsequently, in the distal plethysmogram signal from a popliteal artery at knee-joint level. The measurement is triggered by the R wave of the ECG. The PWV can be determined from the distance and the time difference between the 2 recording sites. The repeatability index and the reproducibility index were good (99% and 87%, respectively).[21] A detailed description of the method,[17, 22] the validation study,[22] and reference values[23] have been reported previously.

Statistical Methods

The comparisons between study participants and nonparticipants (subjects lost to follow-up or excluded) were performed with the use of age- and sex-adjusted linear and logistic regression analysis and the *t* test to examine differences in age. Change in the ideal cardiovascular health index was calculated by subtracting the Index86 from the Index07. To study the associations between the indices and PWV, and between the change in ideal cardiovascular health index and PWV, we used age-, sex-, and heart-rate-adjusted linear regression. Heart rate was added in the analyses because it may be a confounding factor.[24] The statistical analyses were performed with the SPSS for Windows (Release 20.0.0, SPSS Inc). Statistical significance was inferred at a 2-tailed P value <0.05.

Results

The characteristics of the study participants and nonparticipants in 1986 are shown in Table 1. Participants aged 9–18 years were more often female and were more likely to have an ideal physical activity profile and ideal smoking status than nonparticipants. The older (aged

21–24 years) participants more often had an ideal physical activity status, an ideal healthy diet score, an ideal smoking status, and lower systolic blood pressure than nonparticipants. There was no difference in age, BMI, or glucose and total cholesterol levels between participants and nonparticipants.

In the 1986 survey, the mean ideal cardiovascular health index of the younger participants was 3.7 (SD 1.0; Table 2) and that of the older participants 4.3 (SD 1.2; Table 3). Ideal glucose levels (98.4% and 98.8%, respectively) and BMI levels (85.4% and 84.7%, respectively) were the most common. Ideal status in physical activity and smoking (6.5% and 22.8%, respectively) was the most difficult to achieve for younger participants, and none of them scored 0 or a full 7 out of 7 ideal health components in Index86. Of the older participants, only 7 individuals (2.1%) scored 7 out of 7 ideal health components in 1986, but none scored 0. Ideal status in terms of healthy diet, physical activity and blood pressure (22.9%, 49.4%, and 49.4%, respectively) were the most difficult to achieve for the older participants. Remarkable changes could be seen in the levels of individual components between 1986 and 2007 in both groups (Table 2 and 3).

Index86 was associated with Index07 in both groups ($\beta=0.21$, $p<0.001$, for younger and $\beta=0.36$, $p<0.001$, for older participants) in the linear regression model. This association remained significant after adjustment for age and sex ($\beta=0.22$, $p<0.001$, and $\beta=0.31$, $p<0.001$, respectively). Index86 was inversely related to PWV in both groups, but the relationship was significant only for older participants ($\beta=-0.05$, $p=0.16$, and $\beta=-0.16$, $p=0.004$, respectively). Index07 was significantly related to PWV in both groups ($\beta=-0.30$, $p<0.001$, and $\beta=-0.37$, $p<0.001$, respectively) and remained significant ($\beta=-0.30$, $p<0.001$, and $\beta=-0.36$, $p<0.001$, respectively) after adjustment for Index86.

There was wide variation in the change in ideal cardiovascular health index—from -4 to +5 points for the younger and from -5 to +4 points for the older participants. The average change was (mean±SD) 0.1±1.6 and -0.7±1.5, respectively. Female subjects had slightly higher means in both groups (0.6 vs. -0.5, $p<0.001$, and -0.4 vs. -1.1, $p<0.001$, respectively). None of the older subjects could maintain all 7 out of 7 ideal scores from baseline to follow-up. In addition, only 16 (2.0%) younger and 7 (1.5%) older subjects could reach this status in 2007. Changes in the ideal cardiovascular health index according to the Index86 scores are shown in tables 4 and 5.

The change in ideal cardiovascular health index was inversely related to PWV (adjusted for age, sex, and heart-rate) in younger ($\beta=-0.25$, $p<0.001$) and in older ($\beta=-0.23$, $p<0.001$) participants (Figure 2), and the effect was even stronger after adjustment for the Index86 ($\beta=-0.32$, $p<0.001$, and $\beta=-0.37$, $p<0.001$, respectively). In this model, Index86 also had independent significant inverse effect on PWV in both groups ($\beta=-0.19$, $p<0.001$, and $\beta=-0.32$, $p<0.001$, respectively). Negative change in ideal cardiovascular health index (Index86 ≥ 3 and change ≤ -2) was worse than staying unhealthy (Index86 < 3 and no change), PWV 8.4 m/s and 8.2 m/s ($p=0.02$), respectively. Additionally, among the participants with no change, the Index86 was inversely associated with PWV in younger ($\beta=-0.22$, $p=0.002$) and in older ($\beta=-0.38$, $p<0.001$) participants.

Sensitivity analyses

We performed 2 additional analyses. First, because smoking was only evaluated in subjects aged 12 years or older, we repeated all analyses without subjects aged less than 12 years. Second, we repeated analyses excluding the subjects using antihypertensive or cholesterol-

lowering medication. The results of all these additional analyses were similar to those shown. Third, we analyzed associations of PWV and mini-index i.e. the number of clinically important 3 key ideal behaviors: smoking, diet, and physical activity. The change in mini-index was also inversely associated with PWV (adjusted for age, sex, heart-rate, and mini-index in 1986) in both younger (β=-0.09, p=0.04) and in older (β=-0.25, p<0.001) participants.

Discussion

The present study showed that the change in the ideal cardiovascular health index was inversely related to PWV in adulthood. This relationship was significant for the younger (change from childhood to adulthood) and the older (change from young adulthood to middle age) participants and remained significant after adjusting for the ideal cardiovascular health index at baseline.

To the best of our knowledge, this is the first study to demonstrate the association between the change in the ideal cardiovascular health index and PWV. We and others have previously shown associations between traditional as well as lifestyle risk factors and PWV.[17, 25, 26] In these studies, however, either fewer components were used or risk factors were used as continuous variables with no specific classification. In the AHA definition for ideal cardiovascular health, the health-promoting benefits of each of the index components have been well established.[1] The ideal cardiovascular health index has also been shown to predict lower CVD risk and mortality of all causes.[2-4] However, the prevalence of ideal cardiovascular health has been reported to be extremely low in adolescence[6, 7] and in adulthood.[2, 9, 10] To improve the outcomes of the primordial prevention of CVD and to reach the AHA 2020 Impact Goals, there should be a clear change towards ideal cardiovascular

health status. At the same time, it should be known how the changes in ideal cardiovascular health status affect cardiovascular outcomes.

We found an inverse linear association between the change in ideal cardiovascular health index and PWV. The association was even stronger when adjusted for the index at baseline, supporting the hypothesis that a change in an individual's ideal cardiovascular health index has an independent favorable effect on the process of arterial stiffening. Our findings also support the previous studies showing tracking of risk factors from childhood to adulthood,[27, 28] as the average change in the index for the younger participants was 0.1 points. Remarkably, the older participants showed an average change in index of -0.7 points, and only 20.3% demonstrated an increase of +1 or more points. None of them were able to maintain the ideal 7 out of 7 score from baseline to follow-up, and only 16 younger and 7 older subjects were able to achieve this status at follow-up. This corroborates the fact that lifestyle changes towards ideal cardiovascular health are difficult to reach. However, we showed that the change in ideal cardiovascular index was inversely related to PWV in both groups—also after adjustment for the baseline index—suggesting that favorable changes in cardiovascular health could have favorable impact on the stiffening process of arteries.

Arterial stiffness is a surrogate marker for CVD and assessed as PWV, is generally accepted as an independent predictor of cardiovascular events and all-cause mortality.[18] The stiffening process of large arteries is complex and aging and exposure to cardiovascular risk factors accelerate it.[24, 29, 30] This process includes the overproduction of collagen, the degradation and remodeling of normal elastin, enhanced vascular hypertrophy, increased oxidative stress caused by repeated mechanical load, increased local activity of the renin-angiotensin-aldosterone system, and inflammation.[29, 30] Structural stiffening may alter the endothelial

function, thus increasing vascular smooth muscle cell tone and thereby further worsening the stiffening. Blood pressure has been shown to be the most remarkable lifetime risk factor for the stiffening process.[24-26] Cecelja and Chowienczyk reported the dissociation of aortic PWV with traditional CVD risk factors other than hypertension.[24] However, few reports concerning physical activity and PWV and none concerning a healthy diet and PWV were included in their systematic review—the review therefore included no reports concerning all 7 ideal cardiovascular health components and PWV.[24] It is also known that smoking, low physical activity, and an unhealthy diet form an important combination of risk factors when assessing the risk load for CVD.[1] Our present findings support the hypothesis that arterial stiffness measured by PWV reflects the ongoing multifactor pathologic process which could be assessed by means of the ideal cardiovascular health index, with the change in the index in particular.

The strengths of the present study are the well-phenotyped participants at baseline and follow-up and the longitudinal study design. However, our study has some limitations. Firstly, even though measurement of major risk factors is well standardized and therefore reasonably generalizable from one study to the next, the measurement of diet and physical activity is not. At baseline, information on dietary habits was obtained with a non-quantitative food frequency questionnaire, which has some limitations. For example, soft drinks included not only sugar-sweetened beverages but also diet drinks; the category of fruits included fruit juices; and fish was assessed as “fish foods,” which included fish and all fish products. In addition, the intakes of sodium and fiber-rich whole grain, which the AHA also include in their estimates, could not be inferred at baseline. In 2007, a more detailed quantitative food frequency questionnaire that provided an estimate of food consumption in grams per day was adopted. Physical activity was assessed with a subjective method both at baseline and follow-up. Self-reported data on diet, physical activity, and smoking are subject to known biases. However, as reported previously, validation studies showed significant

correlations between the information obtained by the food frequency questionnaire and the 48-hour recall[31], between the physical activity questionnaire and the maximal cycle ergometer test[32], and between the self-reported smoking (a measure similar to that used in our study) and biochemical measurements[33]. These findings support the validity of the self-reports. Secondly, because the present study cohort was racially homogeneous, the generalizability of our results is limited to white European subjects. It is also a limitation that definitions for Ideal Cardiovascular Health were different in childhood and in adulthood, so this may affect the relationship between the change in the index from childhood to adulthood and PWV in adulthood. It is also important to remember that PWV was measured only once in 2007, so it is not possible to analyze changes in PWV and especially age-related changes. Another potential limitation is the nonparticipation in the follow-up study. As shown in Table 1, participants had slightly better characteristics than nonparticipants in 1986, leading to an underestimation of associations. Finally, an observational study cannot establish causality, and the impact of both baseline values and the changes in risk factors during follow-up may have been underestimated or overestimated due to possible regression dilution bias.

In conclusion, we found that the change in the ideal cardiovascular health index was an independent predictor of PWV for younger (change from childhood to adulthood) and older (change from young adulthood to middle age) participants and remained significant after adjustment for the baseline index. Our findings suggest that it is always worthwhile to change one's lifestyle from unfavorable to favorable. Further, the study indicates that the ideal cardiovascular health index is a useful tool for primordial prevention of CVD.

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Disclosures

None.

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Figure Legends

Figure 1.

Study flowchart.

Figure 2.

PWV in 2007 by the change in the ideal cardiovascular health index for participants aged 30–39 years (A) and for participants aged 42–45 years (B). Change was calculated by subtracting the ideal cardiovascular health index in 1986 from the index in 2007. Bars represent sex-, age-, and heart-rate-specific mean plus 95% confidence interval. Dashed line represents population mean and values inside columns indicate the number of subjects in each group.

Table 1.

Characteristics of Study Participants and Nonparticipants (Subjects Missed Follow-up or Excluded) in 1986

Variable	Participants	Nonparticipants	p-value
Children 9–18 y of age			
Number of subjects	803	1210	
Sex, female, %	56.4	48.0	0.0002
Age, y, mean (SD)	13.6 (3.4)	13.3 (3.3)	0.06
BMI, kg/m^2, mean (SD)	19.4 (3.1)	19.1 (3.4)	0.43
Ideal physical activity, %	6.5	4.6	0.03
Ideal healthy diet score, %	23.8	21.2	0.19
Never smoked whole cigarette, %*	22.8	18.3	0.01
Systolic blood pressure, mmHg, mean (SD)	112 (12)	111 (12)	0.22
Diastolic blood pressure, mmHg, mean (SD)	63 (9)	62 (10)	0.58
Glucose, mmol/l, mean (SD)	4.7 (0.4)	4.8 (1.1)	0.13
Total cholesterol, mmol/l, mean (SD)	4.9 (0.9)	5.0 (1.0)	0.28
Adults 21–24 y of age			
Number of subjects	340	426	
Sex, female, %	56.5	51.2	0.15
Age, y, mean (SD)	22.5 (1.5)	22.4 (1.5)	0.41
BMI, kg/m^2, mean (SD)	22.3 (2.9)	22.5 (2.8)	0.42
Ideal physical activity, %	49.4	31.2	<0.0001
Ideal healthy diet score, %	22.9	16.4	0.03
Ideal smoking status, %	60.9	39.2	<0.0001

Systolic blood pressure, mmHg, mean (SD)	121 (12)	123 (12)	0.02
Diastolic blood pressure, mmHg, mean (SD)	71 (9)	71 (11)	0.27
Glucose, mmol/l, mean (SD)	4.6 (0.4)	4.6 (0.5)	0.88
Total cholesterol, mmol/l, mean (SD)	5.1 (0.9)	5.1 (1.0)	0.99

Comparison between participants and nonparticipants were performed using age- and sex-adjusted linear and logistic regression analysis as well as the *t* test to examine differences in age.

* Smoking data were gathered on subjects aged 12–18 years

Table 2. Prevalence of Cardiovascular Health Behaviors and Factors in 1986 and 2007, Participants Aged 9–18 Years in 1986, n=803

Variable	1986	2007
Smoking status*		
Poor (childhood: smoked 1 or more cigarettes; adulthood: current smoker), %	77.2	24.2
Intermediate (adulthood: former ≤12 months), %	-	4.9
Ideal (childhood: never tried or never smoked whole cigarette; adulthood: never or quit >12 months ago), %	22.8	71.0
Body mass index†		
Poor (childhood: >95th percentile; adulthood: ≥30 kg/m^2), %	4.8	16.3
Intermediate (childhood: 85–95th percentile; adulthood: 25–29.9 kg/m^2), %	9.8	35.5
Ideal (childhood: <85th percentile; adulthood: <25 kg/m^2), %	85.4	48.2
Physical activity level		
Poor (none), %	11.3	8.6
Intermediate (childhood: >0 and <7 hours of moderate or vigorous per week; adulthood: >0 and <1 h/wk vigorous or <2–3 h/wk moderate), %	82.2	42.0
Ideal (childhood: ≥7 hours of moderate or vigorous activity per week; adulthood: ≥1 h/wk vigorous intensity or ≥2–3 h/wk moderate intensity or ≥2–3 h/wk moderate plus vigorous), %	6.5	49.4
Healthy diet score‡		
Poor (0 components in 1986; 0–1 components in 2007), %	20.7	20.5
Intermediate (1 component in 1986; 2–3 components in 2007), %	55.5	66.4

Ideal (2-3 components in 1986; 4–5 components in 2007), %	23.8	13.1
Total cholesterol		
Poor (childhood: ≥200 mg/dL; adulthood: ≥240 mg/dL), %	35.3	7.0
Intermediate (childhood: 170–199 mg/dL; adulthood: 200-240 mg/dL or treated to goal), %	35.4	27.7
Ideal (childhood: <170 mg/dL; adulthood: <200 mg/dL), %	29.3	65.3
Blood pressure†		
Poor (childhood: >95th percentile; adulthood: SBP ≥140 or DBP ≥90 mmHg), %	8.6	14.2
Intermediate (childhood: 90–95th percentile; adulthood: SBP 120–139 or DBP 80-89 mmHg or treated to goal), %	9.5	35.5
Ideal (childhood: <90th percentile; adulthood: <120/<80 mmHg), %	81.9	50.3
Fasting plasma glucose		
Poor (≥126 mg/dL), %	-	0.2
Intermediate (100–125 mg/dL or treated to goal in adulthood), %	1.6	18.2
Ideal (<100 mg/dL), %	98.4	81.6
Ideal cardiovascular health index, points, mean (SD) §	3.7 (1.0)	3.8 (1.5)
Pulse wave velocity, m/s, mean (SD) ‖		7.9 (0.6)

* Smoking only aged 12 years and older in 1986

† All percentile limits are age- and sex-specific.

‡ Healthy Diet Components in 1986: fruits and vegetables = consumption of both fruits and vegetables daily; fish = consumption of fish or fish products a couple of times per week or more frequently; soft drinks = consumption of soft drinks a couple of times per week or less

frequently. Components in 2007: fruits and vegetables ≥450 g/d; fish: ≥1 oz/d; whole grains ≥3 oz/d; sodium <1500 mg/d; sugar-sweetened beverages ≤5 oz/d.

§ Corresponds to the number of ideal health factors and behaviors

|| Adjusted for sex, age and heart-rate

Table 3. Prevalence of Cardiovascular Health Behaviors and Factors in 1986 and 2007, Participants Aged 21–24 Years in 1986, n=340

Variable	1986	2007
Smoking status		
Poor (current smoker), %	27.4	17.6
Intermediate (former ≤12 months), %	11.8	4.7
Ideal (never or quit >12 months ago), %	60.9	77.6
Body mass index		
Poor (≥30 kg/m^2), %	1.8	20.0
Intermediate (25–29.9 kg/m^2), %	13.5	36.2
Ideal (<25 kg/m^2), %	84.7	43.8
Physical activity level		
Poor (none), %	20.6	8.5
Intermediate (>0 and <1 h/wk vigorous or <2–3 h/wk moderate), %	30.0	40.6
Ideal (≥1 h/wk vigorous intensity or ≥2–3 h/wk moderate intensity or ≥2–3 h/wk moderate plus vigorous), %	49.4	50.9
Healthy diet score*		
Poor (0 components in 1986; 0–1 components in 2007), %	20.3	13.5
Intermediate (1 component in 1986; 2–3 components in 2007), %	56.8	72.9
Ideal (2–3 components in 1986; 4–5 components in 2007), %	22.9	13.5
Total cholesterol		
Poor (≥240 mg/dL), %	11.5	11.2
Intermediate (200–240 mg/dL or treated to goal), %	29.1	38.2
Ideal (<200 mg/dL), %	59.4	50.6
Blood pressure		

Poor (SBP ≥140 or DBP ≥90 mmHg), %	9.1	24.4
Intermediate (SBP 120–139 or DBP 80–89 mmHg or treated to goal), %	41.5	34.1
Ideal (<120/<80 mmHg), %	49.4	41.5
Fasting plasma glucose		
Poor (≥126 mg/dL), %	-	1.2
Intermediate (100–125 mg/dL or treated to goal), %	1.2	24.4
Ideal (<100 mg/dL), %	98.8	74.4
Ideal health index, points, mean (SD) †	4.3 (1.2)	3.5 (1.5)
Pulse wave velocity, m/s, mean (SD) ‡		8.7 (0.5)

* Healthy Diet Components in 1986: fruits and vegetables = consumption of both fruits and vegetables daily; fish = consumption of fish or fish products a couple of times per week or more frequently; soft drinks = consumption of soft drinks a couple of times per week or less frequently. Components in 2007: fruits and vegetables ≥450 g/d; fish: ≥1 oz/d; whole grains ≥3 oz/d; sodium <1500 mg/d; sugar-sweetened beverages ≤5 oz/d.

†Corresponds to the number of ideal health factors and behaviors

‡ Adjusted for sex, age and heart-rate

Table 4. Prevalence of change in the Ideal Cardiovascular Health Index According to the Index in 1986, participants aged 9–18 years in 1986, n=803

	Ideal Cardiovascular Health Index in 1986, Points								
	All	0	1	2	3	4	5	6	7
n	803		8	83	254	306	133	19	
Change									
2 or more	19.4		37.5	49.4	28.3	11.8	3.0		
1	22.2		37.5	18.1	21.3	28.8	12.8	5.3	
0	24.5		25.0	24.1	24.8	23.2	27.1	26.3	
-1	17.4			8.4	16.5	17.3	24.1	31.6	
-2 or less	16.4				9.1	19.0	33.3	36.8	

Table 5. Prevalence of change in the Ideal Cardiovascular Health Index According to the Index in 1986, participants aged 21–24 years in 1986, n=340

	Ideal Cardiovascular Health Index in 1986, Points								
	All	0	1	2	3	4	5	6	7
n	340		4	19	63	105	105	37	7
Change									
1 or more	20.3		50.0	26.3	39.7	16.2	18.1	2.7	
0	25.3		50.0	52.6	31.7	27.6	19.0	13.5	
-1	23.5			21.1	17.5	23.8	26.7	27.0	28.6
-2	18.8				7.9	26.7	17.1	27.0	42.9
-3 or less	12.1				3.2	5.7	19.0	29.7	28.6

Figure 1.

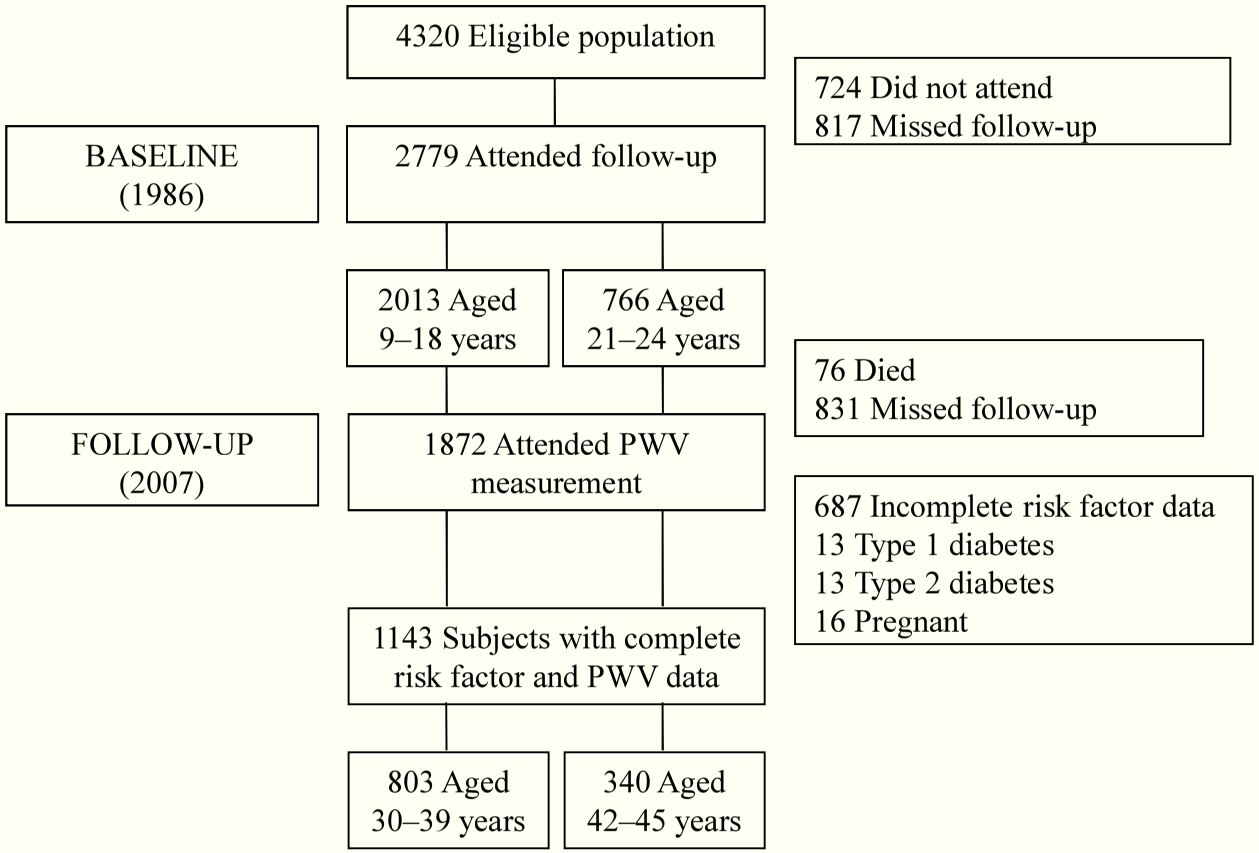
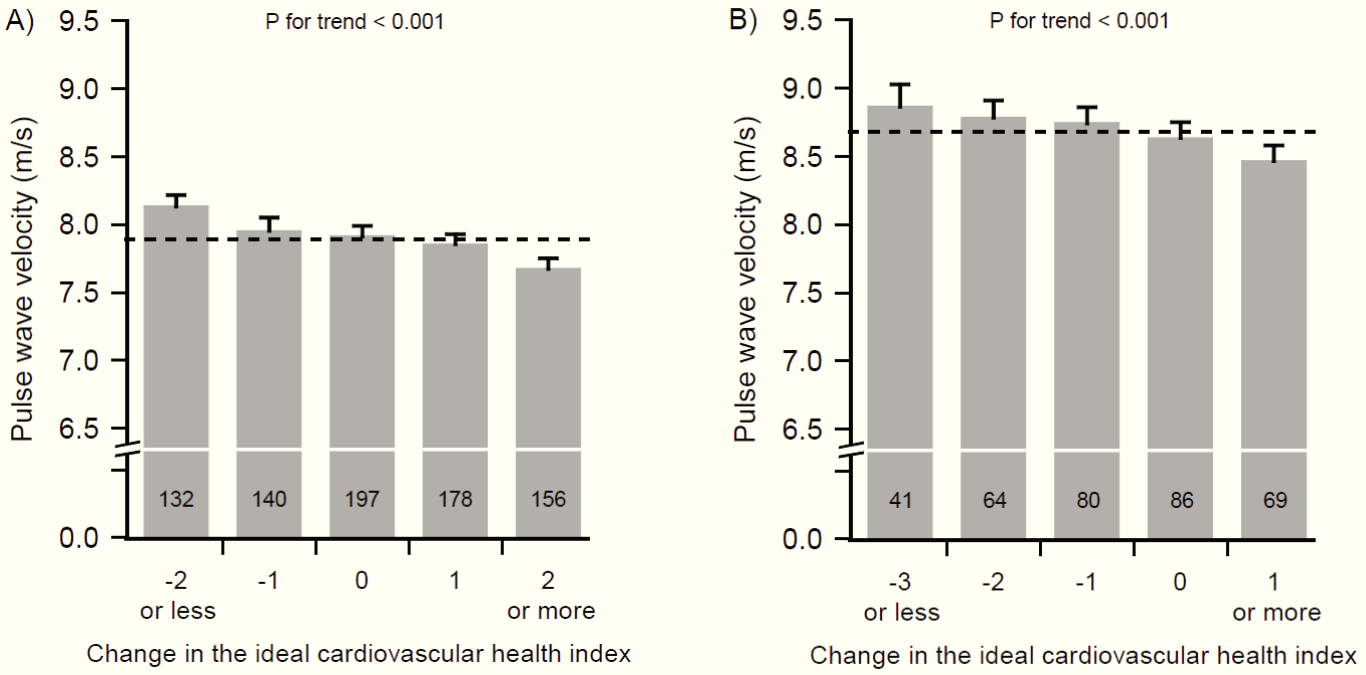

4320 Eligible population
724 Did not attend
817 Missed follow-up
BASELINE
(1986)
2779 Attended follow-up
2013 Aged
9–18 years
766 Aged
21–24 years
76 Died
831 Missed follow-up
FOLLOW-UP
(2007)
1872 Attended PWV
measurement
687 Incomplete risk factor data
13 Type 1 diabetes
13 Type 2 diabetes
16 Pregnant
1143 Subjects with complete
risk factor and PWV data
803 Aged
30–39 years
340 Aged
42–45 years

Figure 2.


A)
P for trend < 0.001
Pulse wave velocity (m/s)
9.5
9.0
8.5
8.0
7.5
7.0
6.5
0.0
132
140
197
178
156
-2 or less
-1
0
1
2 or more
Change in the ideal cardiovascular health index
B)
P for trend < 0.001
Pulse wave velocity (m/s)
41
64
80
86
69
-3 or less
-2
-1
0
1 or more
Change in the ideal cardiovascular health index