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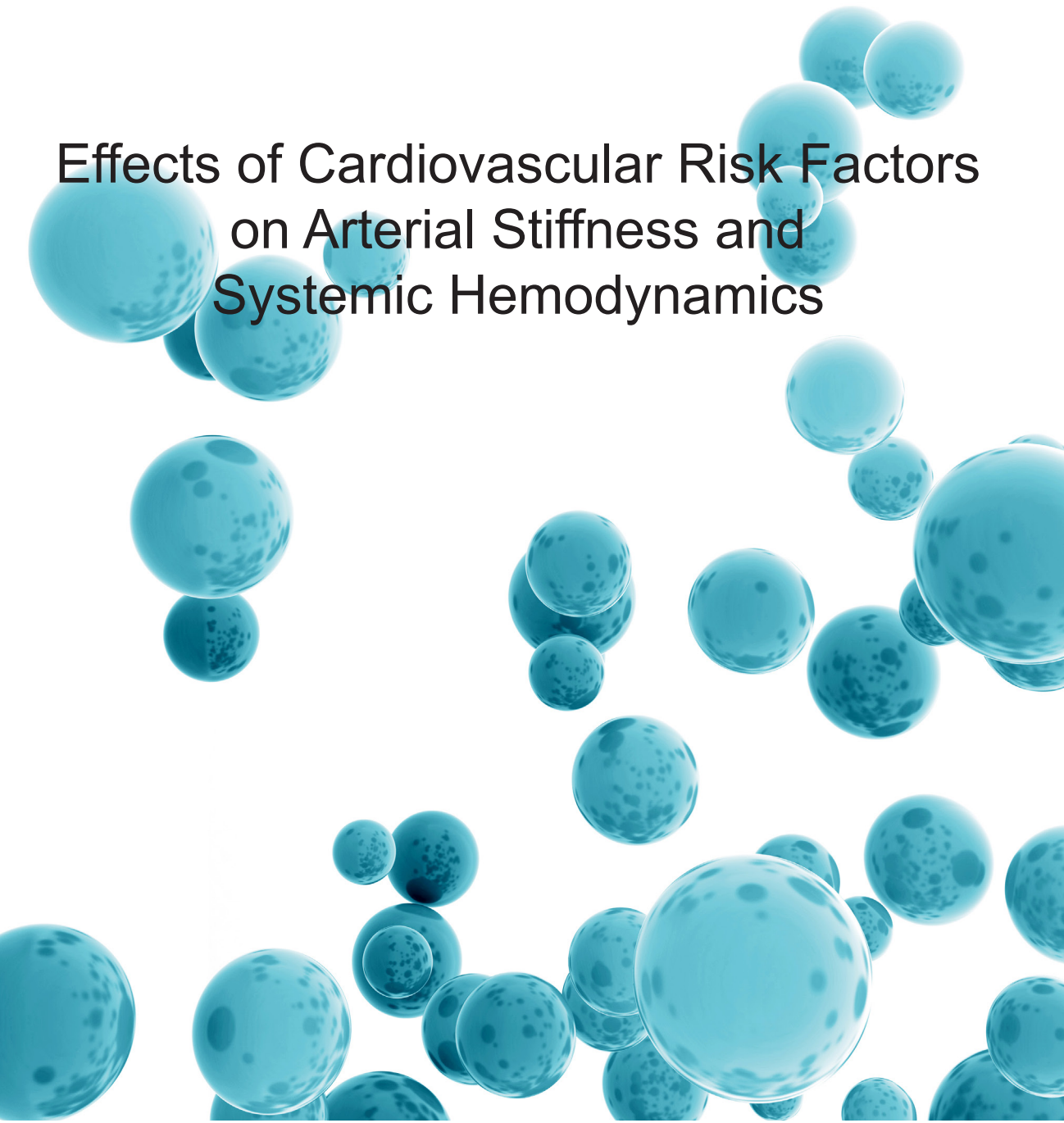
Effects of Cardiovascular Risk Factors on Arterial Stiffness and Systemic Hemodynamics



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Effects of Cardiovascular Risk Factors on Arterial Stiffness and Systemic Hemodynamics

ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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Tiivistelmä

Tausta: Metabolinen oireyhtymä on kasauma sydän- ja verisuonisairauksien riskitekijöitä, mukaan lukien kohonnut verenpaine, dyslipidemia, diabetes ja sen esiasteet (suurentunut paastoglukoosi ja heikentynyt glukoosinsieto), insuliiniresistenssi ja keskivartalolihavuus. Metabolisen oireyhtymän on osoitettu olevan yhteydessä varhaisiin valtimotautimuutoksiin sekä kohonneeseen sydän- ja verisuonisairauksien ja kuolleisuuden riskiin aikuisilla. Myös lapsuuden metabolinen oireyhtymä saattaa lisätä riskiä sydän- ja verisuonisairauksiin aikuisena.

Lihavuusepidemian ohella tyypin 2 diabeteksen ja metabolisen oirehtymän esiintyvyys on lisääntymässä hälyyttävästi. Lisäksi dyslipidemiasta on tullut merkittävä kansanterveydellinen ongelma maailmanlaajuisesti. Vuosikymmenten intensiivisestä tutkimustyöstä huolimatta näiden metabolisten sairauksien vaikutukset sydämen ja verenkiertoelimistön toimintaan ovat vielä osittain selvittämättä.

Tavoitteet: Tutkimuksen tavoitteena oli selvittää sokeriaineenvaihdunnan häiriöiden, lapsuuden ja aikuisiän metabolisen oireyhtymän sekä apolipoproteiinien B ja A-1 yhteyksiä valtimoiden jäykkyyteen. Lisäksi tutkimuksessa selvitettiin metabolisen oireyhtymän ja sokeriaineenvaihdunnan häiriöiden vaikutuksia hemodynaamisiin muuttujiin.

Aineisto ja menetelmät: Tutkimuspopulaatio koostui 1872 henkilöstä (iältään 30–45 vuotta, 46 % miehiä), jotka osallistuivat Lasten Sepelvaltimotaudin Riskitekijät -tutkimukseen, sekä 455 henkilöstä (iältään 46–76 vuotta, 44 % miehiä), jotka osallistuivat Terveys 2000 -tutkimukseen. Pulssiaallon etenemisnopeus, jota pidetään yleisesti luotettavimpana tapana arvioida valtimoiden jäykkyyttä, sekä hemodynaamiset muuttujat (sydämen iskutilavuus, ääreisverenkierron vastus) mitattiin käyttäen koko kehon impedanssikardiografia -laitteistoa.

Tulokset: Metabolinen oireyhtymä sekä glukoosinsiedon heikkeneminen olivat yhteydessä alentuneeseen sydämen iskutilavuuteen sekä kohonneeseen ääreisverenkierron vastukseen ja pulssiaallon etenemisnopeuteen. Henkilöillä, jotka parantuivat metabolisesta oireyhtymästä kuuden vuoden seuranta-aikana, oli korkeampi sydämen iskutilavuus ja matalampi pulssiaallon etenemisnopeus verrattuna henkilöihin, jotka sairastivat metabolista oireyhtymää kuuden vuoden seuranta-ajan. Lapsuudessa metabolista oireyhtymää sairastaneilla oli korkeampi pulssiaallon etenemisnopeus aikuisena verrattuna niihin koehenkilöihin, jotka olivat lapsuudessa terveitä. Myös niillä koehenkilöillä, jotka sairastivat metabolista oireyhtymää sekä lapsuudessa että aikuisena, oli korkeampi pulssiaallon etenemisnopeus verrattuna koehenkilöihin, jotka parantuivat oireyhtymästä 21 vuoden seuranta-aikana. Kohonneen apolipoproteiini B:n todettiin olevan yhteydessä kohonneeseen pulssiaallon etenemisnopeuteen. Lisäksi kohonnut apolipoproteiini B ennusti kohonnutta pulssiaallon etenemisnopeutta kuusi vuotta myöhemmin mitattuna.

Johtopäätökset: Sokeriaineenvaihdunnan häiriöillä ja metabolisella oireyhtymällä on useita haitallisia vaikutuksia sydämen ja verenkiertoelimistön toimintaan, kun taas parantuminen metabolisesta oireyhtymästä voi aikaansaada suotuisia muutoksia sydämen ja verenkiertoelimistön toiminnassa. Lisäksi tutkimuksen tulokset osoittavat, että kohonnut apolipoproteiini B on yhteydessä kohonneeseen valtimoiden jäykkyytteen.

Tutkimuksen tulokset tuovat uusia näkökulmia sydän- ja verisuonisairauksien riskitekijöiden vaikutuksista sydämen ja verenkiertoelimistön toimintaan. Tutkimuksen löydökset painottavat riskitekijöiden ehkäisyn ja hoidon tärkeyttä niin lapsilla kuin aikuisillakin.

Abstract

Backround: Metabolic syndrome is a constellation of metabolic abnormalities including hypertension, dyslipidemia, glucose intolerance (impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes), insulin resistance, and obesity, all well known risk factors for cardiovascular disease. In adult populations, the simultaneous accumulation of these factors carries an increased risk of subclinical atherosclerosis and cardiovascular disease, in addition to increasing mortality. Growing attention has also been directed at metabolic syndrome in children and adolescents as a diagnosis of paediatric metabolic syndrome may predict an increased risk of cardiovascular disease in adulthood.

Parallel with the obesity epidemic, the incidence of type 2 diabetes and metabolic syndrome have increased alarmingly. Moreover, the high prevalence of dyslipidemia has become a worldwide public health problem. Although there has been intensive research in the last decades, the effects of these metabolic abnormalities on cardiovascular function have not been fully elaborated.

Aims: The current study investigated the associations of impaired glucose metabolism, childhood and adulthood metabolic syndrome, and apolipoproteins B and A-1 with arterial stiffness. In addition, the present study examined the relationship between metabolic syndrome, impaired glucose metabolism and systemic hemodynamic parameters.

Subjects and methods: The study population consisted of 1872 participants (aged 30–45 years, 46% males) participating in the Cardiovascular Risk in Young Finns Study, and 455 participants (aged 46–76 years, 44% males) enrolled in the Health 2000 Survey. A whole-body impedance cardiography device was used to measure arterial pulse wave velocity, a commonly used marker of arterial stiffness, and systemic hemodynamic parameters including stroke index and systemic vascular resistance index.

Results: Metabolic syndrome, an increasing number of metabolic sydrome components and a worsening of glucose tolerance were associated with lower stroke index as well as higher systemic vascular resistance index and pulse wave velocity. Participants with persistent metabolic syndrome had a lower stroke index and higher pulse wave velocity when compared to participants who recovered from metabolic syndrome over 6 years' follow up. Participants suffering from metabolic syndrome in childhood had a higher pulse wave velocity after 21-year follow-up when compared with those not afflicted with the syndrome in childhood. Moreover, participants who recovered from metabolic syndrome during the 21-year follow-up period had a lower pulse wave velocity than those with persistent metabolic syndrome. Apolipoprotein B was directly and independently associated with pulse wave velocity, and apolipoprotein B measured in young adulthood was predictive of pulse wave velocity measured 6 years later.

Conclusions: Deteriorating glucose tolerance and metabolic syndrome have adverse effects on arterial stiffness and systemic hemodynamics, and recovery from metabolic syndrome may improve cardiovascular function. The present study also suggests that increased apolipoprotein B is associated with increased arterial stiffness.

The current study brings new insight into the relationships between cardiovascular risk factors and cardiovascular function, and our findings underline the importance of the prevention and control of cardiovascular risk factors in both childhood and adulthood.

Contents

List of original publications

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I–IV:

I Koivistoinen T, Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Laitinen T, Taittonen L, Lehtimäki T, Kööbi T, Raitakari OT, Kähönen M. Systemic hemodynamics in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study. Annals of Medicine. 2010;42:612-621.

II Koivistoinen T, Jula A, Aatola H, Kööbi T, Moilanen L, Lehtimäki T, Kähönen M. Systemic hemodynamics in relation to glucose tolerance: the Health 2000 Survey. Metabolism. 2011;60:557-563.

III Koivistoinen T, Hutri-Kähönen N, Juonala M, Aatola H, Kööbi T, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Metabolic syndrome in childhood and increased arterial stiffness in adulthood: the Cardiovascular Risk In Young Finns Study. Annals of Medicine. 2011;43:312-319.

IV Koivistoinen T, Hutri-Kähönen N, Juonala M, Kööbi T, Aatola H, Lehtimäki T, Viikari JS, Raitakari OT, Kähönen M. Apolipoprotein B is related to arterial pulse wave velocity in young adults: the Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2011;214:220-224.

Abbreviations

ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AHA	American Heart Association
AIx	Augmentation index
ASI	Arterial stiffness index
ATPIII	Adult Treatment Panel III
AUC	Areas under curve
BMI	Body mass index
CAC	Carotid artery compliance
Cdist	Carotid artery distensibility
CI	Cardiac index
CO	Cardiac output
CRP	C-reactive protein
CVD	Cardiovascular disease
DM2	Type 2 diabetes
EGIR	European Group for Study of Insulin Resistance
HDL	High-density lipoprotein
ICG_{TH}	Thoracic impedance cardiography
ICG_{WB}	Whole-body impedance cardiography
IDF	International Diabetes Foundation
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IPG	Impedance plethysmogram
LDL	Low-density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
MetS	Metabolic syndrome
NCEP	National Cholesterol Education Program
NGT	Normal glucose tolerance
NHLBI	National Heart, Lung, and Blood Institute
OGTT	Oral glucose tolerance test

Ped1MetS	First paediatric metabolic syndrome definition
Ped2MetS	Second paediatric metabolic syndrome definition
PP	Pulse pressure
PWV	Pulse wave velocity
ROC	Receiver-operating characteristic
SE	Standard error
SI	Stroke index
SV	Stroke volume
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index
VLDL	Very-low-density lipoprotein
WHO	World Health Organization
YEM	Young’s elastic modulus
YFS	Cardiovascular Risk in Young Finns Study

1 Introduction

Cardiovascular diseases (CVD) are the leading cause of death globally. An estimated 17.5 million people died from CVD in 2012, representing 31% of all deaths worldwide (WHO 2014). The incidence and prevalence of CVD increase steeply with advancing age, and advancing age unequivocally confers a major risk (Lakatta and Levy 2003). Aging gives rise to two pathologies that affect the arteries: Firstly, there is atherosclerosis, a progressive disease in which lipids and fibrous elements accumulate in the arteries, and, secondly, arteriosclerosis, which refers to the age-related stiffening and dilatation of large arteries.

Arterial stiffening is related to increased cardiovascular risk in several patient groups (Lehmann et al. 1998, Blacher et al. 1999a,b, Amar et al. 2001) and healthy individuals alike (Mattace-Raso et al. 2006). It is also a strong independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease (Blacher et al. 1999b), hypertension (Laurent et al. 2001) or diabetes (Cruickshank et al. 2002). Several methods have been introduced to evaluate arterial stiffness, and of these, carotid-femoral pulse wave velocity (PWV) is considered the gold standard (Laurent et al. 2006).

In addition to aging, metabolic syndrome (MetS), impaired glucose metabolism and dyslipidemia are strong predictors of CVD (de Vegt et al. 1999, NCEP Expert panel 2002, Wilson et al. 2005, Huxley et al. 2006). Although these metabolic disorders are widely studied, there is a paucity of information concerning the effects of these on arterial stiffness. PWV has been shown to increase in subjects with MetS when compared to those not afflicted with the syndrome (Li et al. 2005a), but the possible reversibility of PWV in relation to recovery from MetS is unknown. In addition, the relationship between childhood MetS and adulthood PWV has not been previously studied. Moreover, previous studies on the association of impaired glucose metabolism – that is, impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and type 2 diabetes (DM2) – with PWV have been inconclusive (Ohnishi et al. 2003, Cecelja and Chowienczyk 2009, Xu et al. 2010, Shin et al. 2011, Li et al. 2012). Furthermore, it has been suggested that apolipoproteins B (ApoB) and A-1 (ApoA-1) could be better markers of cardiovascular risk than low-density lipoprotein (LDL) and

high-density lipoprotein (HDL) cholesterols (Walldius et al. 2001, Sniderman et al. 2003, Yusuf et al. 2004, Simon et al. 2005), but the relation between apolipoproteins and PWV are examined only in a few studies (Taquet et al. 1993, Amar et al. 2001, Bjornstad et al. 2015).

Arterial pressure and flow are the result of the interaction between left ventricular stroke volume (SV), arterial stiffness, pulse wave reflections and systemic vascular resistance (SVR). Previously, diabetes has been shown to associate with decreased SV (Heckbert et al. 2006) and hypertension and obesity with increased SVR (Abdelhammed et al. 2005, Chirinos et al. 2009). However, the effects of MetS and impaired glucose metabolism on these systemic hemodynamic parameters are largely unknown.

The aim of this thesis was to gain more insight into the associations of cardiovascular risk factors with arterial stiffness and systemic hemodynamics. We evaluated the relationships of impaired glucose metabolism, childhood and adulthood MetS, and apolipoproteins with PWV. In addition, we studied systemic hemodynamics in individuals with impaired glucose metabolism or MetS.

2 Review of the literature

2.1 Pathophysiology

2.1.1 Atherosclerosis, arterial stiffness and vascular resistance

Atherosclerosis is the most common cardiovascular cause of death in the Western world (Lusis 2000, Nichols et al. 2011). Although clinical manifestations of atherosclerosis occur in middle age or later, accumulating evidence shows that atherosclerosis has its roots already in childhood (Berenson et al. 1998, Raitakari et al. 2003, Juonala et al. 2010, Cote et al. 2013). Endothelial dysfunction is considered the earliest marker of atherosclerosis (Veerasamy et al. 2015). Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL cholesterol, hypertension, diabetes, genetic alteration, free radicals caused by cigarette smoking, and combinations of these and other factors (Ross 1999). The endothelial dysfunction that results from the injury leads to increased adhesiveness and permeability of the endothelium (Ross 1999), which allows lipoprotein particles to accumulate in the intima, leading to foam-cell formation, inflammation and inhibition of the nitric oxide production. This, in turn, promotes smooth muscle cell migration and proliferation as well as extracellular matrix production, leading to fibrous plagues. Furthermore, calcification, ulcerations at the luminal surface and intraplague haemorrhages increase the complexity and size of the plagues (Ross 1999, Lusis 2000, Libby et al. 2010). These changes alter arterial blood flow and hemodynamics by narrowing or occluding the arterial lumen and causing abnormality in vascular tone (Nichols et al. 2011).

The lesions of atherosclerosis occur principally in large and medium-sized elastic and muscular arteries (Ross 1999), whereas age-related physical changes of the arterial wall, dilatation and stiffening, are most marked in the aorta and central elastic arteries (O'Rourke and Hashimoto 2007). These age-related changes, including medial fracture of elastin, loss of muscle attachments, deposition of collagen and calcification, as well as age-dependent arterial intimal

media thickening (even in the absence of atherosclerosis), pose pronounced, escalating adverse effects on the cushioning function of elastic arteries, which in turn leads to increased arterial stiffness (Lakatta and Levy 2003, O'Rourke and Hashimoto 2007, Nichols et al. 2011, McEniery et al. 2009). Arterial stiffening is associated with higher cardiovascular risk in several patient groups (Lehmann et al. 1998, Blacher et al. 1999a,b, Amar et al. 2001) as well as in healthy subjects (Mattace-Raso et al. 2006). It is also a strong independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease (Blacher et al. 1999b), hypertension (Laurent et al. 2001) or diabetes (Cruickshank et al. 2002). Although the pathophysiology of atherosclerosis involves many similar features and arterial stiffness and atherosclerosis often coexist, the causality between them remains uncertain (Zieman et al 2005, Cecelja and Chowienczyk 2009, Townsend et al. 2015).

SVR describes the vessels' tendency to oppose blood flow. It is analogous, to some extent, to the concept of electrical resistance, which is defined as the relationship between current and potential drop in a circuit. SVR can be estimated when mean pressure at the beginning and end of the vascular bed, as well as the total blood flow through the bed, are known. Thus, SVR is calculated as the difference between mean aortic pressure and the mean right atrial pressure, divided by the cardiac output (the mean right atrial pressure is assumed to be zero, because the pressure in the great veins is very low compared to the mean aortic pressure) (Nichols et al. 2011). SVR is mainly determined by the microcirculation, i.e. small arteries (< 400 μm), arterioles (< 100 μm) and capillaries, since they present the greatest resistance (O'Rourke and Hashimoto 2007, Westerhof and Westerhof 2013). Although studies on aging have not found specific structural changes in the microcirculation (O'Rourke and Hashimoto 2007), SVR is increased with aging as a consequence of vascular rarefaction (fewer resistance vessels) and decreased arteriolar cross-sectional area (Nichols et al. 2011). Moreover, increased sympathetic activity (Mayet and Hughes 2003), obesity (Chirinos et al. 2009) and impaired insulin-mediated vasodilation (Feldman and Bierbrier 1993) may increase SVR.

2.1.2 Arterial stiffness, wave reflections and left ventricular failure

Traditionally, arterial circulation has been presented as a simple, steady flow system influenced by mean blood pressure, cardiac output and total peripheral resistance. However, this model does not take into account the fact that blood

flow is pulsatile, not constant. In the human body, arterial pulse pressure is a complex interaction between left ventricular (LV) stroke volume (SV), the cushioning capacity of large arteries, pulse wave reflections and SVR (Stergiopulos and Westerhof 1998, Dart and Kingwell 2001, Sabovic et al. 2009, Nichols et al. 2011).

Increased SVR raises both systolic and diastolic pressure to a similar degree, whereas central artery stiffness raises systolic but lowers diastolic pressure (Lakatta and Levy 2003). This phenomenon can be explained by pressure wave reflections. The SV-induced pressure wave can be reflected at each discontinuity of the arterial wall, including branching points, areas of alteration in arterial stiffness and the high-resistance arterioles (Sabovic et al. 2009, Nichols et al. 2011). The timing of the forward- and backward-travelling pressure waves, which determines the final amplitude and shape of the pressure wave, depends on SV, the distance of the reflected site, heart rate and arterial stiffness (Safar et al. 2003, Sabovic et al. 2009).

In young and healthy individuals, the reflected wave reaches the proximal aorta during diastole, thus augmenting diastolic blood pressure and aiding coronary perfusion (Sabovic et al. 2009). In older individuals, the stiffening of the aorta and early return of the reflected waves leads to an increase in systolic blood pressure, thus increasing LV load, promoting LV hypertrophy and increasing LV oxygen requirement. In contrast, the greater peripheral run-off of SV during systole and the impaired elastic recoil of the aorta result in the fall of diastolic blood pressure, thus impairing coronary blood flow. Finally, increased oxygen demand and decreased coronary perfusion predispose to ischaemia, leading to the development of LV failure (McVeigh et al. 2002, O'Rourke and Hashimoto 2007).

2.2 Measurement of arterial stiffness

2.2.1 Pulse wave velocity

PWV provides information on the time it takes for a pressure or flow wave to travel between two sites in the arterial tree. PWV can be used as a surrogate marker of the mechanical properties of an arterial segment, with a higher PWV indicating stiffer arteries (Hughes et al. 2004, Mattace-Raso et al. 2006). PWV is usually assessed by measuring the time delay in upstroke between a proximal

and distal pressure (Asmar et al. 1995), distension (van der Heijden-Spek et al. 2000), Doppler (Cruickshank et al. 2002) or whole-body impedance cardiography (ICG_{WB}) waves (Kööbi et al. 2003). PWV can be calculated when the transit time (Δt) between the feet of the two waveforms and the distance (L) covered by the waves are known, i.e. PWV = L (meters)/Δt (seconds) (Figure 2.1).

The abdominal aorta is the largest contributor to the arterial buffering function and, therefore, it is a major vessel of interest when determining segmental arterial stiffness (Laurent et al. 2006). Carotid-to-femoral-artery PWV has been identified as an independent predictor of cardiovascular events and mortality in several populations (Blacher et al. 1999a, Laurent et al. 2001, Shokawa et al. 2005, Mattace-Raso et al. 2006) and has emerged as the gold standard for assessing central (aortic) arterial stiffness (Laurent et al. 2006). However, it should be noted that carotid-femoral PWV is measured between two peripheral sites and it is therefore not a direct measurement of aortic stiffness (Cavalcante et al. 2011). A more precise evaluation of aortic PWV can be achieved by measuring the pulse transit time of Doppler waves between the left subclavian artery and the bifurcation of the abdominal aorta (Laurent et al. 2006). Although aortic PWV using this method has been shown to predict mortality (Cruickshank et al. 2002, Anderson et al. 2009), it is not known whether it has any specific advantage over carotid-femoral PWV (Laurent et al. 2006). Segmental peripheral arterial stiffness can be evaluated by measuring the carotid-to-radial-artery or femoral-to-posterior-tibial-artery PWV. However, these have not demostrated prognostic value for cardiovascular mortality in end-stage renal disease patients (Pannier et al. 2005). Brachial-ankle PWV combines the measurement of central and peripheral arterial stiffness (Sugawara et al. 2005), and it has been shown to predict cardiovascular events (Tomiyama et al. 2005, Katakami et al. 2014) and mortality (Matsuoka et al. 2005, Turin et al. 2010). With the ICG_{WB} method, PWV is measured between the aortic arch and the popliteal artery. Although prognostic data on ICG_{WB}-based PWV is lacking, it has been demonstrated to be well in agreement with the Doppler ultrasound method (Kööbi et al. 2003).

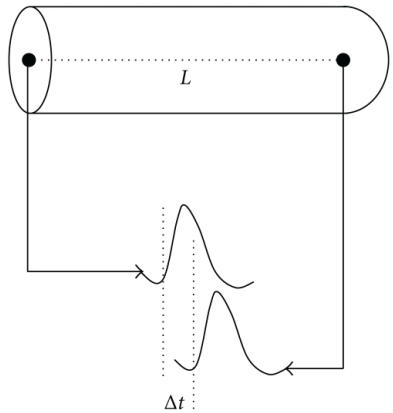

Figure 2.1 Pulse wave velocity calculated as the distance between two points (L) divided by the transit time (Δt) of the pulse wave between these two points.
Reprinted from the International Journal of Nephrology, 2011, Mac-Way F, Leboeuf A, Aqharazii M. Arterial stiffness and dialysis calcium concentration, 839793, Copyright (2011), with permission from Mac-Way et al.

2.2.2 Other methods

Local arterial stiffness can be determined by measuring carotid artery elasticity indices using ultrasound devices. Carotid artery compliance (CAC), defined as a change in volume (ΔV) or diameter (ΔD) for a given change in pressure (ΔP), measures the ability of an artery to expand as a response to pulse pressure (Salomaa et al. 1995, Nichols et al. 2011). Carotid artery distensibility (Cdist) is CAC divided by the initial volume (V) or diameter (D), i.e. relative change in volume or diameter with pressure (Dijk et al. 2005, Nichols et al. 2011). Young's elastic modulus (YEM) gives an estimate of arterial stiffness that is independent of wall (intima-media) thickness (Salomaa et al. 1995, Juonala et al. 2005). The arterial stiffness index (ASI) has been developed to reduce the impact of the curvilinear pressure-stiffness relationship on arterial stiffness measurement, and it is considered to be independent of intraluminal pressure (Hirai et al. 1989, Salomaa et al. 1995, Juonala et al. 2005). Previous studies on the association between carotid artery elasticity indices and cardiovascular events or mortality have reported inconclusive results (Störk et al. 2004, Dijk et al. 2005, Ogawa et al. 2009). Moreover, local measurements of arterial stiffness demand technical expertise and take longer than measuring PWV, and they are therefore suitable for analyses in pathophysiology, pharmacology and therapeutics, rather than for epidemiological studies (Laurent et al. 2006).

Pulse pressure (PP), defined as the difference between systolic and diastolic blood pressure, provides a crude estimate of large conduit artery stiffness (Cohn et al. 2004). However, a number of other physiological factors such as pressure wave reflections influence PP. Moreover, in young individuals, an elevation in PP can be related to an increase in SV rather than an increase in arterial stiffness (Dart and Kingwell 2001).

As discussed in section 2.1.2, the arterial pressure waveform is a composite of the SV-introduced pressure wave and a reflected wave. The augmentation index (AIx) is determined from the arterial pressure wave as a ratio of augmentation pressure and PP (Figure 2.2). Central AIx can be measured from the radial artery waveform, using a transfer function, or from the carotid artery waveform (Laurent et al. 2006). Increased AIx has been shown to associate with cardiovascular and total mortality in individuals with end stage renal failure (London et al. 2001) and in persons with coronary artery disease (Weber et al. 2005). However, in a large community-based sample, AIx was not related to the risk of major CVD events (Mitchell et al. 2010). The AIx is subject to several influencing factors, such as left ventricular outflow, the shape of the forward wave and the timing of the reflected wave, in addition to being affected by height, age, sex, heart rate and arterial stiffness (Kingwell and Gatzka 2002). AIx is therefore not a true indicator of arterial stiffness.

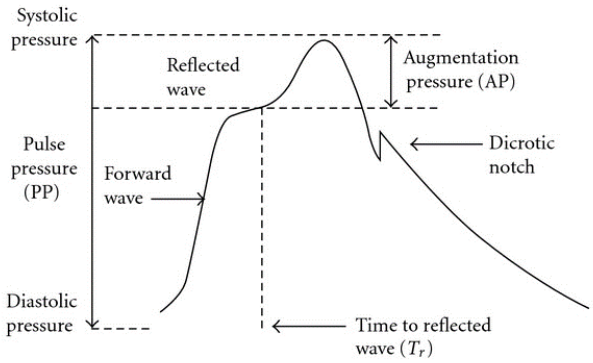

Figure 2.2 Arterial pressure waveform. Augmentation pressure is the additional pressure added to the forward wave by the reflected wave. Augmentation index is defined as a ratio of augmentation pressure and pulse pressure.
Reprinted from the International Journal of Vascular Medicine, 2012, Stoner L, Young JM, Fryer S. Assesments of arterial stiffness and endothelial function using pulse wave analysis, 903107, Copyright (2012), with permission from Lee Stoner et al.

2.3 Measurement of cardiac output

The intermittent thermodilution technique is often considered a 'clinical standard' for cardiac output (CO) assessment (Hofer et al. 2007). A bolus of cold sterile solution is injected into the proximal port of a pulmonary artery catheter located in the right atrium and detected distally by a thermistor located in the pulmonary artery. An area under the curve showing the change in temperature over time is converted into a measurement of CO (Nishikawa and Dohi 1993). Several other methods have also been used to measure CO: transoesophageal or transthoracic echocardiography, transoesophageal aortic Doppler ultrasound, pulse wave analysis from pressure waveforms, the direct Fick method, the partial carbon dioxide rebreathing technique, velocity-encoded magnetic resonance imaging, and the pulsed dye densitrometry method (Hofer et al. 2007, Nichols et al. 2011). All these methods are either invasive or time-consuming and require a high level of operator skills and knowledge, which limits their use in wide-scale epidemiological studies.

The thoracic impedance cardiography (ICG_{TH}) technique to determine CO was introduced by Kubicek in the 1960's (Kubicek et al. 1966) and the ICG_{WB} method by Tishchenko in the 1970's (Tishchenko 1973). In both methods, a high-frequency alternating electrical current with a low amplitude is applied to the body trough current electrodes. Changes in cardiac related blood volume resulting in changes in bio-impedance can be measured with voltage electrodes located between current electrodes, and a mathematical conversion is used to translate the change in bio-impedance into CO (Geerts et al. 2011). ICG_{WB} differs from ICG_{TH} in its placement of electrodes, the frequency of the alternating current used, and the SV equation. In ICG_{TH} electrodes are positioned onto the thoracic area, whereas in ICG_{WB} a pair of electrically connected electrodes are applied to the wrists and another pair to the ankles. The frequency of the alternating current applied in ICG_{WB} (30 kHz) is considerably lower than the frequency usually used in ICG_{TH} (70-200 kHz) (Kööbi et al. 1997a). The over-simplification of the physiological reality by mathematical equations as well as motion artefacts, cardiac valve disease and arrhythmias are considered to contribute to the inaccuracy of ICG (Geerts et al. 2011). The major advantages of the ICG_{WB} method are its operator independence and the low cost of the equipment. Several studies (Kööbi et al. 1997a, Kööbi et al. 1997b, Kööbi et al. 1999, Cotter et al. 2004, Paredes et al. 2006) have shown that ICG_{WB} accurately measures CO when compared with the thermodilution method in different conditions (in the supine

position, during head-up tilt, after anaesthesia induction, after coronary artery bypass surgery).

2.4 Cardiovascular risk factors

2.4.1 Hypertension

The basic problem in hypertension is the increase in peripheral resistance and arterial stiffening, as previously described in chapter 2.1. From the point of view of the central elastic arteries, hypertension can be viewed as a form of accelerated aging – it involves similar pathologic changes in the arterial walls, but they occur at an earlier age (Nichols et al. 2011). The more peripheral muscular arteries suffer accelerated intimal change, accelerated atherosclerosis and endothelial dysfunction with hypertension (Roman et al. 1995, Wallace et al. 2007, Nichols et al. 2011). In advanced disease, aldosterone and angiotensin II cause an increase in blood volume and vasoconstriction, respectively, leading to increased CO and further increased peripheral resistance (Nichols et al. 2011). Moreover, increased left ventricular afterload leads to myocardial hypertrophy (Gatzka and Kingwell 2003).

In the review by Cecelja and Chowienczyk (2009), blood pressure was independently associated with carotid-femoral PWV in 90% of 77 studies. In addition, blood pressure measured in childhood and/or adolescence has been found to associate with PWV in adulthood (Aatola et al. 2010a). PWV has been shown to predict cardiovascular events above and beyond mean arterial pressure, as well as 24-hour mean arterial pressure (Willum-Hansen et al. 2006), and it is thus suggested that PWV relates more closely to the duration and severity of hypertension than does a single blood pressure measurement, and that PWV could be a better measure of blood pressure than the conventional office measurement (Cecelja and Chowienczyk 2009).

2.4.2 Lipid risk factors

Lipoproteins transport hydrophobic molecules in the blood stream, and they are comprised of a coat of phospholipid and protein, and a core of cholesterol and triglyceride. Three major classes of lipoproteins can be found in serum: low-

density lipoproteins (LDL), high-density lipoproteins (HDL) and very-low-density lipoproteins (VLDL). LDL cholesterol typically makes up 60–70 percent, HDL cholesterol 20–30 percent, and the triglyceride-rich lipoprotein VLDL 10–15 percent of the total serum cholesterol (NCEP Expert panel 2002). ApoB is a structural protein for lipoproteins carrying lipids from the liver and gut to the sites of use (i.e. VLDL-LDL spectrum), whereas ApoA-1 is a structural protein for lipoproteins returning cholesterol from the periphery to the liver (i.e. HDL) (Marcovina and Packard 2006).

High LDL and low HDL cholesterol are strong independent predictors of atherosclerosis and coronary heart disease (NCEP Expert panel 2002). Data on the association of LDL and HDL cholesterol with arterial stiffness is, to a degree, controversial. A systematic review of the independent association of PWV with cardiovascular risk factors found a significant association between LDL cholesterol and PWV only in 1 out of 21 studies, and between HDL cholesterol and PWV in 4 out of 37 studies (Cecelja and Chowienczyk 2009). Juonala et al. (2005) reported an independent association of carotid artery elasticity indices (CAC, YEM, ASI) with LDL cholesterol, but not with HDL cholesterol, in young adults. In contrast, in a population of young adults, Urbina et al. (2004) found an independent correlation between YEM and HDL cholesterol, whereas there was no association between YEM and LDL cholesterol. Moreover, Della-Morte et al. (2010) did not find an independent association of low HDL cholesterol, as a component of MetS, with ASI in a population of elderly subjects with MetS.

Accumulating evidence suggests that ApoB and ApoA-1 could be better markers of cardiovascular risk than LDL and HDL cholesterol (Walldius et al. 2001, Sniderman et al. 2003, Yusuf et al. 2004, Simon et al. 2005). ApoB levels reflect the total number of atherogenic particles (VLDL, intermediate-density lipoprotein, LDL), and ApoB dosage is therefore more representative of the atherogenic burden than each of these fractions (Sniderman et al. 2001, Rasouli et al. 2006). In addition, it has been suggested that ApoB, but not cholesterol, plays a major role in the LDL-induced dysfunction of the vascular endothelium (Yu et al. 2015). ApoA-1 is considered to be the ‘active ingredient’ in HDL, mediating cell-lipoprotein interactions. It also has anti-inflammatory and anti-oxidative properties, and this may contribute to its cardioprotective role (Marcovina and Packard 2006). A limited number of relative small-scale studies have previously addressed the relationship between apolipoproteins (B and A-1) and arterial stiffness. ApoB has been found to associate with PWV in adolescents with type 1 diabetes (Bjornstad et al. 2015) and in patients treated for

cardiovascular risk factors (Amar et al. 2001). ApoB has also been shown to correlate with YEM (Schmidt-Trucksäss et al. 1999), whereas ApoA-1 was not found to associate with PWV in healthy middle-aged women (Taquet et al. 1993).

It has been suggested that non-HDL cholesterol, a content of the cholesterol in atherogenic ApoB-containing lipoproteins, could be used as a surrogate measure for ApoB, especially in subjects with elevated triglycerides (NCEP Expert panel 2002). However, there are two major differences between these two measures. A significant proportion of non-HDL cholesterol is found in intermediate-density lipoprotein and VLDL, whereas ApoB primarily reflects LDL (Marcovina and Packard 2006). In addition, ApoB gives a measure of particle number, and if the number of particles rather than their cholesterol load is the more important factor, then the measurement of ApoB should be better in risk prediction (Marcovina and Packard 2006). Some (Pischon et al. 2005, Simon et al. 2005), but not all (Ridker et al. 2005), clinical studies support this hypothesis.

2.4.3 Impaired glucose metabolism

Diabetes is one of the most common metabolic disorders, affecting more than 380 million people worldwide. This number is expected to rise to 592 million by 2035 (Guariguata et al. 2014). The majority (90%–95%) of diabetic patients suffer from type 2 diabetes mellitus (DM2) (Creager et al. 2003). DM2 is preceded by a pre-diabetic stage, which includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Stancakova et al. 2009). It has been suggested that impaired insulin release is a predominant feature of isolated IFG, whereas peripheral insulin resistance characterizes isolated IGT (Stancakova et al. 2009). During the pre-diabetic stage, the risk of CVD events is modestly increased, and with the development of DM2, there is a large increase in the risk (Nathan et al. 2007).

Many of the metabolic abnormalities known to occur in diabetes, including hyperglycemia, free fatty acids and insulin resistance, provoke several mechanisms that alter the structure and function of arteries. These include decreased endothelium-derived NO, reduced endothelium-dependent vasodilation, the production of oxygen-derived free radicals, increased intracellular production of advanced glycation end products, and vascular smooth muscle cell contraction and growth (Creager et al. 2003). These abnormalities contribute to the cellular events that cause atherosclerosis. Moreover, endothelial

nitric oxide dysregulation and advanced glycation end products have critical roles in the pathogenesis of arterial stiffness (Prenner and Chirinos 2015).

Individuals with IGT have shown increased PWV when compared to those with normal glucose tolerance (NGT) (Xu et al. 2010, Li et al. 2012), whereas studies on the relationship between IFG and PWV have reported conflicting results (Ohnishi et al. 2003, Xu et al. 2010, Shin et al. 2011, Li et al. 2012). In the review by Cecelja and Chowienczyk (2009), diabetes was found to associate with PWV in 12 (52%) out of 23 studies. Moreover, diabetes accounted for only 1%–8% of the variation in PWV (Cecelja and Chowienczyk 2009). One plausible explanation is that independent effects of diabetes on arterial stiffness are diluted, to some extent, by the association of hypertension with diabetes (Prenner and Chirinos 2015). In addition to vascular changes, impaired glucose metabolism has direct adverse effects on the heart. IGT and DM2 are accompanied by cardiac steatosis (i.e. myocardial lipid overstorage), which precedes the onset of LV systolic dysfunction (McGavock et al. 2007). Moreover, abnormalities in cardiac metabolism in diabetics augment the ill effects of arterial stiffening on the heart (Nichols et al. 2011).

2.4.4 Obesity

Worldwide, more than 1.9 billion adults are overweight (body mass index [BMI] $\geq$ 25 kg/m2), and over 600 million of these are obese (BMI $\geq$ 30 kg/m2) (WHO 2015). Obesity is associated with DM2, hypertension, CVD and mortality as well as a reduced life expectancy (Poirier et al. 2006). A variety of alterations in cardiovascular structure and function occur as excessive adipose tissue accumulates. In obese subjects, endothelial dysfunction and overactivity of the sympathetic nervous system increase SVR, thus leading to higher blood pressure (Poirier et al. 2006). Moreover, the abdominal adiposity contributes to an increase in arterial stiffness (Schillaci et al. 2005). Furthermore, to meet the increased metabolic needs in obesity, the circulating blood volume increases, which leads to an increased venous return, the dilation of ventricles, increased wall tension, left ventricular hypertrophy (LVH) and, eventually, to an increase in LV filling pressure and LV enlargement. As the LVH becomes unable to accommodate the accelerating LV dilation, the wall tension becomes even more increased, which results in systolic dysfunction (Poirier et al. 2006).

2.4.5 Metabolic syndrome

MetS is a cluster of cardiovascular risk factors, including hypertension, dyslipidemia, glucose intolerance (IFG, IGT, or DM2), insulin resistance and obesity (Eckel et al. 2005). When grouped together, they are associated with an increased risk of subclinical atherosclerosis (Mattsson et al. 2008), CVD and mortality (Isomaa et al 2001, Lakka et al. 2002). With the high rate of paediatric obesity, interest in MetS among adolescents is increasing because a diagnosis of paediatric MetS might identify those at an increased risk of CVD in adulthood (Gustafson et al. 2009).

There are various definitions for MetS in adulthood. In 1998, the World Health Organization (WHO) introduced the first simple criteria for MetS. A diagnosis of MetS according to WHO criteria included insulin resistance plus two additional risk factors. In 1999, the European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO MetS definition, requiring elevated plasma insulin plus two other factors. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) introduced a new definition of MetS. The ATP III criteria required the presence of 3 out of 5 factors, whereas the International Diabetes Foundation (IDF) definition, introduced in 2005, required the presence of abdominal obesity plus two additional factors. In 2005, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) maintained the ATP III criteria with minor modifications. The AHA/NHLBI based their decision on the conclusion that the ATP III criteria are simple to use in a clinical setting and a large number of studies have been carried out to evaluate the ATP III criteria (Grundy et al. 2005). In addition, the IDF and AHA/NHLBI introduced unified MetS criteria in 2009, requiring 3 abnormal findings out of a total of 5 (Alberti et al. 2009). For children and adolescents, there are at least 40 definitions of MetS, and most criteria used in paediatric studies have been variably adapted from adult standards with the use of sex- and age-dependent normal values (Ford and Li 2008, Steinberger et al. 2009).

Local arterial stiffness, as measured by ASI, has been found to increase in obese children with MetS (Iannuzzi et al. 2006), and local arterial distensibility has been shown to decrease in adolescents with an increase in the number of MetS components (Whincup et al. 2005). In adults, PWV has been demonstrated to be increased in subjects with MetS as compared to those not afflicted with the syndrome (Li et al. 2005a), and echocardiographic studies have suggested the presence of impaired global LV function (Turhan et al. 2009) and impaired LV

systolic and diastolic functions (Gong et al. 2009) in patients with MetS. The detailed effects of the individual components of MetS on cardiovascular structure and function are discussed in sections 2.4.1–2.4.4.

2.4.6 Other risk factors

Despite the fact that cigarette smoking increases inflammation, thrombosis and the oxidation of LDL cholesterol (Ambrose and Barua 2004), it has been suggested that arterial stiffness may be an underlying mechanism through which smoking contributes to CVD (Nichols et al. 2011). This suggestion is supported by the direct association between AIx and smoking (Mahmud and Feely 2003, Rehill et al. 2006), as well as by the reversibility of AIx and improvement in reflected waves after smoking cessation (Rehill et al. 2006, Polonia et al. 2009). However, the majority of previous studies have not found a relationship between cicarette smoking and PWV. In the review by Cecelja and Chowienczyk (2009), smoking was associated with carotid-femoral PWV in only 6 (14%) of the 44 studies, and smoking accounted for only 0.3%–2.2% of the variation in PWV. One plausible explanation is that, at least in its early stages, PWV does not reflect the atherosclerotic process but an alternative pathology of the vascular wall (Cecelja and Chowienczyk 2009, Townsend et al. 2015). Cicarette smoking also has negative effects on systemic hemodynamics; smokers have been shown to have decreased SV (Heckbert et al. 2006) and increased SVR (Li et al. 2005b) when compared to nonsmokers.

Several dietary factors have a significant impact on arterial stiffness. Dietary cholesterol intake has been found to associate directly with arterial stiffness (Hallikainen et al. 2013). Moreover, increased arterial stiffness has been reported in subjects with excessive alcohol consumption (Mahmud and Feely 2002) and higher salt intake (Avolio et al. 1985). In contrast, higher regular intake of plant-derived phytoestrogens (van der Schouw et al. 2002) and isoflavones (Pase et al. 2011) has been found to reduce arterial stiffness. Moreover, we have previously shown that vegetable consumption in childhood is inversely associated with PWV in adulthood (Aatola et al. 2010b). Habitual cocoa consumption has also been shown to associate with decreased arterial stiffness and with improved central hemodynamics (Vlachopoulos et al. 2007).

Physical inactivity is a risk factor for cardiovascular disease in the general population (Shiroma and Lee 2010). Over twenty years ago, Vaitkevicius et al. (1993) demonstrated that individuals with a low physical activity level had higher

arterial stiffness than physically active individuals. Since then, several other studies have shown a beneficial relationship between physical activity and arterial stiffness (Kozakova et al. 2007, Sakuragi et al. 2009, Gando et al. 2010, Edwards et al. 2012). In addition, it has been shown that exercise training can improve left ventricular systolic performance (Ehsani et al. 1991) as well as decrease blood pressure by decreasing SVR (Cornelissen and Fagard 2005).

C-reactive protein (CRP) is a leading biomarker of inflammation for clinical application, and high-sensitivity CRP has been found to predict cardiovascular events even after adjustment for the traditional risk factors (Libby et al. 2009). High CRP levels have been independently related to increased PWV in some (Mattace-Raso et al. 2004, Yasmin et al. 2004), but not in all (Kullo et al. 2005), previous studies.

There are clear differences between men and women in regard to several cardiovascular parameters, which could at least partly be explained by differing bodily habitus (females as a group are shorter and weigh less than males) (Nichols et al. 2011). In the review by Cecelja and Chowienczyk (2009), sex was associated with PWV in 15 (27%) out of 54 studies (males having higher PWV than females), whereas in the review by the Reference Values for Arterial Stiffness' Collaboration (Mattace-Raso et al. 2010), the influence of sex on PWV was negligible (<0.1 m/s difference, $p=0.04$).

3 Aims of the study

The aim of this study was to gain more insight into the associations of cardiovascular risk factors with arterial stiffness and systemic hemodynamics. The specific objectives were:

1. To examine the effects of impaired glucose metabolism and metabolic syndrome on arterial stiffness and systemic hemodynamics (I, II).

2. To study the effects of spontaneus recovery from metabolic syndrome on arterial stiffness and systemic hemodynamics (I).

3. To investigate the associations of childhood metabolic syndrome and recovery from childhood metabolic syndrome with arterial stiffness in adulthood (III).

4. To investigate the associations of apolipoproteins B and A-1 with arterial stiffness (IV).

4 Subjects and methods

4.1 Subjects

4.1.1 The Health 2000 Survey

The source of the study population was a large Finnish health examination survey (the Health 2000 Survey) carried out in 2000–2001 (Aromaa and Koskinen 2004). The overall study cohort was a two-stage stratified cluster sample (7419 participants, participation rate 92%) representing the entire Finnish population aged 30 years and older. A supplemental study was carried out to study cardiovascular diseases and diabetes more thoroughly (1867 participants, participation rate 82%). Because specialized equipment was required, the supplemental study was carried out in the catchment areas of the five Finnish Universal Hospitals. The mean interval between the Health 2000 Survey and the supplemental study was 16 months (range 10–23 months). In the catchment areas of Tampere and Turku University Hospitals, 455 participants (aged 46–76 years, 44% males) underwent in ICG_{WB} measurement.

4.1.2 The Cardiovascular Risk in Young Finns Study

The Cardiovascular Risk in Young Finns Study (YFS) is an on-going multicentre study of atherosclerosis risk in Finnish children and young adults (Raitakari et al. 2008). The first cross-sectional survey was conducted in 1980. Altogether 4320 children and adolescents in 6 age cohorts (aged 3, 6, 9, 12, 15 and 18) were randomly chosen from the population register to produce a representative sample of Finnish children. A total of 3596 participants (83% of those invited) participated the study in 1980. Thereafter, several follow-up studies with physical examinations and blood sampling have been performed: in 1983 (n=2991, participation rate 83%), 1986 (n=2779, participation rate 78%), 2001 (n=2283, participation rate 64%), 2007 (n=2204, participation rate 61%), and in 2011–2012

(n=2063, participation rate 57%). In the 27-year follow-up in 2007, 1872 participants (aged 30–45 years, 46% males) underwent in ICG_{WB} monitoring.

4.1.3 Study populations

Study I

In study I, 1741 non-pregnant females and males without type 1 diabetes (aged 30–45 years, 45% males) who participated in the YFS 2007 follow-up had complete metabolic risk factor, PWV and systemic hemodynamics data (SI, SVRI) available. Furthermore, 1391 non-pregnant females and males without type 1 diabetes (aged 30–45 years, 46% males) with complete metabolic risk factor data measured in 2001 and 2007 comprised a sub-group which was used to evaluate the effect of spontaneous recovery from MetS over 6 years' follow-up (2001–2007) on PWV and systemic hemodynamics.

Study II

In the Health 2000 Survey (supplemental study), 402 participants underwent ICG_{WB} measurement and oral glucose tolerance testing (OGTT). Participants with missing data on cardiovascular risk factors, OGTT, PWV or systemic hemodynamics (n =11), and those with type 1 diabetes or undetermined diabetes (n = 2), were excluded. Therefore, a total of 389 participants (aged 46–76 years, 43% males) were included in the analysis.

Study III

The study population comprised 945 non-pregnant females and males who participated in the 1986 YFS survey at the ages of 9, 12, 15, or 18 years as well as the adult follow-up in 2007 (then aged 30–39 years, 45% males), and for whom complete risk factor data were available in 1986, in addition to risk factor and PWV data in 2007. Subjects participating in the 1986 survey were selected to comprise the baseline study sample, because fasting glucose was not measured in the 1980 survey.

Study IV

After excluding participants with incomplete cardiovascular risk factor data (n=82), those with type 1 or type 2 diabetes (n=12), pregnant women (n=19) and participants using antihypertensive (n=120) or cholesterol-lowering medication (n=21), a total of 1618 individuals (aged 30–45 years, 45% males) who participated in the YFS 2007 follow-up were included in the analysis. A sub-sample group was formed to study whether ApoB and ApoA-1 measured in young adulthood are predictive of PWV assessed 6 years later. The sub-group was comprised of those 1264 participants (aged 30–45 years, 46% males) for whom complete cardiovascular risk factor data (after the above-mentioned exclusions) was available in 2001 and whose PWV was measured in 2007.

4.2 Methods

4.2.1 Medical examination and questionnaire

Height and weight were measured, and BMI was calculated by dividing the weight in kilograms by the square of the height in metres. In the Health 2000 Survey supplemental study, continuous blood pressure was measured using a Finapres digital plethysmograph (Ohmeda, Engelwood, CO). An average blood pressure value of a 30-second measurement was used and the results verified by an Omron manometer (Omron, Matsusaka, Japan and Omron Healthcare Europe, Hoofddorp, the Neatherlands). In the YFS, blood pressure was measured with a random zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, United Kingdom) and the mean of three measurements was used. In the YFS, waist circumference was measured only in 2001 and 2007. In the Health 2000 Survey supplemental study, waist circumference data was not available. Smoking habits were ascertained with a questionnaire, and smoking was defined as smoking on a daily basis. In the Health 2000 Survey supplemental study, smoking data was not available and it was collected from the Health 2000 Survey data.

4.2.2 Laboratory analyses

The Health 2000 Survey

Venous blood samples were collected after an overnight fast. Total cholesterol, HDL cholesterol and triglyceride concentrations were determined enzymatically (Olympus System Reagent, Olympus Diagnostica GmbH, Hamburg, Germany, for total cholesterol and triglycerides; Roche Diagnostics, Mannheim, Germany, for HDL cholesterol) with a clinical chemistry analyzer (Olympus, AU400, Hamburg, Germany). LDL cholesterol concentration was calculated using the Friedewald formula. The OGTT was carried out after 10 to 12 hours of fasting. The participants were given 75 g of glucose in a 10% solution, and venous blood samples for glucose and insulin determinations were taken before and 2 hours after the glucose load. Plasma glucose was determined by the glucose dehydrokinase method (Diagnostica Merck, Darmstadt, Germany) in a clinical chemistry analyzer (Konelab, Vantaa, Finland). Plasma insulin was determined by the radio immunoanalysis method (Pharmacia, Uppsala, Sweden).

The Cardiovascular Risk in Young Finns Study

Venous blood samples were taken after 12 hours of fasting. Serum total cholesterol and triglyceride concentrations were measured using a fully enzymatic method (Boehringer Mannheim, Mannheim, Germany) in 1986, and enzymatically (Olympus System Reagent) in a clinical chemistry analyzer (Olympus, AU400) in 2001 and 2007. HDL cholesterol was analysed after precipitation of VLDL and LDL with dextrane sulphate 500 000 (Kostner 1976). LDL cholesterol concentration was calculated with the Friedewald formula, and non-HDL cholesterol concentration was calculated by subtracting the HDL cholesterol from the total cholesterol. In 2001 and 2007, ApoB and ApoA-1 were determined immunoturbidometrically (Orion Diagnostica, Espoo, Finland). Fasting plasma glucose concentrations were analysed enzymatically (Olympus Diagnostica GmbH). Serum insulin was measured with a modification of the immunoassay method (Herbert et al. 1965) in 1986, and with an immunoassay kit (Abbott Laboratories, Diagnostic Division, Dainabot, USA) in 2001 and 2007. CRP was analysed by an automated analyzer (Olympus AU400) using a turbidimetric immunoassay kit (Wako Chemicals, Neuss, Germany) in 2001 and 2007. All assays were done in the same laboratory.

4.2.3 Metabolic syndrome

Because no general consensus exists regarding the definition of MetS (Kassi et al. 2011), we used three different definitions for MetS in study I. According to the updated NCEP definition (Grundy et al. 2005), three or more of the following criteria constitute a diagnosis of MetS: 1) increased waist circumference (men ≥ 102 cm, women ≥ 88 cm), 2) triglycerides ≥ 1.7 mmol/l or drug treatment, 3) low HDL cholesterol (men < 1.03 mmol/l, women < 1.3 mmol/l) or treatment for dyslipidemia, 4) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or drug treatment, 5) fasting glucose ≥ 5.6 mmol/l or drug treatment. According to the IDF definition (Alberti et al. 2005), increased waist circumference (≥ 94 cm for men and ≥ 80 cm for women) and at least two of the following factors are present: 1) triglycerides > 1.7 mmol/l or specific treatment; 2) HDL cholesterol < 1.03 mmol/l in men and < 1.29 mmol/l in women or specific treatment; 3) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment of previously diagnosed hypertension; 4) fasting plasma glucose ≥ 5.6 mmol/l or previously diagnosed type 2 diabetes. The IDF definition has ethnicity-specific values for waist circumference. According to the EGIR definition (Balkau and Charles 1999), MetS is present if hyperinsulinemia (defined as non-diabetic subjects having a fasting insulin level in the highest quartile, which in our study was 11 mU/l) is accomppanied by at least two of the following abnormalities: 1) fasting blood glucose ≥ 6.1 mmol/l; 2) blood pressure ≥140/90 mmHg or treatment for hypertension; 3) triglycerides >2.0 mmol/l or HDL cholesterol < 1.0 mmol/l, or treatment for dyslipidemia; 4) waist circumference ≥ 94 cm in men and ≥ 80 cm in women. The sub-sample study population (n = 1391) was classified further into four different groups according to their MetS status at 2001 and 2007: control group (no MetS at 2001 or 2007), recovery group (MetS at 2001 but not at 2007), incident group (no MetS at 2001 but MetS at 2007) and persistent group (MetS both at 2001 and 2007).

Because there is no universally accepted definition for paediatric MetS (Steinberger et al. 2009), in study III we created two paediatric MetS definitions similar to the previous study by Lambert et al. (Lambert et al. 2004). Values of age- and sex-specific cut-off points used to define risk factors were estimated from the study population. Overweight was defined as BMI ≥ 85th percentile (Himes and Dietz 1994). High triglycerides, high systolic blood pressure, hyperinsulinemia and low HDL cholesterol were defined as values in the respective extreme quartiles (triglycerides, systolic blood pressure, and fasting

insulin ≥ 75th percentile, HDL cholesterol ≤ 25th percentile). Similar cut-off points were also used in the Bogalusa Heart Study (Chen et al. 1999). Hyperglycaemia was defined as fasting blood glucose ≥ 6.1 mmol/L (Fagot-Campagna et al. 2001). The first paediatric MetS (Ped1MetS) definition required the presence of any three of these six risk factors. The second paediatric MetS (Ped2MetS) definition required the presence of hyperinsulinemia and any two of the other five risk factors. For adult participants, the NCEP definition for MetS was used in study III. The study population was classified further into four different groups according to MetS status in 1986 and 2007: control group (no MetS in 1986 or 2007), recovery group (MetS in 1986 but not in 2007), incident group (no MetS in 1986 but MetS in 2007) and the persistent group (MetS in both 1986 and 2007). These groups were comprised separately for the two paediatric MetS definitions (Ped1MetS and Ped2MetS).

4.2.4 Glucose tolerance

In study II, the WHO criteria for diabetes mellitus (WHO 1999) was used in the classification of participants with no previously diagnosed diabetes: 1) Normal glucose tolerance (NGT) – fasting plasma glucose < 6.1 mmol/l and 2-h plasma glucose < 7.8 mmol/l in an OGTT; 2) Impaired fasting glucose (IFG) – fasting plasma glucose 6.1–6.9 mmol/l and 2-h plasma glucose < 7.8 mmol/l; 3) Impaired glucose tolerance (IGT) – fasting plasma glucose < 7.0 mmol/l and 2-h plasma glucose 7.8–11.0 mmol/l; and 4) Type 2 diabetes (DM2) – fasting plasma glucose ≥ 7.0 mmol/l or 2-h plasma glucose ≥ 11.1 mmol/l. Participants taking oral diabetes medication were considered to have DM2 regardless of their OGTT results.

4.2.5 Whole-body impedance cardiography measurement

Systemic hemodynamic parameters were measured by using a commercially available whole-body impedance cardiography monitor, CircMon B202 (CircMon, JR Medical Ltd, Tallinn, Estonia). After the interview, participants lay in the supine position for at least 15 min prior to the measurement. Alternating electrical current (30 kHz, 0.7 mA) was applied to the current electrodes (Blue sensor type R-00-S, Medicotest A/S, Olstykke, Denmark) on the distal parts of the extremities, and heart-synchronous pulsation-induced impedance variation

trough the main vascular trees was measured from voltage electrodes placed proximally to the current electrodes (Figure 4.1A). The amplitude of heart-synchronous variations of the whole-body impedance correlates closely with the SV, and the CircMon software calculates SV using the Tishchenko SV equation (Tishchenko 1973, Kööbi et al. 1997a, Kööbi et al. 1999):

$$SV = k \cdot H^2 \cdot \frac{dZ / Z_C}{Z_0} \cdot \frac{C}{D}$$

where coefficient k is an empirical correction factor (k = 0.275 for males and k = 0.247 for females) (Tishchenko, 1973), H is the subject's height (cm), dZ is the amplitude of heart synchronous impedance variation (Ω), Zc is the calibration factor (0.1 Ω), Z_0 is the baseline impedance of the body (Ω), C is the duration of the cardiac cycle (ms), and D is the duration from the lowest value of whole-body impedance to the onset of the next cardiac cycle (ms).

An additional pair of electrodes was placed on the knee-joint level and the calf to measure PWV (Figure 4.1A). The CircMon software estimates the foot of the ICG signal that coincides with pulse transmission in the aortic arch and, later, the foot of the impedance plethysmogram (IPG) signal that coincides with pulse transmission in the popliteal artery (Kööbi et al. 2003) (Figure 4.1B). By means of the measured pulse transit time (Δt) and estimated distance (L) between these two sites, the CircMon software calculates PWV using the equation:

$$PWV\ (m/s) = L/\Delta t$$

The repeatability index (the variation between two consecutive PWV measurements) and the reproducibility index (the variation in the PWV measurements performed on four separate days) were 99% and 87%, respectively (Tahvanainen et al. 2009). Whole-body impedance cardiography slightly overestimates PWV values when compared to the Doppler method, and this small bias was corrected using the empirical equation (Kööbi et al. 2003):

$$PWV\ (m/s) = 0.696 \times PWVicg + 0.864$$

The CircMon software calculates SVR automatically by dividing mean blood pressure by CO. CO was estimated as heart rate * SV. SV, CO and SVR were

indexed to body surface area to derive the stroke index (SI, ml/m2), cardiac index (CI, l/min/m2), and systemic vascular resistance index (SVRI, dyn*s/cm5*m2). The time resolution of the recordings was 5 ms, and hemodynamic parameters represent the mean of recordings over 30 s.

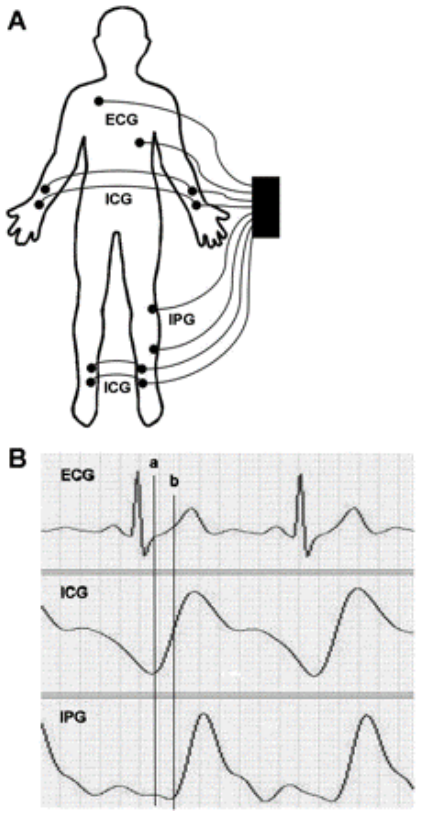

Figure 4.1 A) Placement of electrodes in whole-body impedance cardiography with an additional voltage-sensing channel on the left calf for PWV measurement. B) Synchronous recordings of ECG, whole-body ICG and IPG. Time difference between the feet of the ICG (a) and IPG (b) indicates the pulse transit time from the aortic arch to the popliteal artery.
Reprinted from Hypertension, 55, 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, 806-811, Copyright (2010), with permission from Wolters Kluwer Health.

4.2.6 Statistical methods

The statistical comparison of the receiver-operating characteristic (ROC) curves was carried out with a Statistical Analysis System (SAS Institute Inc., Cary, NC,

USA) macro. Other statistical analyses were performed using SPSS for Windows (version 16.0, SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant. The skewed distribution of triglycerides (all studies), CRP (studies I and IV) and insulin (studies I, III and IV) were corrected logaritmically before statistical analyses. There were no interactions between sex and glucose tolerance groups (study II), hemodynamic parameters (studies I and II), MetS (studies I and III), cardiovascular risk factors (study IV), and PWV (studies III and IV). Therefore, the analyses were performed with the sexes combined in all studies. T-test (comparison between two groups) or analysis of variance with the Dunnet T3 post hoc test (comparison between multiple groups) was used to compare the means of continuous variables. The Chi-square test was used to compare categorical variables.

Regression analysis was used to study the univariate relationships between PWV and cardiovascular risk factors (study IV) as well as the univariate relationships between PWV and MetS components (study III). Adjusted multivariable linear regression models were constructed to study the independent effects of glucose (study II), insulin (study II), MetS components (study I and III) and cardiovascular risk factors (study IV) on PWV or hemodynamic parameters. Heart-rate-specific z-scores for PWV were used in the regression analysis (studies III and IV), because heart rate may be a confounding factor (Lantelme et al. 2002). Adjusted mean PWV and systemic hemodynamic parameters were analysed using general linear models (all studies).

In study IV, regression models were assessed for multicollinearity before the analysis, because there were strong bivariate correlations for LDL, triglycerides and non-HDL cholesterol with ApoB. Variance inflation factors for ApoB, LDL cholesterol, triglycerides and non-HDL cholesterol ranged from 12.0 to 191.7 (tolerances ranging from 0.006 to 0.083), and lipid measures were therefore analysed separately in multivariable models. In study II, to limit the effects of collinearity and control the number of covariates, glucose and insulin measures were analysed separately in multivariable models.

In study IV, Fisher's least significant difference test was used to evaluate differences in PWV between the ApoB tertiles groups. ROC analyses – including areas under curves (AUC) – were generated to study the utility of ApoB and non-HDL cholesterol in order to detect participants with $\geq$ 90th-percentile adulthood PWV (study IV). Variation in risk variables during the 21-year follow-up was studied by subtracting the baseline value from the follow-up value (study III).

5 Results

5.1 Characteristics of the study population

The combined clinical characteristics of the Health 2000 Survey supplemental study and the Cardiovascular Risk in Young Finns Study populations with available systemic hemodynamics and PWV data are shown in Table 5.1.

Table 5.1 Clinical characteristics of the Health 2000 Survey supplemental study population (H2000) and The Cardiovascular Risk in Young Finns Study population (YFS) in 1986, 2001 and 2007.

	H2000	YFS		
Variable		1986	2001	2007
Number of participants	395–401*	990–1023*	1513–1547*	1828–1867*
Age (years)	58.3 ± 7.9	13.5 ± 3.4	31.9 ± 5.0	37.6 ± 5.0
Male participants (%)	43.9	45.1	44.7	45.7
BMI (kg/m^2)	27.1 ± 4.3	19.3 ± 3.1	24.9 ± 4.3	26.0 ± 4.8
Glucose (mmol/l)	5.8 ± 1.3	4.7 ± 0.9	5.0 ± 0.8	5.3 ± 0.8
SBP (mmHg)	129.8 ± 21.8	111.1 ± 12.0	116.1 ± 13.0	120.5 ± 14.3
DBP (mmHg)	67.2 ± 12.7	62.8 ± 9.4	70.2 ± 10.6	75.5 ± 11.3
Total cholesterol (mmol/l)	5.6 ± 0.9	4.9 ± 1.0	5.1 ± 1.0	5.0 ± 0.9
LDL cholesterol (mmol/l)	3.4 ± 0.9	3.0 ± 0.9	3.3 ± 0.8	3.1 ± 0.8
HDL cholesterol (mmol/l)	1.6 ± 0.4	1.5 ± 0.3	1.3 ± 0.3	1.3 ± 0.3
Triglycerides (mmol/l)	1.3 (0.9–1.7)	0.9 (0.7–1.1)	1.2 (0.8–1.6)	1.2 (0.9–1.7)
Smoking (%)	23.2	10.2†	22.6	19.3
Waist circumference (cm)	…	…	83.9 ± 12.0	88.7 ± 13.3
Apolipoprotein A-1 (g/l)	…	…	1.5 ± 0.3	1.6 ± 0.2
Apolipoprotein B (g/l)	…	…	1.1 ± 0.3	1.0 ± 0.3

Values presented as unadjusted means ± standard deviation or geometric mean (25th–75th percentiles) or percentages of participants. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *Some variables have missing data. †Smoking data was gathered on participants aged 12–18 years.

5.2 Cardiovascular risk factors and PWV

5.2.1 Metabolic syndrome (studies I and III)

There were a total of 945 subjects who participated in the base-line study in 1986 (then aged 9–18 years) and the follow-up in 2007 (then aged 30–39 years) (study III). The prevalences of MetS in the base-line paediatric population in 1986 were 14.1% for the Ped1MetS definition and 11.1% for the Ped2MetS definition. In the follow-up adult population in 2007, the prevalence of MetS was 18.1%. Of the continuous paediatric risk variables, age, sex, systolic blood pressure and triglycerides were independently associated with PWV in adulthood ($p < 0.02$ for all). In addition, hyperinsulinemia as a component of paediatric MetS was directly and independently related to PWV in adulthood ($p = 0.021$) (Table 5.2).

Table 5.2 Multivariable associations of continuous paediatric risk variables and components of paediatric MetS (ages 9–18 years in 1986) with adult PWV (in 2007) (n=945).

	PWV	
	β ± SE	P
Continuous paediatric risk variables		
Age	0.039 ± 0.011	0.001
Sex	0.607 ± 0.062	<0.001
Systolic blood pressure (mmHg)	0.008 ± 0.003	0.007
Triglycerides (mmol/l)	0.541 ± 0.217	0.013
Body mass index (kg/m^2)	-0.004 ± 0.013	0.750
Insulin (mmol/l)	0.182 ± 0.155	0.241
HDL cholesterol (mmol/l)	-0.029 ± 0.117	0.805
Components of paediatric MetS		
Age	0.059 ± 0.009	<0.001
Sex	0.608 ± 0.060	<0.001
Hyperinsulinemia	0.164 ± 0.071	0.021
Hypertension	0.126 ± 0.069	0.068
Overweight	0.039 ± 0.089	0.661
Low HDL cholesterol	-0.036 ± 0.072	0.613
High triglycerides	0.082 ± 0.073	0.260
Hyperglycaemia	-0.200 ± 0.526	0.703

Heart rate-specific z scores were used for PWV. β, regression coefficient; SE, standard error.

Participants suffering from MetS in childhood or adulthood had higher PWV in adulthood when compared with those not afflicted with the syndrome ($p<0.007$) (Figure 5.1A). An increasing number of the MetS components in childhood were associated with increased PWV in adulthood (p for trend = 0.005) (Figure 5.1B). Participants with persistent MetS over the 21-year follow-up had higher PWV than those without MetS at base-line and follow-up ($p<0.001$). Moreover, participants who recovered from MetS over the 21-year follow up had lower PWV when compared to those with persistent MetS ($p<0.001$) (Figure 5.1C).

In a population of 1741 young adults (aged 30–45 years, 45% males), the prevalence of MetS was 19.7% using the NCEP definition, 22.7% using the IDF definition, and 13.4 % using the EGIR definition (study I). As individual components of MetS, obesity and hypertension by all definitions, high triglycerides by the NCEP and IDF definitions, and dyslipidemia by the EGIR definition were independently associated with PWV ($p<0.02$ for all) (Table 5.3).

Table 5.3 Relationship between MetS (NCEP, IDF, EGIR) components and PWV (adjusted for age, sex and other metabolic syndrome components).

	PWV	
	β ± SE	P
NCEP		
Obesity	0.251 ± 0.073	0.001
High triglycerides	0.196 ± 0.083	0.018
Low HDL	0.067 ± 0.067	0.317
Hypertension	0.788 ± 0.070	<0.001
High glucose	0.087 ± 0.076	0.251
IDF		
Obesity	0.202 ± 0.066	0.002
High triglycerides	0.202 ± 0.083	0.015
Low HDL	0.061 ± 0.068	0.369
Hypertension	0.789 ± 0.070	<0.001
High glucose	0.093 ± 0.076	0.217
EGIR		
Hyperinsulinemia	-0.004 ± 0.082	0.958
Obesity	0.257 ± 0.069	<0.001
Dyslipidemia	0.234 ± 0.081	0.004
Hypertension	0.778 ± 0.100	<0.001
High glucose	0.229 ± 0.130	0.078

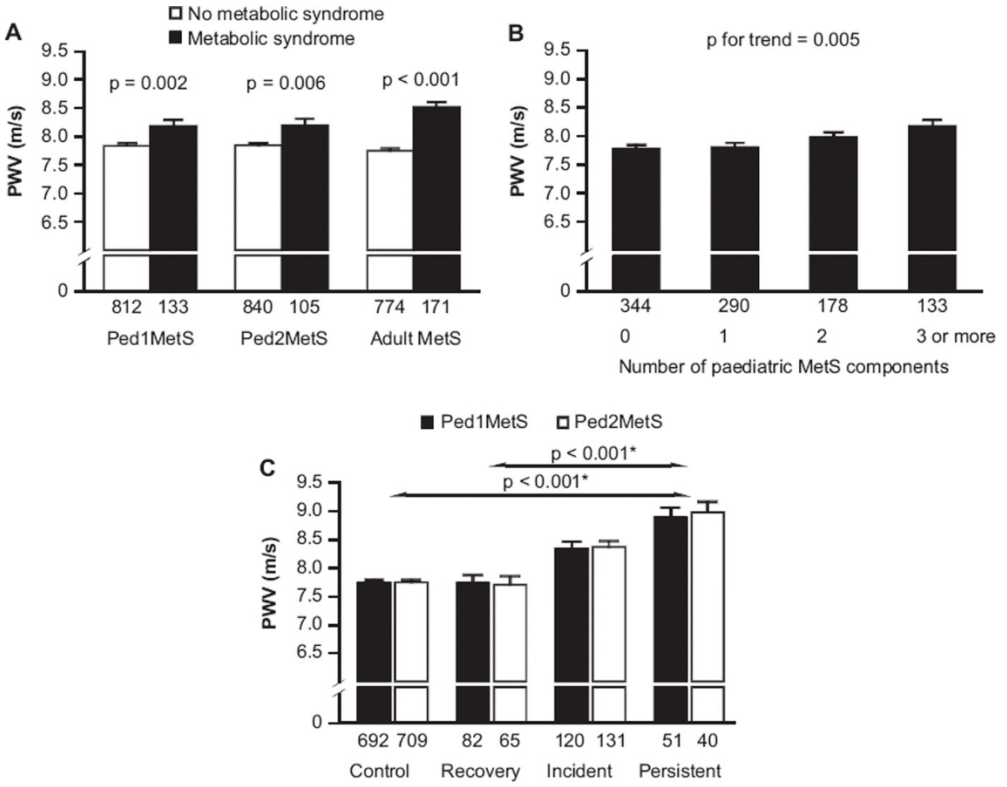

Figure 5.1 A) Comparison of adult PWV between participants with and without MetS according to the paediatric MetS definitions (Ped1MetS and Ped2MetS) (ages 9 to 18 years in 1986) and the adult MetS definition (ages 30 to 39 years in 2007). B) Adult PWV by the number of paediatric MetS components (ages 9 to 18 years in 1986). C) Comparison of adult PWV between the 21-year changes in MetS status.
PWV values are age-, sex- and heart-rate-adjusted means and standard errors. Values under columns indicate the number of participants in each group. * for both paediatric MetS definitions (Ped1MetS and Ped2MetS).
Reprinted from Annals of Medicine, 43, Koivistoinen T, Hutri-Kähönen N, Juonala M, Aatola H, Kööbi T, Lehtimäki T, Viikari JSA, Raitakari OT, Kähönen M. Metabolic syndrome in childhood and increased arterial stiffness in adulthood-The Cardiovascular Risk in Young Finns Study, 312-319, Copyright (2011), with permission from Taylor&Francis.

Participants with MetS had higher PWV values (age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted) when compared with those not afflicted with the syndrome (study I): 8.7 ± 0.07 m/s vs. 8.0 ± 0.04 m/s by the NCEP definition; 8.7 ± 0.07 m/s vs. 8.0 ± 0.04 m/s by the IDF definition; and 8.4 ± 0.09 m/s vs. 8.1 ± 0.03 m/s by the EGIR definition ($p<0.005$ for all). Moreover, PWV increased with an increasing amount of MetS components ($p<0.001$ for all definitions) (Figure

5.2A). The association of recovery from MetS with PWV was studied on a subpopulation of 1391 participants who had complete risk factor data available at 2001 and at 2007, and PWV measured at 2007 (study I). Higher PWV was observed in the MetS persistent group (MetS both at 2001 and 2007) compared to the MetS recovery group (MetS at 2001 but not at 2007), whereas there was no difference in PWV in the MetS control (no MetS at 2001 or 2007) and MetS recovery groups (Figure 5.2B). All analyses were repeated after adjusting PWV for heart rate with essentially similar results.

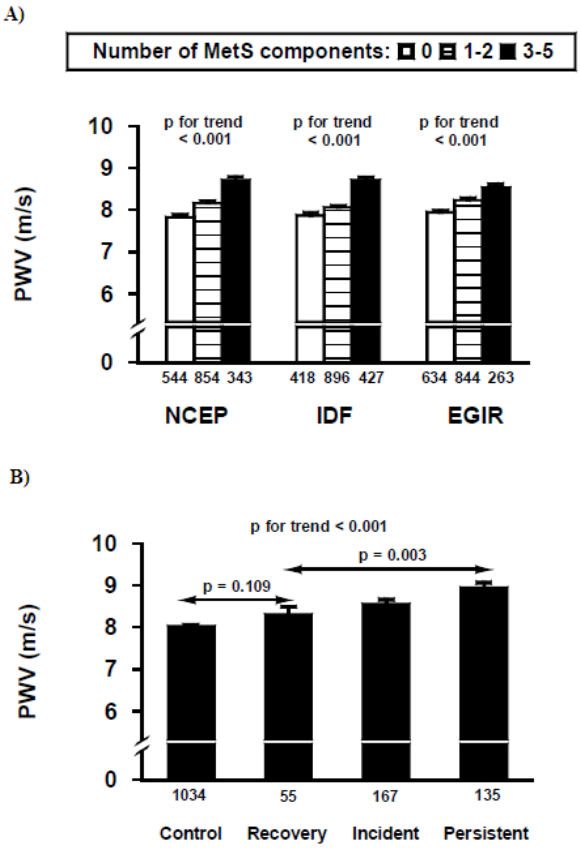

Figure 5.2 A) Mean level of PWV by the number of MetS components by the NCEP, IDF or EGIR definition. B) Comparison of PWV between the 6-year change in MetS status by IDF definition. Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of participants in each group.
Adapted from Annals of Medicine, 42, Koivistonen T, Aatola H, Hutri-Kähönen N, Juonala M, Viikari JSA, Laitinen T, Taittonen L, Lehtimäki T, Kööbi T, Raitakari OT, Kähönen M. Systemic hemodynamics in young adults with the metabolic syndrome: The Cardiovascular Risk in Young Finns Study, 612-621, Copyright (2010), with permission from Taylor&Francis.

5.2.2 ApoB and ApoA-1 (study IV)

The study population comprised 1618 young adults (aged 30–45 years, 45% males) with complete cardiovascular and PWV data available in 2007 (study IV). A sub-sample group comprised 1264 young adults for whom complete cardiovascular data was available in 2001 (then aged 24–39 years, 46% males) and whose PWV was measured in 2007. All risk factors, expect for smoking, ApoA-1 in 2007 and CRP in 2001, were univariately associated with PWV ($p<0.03$ for all) (Table 5.4). Of the lipid risk factors, ApoB (2001: $p=0.005$; 2007: $p=0.003$), the ApoB/ApoA-1 ratio (2001: $p=0.002$; 2007: $p=0.004$) and the LDL/HDL ratio (2001: $p=0.012$; $p=0.008$) were independently associated with PWV in the multivariable analyses (Table 5.4). In addition, triglycerides ($p=0.004$) and non-HDL cholesterol ($p=0.025$) measured in 2007 were independently associated with PWV.

There was an increasing trend of PWV across the ApoB tertiles measured in 2001 (Figure 5.3A) and 2007 (Figure 5.3B). The AUC for ApoB (measured in 2001 or 2007) was higher than for non-HDL cholesterol in predicting $\geq$ 90th percentile PWV. However, in 2001 the difference remained significant only when the model additionally included heart rate (0.673 vs. 0.654, respectively, $p = 0.008$), but it was diluted after adding age and sex in the model ($p=0.10$). Moreover, in 2007 the difference remained significant when heart rate, age and sex were included in the model (0.756 vs. 0.749, respectively, $p=0.025$), but it was diluted after including all non-lipid risk factors independently associated with PWV in the model ($p=0.067$).

Table 5.4 Univariate and multivariable relations between risk factors and PWV.

	Risk variables measured in 2001 and PWV in 2007		Risk variables and PWV measured in 2007	
	β (SE)	P	β (SE)	P
Univariate relations				
ApoA-I (g/l)	-0.259 (0.112)	0.022	-0.166 (0.099)	0.094
ApoB (g/l)	0.969 (0.110)	< 0.001	1.154 (0.093)	< 0.001
ApoB/ApoA-1 ratio	1.069 (0.123)	< 0.001	1.285 (0.115)	< 0.001
HDL cholesterol (mmol/)	-0.414 (0.090)	< 0.001	-0.385 (0.076)	< 0.001
LDL cholesterol (mmol/)	0.195 (0.033)	< 0.001	0.241 (0.030)	< 0.001
Non-HDL cholesterol (mmol/)	0.213 (0.030)	< 0.001	0.274 (0.026)	< 0.001
LDL/HDL ratio	0.185 (0.024)	< 0.001	0.235 (0.024)	< 0.001
Triglycerides (mmol/l)	0.896 (0.143)	< 0.001	1.291 (0.119)	< 0.001
Systolic blood pressure (mmHg)	0.031 (0.002)	< 0.001	0.032 (0.002)	< 0.001
Body mass index (kg/m^2)	0.040 (0.007)	< 0.001	0.039 (0.005)	< 0.001
Insulin (mU/l)	0.486 (0.122)	< 0.001	0.520 (0.075)	< 0.001
Fasting glucose (mmol/l)	0.520 (0.064)	< 0.001	0.521 (0.048)	< 0.001
C-reactive protein (mg/l)	0.070 (0.053)	0.187	0.207 (0.052)	< 0.001
Smoking	-0.025 (0.065)	0.696	-0.082 (0.062)	0.186
Multivariable relations				
ApoA-1* (g/l)	-0.110 (0.106)	0.301	0.034 (0.090)	0.704
ApoB* (g/l)	0.310 (0.111)	0.005	0.292 (0.098)	0.003
Sex	0.374 (0.059)	< 0.001	0.323 (0.050)	< 0.001
Insulin (mU/l)	0.385 (0.130)	0.003	0.229 (0.082)	0.005
Fasting glucose (mmol/l)	0.005 (0.065)	0.943	0.099 (0.048)	0.041
Age (years)	0.053 (0.005)	< 0.001	0.045 (0.004)	< 0.001
Body mass index (kg/m^2)	-0.013 (0.007)	0.090	-0.011 (0.006)	0.079
C-reactive protein (mg/l)	…	…	0.094 (0.049)	0.058
Systolic blood pressure (mmHg)	0.024 (0.002)	< 0.001	0.024 (0.002)	< 0.001

Heart rate-specific z-scores were used for PWV.

* When ApoA-1 and ApoB were replaced with their ratio, or with HDL and LDL cholesterol, the LDL/HDL ratio, the non-HDL cholesterol, or triglycerides, an independent association was found between the 2001 ApoB/ApoA-1 ratio (β [SE] = 0.397 [0.128], p = 0.002), the 2001 LDL/HDL ratio (0.061 [0.024], p = 0.012), the 2007 ApoB/ApoA-1 ratio (0.353 [0.123], p = 0.004), the 2007 LDL/HDL ratio (0.064 [0.024], p = 0.008), the 2007 triglycerides (0.369 [0.128], p = 0.004), the 2007 non-HDL cholesterol (0.057 [0.025], p = 0.025), and PWV assessed in 2007.

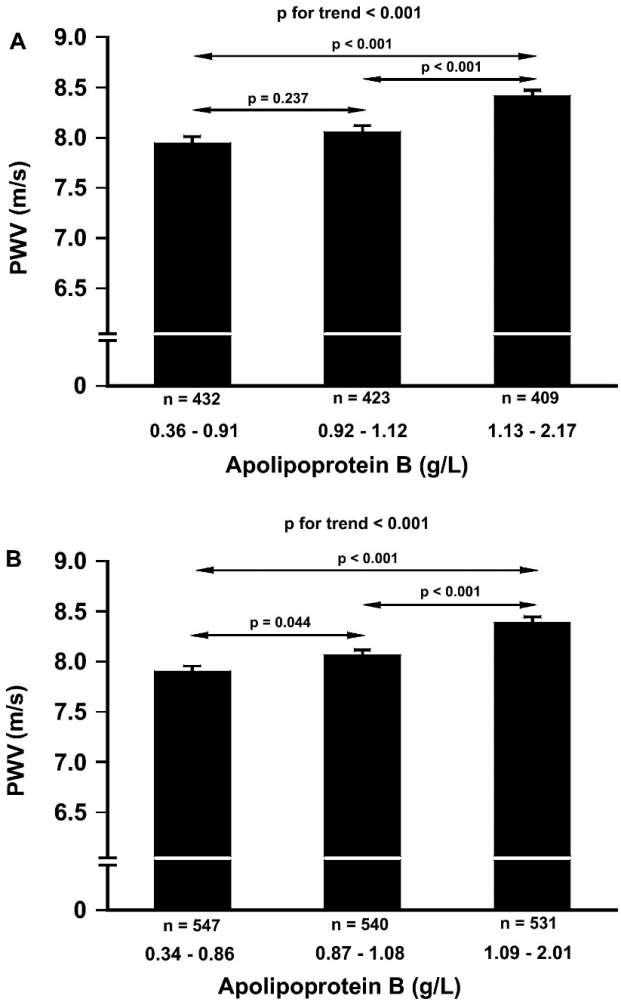

Figure 5.3 A) Heart-rate-, age- and sex-adjusted PWV means and standard errors (measured in 2007) across apolipoprotein B tertiles measured in 2001 (n = 1264, participants aged 24–39 years). B) Heart-rate-, age- and sex-adjusted PWV means and standard errors (measured in 2007) across apolipoprotein B tertiles measured in 2007 (n = 1618, participants aged 30–45 years).
Reprinted from Atherosclerosis, 214, Koivistoinen T, Hutri-Kähönen N, Juonala M, Kööbi T, Aatola H, Lehtimäki T, Viikari JSA, Raitakari OT, Kähönen M. Apolipoprotein B is related to arterial pulse wave velocity in young adults: The Cardiovascular Risk in Young Finns Study, 220-224, Copyright (2011), with permission from Elsevier.

5.2.3 Impaired glucose metabolism (study II)

The effect of impaired glucose metabolism on PWV was studied in a population of 389 participants (aged 46–76 years, 43% males) (study II). The prevalence of IFG, IGT and DM2 was 9.3%, 19.5% and 8.7%, respectively. In multivariable regression models, fasting glucose (p=0.034) and 2-h glucose in OGTT (p=0.005) were directly and independently associated with PWV (Table 5.5).

Table 5.5 Independent glucose/insulin effects on PWV.

	PWV	
	β ± SE*	P
Fasting glucose (mmol/l)	0.193 ± 0.091	0.034
2-h glucose in OGTT (mmol/l)	0.085 ± 0.030	0.005
Fasting insulin (mmol/l)	0.033 ± 0.019	0.075
2-h insulin in OGTT (mmol/l)	0.002 ± 0.002	0.331

*adjusted for age, sex, heart rate, body mass, systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, and smoking.

There was a trend of increasing PWV according to the worsening of glucose tolerance (Figure 5.4). The trend remained significant after adjusting for age, sex, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, and smoking (p for trend 0.021).

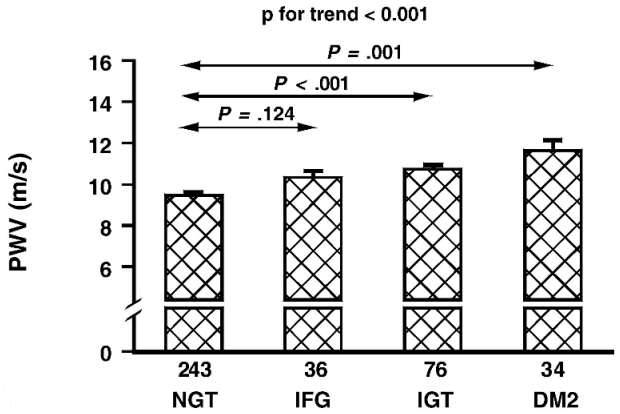

Figure 5.4 PWV means and standard errors according to glucose tolerance status. Values under columns indicate the number of participants in each group.
Adapted from Metabolism, 60, Koivistoinen T, Jula A, Aatola H, Kööbi T, Moilanen L, Lehtimäki T, Kähönen M. Systemic hemodynamics in relation to glucose tolerance: the Health 2000 Survey, 557-563, Copyright (2011), with permission from Elsevier.

5.3 Metabolic syndrome, impaired glucose metabolism and systemic hemodynamics (studies I and II)

The effect of MetS on systemic hemodymics was studied in a population of 1741 young adults (aged 30–45 years, 45% males) (study I). In addition, a subgroup of 1391 participants was created to evaluate the effect of spontaneous recovery from MetS over 6 years' follow-up (2001–2007) on systemic hemodynamics. Moreover, the effect of impaired glucose metabolism on systemic hemodynamics was studied in a population of 389 older adults (aged 46–76 years, 43% males) with NGT, IFG, IGT, or DM2 (study II).

As individual components of MetS, low HDL cholesterol by the NCEP ($p=0.002$) and IDF ($p=0.037$) criteria, obesity ($p<0.001$), hypertension ($p<0.003$), and hyperinsulinemia by the EGIR criteria ($p=0.002$) were inversely and independently associated with SI. As expected, obesity ($p<0.003$) and hypertension ($p<0.001$) were independent determinants of SVRI (Table 5.6).

Table 5.6 Relationship between MetS components and hemodynamic parameters adjusted for age, sex and other MetS components.

	SI		SVRI	
	β ± SE	P	β ± SE	P
NCEP				
Obesity	-1.421 ± 0.326	<0.001	120.419 ± 30.018	<0.001
High triglycerides	-0.515 ± 0.369	0.162	-16.155 ± 33.888	0.634
Low HDL	-0.922 ± 0.300	0.002	36.063 ± 27.594	0.191
Hypertension	-1.445 ± 0.310	<0.001	255.311 ± 38.493	<0.001
High glucose	-0.084 ± 0.338	0.803	-17.200 ± 31.074	0.580
IDF				
Obesity	-1.975 ± 0.292	<0.001	154.219 ± 26.918	<0.001
High triglycerides	-0.368 ± 0.366	0.315	-25.623 ± 33.783	0.448
Low HDL	-0.630 ± 0.302	0.037	15.000 ± 27.808	0.590
Hypertension	-1.364 ± 0.308	<0.001	249.950 ± 28.382	<0.001
High glucose	-0.083 ± 0.334	0.805	-16.726 ± 30.795	0.587
EGIR				
Hyperinsulinemia	-1.131 ± 0.357	0.002	-25.068 ± 33.185	0.450
Obesity	-1.886 ± 0.300	<0.001	169.967 ± 27.877	<0.001
Dyslipidemia	-0.426 ± 0.349	0.222	21.672 ± 32.497	0.505
Hypertension	-1.328 ± 0.433	0.002	254.584 ± 40.263	<0.001
High glucose	0.760 ± 0.563	0.178	-41.732 ± 52.435	0.426

Participants with MetS had lower SI and higher SVRI by all definitions ($p<0.005$) (Figure 5.5A and 5.5B). There was also a trend of decreasing SI and increasing SVRI with an increase in the amount of MetS components by all three definitions ($p<0.001$ for all) (Figure 5.6A and 5.6B).

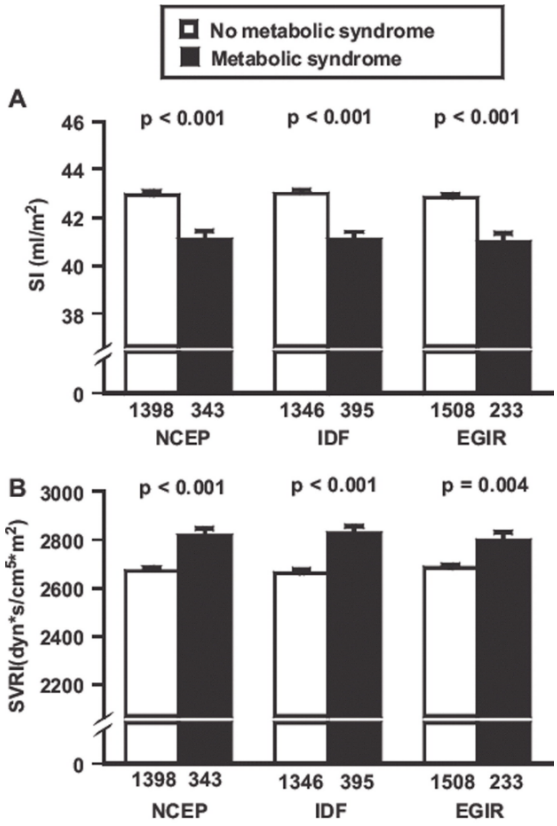

Figure 5.5 Comparison of SI (A) and SVRI (B) between the participants with and without MetS by the NCEP, IDF, or EGIR definition. Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of participants in each group.

Adapted from Annals of Medicine, 42, Koivistonen T, Aatola H, Hutri-Kähönen N, Juonala M, Viikari JSA, Laitinen T, Taittonen L, Lehtimäki T, Kööbi T, Raitakari OT, Kähönen M. Systemic hemodynamics in young adults with the metabolic syndrome: The Cardiovascular Risk in Young Finns Study, 612-621, Copyright (2010), with permission from Taylor&Francis.

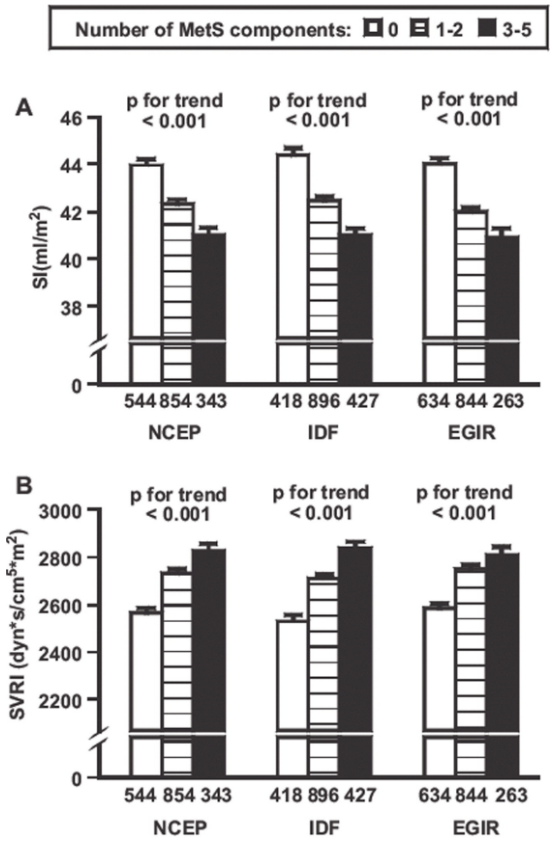

Figure 5.6 Mean levels of SI (A) and SVRI (B) by the number of MetS components according to the NCEP, IDF or EGIR definition. Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of participants in each group.
Adapted from Annals of Medicine, 42, Koivistonen T, Aatola H, Hutri-Kähönen N, Juonala M, Viikari JSA, Laitinen T, Taittonen L, Lehtimäki T, Kööbi T, Raitakari OT, Kähönen M. Systemin hemodynamics in young adults with the metabolic syndrome: The Cardiovascular Risk in Young Finns Study, 612-621, Copyright (2010), with permission from Taylor&Francis.

Lower SI (p=0.024) was observed in the MetS persistent group (MetS both at 2001 and 2007 by the IDF definition) compared to the MetS recovery group (MetS at 2001 but not at 2007 by the IDF definition) (Figure 5.7A). The difference in SVRI between the MetS persistent and MetS recovery groups was not statistically significant (p=0.082) (Figure 5.7B). Statistically significant trends for SI and SVRI according to a 6-year change in MetS status were also observed using the NCEP and EGIR definitions (p<0.001 for both). Heart rate was higher in participants with MetS than in those without MetS by all three definitions (69

± 10 beats/min vs. 64 ± 9 beats/min, respectively, p<0.001). There was no statistically significant difference in CI between participants with or without MetS.

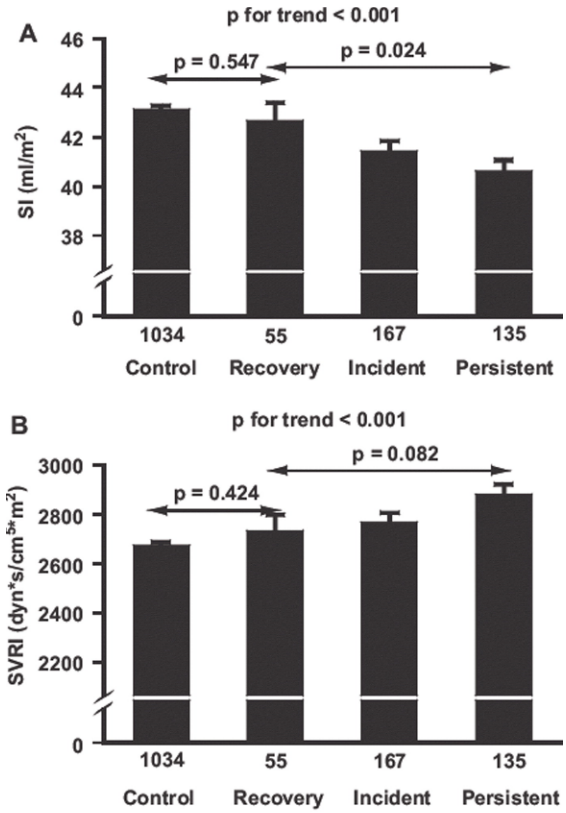

Figure 5.7 Comparison of SI (A) and SVRI (B) between the 6-year change in MetS status by the IDF definition.Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of participants in each group.
Adapted from Annals of Medicine, 42, Koivistonen T, Aatola H, Hutri-Kähönen N, Juonala M, Viikari JSA, Laitinen T, Taittonen L, Lehtimäki T, Kööbi T, Raitakari OT, Kähönen M. Systemic hemodynamics in young adults with the metabolic syndrome: The Cardiovascular Risk in Young Finns Study, 612-621, Copyright (2010), with permission from Taylor&Francis.

Two-hour glucose in OGTT (p<0.001) and two-hour insulin in OGTT (p=0.006) were directly and independently associated with SVRI, whereas glucose or insulin measures were not independently related with SI in multivariable regression models (Table 5.7) (study II).

Table 5.7 Independent glucose/insulin effects on SI and SVRI.

	SI		SVRI	
	β ± SE*	P	β ± SE*	P
Fasting glucose (mmol/l)	-0.277 ± 0.381	0.467	58.217 ± 36.654	0.113
2-hour glucose in OGTT (mmol/l)	-0.153 ± 0.127	0.227	45.352 ± 11.717	<0.001
Fasting insulin (mmol/l)	0.014 ± 0.078	0.857	-2.026 ± 7.627	0.791
2-hour insulin in OGTT (mmol/l)	-0.012 ± 0.010	0.223	2.666 ± 0.970	0.006

*adjusted for age, sex, heart rate, body mass, systolic and diastolic blood pressure (for SI only), HDL and LDL cholesterol, triglycerides, and smoking.

SI was observed to decrease (p for trend <0.001) and SVRI to increase (p for trend = 0.002) with the worsening of glucose tolerance (Figure 5.8). In pairwise comparisons, SI was lower in the IFG and IGT groups when compared with the NGT group ($p<0.05$ for both), but there was no statistically significant difference between the DM2 and NGT groups ($p=0.221$). SVRI was higher in the IGT and DM2 groups than in the NGT group ($p<0.05$ for both). After adjusting for age, sex, HDL and LDL cholesterol, triglycerides, smoking, and systolic and diastolic blood pressure (for SI only), the trend of decreasing SI and increasing SVRI with the worsening of glucose tolerance remained statistically significant (p for trend < 0.03 for both). There were no statistically significant differences in CI or heart rate between the groups.

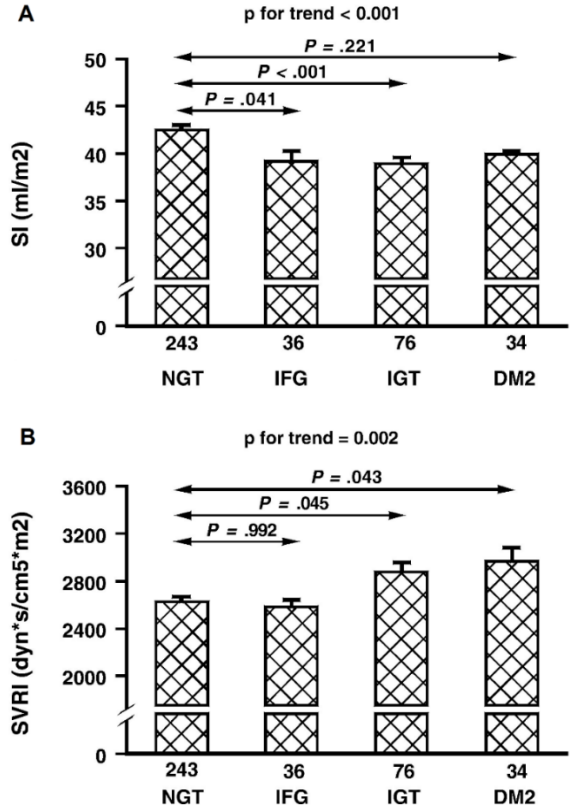

Figure 5.8 SI (A) and SVRI (B) means and standard errors according to glucose tolerance status. Values under columns indicate the number of participants in each group.
Adapted from Metabolism, 60, Koivistoinen T, Jula A, Aatola H, Kööbi T, Moilanen L, Lehtimäki T, Kähönen M. Systemic hemodynamics in relation to glucose tolerance: the Health 2000 Survey, 557-563, Copyright (2011), with permission from Elsevier.

5.4 Interrelationship between arterial stiffness and systemic hemodynamic parameters

Arterial stiffness index (ASI) has been developed to reduce the impact of the curvilinear pressure-stiffness relationship on arterial stiffness measurement, and it is considered to be independent of blood pressure. To examine whether arterial stiffness reflects a similar or different entity of cardiovascular structure and function when compared to systemic hemodynamic parameters, the interrelationship between ASI and systemic hemodynamic parameters was studied on a population of 350 adults (the Health 2000 Supplemental study population, participants aged 46–76 years, 44% males) (unpublished data). ASI

was measured from the carotid artery using high-resolution B-mode ultrasound. The measurement protocol has been described in detail previously (Niiranen et al. 2007, Kettunen et al. 2011). There was no correlation between ASI and SVRI (r=0.1, p=0.07) (Figure 5.9A). A weak, but statistically significant, univariate correlation was found between ASI and SI (r=-0.15, p=0.004) (Figure 5.9B).

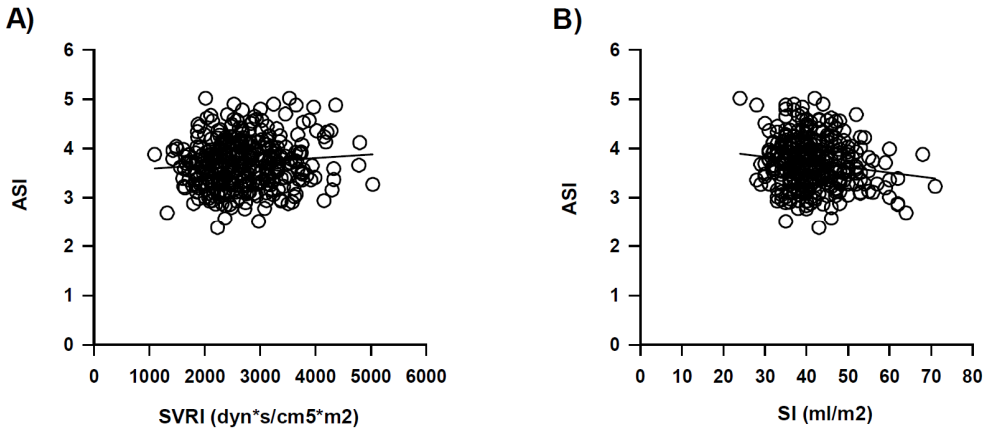

Figure 5.9 Arterial stiffness index (ASI) in relation to systemic vascular resistance index (SVRI) (A) and stroke index (SI) (B). The central line is the standard linear regression line.

6 Discussion

6.1 Cardiovascular risk factors and PWV

Previously, elevated cardiovascular risk factor levels in childhood have been shown to predict increased carotid artery intima-media thickness in adulthood (Raitakari et al. 2003). In addition, decreased CAC, as well as increased YEM and PWV, have been found in adults with an increasing number of cardiovascular risk factors measured in childhood (Juonala et al. 2005, Aatola et al. 2010a). However, the relationship between childhood MetS and arterial stiffness has received little academic interest to date. Iannuzzi et al. (2006) found an increased ASI in obese children with MetS (Iannuzzi et al. 2006), and Whincup et al. (2005) reported the local arterial distensibility in adolescents to decrease with the increase in the number of MetS components. The present study provided further insight into the possible adverse effects of childhood MetS on arterial stiffness by showing that participants with MetS in childhood have increased PWV in adulthood. Moreover, hypersinsulinemia as a component of childhood MetS was associated with increased PWV in adulthood, a finding which is in line with the notion that insulin levels in childhood correlate inversely with CAC and directly with YEM in adulthood (Juonala et al. 2005). In the adult population, participants with MetS had higher PWV values than those not afflicted with the syndrome, a finding which is in concert with earlier reports in young (Li et al. 2005a) and middle-aged adults (Sipilä et al. 2007). As have others (Schillaci et al. 2005), we found that hypertension and obesity as individual components of MetS were independent determinants of PWV. Previously, triglycerides have been shown to associate directly with PWV in some (Mitchell et al. 2004, Aatola et al. 2010a), but not in all studies (Cecelja and Chowienczyk 2009). In the present study, trigyclyserides as a continuous variable and as a component of adult MetS were directly associated with PWV.

Participants with persistent MetS had higher PWV than those who recovered or were free from MetS during the 6-year (adult population) or 21-year (pediatric population) follow-up. This difference (0.8–1.3 m/s) is noteworthy, since there is a 14%–15% increase in cardiovascular events, cardiovascular mortality, and all-

cause mortality for each 1 m/s increase in aortic PWV (Vlachopoulos et al. 2010). Participants in the MetS persistent group had a higher BMI or waist circumference, fasting glucose, blood pressure, triglycerides, as well as lower HDL cholesterol, as compared to MetS recovery group. Our results thus suggest that reduced arterial stiffness in subjects with MetS could be achieved by improving the metabolic risk factor profile and by weight reduction. Further evidence to support this view has been provided by the previous studies demonstrating a decrease in carotid-femoral PWV after weight reduction in middle-aged men (Miyaki et al. 2009), a reduction in carotid-femoral PWV after long-term trandolapril treatment in older adults (Mitchell et al. 2007), and a decrease in femoral-ankle PWV after atorvastatin treatment in patients with DM2 (Shinohara et al. 2005).

Increased PWV was observed in middle-aged participants with IGT and DM2 compared with participants with NGT, which is in line with previous reports (Taniwaki et al. 1999, Ohnishi et al. 2003, Rahman et al. 2008, Xu et al. 2010). Moreover, there was a trend of increasing PWV with the worsening of glucose tolerance. Furthermore, fasting glucose and 2-hour glucose on OGTT were independent determinants of PWV. Therefore, the present findings suggest that glucose intolerance, even without DM2, has adverse effects on arterial stiffness and that glucose tolerance measurements should be included in the risk evaluation of the middle-aged population.

Previously, in relative small-scale studies, ApoB has been found to associate with PWV in adolescents with type 1 diabetes (Bjornstad et al. 2015) and in patients treated for cardiovascular risk factors (Amar et al. 2001). In addition, ApoB has been shown to correlate with local (carotid artery) arterial stiffness (Schmidt-Trucksäss et al. 1999). In the current study, ApoB was directly and independently associated with PWV in young adults. Moreover, ApoB was found to predict increased PWV measured 6 years later. In contrast, LDL cholesterol was not independently associated with PWV and did not predict PWV during the 6-year follow up. The current findings thus suggest that ApoB is associated with arterial stiffness in young adults and that ApoB may be a better dyslipidemia risk marker of increased arterial stiffness than LDL cholesterol. However, the ROC analysis demonstrated that there were no differences between non-HDL cholesterol and ApoB in identifying increased PWV and, therefore, we conclude that ApoB is not superior to non-HDL cholesterol in detecting increased arterial stiffness in young adults. Furthermore, in the current study, ApoA-1 was not

associated with PWV, as was also shown previously in a population of 429 healthy middle-aged women (Taquet et al. 1993).

The pathophysiological mechanisms underlying the association between cardiovascular risk factors and arterial stiffness are incompletely understood (Zieman et al. 2005, Stehouwer et al. 2008, Cecelja and Chowienczyk 2009, Prenner and Chirinos 2015). Nevertheless, it has been suggested that hyperglycaemia increases the formation of advanced glycation end products on the arterial wall, causing cross-linking of collagen (Stehouwer et al. 2008, Prenner and Chirinos 2015). Hyperglycaemia and hyperinsulinemia also promote the development of wall hypertrophy and fibrosis by increasing the local activity of the renin-angiotensin-aldosterone system (Stehouwer et al. 2008). In addition, hypertension may result in structural alterations in the arterial wall, including decreased elastin content, increased collagen content, and change in the type of collagen (Cecelja and Chowienczyk 2009). Moreover, low-grade inflammation and endothelial dysfuntion related to cardiovascular risk factors may increase stiffness (Stehouwer et al. 2008, Townsend et al. 2015).

In summary, the present study demonstrated the adverse effects of cardiovascular risk factors, particularly impaired glucose metabolism, increased ApoB and MetS, on arterial stiffness. Moreover, the current findings suggest that recovery from MetS is associated with decreased arterial stiffness.

6.2 Cardiovascular risk factors and systemic hemodynamics

The main findings of this study on the relationship between MetS, glucose tolerance and systemic hemodynamic parameters were as follows. Firstly, MetS, an increasing number of MetS components, and deteriorating glucose tolerance were associated with decreased SI and increased SVRI. Secondly, as individual components of MetS, low HDL cholesterol, obesity, hypertension, and hyperinsulinemia were inversely and independently associated with SI, and obesity and hypertension were independent determinants of SVRI. Thirdly, 2-hour glucose and insulin in OGTT were directly and independently associated with SVRI. The fourth main finding was that participants who recovered from MetS during the 6-year follow-up had higher SI when compared to participants with persistent MetS.

Previous studies have provided several plausible explanations for the adverse changes in systemic hemodynamics in subjects with MetS and/or

impaired glucose metabolism. All the components of MetS can individually impair endothelial function, leading to a higher tone in resistance arteries (Su et al. 2008, Tziomalos et al. 2010). In addition, in hypertensive and obese individuals, impairment of insulin-mediated vasodilation may contribute to the increase in peripheral resistance (Feldman and Bierbrier 1993). Moreover, persons with MetS have increased sympathetic tone (Koskinen et al. 2009).

Increased insulin levels, glucose intolerance and hypertension have been shown to relate to LV hypertrophy and mass (Sasson et al. 1993, Hara-Nakamura et al. 1994, Palmieri et al. 2001), which in turn are related to decreased contractility (Grossman et al. 1994, Dahan et al. 1997). Moreover, alterations in myocardial cells caused by diabetes may lead to myocardial cell injury, interstitial fibrosis and, ultimately, to LV dysfunction, especially when the diabetes is accompanied by hypertension (Kawaguchi et al. 1997). Furthermore, IGT may be an independent aetiological factor for low coronary flow (Binak et al. 2006), and alterations in intracellular calcium homeostasis in the diabetic heart may lead to depressed contractility (Lopaschuk 2002). However, it should be noted that, in addition to the direct influence of MetS and/or deteriorating glucose tolerance on SI, increased arterial load caused by increased stiffness and SVR could be responsible for the lower SI in subjects with MetS and/or glucose metabolism disorder.

The present findings are in line with previous findings showing increased SVRI in hypertensive patients (Abdelhammed et al. 2005) and subjects with abdominal obesity (Chirinos et al. 2009). Moreover, low HDL cholesterol has been associated with subclinical LV dysfunction (Wang et al. 1999) and central obesity with lower CO (Jern et al. 1992). Furthermore, antidiabetic medication has been shown to decrease SVR (Shargorodsky et al. 2003), and antihypertensive medication has been found to reduce total peripheral resistance and slightly improve cardiac pump function (Omvik et al. 2000).

Taken together, the current findings suggest that MetS and impaired glucose metabolism have adverse effects on systemic hemodynamics, and recovery from MetS may improve cardiac pump function.

6.3 Methodological considerations and study limitations

Although the large study population from the two distinct cohorts and the long follow-up in YFS are the greatest strengths of the presents study, there are also

some limitations concerning this population. The overall cohort of the Health 2000 Survey (8028 participants) represents the entire Finnish population aged 30 and over. To study CVD and diabetes more thoroughly, the supplemental study (1867 participants) was carried out in the catchment areas of five Finnish University Hospitals, and in the catchment areas of Tampere and Turku University Hospitals, 455 subjects participated in ICG_{WB} measurement. This sub-sample is therefore a cross-section of the middle-aged and elderly Finnish population living in urban areas, rather than being representative of the whole Finnish population. In YFS, a representative sample of Finnish children (3596 subjects) participated the study in 1980. After that, several follow-up studies of this cohort have been conducted, and the participation rates have varied from 80% (in 1983) to 60% (in 2007). The dropout rate in the YFS cohort has thus been substantial. However, the risk profile during the 21-year follow-up period among the remaining participants is well-representative of the original population (Juonala et al. 2004).

Some limitations concerning MetS and the current study protocol should be noted. There is accumulating skepticism towards the usefulness of MetS as a diagnostic or disease management tool (Borch-Johnsen and Wareham 2010, Simmons et al. 2010). One of the main concerns is that MetS seems not to be a greater cardiovascular risk factor than the sum of its parts. However, it has been suggested that MetS could act as an early warning sign, particularly among young individuals with a relatively low risk according to the individual risk factors (Cameron et al. 2009). In the present study, MetS status was defined at baseline and at follow-up, but ICG_{WB} measurements were only taken at follow-up. Therefore, the current study does not allow the evaluation of longitudinal changes in ICG_{WB} parameters in relation to MetS status. Moreover, the lack of standard paediatric MetS definitions may limit the generalizability of the present results.

The measurement of PWV and systemic hemodynamic parameters with ICG_{WB} could be considered a methodological limitation. Although ICG_{WB} has been found to be well in agreement with the Doppler method in the measurement of PWV (Kööbi et al. 2003), and with the thermodilution method in the measurement of CO (Kööbi et al. 1997a, Kööbi et al. 1997b, Kööbi et al. 1999), ICG_{WB} is not widely used in epidemiological studies, obviously limiting the comparability of the present findings with the observations from other cohorts. However, it should be noted that ICG_{WB} is ideal for epidemiological settings because it is an inexpensive, fast and operator-independent method for measuring PWV and systemic hemodynamic parameters simultaneously.

The arterial wall includes a diversity of molecular, cellular and histological structures, which renders the elastic properties of various conduit arteries along the arterial tree quite heterogeneous (Laurent et al. 2006). Moreover, aging and cardiovascular risk factors effect the dynamic properties of the arterial tree in an inhomogeneous fashion (Nichols et al. 2011). Measuring PWV over arteries with different properties could therefore be considered a limitation. However, the inclusion of the femoral artery in the measurement protocol could prove important as it has been proposed that the deleterious effects of cardiovascular risk factors on local arterial stiffness are more pronounced in the more muscular than the more elastic arteries (Schram et al. 2004, Ferreira et al. 2005). Furthermore, the longer pathway (aorta-poplitea) could provide a more global index of vascular health.

Several different methods have been developed to estimate structural and functional changes in the cardiovascular system. Stroke volume, as a measure of cardiac function, refers to to the quantity of blood pumped out of the left ventricle with every heart beat, and its major determinants are preload, afterload and contractility. Arterial stiffness describes the cushioning function of large arteries, whereas systemic vascular resistance describes the vessels' tendency to oppose blood flow and it is mainly determined by the microcirculation, i.e. small arteries, arterioles and capillaries, since they present the greatest resistance (O'Rourke and Hashimoto 2007, Westerhof and Westerhof 2013). In the present study, the arterial stiffness index did not correlate with SVRI and correlated only weakly with SI. These findings suggest that arterial stiffness reflects, at least partly, a different entity of cardiovascular function than systemic hemodynamic parameters, thus supporting the current approach to study the effects of cardiovascular risk factors on arterial stiffness and systemic hemodynamics seperately.

6.4 Clinical implications and future perspectives

The incidence of MetS and diabetes have increased alarmingly, and studying these metabolic abnormalities is therefore essential. This study showed in young adults that MetS yields adverse effects on arterial stiffness and systemic hemodynamics and recovery from MetS may improve cardiovascular function. Moreover, childhood MetS was found to associate with increased arterial stiffness in adulthood, and recovery from childhood MetS during a 21-year follow-up period had positive effects on arterial stiffness. The current study also expanded

the understanding of the adverse alterations in arterial stiffness and systemic hemodynamics caused by deteriorating glucose tolerance. Thus, the present findings underline the importance of the prevention and controlling of cardiovascular risk factors in both childhood and adulthood. Especially the prevention of excessive weight gain and obesity is essential, since the risk of diabetes, cardiovascular disease and hypertension rises continuously with increasing weight (WHO 2003). Possible factors that could protect against weight gain include regular physical activity, home and school enviroments that support healthy food choices, lower alcohol consumption, low glycaemic index foods and a high dietary fibre intake (WHO 2003).

The present study also suggests that increased ApoB is associated with increased arterial stiffness. Moreover, the 6 years of dyslipidemia may influence the arterial stiffening in young adults, and our findings therefore reinforce the focus on primary prevention and the possibility of modulating the arterial aging process.

7 Summary and conclusions

The effects of impaired glucose metabolism, apolipoproteins B and A-1, and childhood and adulthood MetS on PWV were investigated among participants of the Cardiovascular Risk in Young Finns Study and the Health 2000 Survey. In addition, the present study examined the relationship between MetS, impaired glucose metabolism and systemic hemodynamic parameters. The results of this large-scale study with data from two cohorts can be summarised as follows:

1. A worsening of glucose tolerance, increased ApoB, and MetS in childhood and adulthood were related to an increase in PWV. Moreover, ApoB measured in young adulthood was predictive of PWV measured 6 years later. This study thus highlights the importance of the prevention and controlling of cardiovascular risk factors in both childhood and adulthood.

2. Recovery from MetS during 6-year and 21-year follow-up was associated with decreased arterial stiffness. Therefore, our findings suggest that favourable changes in the vasculature can be achieved by improving cardiovascular risk factors.

3. MetS, an increasing number of MetS components and deteriorating glucose tolerance were associated with decreased SI and increased SVRI. Moreover, recovery from MetS was associated with increased SI. Therefore, this investigation brings new insight into the relationships between cardiovascular risk factors and systemic hemodynamics, and our findings emphasize the importance of an evaluation of glucose tolerance status and MetS in the estimation of cardiovascular risk.

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Teemu Koivistoinen

9 References

Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, Taittonen L, Lehtimäki T, Raitakari OT, Kähönen M (2010a): Lifetime risk factors and arterial pulse wave velocity in adulthood: the cardiovascular risk in young Finns study. Hypertension 55:806-811.

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

Abdelhammed AI, Smith RD, Levy P, Smits GJ, Ferrario CM (2005): Noninvasive hemodynamic profiles in hypertensive subjects. Am J Hypertens 18:51S-59S.

Alberti KG, Zimmet P, Shaw J (2005): The metabolic syndrome – a new worldwide definition. Lancet 366:1059-1062.

Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr (2009): Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640-1645.

Amar J, Ruidavets JB, Chamontin B, Drouet L, Ferrières J (2001): Arterial stiffness and cardiovascular risk factors in a population-based study. J Hypertens 19:381-387.

Ambrose JA, Barua RS (2004): The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 43:1731-1737.

Anderson SG, Sanders TA, Cruickshank JK (2009): Plasma fatty acid composition as a predictor of arterial stiffness and mortality. Hypertension 53:839-845.

Aromaa A and Koskinen S (2004): Health and functional capacity in Finland. Baseline results of Health 2000 health exmination survey. Publications of National Public Health Institute, Helsinki. B12/2004:1-175.

Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI (1995): Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 26:485-490.

Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF (1985): Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation 71:202-210.

Balkau B, Charles MA (1999): Comment on the provisional report from the WHO consultation. Diabetic Medicine 16:442-443.

Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA (1998): Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 338:1650-1656.

Binak E, Gunduz H, Sahin M, Kurtoglu N, Dindar I (2006): The relation between impaired glucose tolerance and slow coronary flow. Int J Cardiol 111:142-146.

Bjornstad P, Nguyen N, Reinick C, Maahs DM, Bishop FK, Clements SA, Snell-Bergeon JK, Lieberman R, Pyle L, Daniels SR, Paul Wadwa R (2015): Association of apolipoprotein B, LDL-C and vascular stiffness in adolescents with type 1 diabetes. Acta Diabetol 52:611-619.

Blacher J, Asmar R, Djane S, London GM, Safar ME (1999a): Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 33:1111-1117.

Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM (1999b): Impact of aortic stiffness on survival in end-stage renal disease. Circulation 99:2434-2439.

Borch-Johnsen K, Wareham N (2010): The rise and fall of the metabolic syndrome. Diabetologia 53:597-599.

Cameron AJ, Zimmet PZ, Shaw JE, Alberti KG (2009): The metabolic syndrome: in need of a global mission statement. Diabet Med 26:306-309.

Cavalcante JL, Lima JA, Redheuil A, Al-Mallah MH (2011): Aortic stiffness: current understanding and future directions. J Am Coll Cardiol 57:1511-1522.

Cecelja M, Chowienczyk P (2009): Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 54:1328-1336.

Chen W, Srinivasan SR, Elkasabany A, Berenson GS (1999): Cardiovascular risk factors clustering features of insulin resistance syndrome (Syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: the Bogalusa Heart Study. Am J Epidemiol 150:667-674.

Chirinos JA, Rietzschel ER, De Buyzere ML, De Bacquer D, Gillebert TC, Gupta AK, Segers P; Asklepios investigators (2009): Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. Hypertension 54:558-566.

Cohn JN, Quyyumi AA, Hollenberg NK, Jamerson KA (2004): Surrogate markers for cardiovascular disease: functional markers. Circulation 109:IV31-46.

Cornelissen VA, Fagard RH (2005): Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. Hypertension 46:667-675.

Cote AT, Harris KC, Panagiotopoulos C, Sandor GG, Devlin AM (2013): Childhood obesity and cardiovascular dysfunction. J Am Coll Cardiol 62:1309–1319.

Cotter G, Moshkovitz Y, Kaluski E, Cohen AJ, Miller H, Goor D, Vered Z (2004): Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. Chest 125:1431-1440.

Creager MA, Lüscher TF, Cosentino F, Beckman JA (2003): Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. Circulation 108:1527-1532.

Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG (2002): Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 106:2085-2090.

Dahan M, Siohan P, Viron B, Michel C, Paillole C, Gourgon R, Mignon F (1997): Relationship between left ventricular hypertrophy, myocardial contractility, and load conditions in hemodialysis patients: an echocardiographic study. Am J Kidney Dis 30:780-785.

Dart AM, Kingwell BA (2001): Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol 37:975-984.

de Vegt F, Dekker JM, Ruhé HG, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ (1999): Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia 42:926-931.

Della-Morte D, Gardener H, Denaro F, Boden-Albala B, Elkind MS, Paik MC, Sacco RL, Rundek T (2010): Metabolic syndrome increases carotid artery stiffness: the Northern Manhattan Study. Int J Stroke 5:138-144.

Dijk JM, Algra A, van der Graaf Y, Grobbee DE, Bots ML; SMART study group (2005): Carotid stiffness and the risk of new vascular events in patients with manifest cardiovascular disease. The SMART study. Eur Heart J 26:1213-1220.

Eckel RH, Grundy SM, Zimmet PZ (2005): The metabolic syndrome. Lancet 365:1415-1428.

Edwards NM, Daniels SR, Claytor RP, Khoury PR, Dolan LM, Kimball TR, Urbina EM (2012): Physical activity is independently associated with multiple

measures of arterial stiffness in adolescents and young adults. Metabolism 61:869-872.

Ehsani AA, Ogawa T, Miller TR, Spina RJ, Jilka SM (1991): Exercise training improves left ventricular systolic function in older men. Circulation 83:96-103.

Fagot-Campagna A, Saaddine JB, Flegal KM, Beckles GL (2001): Diabetes, impaired fasting glucose, and elevated HbA1c in U.S. adolescents: the Third National Health and Nutrition Examination Survey. Diabetes Care 24:834-837.

Feldman RD, Bierbrier GS (1993): Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. Lancet 342:707-709.

Ferreira I, Henry RM, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD; Amsterdam Growth and Health Longitudinal Study (2005): The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. Arch Intern Med 165:875-882.

Ford ES, Li C (2008): Defining the metabolic syndrome in children and adolescents: will the real definition please stand up? J Pediatr 152:160-164.

Gando Y, Yamamoto K, Murakami H, Ohmori Y, Kawakami R, Sanada K, Higuchi M, Tabata I, Miyachi M (2010): Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. Hypertension 56:540-546.

Gatzka CD, Kingwell BA (2003): Arterial hypertension: cardiac structure and arterial stiffness. J Hypertens 21:691-693.

Geerts BF, Aarts LP, Jansen JR (2011): Methods in pharmacology: measurement of cardiac output. Br J Clin Pharmacol 71:316-330.

Gong HP, Tan HW, Fang NN, Song T, Li SH, Zhong M, Zhang W, Zhang Y (2009): Impaired left ventricular systolic and diastolic function in patients with metabolic syndrome as assessed by strain and strain rate imaging. Diabetes Res Clin Pract 83:300-307.

Grossman E, Oren S, Messerli FH (1994): Left ventricular mass and cardiac function in patients with essential hypertension. J Hum Hypertens 8:417-421.

Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute (2005): Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112:2735-2752.

Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE (2014): Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 103:137-149.

Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, Sebring NG, Han JC, Yanovski SZ, Hubbard VS, Yanovski JA (2009): The stability of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab 94:4828-4834.

Hallikainen M, Halonen J, Konttinen J, Lindholm H, Simonen P, Nissinen MJ, Gylling H (2013): Diet and cardiovascular health in asymptomatic normo- and mildly-to-moderately hypercholesterolemic participants - baseline data from the BLOOD FLOW intervention study. Nutr Metab (Lond) 10:62.

Hara-Nakamura N, Kohara K, Sumimoto T, Lin M, Hiwada K (1994): Glucose intolerance exaggerates left ventricular hypertrophy and dysfunction in essential hypertension. Am J Hypertens 7:1110-1114.

Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, Hundley WG, Lima JA, Bluemke DA (2006): Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol 48:2285-2292.

Herbert V, Lau KS, Gottlieb CW, Bleicher SJ (1965): Coated charcoal immunoassay of insulin. J Clin Endocrinol Metab 25:1375-1384.

Himes JH, Dietz WH (1994): Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. Am J Clin Nutr 59:307-316.

Hirai T, Sasayama S, Kawasaki T, Yagi S (1989): Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. Circulation 80:78-86.

Hofer CK, Ganter MT, Zollinger A (2007): What technique should I use to measure cardiac output? Curr Opin Crit Care 13:308-317.

Hughes SM, Dixon LJ, McVeigh GE (2004): Arterial stiffness and pulse wave velocity: problems with terminology. Circulation 109:e3.

Huxley R, Barzi F, Woodward M (2006): Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 332:73-78.

Iannuzzi A, Licenziati MR, Acampora C, Renis M, Agrusta M, Romano L, Valerio G, Panico S, Trevisan M (2006): Carotid artery stiffness in obese children with the metabolic syndrome. Am J Cardiol 97:528-531.

Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, Taskinen MR, Groop L (2001): Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 24:683-689.

Jern S, Bergbrant A, Björntorp P, Hansson L (1992): Relation of central hemodynamics to obesity and body fat distribution. Hypertension 19:520-527.

Juonala M, Viikari JS, Hutri-Kähönen N, Pietikäinen M, Jokinen E, Taittonen L, Marniemi J, Rönnemaa T, Raitakari OT (2004): The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. J Intern Med 255:457-468.

Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS, Raitakari OT (2005): Risk factors identified in childhood and decreased carotid artery elasticity

in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 112:1486-1493.

Juonala M, Magnussen CG, Venn A, Dwyer T, Burns TL, Davis PH, Chen W, Srinivasan SR, Daniels SR, Kähönen M, Laitinen T, Taittonen L, Berenson GS, Viikari JS, Raitakari OT (2010): Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation 122:2514-2520.

Kassi E, Pervanidou P, Kaltsas G, Chrousos G (2011): Metabolic syndrome: definitions and controversies. BMC Med 9:48.

Katakami N, Osonoi T, Takahara M, Saitou M, Matsuoka TA, Yamasaki Y, Shimomura I (2014): Clinical utility of brachial-ankle pulse wave velocity in the prediction of cardiovascular events in diabetic patients. Cardiovasc Diabetol 13:128.

Kawaguchi M, Techigawara M, Ishihata T, Asakura T, Saito F, Maehara K, Maruyama Y (1997): A comparison of ultrastructural changes on endomyocardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. Heart Vessels 12:267-274.

Kettunen T, Eklund C, Kähönen M, Jula A, Päivä H, Lyytikäinen LP, Hurme M, Lehtimäki T (2011): Polymorphism in the C-reactive protein (CRP) gene affects CRP levels in plasma and one early marker of atherosclerosis in men: The Health 2000 Survey. Scand J Clin Lab Invest 71:353-361.

Kingwell BA, Gatzka CD (2002): Arterial stiffness and prediction of cardiovascular risk. J Hypertens 20:2337-2340.

Koskinen T, Kähönen M, Jula A, Mattsson N, Laitinen T, Keltikangas-Järvinen L, Viikari J, Välimäki I, Rönnemaa T, Raitakari OT (2009): Metabolic syndrome and short-term heart rate variability in young adults. The cardiovascular risk in young Finns study. Diabet Med 26:354-361.

Kostner GM (1976): Letter: enzymatic determination of cholesterol in high-density lipoprotein fractions prepared by polyanion precipitation. Clin Chem 22:695.

Kozakova M, Palombo C, Mhamdi L, Konrad T, Nilsson P, Staehr PB, Paterni M, Balkau B; RISC Investigators (2007): Habitual physical activity and vascular aging in a young to middle-age population at low cardiovascular risk. Stroke 38:2549-2555.

Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH (1966): Development and evaluation of an impedance cardiac output system. Aerosp Med 37:1208-1212.

Kullo IJ, Seward JB, Bailey KR, Bielak LF, Grossardt BR, Sheedy PF 2nd, Peyser PA, Turner ST (2005): C-reactive protein is related to arterial wave reflection and stiffness in asymptomatic subjects from the community. Am J Hypertens 18:1123-1129.

Kööbi T, Kaukinen S, Turjanmaa VM, Uusitalo AJ (1997a): Whole-body impedance cardiography in the measurement of cardiac output. Crit Care Med 25:779-785.

Kööbi T, Kaukinen S, Ahola T, Turjanmaa VM (1997b): Non-invasive measurement of cardiac output: whole-body impedance cardiography in simultaneous comparison with thermodilution and direct oxygen Fick methods. Intensive Care Med 23:1132-1137.

Kööbi T, Kaukinen S, Turjanmaa VM (1999): Cardiac output can be reliably measured noninvasively after coronary artery bypass grafting operation. Crit Care Med 27:2206-2211.

Kööbi T, Kähönen M, Iivainen T, Turjanmaa V (2003): Simultaneous non-invasive assessment of arterial stiffness and hemodynamics - a validation study. Clin Physiol Funct Imaging 23:31-36.

Lakatta EG, Levy D (2003): Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation 107:138-146.

Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT (2002): The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288:2709-2716.

Lambert M, Paradis G, O'Loughlin J, Delvin EE, Hanley JA, Levy E (2004): Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. Int J Obes Relat Metab Disord 28:833-841.

Lantelme P, Mestre C, Lievre M, Gressard A, Milon H (2002) : Heart rate: an important confounder of pulse wave velocity assessment. Hypertension 39:1083-1087.

Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A (2001): Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37:1236-1241.

Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries (2006): Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27:2588-2605.

Lehmann ED, Hopkins KD, Rawesh A, Joseph RC, Kongola K, Coppack SW, Gosling RG (1998): Relation between number of cardiovascular risk factors/events and noninvasive Doppler ultrasound assessments of aortic compliance. Hypertension 32:565-569.

Li S, Chen W, Srinivasan SR, Berenson GS (2005a): Influence of metabolic syndrome on arterial stiffness and its age-related change in young adults: the Bogalusa Heart Study. Atherosclerosis 180:349-354.

Li H, Srinivasan SR, Chen W, Xu JH, Li S, Berenson GS (2005b): Vascular abnormalities in asymptomatic, healthy young adult smokers without other major cardiovascular risk factors: the Bogalusa Heart Study. Am J Hypertens 18:319-324.

Li CH, Wu JS, Yang YC, Shih CC, Lu FH, Chang CJ (2012): Increased arterial stiffness in subjects with impaired glucose tolerance and newly diagnosed

diabetes but not isolated impaired fasting glucose. J Clin Endocrinol Metab 97:E658-662.

Libby P, Ridker PM, Hansson GK; Leducq Transatlantic Network on Atherothrombosis (2009): Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol 54:2129-2138.

Libby P, Okamoto Y, Rocha VZ, Folco E (2010): Inflammation in atherosclerosis: transition from theory to practice. Circulation Journal 74:213-220.

London GM, Blacher J, Pannier B, Guérin AP, Marchais SJ, Safar ME (2001): Arterial wave reflections and survival in end-stage renal failure. Hypertension 38:434-438.

Lopaschuk GD (2002): Metabolic abnormalities in the diabetic heart. Heart Fail Rev 7:149-159.

Lusis AJ (2000): Atherosclerosis. Nature 407:233-241.

Mahmud A, Feely J (2002): Divergent effect of acute and chronic alcohol on arterial stiffness. Am J Hypertens 15:240-243.

Mahmud A, Feely J (2003): Effect of smoking on arterial stiffness and pulse pressure amplification. Hypertension 41:183-187.

Marcovina S, Packard CJ (2006): Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern Med 259:437-446.

Matsuoka O, Otsuka K, Murakami S, Hotta N, Yamanaka G, Kubo Y, Yamanaka T, Shinagawa M, Nunoda S, Nishimura Y, Shibata K, Saitoh H, Nishinaga M, Ishine M, Wada T, Okumiya K, Matsubayashi K, Yano S, Ichihara K, Cornélissen G, Halberg F, Ozawa T (2005): Arterial stiffness independently predicts cardiovascular events in an elderly community -- Longitudinal Investigation for the Longevity and Aging in Hokkaido County (LILAC) study. Biomed Pharmacother 59 Suppl 1:S40-44.

Mattace-Raso FU, van der Cammen TJ, van der Meer IM, Schalekamp MA, Asmar R, Hofman A, Witteman JC (2004): C-reactive protein and arterial stiffness in older adults: the Rotterdam Study. Atherosclerosis 176:111-116.

Mattace-Raso FU, van der Cammen TJ, Hofman A, van Popele NM, Bos ML, Schalekamp MA, Asmar R, Reneman RS, Hoeks AP, Breteler MM, Witteman JC (2006): Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 113:657-663.

Mattace-Raso F, Hofman A, Verwoert GC, Wittemana JC, Wilkinson I, Cockcroft J, McEniery C, Yasmin, Laurent S, Boutouyrie P, Bozec E, Hansen TW, Torp-Pedersen C, Ibsen H, Jeppesen J, Vermeersch SJ, Rietzschel E, De Buyzere M, Gillebert TC, Van Bortel L, Segers P, Vlachopoulos C, Aznaouridis C, Stefanadis C, Benetos A, Labat C, Lacolley P, Stehouwer C, Nijpels G, Dekker JM, Stehouwer C, Ferreira I, Twisk JW, Czernichow S, Galan P, Hercberg S, Pannier B, Guérin A, London G, Cruickshank JK, Anderson SG, Paini A, Agabiti Rosei E, Muiesan ML, Salvetti M, Filipovsky J, Seidlerova J, Dolejsova M (2010): Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 31:2338-2350.

Mattsson N, Rönnemaa T, Juonala M, Viikari JS, Jokinen E, Hutri-Kähönen N, Kähönen M, Laitinen T, Raitakari OT (2008): Arterial structure and function in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study. Eur Heart J 29:784-791.

Mayet J, Hughes A (2003): Cardiac and vascular pathophysiology in hypertension Heart 89:1104-1109.

McEniery CM, McDonnell BJ, So A, Aitken S, Bolton CE, Munnery M, Hickson SS, Yasmin, Maki-Petaja KM, Cockcroft JR, Dixon AK, Wilkinson IB; Anglo-Cardiff Collaboration Trial Investigators (2009): Aortic calcification is associated with aortic stiffness and isolated systolic hypertension in healthy individuals. Hypertension 53:524-531.

McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS (2007): Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. Circulation 116:1170-1175.

McVeigh GE, Hamilton PK, Morgan DR (2002): Evaluation of mechanical arterial properties: clinical, experimental and therapeutic aspects. Clin Sci (Lond 102:51-67.

Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D (2004): Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Fragmingham Heart Study. Hypertension 43:1239-1245.

Mitchell GF, Dunlap ME, Warnica W, Ducharme A, Arnold JM, Tardif JC, Solomon SD, Domanski MJ, Jablonski KA, Rice MM, Pfeffer MA; Prevention of Events With Angiotensin-Converting Enzyme Inhibition Investigators (2007): Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. Hypertension 49:1271-1277.

Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ (2010): Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 121:505-511.

Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, Endo T, Nakata Y, Tanaka K, Ajisaka R (2009): Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men. Angiology 60:351-357.

Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, Zinman B; American Diabetes Association (2007): Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 30:753-759.

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

Nichols WW, O'Rourke MF and Vlachopoulos C (2011): McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 6th edition. London: Hodder Arnold.

Niiranen T, Jula A, Kantola I, Moilanen L, Kähönen M, Kesäniemi YA, Nieminen MS, Reunanen A (2007): Home-measured blood pressure is more strongly associated with atherosclerosis than clinic blood pressure: the Finn-HOME Study. J Hypertens 25:1225-1231.

Nishikawa T, Dohi S (1993): Errors in the measurement of cardiac output by thermodilution. Can J Anaesth 40:142-153.

Ogawa T, Shimada M, Ishida H, Matsuda N, Fujiu A, Ando Y, Nitta K (2009): Relation of stiffness parameter beta to carotid arteriosclerosis and silent cerebral infarction in patients on chronic hemodialysis. Int Urol Nephrol 41:739-745.

Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, Takeuchi H, Shimamoto K (2003): Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study. Diabetes Care 26:437-440.

Omvik P, Gerdts E, Myking OL, Lund-Johansen P (2000): Long-term central hemodynamic effects at rest and during exercise of losartan in essential hypertension. Am Heart J 140:624-630.

O'Rourke MF, Hashimoto J (2007): Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 50:1-13.

Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, Kitzman DW, Hopkins PN, Morgan D, Rao DC, Devereux RB (2001): Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. Circulation 103:102-107.

Pannier B, Guérin AP, Marchais SJ, Safar ME, London GM (2005): Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 45:592-596.

Paredes OL, Shite J, Shinke T, Watanabe S, Otake H, Matsumoto D, Imuro Y, Ogasawara D, Sawada T, Yokoyama M (2006): Impedance cardiography for cardiac output estimation: reliability of wrist-to-ankle electrode configuration. Circ J 70:1164-1168.

Pase MP, Grima NA, Sarris J (2011): The effects of dietary and nutrient interventions on arterial stiffness: a systematic review. Am J Clin Nutr 93:446-454.

Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB (2005): Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 112:3375-3383.

Polonia J, Barbosa L, Silva JA, Rosas M (2009): Improvement of aortic reflection wave responses 6 months after stopping smoking: a prospective study. Blood Press Monit 14:69-75.

Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH; American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism (2006): Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation 113:898-918.

Prenner SB, Chirinos JA (2015): Arterial stiffness in diabetes mellitus. Atherosclerosis 238:370-379.

Rahman S, Ismail AA, Ismail SB, Naing NN, Rahman AR (2008): Early manifestation of macrovasculopathy in newly diagnosed never treated type II diabetic patients with no traditional CVD risk factors. Diabetes Res Clin Pract 80:253-258.

Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, Järvisalo MJ, Uhari M, Jokinen E, Rönnemaa T, Åkerblom HK, Viikari J (2003): Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood-The cardiovascular risk in young Finns study. JAMA 17:2277-2283.

Raitakari OT, Juonala M, Rönnemaa T, Keltikangas-Järvinen L, Räsänen L, Pietikäinen M, Hutri-Kähönen N, Taittonen L, Jokinen E, Marniemi J, Jula A, Telama R, Kähönen M, Lehtimäki T, Akerblom HK, Viikari JS (2008): Cohort profile: the cardiovascular risk in Young Finns Study. Int J Epidemiol 37:1220-1226.

Rasouli M, Kiasari AM, Mokhberi V (2006): The ratio of apoB/apoAI, apoB and lipoprotein(a) are the best predictors of stable coronary artery disease. Clin Chem Lab Med 44:1015-1021.

Rehill N, Beck CR, Yeo KR, Yeo WW (2006): The effect of chronic tobacco smoking on arterial stiffness. Br J Clin Pharmacol 61:767-773.

Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE (2005): Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA 294:326-333.

Roman MJ, Pickering TG, Pini R, Schwartz JE, Devereux RB (1995): Prevalence and determinants of cardiac and vascular hypertrophy in hypertension. Hypertension 26:369-373.

Ross R (1999): Atherosclerosis--an inflammatory disease. N Engl J Med 340:115-126.

Sabovic M, Safar ME, Blacher J (2009): Is there any additional prognostic value of central blood pressure wave forms beyond peripheral blood pressure? Curr Pharm Des 15:254-266.

Safar ME, Levy BI, Struijker-Boudier H (2003): Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 107:2864-2869.

Sakuragi S, Abhayaratna K, Gravenmaker KJ, O'Reilly C, Srikusalanukul W, Budge MM, Telford RD, Abhayaratna WP (2009): Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. Hypertension 53:611-616.

Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR (1995): Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. Circulation 91:1432-1443.

Sasson Z, Rasooly Y, Bhesania T, Rasooly I (1993): Insulin resistance is an important determinant of left ventricular mass in the obese. Circulation 88:1431-1436.

Schillaci G, Pirro M, Vaudo G, Mannarino MR, Savarese G, Pucci G, Franklin SS, Mannarino E (2005): Metabolic syndrome is associated with aortic stiffness in untreated essential hypertension. Hypertension 45:1078-1082.

Schmidt-Trucksäss AS, Grathwohl D, Frey I, Schmid A, Boragk R, Upmeier C, Keul J, Huonker M (1999): Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis 145:107-114.

Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Westerhof N, Stehouwer CD (2004): Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. Hypertension 43:176-181.

Shargorodsky M, Wainstein J, Gavish D, Leibovitz E, Matas Z, Zimlichman R (2003): Treatment with rosiglitazone reduces hyperinsulinemia and improves arterial elasticity in patients with type 2 diabetes mellitus. Am J Hypertens 16:617-622.

Shin JY, Lee HR, Lee DC (2011): Increased arterial stiffness in healthy subjects with high-normal glucose levels and in subjects with pre-diabetes. Cardiovasc Diabetol 10:30.

Shinohara K, Shoji T, Kimoto E, Yokoyama H, Fujiwara S, Hatsuda S, Maeno T, Shoji T, Fukumoto S, Emoto M, Koyama H, Nishizawa Y (2005): Effect of atorvastatin on regional arterial stiffness in patients with type 2 diabetes mellitus. J Atheroscler Thromb 12:205-210.

Shiroma EJ, Lee IM (2010): Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation 122:743-752.

Shokawa T, Imazu M, Yamamoto H, Toyofuku M, Tasaki N, Okimoto T, Yamane K, Kohno N (2005): Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. Circ J 69:259-264.

Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, Ramachandran A, Tajima N, Brajkovich Mirchov I, Ben-Nakhi A, Reaven G, Hama Sambo B, Mendis S, Roglic G (2010): The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia 53:600-605.

Simon A, Chironi G, Gariepy J, Del Pino M, Levenson J (2005): Differences between markers of atherogenic lipoproteins in predicting high cardiovascular risk and subclinical atherosclerosis in asymptomatic men. Atherosclerosis 179:339-344.

Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, Salomaa V, Kaaja R, Kööbi T, Kukkonen-Harjula K, Majahalme S, Kähönen M (2007): Metabolic syndrome and arterial stiffness: the Health 2000 Survey. Metabolism 56:320-326.

Sniderman AD, Scantlebury T, Cianflone K (2001): Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med 135:447-459.

Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldius G (2003): Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. Lancet 361:777-780.

Stancakova A, Javorsky M, Kuulasmaa T, Haffner SM, Kuusisto J, Laakso M (2009): Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish men. Diabetes 58:1212-1221.

Stehouwer CD, Henry RM, Ferreira I (2008): Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 51:527-539.

Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, Mietus-Snyder ML (2009): Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Circulation 119:628-647.

Stergiopulos N, Westerhof N (1998): Determinants of pulse pressure. Hypertension 32:556-559.

Störk S, van den Beld AW, von Schacky C, Angermann CE, Lamberts SW, Grobbee DE, Bots ML (2004): Carotid artery plaque burden, stiffness, and mortality risk in elderly men: a prospective, population-based cohort study. Circulation 110:344-348.

Su Y, Liu XM, Sun YM, Wang YY, Luan Y, Wu Y (2008): Endothelial dysfunction in impaired fasting glycemia, impaired glucose tolerance, and type 2 diabetes mellitus. Am J Cardiol 102:497-498.

Sugawara J, Hayashi K, Yokoi T, Cortez-Cooper MY, DeVan AE, Anton MA, Tanaka H (2005): Brachial-ankle pulse wave velocity: an index of central arterial stiffness? J Hum Hypertens 19:401-406.

Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kähönen M, Nieminen T, Kööbi T, Mustonen J, Pörsti I (2009): Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. Scand J Clin Lab Invest 69:128-137.

Taniwaki H, Kawagishi T, Emoto M, Shoji T, Kanda H, Maekawa K, Nishizawa Y, Morii H (1999): Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. Diabetes Care 22:1851-1857.

Taquet A, Bonithon-Kopp C, Simon A, Levenson J, Scarabin Y, Malmejac A, Ducimetiere P, Guize L (1993): Relations of cardiovascular risk factors to aortic pulse wave velocity in asymptomatic middle-aged women. Eur J Epidemiol 9:298-306.

Tishchenko MI (1973): Estimation of the stroke volume by integral rheogram of the human body. Sechenov Physiol J 59:1216-1224.

Tomiyama H, Koji Y, Yambe M, Shiina K, Motobe K, Yamada J, Shido N, Tanaka N, Chikamori T, Yamashina A (2005): Brachial -- ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. Circ J 69:815-822.

Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, Najjar SS, Nichols WW, Urbina EM, Weber T (2015): Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension 66:698-722.

Turhan H, Yasar AS, Yagmur J, Kurtoglu E, Yetkin E (2009): The impact of metabolic syndrome on left ventricular function: evaluated by using the index of myocardial performance. Int J Cardiol 132:382-386.

Turin TC, Kita Y, Rumana N, Takashima N, Kadota A, Matsui K, Sugihara H, Morita Y, Nakamura Y, Miura K, Ueshima H (2010): Brachial-ankle pulse wave velocity predicts all-cause mortality in the general population: findings from the Takashima study, Japan. Hypertens Res 33:922-925.

Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP (2010): Endothelial dysfunction in metabolic syndrome: prevalence, pathogenesis and management. Nutr Metab Cardiovasc Dis 20:140-146.

Urbina EM, Srinivasan SR, Kieltyka RL, Tang R, Bond MG, Chen W, Berenson GS (2004): Correlates of carotid artery stiffness in young adults: The Bogalusa Heart Study. Atherosclerosis 176:157-164.

Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FC, Lakatta EG (1993): Effects of age and aerobic capacity on arterial stiffness in healthy adults. Circulation 88:1456-1462.

van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM (2000): Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension 35:637-642.

van der Schouw YT, Pijpe A, Lebrun CE, Bots ML, Peeters PH, van Staveren WA, Lamberts SW, Grobbee DE (2002): Higher usual dietary intake of phytoestrogens is associated with lower aortic stiffness in postmenopausal women. Arterioscler Thromb Vasc Biol 22:1316-1322.

Veerasamy M, Bagnall A, Neely D, Allen J, Sinclair H, Kunadian V (2015): Endothelial dysfunction and coronary artery disease: a state of the art review. Cardiol Rev 23:119-129.

Vlachopoulos CV, Alexopoulos NA, Aznaouridis KA, Ioakeimidis NC, Dima IA, Dagre A, Vasiliadou C, Stefanadi EC, Stefanadis CI (2007): Relation of habitual cocoa consumption to aortic stiffness and wave reflections, and to central hemodynamics in healthy individuals. Am J Cardiol 99:1473-1475.

Vlachopoulos C, Aznaouridis K, Stefanadis C (2010): Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 55:1318-1327.

Wallace SM, Yasmin, McEniery CM, Mäki-Petäjä KM, Booth AD, Cockcroft JR, Wilkinson IB (2007): Isolated systolic hypertension is characterized by increased aortic stiffness and endothelial dysfunction. Hypertension 50:228-233.

Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E (2001): High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 358:2026-2033.

Wang TD, Lee CM, Wu CC, Lee TM, Chen WJ, Chen MF, Liau CS, Sung FC, Lee YT (1999): The effects of dyslipidemia on left ventricular systolic function in patients with stable angina pectoris. Atherosclerosis 146:117-124.

Weber T, Auer J, O'rourke MF, Kvas E, Lassnig E, Lamm G, Stark N, Rammer M, Eber B (2005): Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. Eur Heart J 26:2657-2663.

Westerhof N, Westerhof BE (2013): A review of methods to determine the functional arterial parameters stiffness and resistance. J Hypertens 31:1769-1775.

Whincup PH, Gilg JA, Donald AE, Katterhorn M, Oliver C, Cook DG, Deanfield JE (2005): Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. Circulation 112:1789-1797.

WHO (1999): Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation. Part 1: diagnosis and classification of diabetes mellitus. World Health Organization Report, No 99.2:1-59. Available at: http://www.who.int/diabetes/currentpublications/en/.

WHO (2003): Diet, nutrition and the prevention of chronic diseases. Report on the joint WHO/FAO expert consultation. WHO Technical Report Series, No 916:1-149. Available at: http://www.who.int/dietphysicalactivity/publications/trs916/download/en/.

WHO (2014): Global status report on noncommunicable diseases 2014. Available at: www.who.int/nmh/publications/ncd-status-report-2014/en/.

WHO (2015): Obesity and overweight. Fact sheet No 311. Updated January 2015. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/.

Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J (2006): Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 113:664-670.

Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB (2005): Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 112:3066-3072.

Xu L, Jiang CQ, Lam TH, Cheng KK, Yue XJ, Lin JM, Zhang WS, Thomas GN (2010): Impact of impaired fasting glucose and impaired glucose tolerance on

arterial stiffness in an older Chinese population: the Guangzhou Biobank Cohort Study-CVD. Metabolism 59:367-372.

Yasmin, McEniery CM, Wallace S, Mackenzie IS, Cockcroft JR, Wilkinson IB (2004): C-reactive protein is associated with arterial stiffness in apparently healthy individuals. Arterioscler Thromb Vasc Biol 24:969-974.

Yu Q, Zhang Y, Xu CB (2015): Apolipoprotein B, the villain in the drama? Eur J Pharmacol 748:166-169.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators (2004): Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 364:937-952.

Zieman SJ, Melenovsky V, Kass DA (2005): Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 25:932-943.

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ORIGINAL ARTICLE

Systemic hemodynamics in young adults with the metabolic syndrome: The Cardiovascular Risk in Young Finns Study

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Abstract

Objective. We conducted the present study to examine associations of three different metabolic syndrome (MetS) definitions and their components to arterial stiffness, systemic vascular resistance, and left ventricular function at population level. In addition, the objective of the study was to examine associations of spontaneous recovery from MetS over 6 years' follow-up to systemic hemodynamics.

Methods. The study population consisted of 1,741 Finnish young adults (aged 30–45 years) who had complete MetS risk factor and hemodynamic data available at 2007. Associations of spontaneous recovery from MetS to systemic hemodynamics was studied on a subpopulation of 1,391 subjects who had also complete MetS risk factor data available at 2001. Hemodynamic measurements were performed using a whole-body impedance cardiography device.

Results. MetS and increasing number of MetS components were associated with lower stroke index ($P < 0.001$) and higher systemic vascular resistance index ($P < 0.005$) and arterial pulse wave velocity ($P < 0.005$). In MetS persistent group, stroke index was lower ($P = 0.024$), and pulse wave velocity was higher ($P = 0.003$) compared to MetS recovery group.

Conclusion. All current MetS definitions identify young adults with altered systemic hemodynamics, and recovery from MetS is associated with a favorable hemodynamic profile.

Key words: *Arterial stiffness, cardiovascular health, epidemiology, hemodynamics, metabolic syndrome, young adults*

Introduction

Metabolic syndrome (MetS) is a cluster of multiple cardiovascular risk factors such as obesity, hypertension, dyslipidemia, and impaired glucose tolerance. Previous reports have shown that young adults with MetS have increased subclinical atherosclerosis (1,2), and subjects with MetS are at increased risk of cardiovascular disease (CVD) and mortality (3). Previously we (4) and others (5) have shown that pulse wave velocity (PWV), a commonly used marker of arterial stiffness and independent predictor of coronary events as well as all-cause and cardiovascular mortality (6–8),

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Key messages

- Previously, limited data have been available concerning relationships between different metabolic syndrome (MetS) definitions, their components, recovery from MetS, and systemic hemodynamics.
- MetS and its components have adverse effects on systemic hemodynamics in a large cohort of young adults, and recovery from MetS may improve cardiovascular function.

Abbreviations

BMI	body mass index
CI	cardiac index
CO	cardiac output
CRP	C-reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
EGIR	The European Group for the Study of Insulin Resistance guideline
HDL	high-density lipoprotein
HR	heart rate
ICG_{WB}	whole-body impedance cardiography
IDF	The International Diabetes Federation guideline
LDL	low-density lipoprotein
LV	left ventricular
MetS	metabolic syndrome
NCEP	The National Institute of Health Adult treatment Panel III guideline
PWV	pulse wave velocity
SBP	systolic blood pressure
SI	stroke index
SV	stroke volume
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
β	regression coefficient

is increased in subjects with MetS compared to those without the syndrome. Echocardiographic studies have also suggested the presence of impaired global left ventricular (LV) function (9) and impaired LV systolic and diastolic functions in patients with MetS (10,11).

Arterial pressure and flow are the result from the interaction between the left ventricle and the systemic arterial load. Assuming unchanged pump function of the heart, increased arterial load (reduced compliance/increased stiffness, increased systemic vascular resistance (SVR), or both) results in a lower stroke volume (SV), which is one indicator of cardiac function. Decrease in SV may also be associated with LV hypertrophy and other structural changes of heart. Increased SVR and systemic vascular resistance index (SVRI) have been shown in subjects with hypertension (12,13) and abdominal obesity (14,15). However, limited data are available concerning relationships between MetS, its components, and systemic hemodynamics in young adults. Recently, we have shown that arterial structure and function may be restored in young adults after recovery from MetS (16), but the reversibility of arterial PWV, systemic vascular resistance, and LV function in relation with recovery from MetS is unknown.

The aim of this study was to address these gaps in the literature. We evaluated the relations of MetS and its components to stroke index (SI), cardiac index (CI), heart rate (HR), SVRI, and PWV in young adults using three different MetS guidelines. Furthermore, we used longitudinal data to examine whether recovery from MetS over 6 years' follow-up has favorable effects on systemic hemodynamics in young adults.

Methods

Study population

The Cardiovascular Risk in Young Finns Study is an on-going multicenter study of atherosclerosis risk factors of Finnish children and young adults. The first cross-sectional survey was conducted in 1980 including 3,596 randomly selected participants aged 3–18 years (17). Thereafter, several follow-up studies have been performed. The latest study was conducted in 2007, and 1,872 subjects (aged 30–45 years) participated in the whole-body impedance cardiography (ICG_{WB}) monitoring. The subjects with incomplete metabolic risk factor or systemic hemodynamics data ($n = 105$), subjects with type 1 diabetes ($n = 11$), and pregnant subjects ($n = 15$) were excluded. Therefore, a total of 1,741 subjects were included in the present analysis. To evaluate the effect of spontaneous recovery from MetS over 6 years' follow-up (2001–2007) to systemic hemodynamics, we also created a subgroup of subjects who participated in ICG_{WB} measurements in 2007 and who had the complete MetS risk factor data measured in 2001 and 2007. The same exclusion criteria were used in this subsample group, and a total of 1,391 subjects (aged 30–45 years) were included in the analysis.

Clinical characteristics

Venous blood samples were collected after an overnight fast. Lipid determinations for triglycerides, total cholesterol, and high-density lipoprotein (HDL)-cholesterol were done using standard methods. Low-density lipoprotein (LDL)-cholesterol concentration was calculated by the Friedewald formula. Glucose concentrations were analyzed enzymatically, and serum

insulin concentration was measured by microparticle enzyme immunoassay kit. High-sensitivity serum C-reactive protein (CRP) was analyzed by an automated analyzer using a latex turbidimetric immunoassay kit. Details of methods have been described previously (18).

Height, weight, and waist circumference were measured, and body mass index (BMI) (kg/m^2) was calculated. Blood pressure was measured by using a random zero sphygmomanometer, and the mean of three measurements was used in the analysis. Smoking habits were ascertained with a questionnaire, and smoking was defined as smoking on a daily basis. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

Hemodynamic measurements

An ICG_{WB} device (CircMon B202, JR Medical Ltd, Tallinn, Estonia) was used to determine HR, SI (SV/body surface area, mL/m^2), CI (cardiac output (CO)/body surface area, L/min/m^2), SVRI (SVR/body surface area, dyn*s/cm^{5}m^2) and PWV (m/s). In brief, CircMon measures the pulsatile changes in voltage that occur due to pulsatile changes in whole-body impedance as related to the change in the size of the aorta, reflecting SV. CO was estimated as HR* SV and SVR as mean blood pressure divided by CO. To determine the PWV, the CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal caused by pulse wave in the aortic arch and, subsequently, the popliteal artery signal. By means of this time difference and distance between two measurement sites, the software calculates the PWV. SV, CO, and SVR were indexed to body surface area to reduce the influence of body size on measurement result. The procedure of the ICG_{WB} method, as well as the electrode configuration, has been described in detail previously (19–24).

Definition of metabolic syndrome

We used three different definitions for MetS: The National Institute of Health Adult treatment Panel III guideline (NCEP) definition (25): three or more criteria constitute diagnosis of MetS: 1) waist circumference (men $\geq$ 102 cm, women $\geq$ 88 cm), 2) triglycerides $\geq$ 1.7 mmol/L, or drug treatment, 3) HDL-cholesterol (men $<$ 1.03 mmol/L, women $<$ 1.3 mmol/L), or drug treatment, 4) systolic blood pressure $\geq$ 130 mmHg, or diastolic blood pressure $\geq$ 85 mmHg, or drug treatment, 5) fasting glucose $\geq$ 5.6 mmol/L, or drug treatment.

The International Diabetes Federation guideline (IDF) definition (26): waist circumference ($\geq$ 94 cm for men and $\geq$ 80 cm for women) and at least two of the following factors are present: 1) triglycerides $>$ 1.7 mmol/L, or specific treatment for this lipid abnormality, 2) HDL-cholesterol $<$ 1.03 mmol/L in men and $<$ 1.29 mmol/L in women, or specific treatment, 3) systolic blood pressure $\geq$ 130 mmHg, or diastolic blood pressure $\geq$ 85 mmHg, or treatment of previously diagnosed hypertension, 4) fasting plasma glucose $\geq$ 5.6 mmol/L, or previously diagnosed type 2 diabetes. The IDF definition has ethnic-specific values for waist circumference.

The European Group for the Study of Insulin Resistance guideline (EGIR) definition (27): The presence of hyperinsulinemia (defined as non-diabetic subjects having fasting insulin level in the highest quartile, which in our study was 11 mU/L), and at least two of the following abnormalities: 1) fasting blood glucose $\geq$ 6.1 mmol/L, 2) blood pressure $\geq$ 140/90 mmHg, or treated for hypertension, 3) triglycerides $>$ 2.0 mmol/L, or HDL-cholesterol $<$ 1.0 mmol/L, or treated for dyslipidemia, 4) waist circumference $\geq$ 94 cm in men and $\geq$ 80 cm in women.

The subsample study population (n = 1,391) was classified further into four different groups according to their MetS status at 2001 and 2007: Control group (no MetS at 2001 or 2007), recovery group (MetS at 2001, but not at 2007), incident group (no MetS at 2001, but MetS at 2007), and persistent group (MetS both at 2001 and 2007).

Statistics

Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Comparison of base-line characteristics between study groups was performed using t test for continuous variables and chi-square for categorical variables. The skewed distributions of triglycerides, CRP, and insulin were corrected logarithmically before statistical analyses. Adjusted mean systemic hemodynamic parameters were analyzed using general linear models. Linear regression analysis adjusted for age and sex was performed to examine the association of MetS components to hemodynamic parameters. There was no interaction between sexes in hemodynamic parameters and MetS definitions as analyzed by using the variance analysis, except that the association between SVRI and MetS was stronger in women. Therefore, analyses were performed as sexes pooled. Statistical significance was determined as two-tailed $P < 0.05$.

Results

Table I shows the base-line characteristics of the study population according to used MetS definitions. The

prevalence of MetS using the NCEP definition was 19.7%, 22.7% using the IDF definition, and 13.4% using the EGIR definition. By all definitions, the subjects with MetS were older, had higher waist circumference, BMI, total cholesterol, LDL-cholesterol, triglycerides, systolic and diastolic blood pressure, CRP, fasting glucose, and insulin, and lower HDL-cholesterol. Smoking was more common in subjects with MetS using the NCEP and IDF definitions than subjects without MetS.

HR was higher in subjects with MetS than in subjects without MetS ($P < 0.001$) (Table I). Age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means of SI were significantly higher in subjects without MetS by all definitions ($P < 0.001$) (Figure 1A). Subjects without MetS had lower SVRI and PWV compared to subjects with MetS by all three definitions ($P < 0.005$ for both) (Figures 1B and 1C). There was no significant difference in CI between subjects with or without MetS (data not shown). Age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted levels of SI, SVRI, and PWV for subjects with a different number of MetS components (0, 1–2, 3–5) are shown in Figure 2. SI decreased, and SVRI and PWV increased with the increasing amount of MetS components by all three definitions ($P < 0.001$ for all).

The results of multivariable regression analyses including individual components of MetS in predicting hemodynamic parameters are shown in Table II. Low HDL-cholesterol by the NCEP ($P = 0.002$) and IDF ($P = 0.037$) criteria, obesity ($P < 0.001$), hypertension ($P < 0.003$), and hyperinsulinemia by the EGIR criteria ($P = 0.002$) were inversely and independently associated with SI. Obesity ($P < 0.003$) and hypertension ($P < 0.001$) were independent determinants of SVRI and PWV. Also, high triglycerides by the NCEP ($P = 0.018$) and IDF ($P = 0.015$) definitions, and dyslipidemia by the EGIR definition ($P = 0.004$) were independently associated with PWV.

Figure 3 shows age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted mean values of SI, SVRI, and PWV according to a 6-year change in MetS status by the IDF definition. Lower SI (mean ± SE; 40.6 ± 0.5 mL/m^2) and higher PWV (8.9 ± 0.1 m/s) were observed in MetS persistent group (MetS both at 2001 and 2007) compared to MetS recovery group (MetS at 2001 but not at 2007) (SI 43.1 ± 0.2 mL/m^2, $P = 0.024$; PWV 8.0 ± 0.04 m/s, $P = 0.003$). The difference in SVRI between MetS persistent and MetS recovery groups was not statistically significant (2875 ± 46.8 dyn*s/cm^{5}m^2 versus 2670 ± 16.6 dyn*s/cm^{5}m^2, $P = 0.082$). In addition, there was no difference in SI, SVRI, or PWV between MetS control (no MetS at 2001 or 2007) and MetS recovery groups. Statistically significant trends were observed also using the NCEP and EGIR definitions ($P < 0.001$ for both, data not shown).

All analyses were repeated using a recently reported new MetS definition (28) with essentially similar results. Moreover, all analyses were repeated after excluding subjects having previously diagnosed type 2 diabetes and subjects using cholesterol-lowering or antihypertensive medication with essentially similar results,

Table I. Characteristics of the study cohort with and without metabolic syndrome (MetS) according to three definitions (NCEP, IDF, EGIR). Values are presented as unadjusted mean ± standard deviation or geometric mean (25th–75th percentiles) or percentages of subjects.

Variable	All	No MetS	NCEP	IDF	EGIR
Number of subjects	1741	1274	343	395	233
Age (years)	37.6 ± 5.0	37.2 ± 5.0	39.0 ± 4.7	38.8 ± 4.8	38.4 ± 4.9
Sex (men, %)	45.1	41.7	55.1	53.2	54.9
Waist (cm)	88.4 ± 13.0	84.1 ± 10.7	102.0 ± 11.5	101.0 ± 11.2	104.3 ± 11.7
Body mass index (kg/m^2)	25.9 ± 4.6	24.4 ± 3.7	30.6 ± 4.8	30.2 ± 4.6	31.6 ± 5.1
Total cholesterol (mmol/L)	5.0 ± 0.9	4.9 ± 0.8	5.3 ± 1.0	5.4 ± 0.9	5.3 ± 1.0
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.4 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
LDL cholesterol (mmol/L)	3.1 ± 0.8	3.0 ± 0.8	3.3 ± 0.9	3.3 ± 0.9	3.2 ± 0.9
Triglycerides (mmol/L)	1.2 (0.9–1.6)	1.0 (0.8–1.3)	1.9 (1.6–2.6)	1.8 (1.5–2.4)	2.0 (1.6–2.8)
SBP (mmHg)	120.3 ± 14.3	117.1 ± 12.7	130.1 ± 14.7	129.7 ± 14.5	127.2 ± 15.1
DBP (mmHg)	75.5 ± 11.2	73.0 ± 10.0	83.4 ± 11.0	83.0 ± 10.9	82.5 ± 11.5
Heart rate (beats/min)	65 ± 10	64 ± 9	69 ± 10	69 ± 10	69 ± 10
CRP (mg/L)	0.9 (0.4–1.8)	0.7 (0.3–1.4)	1.6 (0.8–3.3)	1.6 (0.8–3.2)	2.0 (1.0–4.1)
Fasting glucose (mmol/L)	5.3 ± 0.6	5.2 ± 0.4	5.8 ± 0.8	5.7 ± 0.8	5.8 ± 1.0
Insulin (mU/L)	6.6 (4.2–10.6)	5.3 (3.6–8.2)	12.8 (8.6–18.5)	12.3 (8.2–17.8)	17.9 (13.1–22.2)
Current smoking (%)	19.2	17.8	23.0	23.3	22.7

In all pairwise comparisons (NCEP versus No MetS, IDF versus No MetS, EGIR versus No MetS) $P < 0.001$, except for age $P < 0.002$ (EGIR versus No MetS), and for smoking $P < 0.04$ (NCEP versus No MetS, IDF versus No MetS) and $P > 0.05$ (EGIR versus No MetS).
SBP = systolic blood pressure; DBP = diastolic blood pressure; CRP = C-reactive protein; No MetS = no metabolic syndrome by any of the three MetS definitions (NCEP, IDF, EGIR); NCEP = The National Institute of Health Adult treatment Panel III guideline; IDF = The International Diabetes Federation guideline; EGIR = The European Group for the Study of Insulin Resistance guideline.

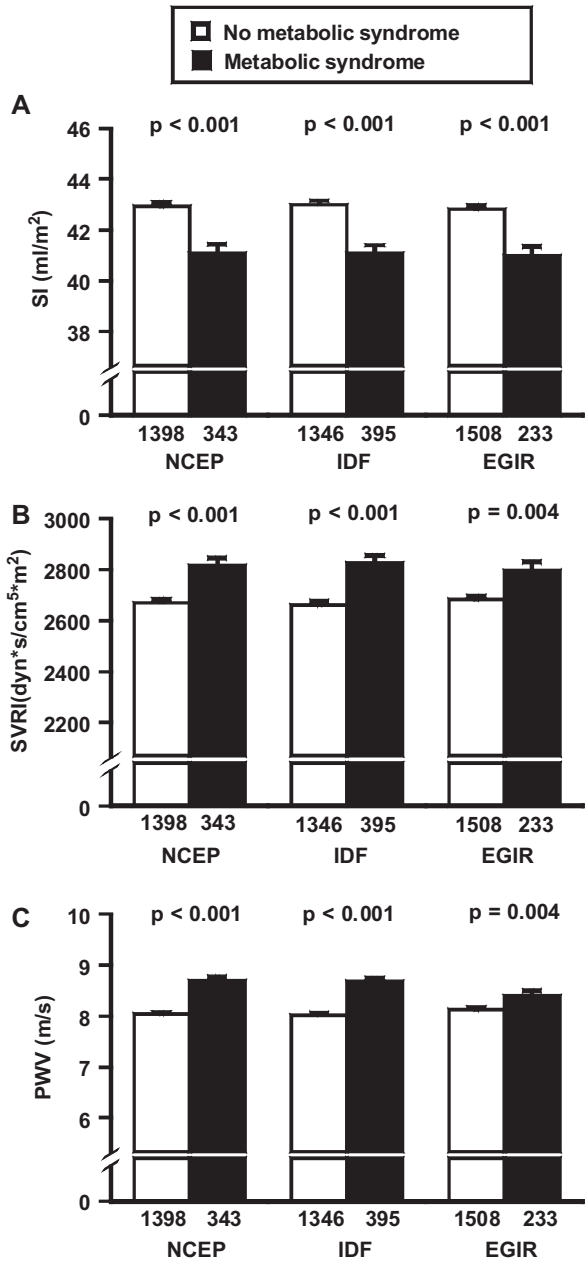

Figure 1. Comparison of SI (A), SVRI (B), and PWV (C) between the subjects without MetS and with MetS by NCEP, IDF, or EGIR definition. Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of subjects in each group. (SI = stroke index; SVRI = systemic vascular resistance index; PWV = pulse wave velocity; NCEP = The National Institute of Health Adult treatment Panel III guideline; IDF = The International Diabetes Federation guideline; EGIR = The European Group for the Study of Insulin Resistance guideline.)

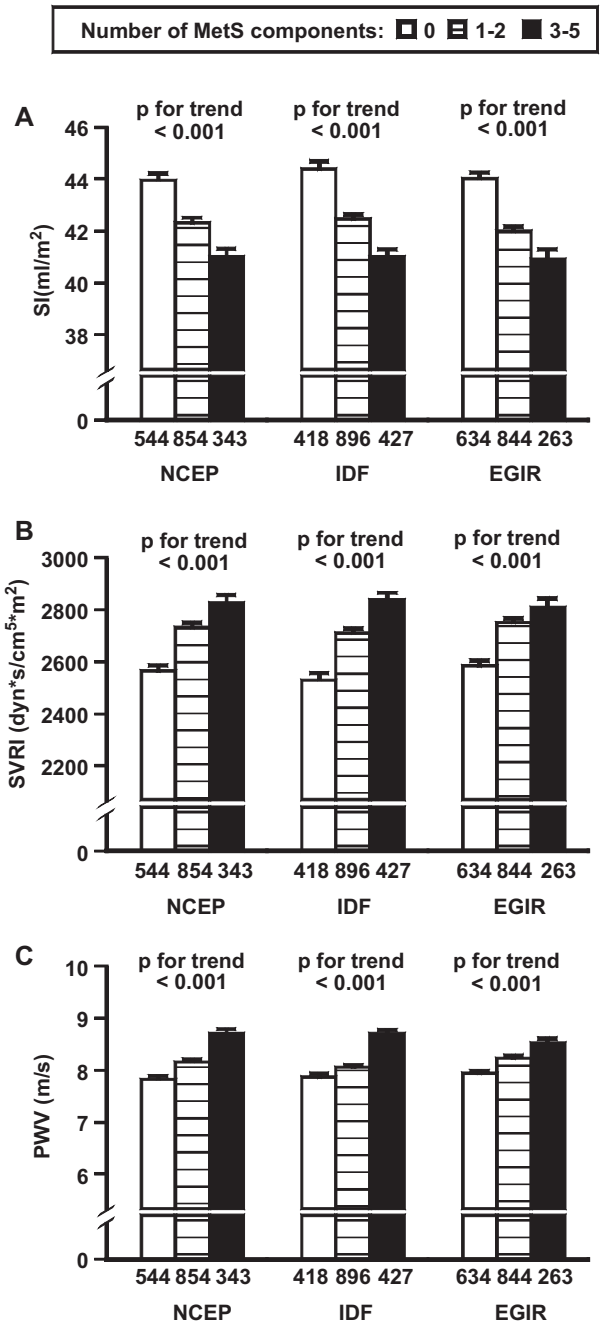

Figure 2. Mean levels on SI (A), SVRI (B), and PWV (C) by the number of MetS components by NCEP, IDF, or EGIR definition. Values are age-, sex-, CRP-, smoking- and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of subjects in each group. (Abbreviations as in Figure 1)

except CI was slightly but statistically significantly higher in subjects with MetS by the NCEP definition (mean ± SE; 2.83 ± 0.03 L/min/m^2) compared to subjects without MetS (2.75 ± 0.01 L/min/m^2, P = 0.013). Furthermore, all analyses were repeated after adjusting PWV for HR with essentially similar results.

Discussion

In this cohort of young Finnish adults, we found four main results. First, the present study demonstrates that young adults with MetS had decreased SI, and increased SVRI and PWV. Second, as individual components of MetS, low HDL-cholesterol, obesity, hypertension, and hyperinsulinemia were inversely

Table II. Linear regression model for the relationship between metabolic syndrome (NCEP, IDF, EGIR) components and hemodynamic parameters adjusted for age, sex, and other metabolic syndrome components.

	SI		SVRI		PWV	
	β ± SE	*P*	β ± SE	*P*	β ± SE	*P*
NCEP						
Obesity	−1.421 ± 0.326	<0.001	120.419 ± 30.018	<0.001	0.251 ± 0.073	0.001
High triglycerides	−0.515 ± 0.369	0.162	−16.155 ± 33.888	0.634	0.196 ± 0.083	0.018
Low HDL	−0.922 ± 0.300	0.002	36.063 ± 27.594	0.191	0.067 ± 0.067	0.317
Hypertension	−1.445 ± 0.310	<0.001	255.311 ± 38.493	<0.001	0.788 ± 0.070	<0.001
High glucose	−0.084 ± 0.338	0.803	−17.200 ± 31.074	0.580	0.087 ± 0.076	0.251
IDF						
Obesity	−1.975 ± 0.292	<0.001	154.219 ± 26.918	<0.001	0.202 ± 0.066	0.002
High triglycerides	−0.368 ± 0.366	0.315	−25.623 ± 33.783	0.448	0.202 ± 0.083	0.015
Low HDL	−0.630 ± 0.302	0.037	15.000 ± 27.808	0.590	0.061 ± 0.068	0.369
Hypertension	−1.364 ± 0.308	<0.001	249.950 ± 28.382	<0.001	0.789 ± 0.070	<0.001
High glucose	−0.083 ± 0.334	0.805	−16.726 ± 30.795	0.587	0.093 ± 0.076	0.217
EGIR						
Hyperinsulinemia	−1.131 ± 0.357	0.002	−25.068 ± 33.185	0.450	−0.004 ± 0.082	0.958
Obesity	−1.886 ± 0.300	<0.001	169.967 ± 27.877	<0.001	0.257 ± 0.069	<0.001
Dyslipidemia	−0.426 ± 0.349	0.222	21.672 ± 32.497	0.505	0.234 ± 0.081	0.004
Hypertension	−1.328 ± 0.433	0.002	254.584 ± 40.263	<0.001	0.778 ± 0.100	<0.001
High glucose	0.760 ± 0.563	0.178	−41.732 ± 52.435	0.426	0.229 ± 0.130	0.078

SI = stroke index; SVRI = systemic vascular resistance index; PWV = pulse wave velocity; β = regression coefficient; SE = standard error; NCEP = The National Institute of Health Adult treatment Panel III guideline; IDF = The International Diabetes Federation guideline; EGIR = The European Group for the Study of Insulin Resistance guideline.

and independently associated with SI, and obesity and hypertension were independent determinants of SVRI and PWV. In addition, high triglycerides and dyslipidemia were independently associated with PWV. Third, the number of MetS components was inversely associated with SI, and directly with SVRI and PWV. Fourth, subjects who recovered from MetS had higher SI and lower PWV when compared to subjects with persistent MetS.

In the present study PWV was higher in subjects with MetS, a finding which is in concert with earlier reports in young (5) and middle-aged adults (4). As have others (29), we found that hypertension and obesity as individual components of MetS were independent determinants of PWV. We also found an association between high triglycerides and increased PWV, a finding which is in agreement with the view that high triglyceride level is an independent risk factor of ischemic heart disease (30). There was an increasing trend of PWV with increasing quantities of MetS components as also shown previously (5). Altogether, the observations regarding PWV in the present study are in general in line with the previous studies.

Relationships of MetS and its components with SI in young adults are largely unknown. We found decreased SI in young adults with MetS, a finding which is also in agreement with previous reports showing decreased LV function in adolescent and middle-aged subjects with MetS (9–11). To the best of our knowledge, this is the first examination showing decrease in SI with the increasing quantity of MetS components. Although the mechanism of LV dysfunction in MetS is not completely understood, components of MetS probably produce cardiac structural and functional alterations leading to diminished SI. In the present study, low HDL-cholesterol, obesity, hypertension, and hyperinsulinemia as individual components of MetS were inversely and independently associated with SI. Previously, it has been suggested that insulin levels and hypertension are directly related to LV hypertrophy and mass (31–33), which in turn are related to decreased contractility (34,35). Moreover, glucose intolerance has been shown to relate to increased LV hypertrophy and decreased LV diastolic function in essential hypertension (36). In addition, Wang et al. found independent association between low HDL-cholesterol and subclinical LV systolic dysfunction (37). Furthermore, Jern et al. reported that central obesity is associated with lower cardiac output (15). On the other hand, in addition to direct influences of MetS components to LV function, lower SI in MetS could be caused by increased arterial load (reduced compliance/increased stiffness, increased systemic vascular resistance, or both).

In the current study, there was no difference in CI between subjects with or without MetS, while HR was higher in subjects with MetS as also shown previously (38). Since CI is defined as HR* SI, lower SI and higher HR on subjects with MetS explain the unchanged CI between groups. Taken together, the above-mentioned findings related to cardiac function are in agreement with the previous findings, but

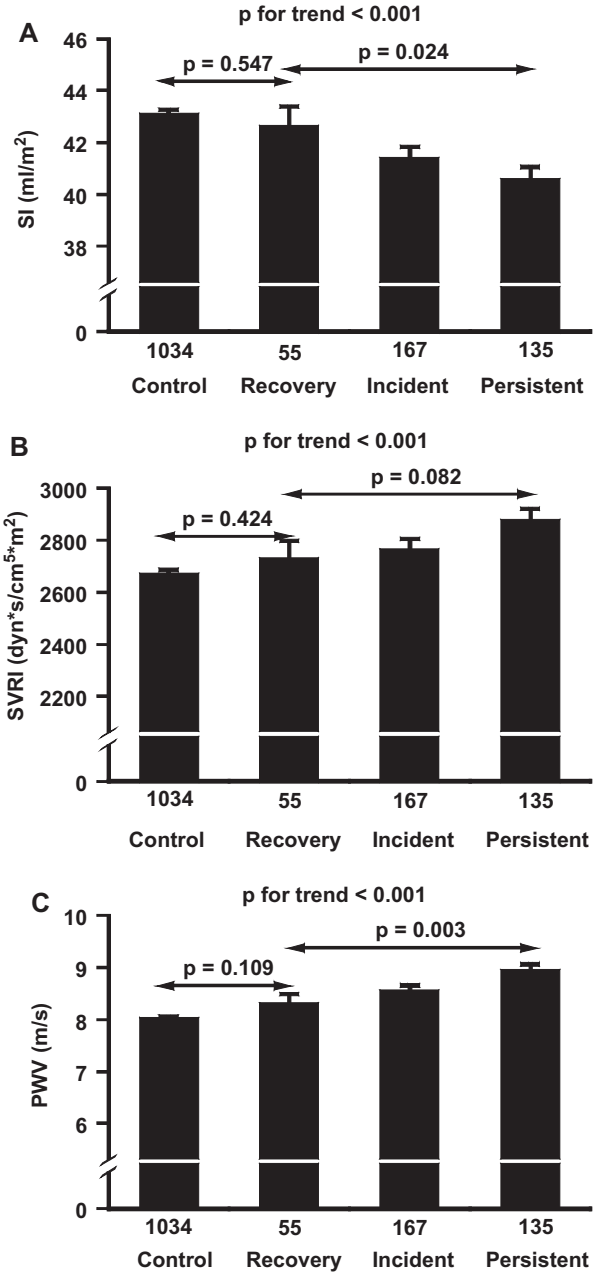

Figure 3. Comparison of SI (A), SVRI (B), and PWV (C) between the 6-year change in MetS status by IDF definition. Values are age-, sex-, CRP-, smoking-, and LDL-cholesterol-adjusted means and standard errors. Values under columns indicate the number of subjects in each group. (SI = stroke index; SVRI = systemic vascular resistance index; PWV = pulse wave velocity; Control = no MetS at 2001 or 2007; Recovery = MetS at 2001 but not at 2007; Incident = no MetS at 2001 but MetS at 2007; Persistent = MetS both at 2001 and 2007.)

provide further insights on the associations of individual MetS components on left ventricular function in young adults.

The present study shows that SVRI was increased in subjects with MetS. Interestingly, there was also a clear increasing trend of SVRI levels with the increasing number of MetS components. In multivariable models, hypertension and obesity as individual components of MetS were independently associated with high SVRI. Previously, it has been shown that SVR and SVRI are increased and arterial compliance is decreased in hypertensive patients (12,13) and subjects with abdominal obesity (14,15) as measures of higher arterial load. In hypertensive and obese subjects, impairment of insulin-mediated vasodilation may contribute to the increase in peripheral resistance (39). In addition, all components of MetS are known risk factors of endothelial dysfunction, and subjects with MetS have impaired endothelium-dependent vasodilatation (40). Thus, one potential mechanism behind increased systemic vascular resistance in subjects with MetS may be endothelial dysfunction leading to higher tone in resistance arteries (40). Another plausible mechanism is increased sympathetic tone in subjects with MetS (41). Further studies are clearly needed on the pathophysiological mechanisms behind an unfavorable systemic hemodynamics profile in subjects with MetS.

To our knowledge, this is the first report to demonstrate the associations of recovery from MetS to systemic hemodynamics. We found lower SI and higher PWV between persistent and recovery groups. Possibly due to the relatively small number of observations, there was no statistically significant difference in SVRI between persistent and recovery groups, although the mean level of SVRI was higher in persistent group compared to recovery group. Details of changes in the risk factor profile and potential explanatory factors behind recovery from MetS have been discussed in detail elsewhere (16). Briefly, subjects in the recovery group had significantly lower total cholesterol, triglycerides, waist circumference, fasting glucose, blood pressure, and higher HDL-cholesterol compared to the persistent group. Significant reduction in waist circumference was independently associated with increased physical activity and increased attention paid to health habits during the follow-up (16). In addition, it has been shown that weight reduction in obese men and antihypertensive or dyslipidemia medication leads to significant decrease in PWV (42–44). Furthermore, antidiabetic medication has been shown to decrease SVR (45), and antihypertensive medication has been found to reduce total peripheral resistance and slightly improve cardiac pump function in clinical trials (46). Recently, we showed that recovery from MetS in young adults was associated with the reversibility of carotid intima-media thickness and carotid artery distensibility, suggesting that arterial structure and function may be restored in young adults with MetS by improving metabolic risk factors and weight reduction (16). In line with this, the findings of the present study suggest that by improving MetS risk

factors, a more favorable systemic hemodynamic profile can be achieved.

ICG_{WB} is not a widely used method to evaluate systemic hemodynamics, apparently limiting comparability of the present findings with the observations from other cohorts. However, previous evaluation studies (19–21) have shown that ICG_{WB} accurately measures CO when compared with the thermodilution and direct Fick methods in different conditions (in the supine position, during head-up tilt, after anesthesia induction, after coronary artery by-pass surgery). The difference in CO values between ICG_{WB} and thermodilution were comparable with those attained between direct Fick and thermodilution, and the repeatability of ICG_{WB} was nearly twice as good as in thermodilution (19,20). The major advantages of the ICG_{WB} method are the possibility of measuring simultaneously several systemic hemodynamic parameters, operator-independence, and the low cost of the equipment. Previously, Ferreira et al. (47) showed that deleterious effects of MetS on arterial stiffness are stronger in the more muscular (i.e. the femoral) than the more elastic (i.e. the carotid) arteries. Advantage of ICG_{WB} in the evaluation of arterial stiffness is that PWV measurement includes also the femoral artery region. Moreover, PWV measured between the aortic arch and popliteal artery using the ICG_{WB} has been shown to be well in agreement with the Doppler ultrasound method (23). All in all, whole-body impedance cardiography provides handy and reliable means of evaluating systemic hemodynamics in large-scale epidemiologic studies.

This study has some other limitations. The 6-year change in MetS status was monitored between the follow-ups in 2001 and 2007, but the hemodynamic parameters were only measured in 2007. Therefore, at this point the present study setting does not allow evaluation of longitudinal changes in systemic hemodynamics in relation to changes in risk factor levels. In addition, the number of subjects in the MetS recovery group by all three definitions was relatively modest. Finally, there is accumulating skepticism of the usefulness of the MetS as a diagnostic or disease management tool (48,49). One of the main concerns about the MetS is that cardiovascular risk associated with the syndrome seems to be no greater than the sum of its parts. However, to the best of our knowledge, there is a paucity of information concerning the association of MetS components with systemic hemodynamic parameters. Thus, one of the main aims of the present study was to examine relations of MetS components with SI, SVRI, and PWV. The strengths of the present study are based on the inclusion of a large cohort of young adults without clinical cardiovascular diseases and use of several MetS definitions. Moreover, we used indexed hemodynamic parameters (SI, SVRI, CI) which reduce the influence on body size to the measurement results, allowing more direct evaluation of associations of risk factors on these parameters.

In conclusion, our results indicate that in young adults MetS and its components have adverse effects on systemic hemodynamics, and recovery from MetS may improve cardiovascular function. This investigation brings new insights into the relationships between MetS and systemic hemodynamics, and our findings underline the importance of early diagnosis and the management of metabolic syndrome.

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References

1. Koskinen J, Kähönen M, Viikari JS, Taittonen L, Laitinen T, Rönnemaa T, et al. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. Circulation. 2009;120:229–36.
2. Mattsson N, Rönnemaa T, Juonala M, Viikari JS, Jokinen E, Hutri-Kähönen N, et al. Arterial structure and function in young adults with the metabolic syndrome: the Cardiovascular Risk in Young Finns Study. Eur Heart J. 2008;29:784–91.
3. Ford ES. Risk for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. Diabetes Care. 2005;28:1769–78.
4. Sipilä K, Koivistoinen T, Moilanen L, Nieminen T, Reunanen A, Jula A, et al. Metabolic syndrome and arterial stiffness: the Health 2000 Survey. Metabolism. 2007;56:320–6.
5. Li S, Chen W, Srinivasan SR, Berenson GS. Influence of metabolic syndrome on arterial stiffness and its age-related change in young adults: the Bogalusa Heart Study. Atherosclerosis. 2005;180:349–54.
6. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37:1236–41.
7. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension. 2002;39:10–15.
8. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an

integrated index of vascular function? Circulation. 2002; 106:2085–90.
9. Turhan H, Yasar AS, Yagmur J, Kurtoglu E, Yetkin E. The impact of metabolic syndrome on left ventricular function: evaluated by using the index of myocardial performance. Int J Cardiol. 2009;132:382–6.
10. Gong HP, Tan HW, Fang NN, Song T, Li SH, Zhong M, et al. Impaired left ventricular systolic and diastolic function in patients with metabolic syndrome as assessed by strain and strain rate imaging. Diabetes Res Clin Pract. 2009;83: 300–7.
11. Chinali M, de Simone G, Roman MJ, Best LG, Lee ET, Russell M, et al. Cardiac markers of pre-clinical disease in adolescents with the metabolic syndrome: the strong heart study. J Am Coll Cardiol. 2008;52:932–8.
12. Chemla D, Antony I, Lecarpentier Y, Nitenberg A. Contribution of systemic vascular resistance and total arterial compliance to effective arterial elastance in humans. Am J Physiol Heart Circ Physiol. 2003;285:H614–20.
13. Abdelhammed AI, Smith RD, Levy P, Smits GJ, Ferrario CM. Noninvasive hemodynamic profiles in hypertensive subjects. Am J Hypertens. 2005;18:51S–9S.
14. Chirinos JA, Rietzschel ER, De Buyzere ML, De Bacquer D, Gillebert TC, Gupta AK, et al. Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. Hypertension. 2009;54:558–66.
15. Jern S, Bergbrant A, Björntorp P, Hansson L. Relation of central hemodynamics to obesity and body fat distribution. Hypertension. 1992;19:520–7.
16. Koskinen J, Magnussen CG, Taittonen L, Räsänen L, Mikkilä V, Laitinen T, et al. Arterial structure and function after recovery from the metabolic syndrome. The Cardiovascular Risk in Young Finns Study. Circulation. 2010;121: 392–400.
17. Åkerblom HK, Viikari J, Uhari M, Räsänen L, Byckling T, Louhivuori K, et al. Atherosclerosis precursors in Finnish children and adolescents. I. General description of the cross-sectional study of 1980, and an account of the children's and families' state of health. Acta Paediatr Scand Suppl. 1985;318: 49–63.
18. Raiko JR, Viikari JS, Ilmanen A, Hutri-Kähönen N, Taittonen L, Jokinen E, et al. Follow-ups of the Cardiovascular Risk in Young Finns Study in 2001 and 2007: Levels and 6-year changes in risk factors. J Intern Med. 2010;267: 370–84.
19. Kööbi T, Kaukinen S, Turjanmaa V, Uusitalo AJ. Whole-body impedance cardiography in the measurement of cardiac output. Crit Care Med. 1997;25:779–85.
20. Kööbi T, Kaukinen S, Ahola T, Turjanmaa VM. Non-invasive measurement of cardiac output: whole-body impedance cardiography in simultaneous comparison with thermodilution and direct oxygen Fick methods. Intensive Care Med. 1997; 23:1132–7.
21. Kööbi T, Kaukinen S, Turjanmaa VM. Cardiac output can be reliably measured noninvasively after coronary artery bypass grafting operation. Crit Care Med. 1999;27:2206–11.
22. Kaukinen S, Kööbi T, Bi Y, Turjanmaa VM. Cardiac output measurement after coronary artery bypass grafting using bolus thermodilution, continuous thermodilution, and whole-body impedance cardiography. J Cardiothorac Vasc Anesth. 2003;17: 199–203.
23. Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and hemodynamics—a validation study. Clin Physiol Funct Imaging. 2003;23:31–6.
24. Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood. The Cardiovascular Risk in Young Finns Study. Hypertension. 2010;55:806–11.
25. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement. Circulation. 2005;112:e285–90.
26. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. Lancet. 2005;366:1059–62.
27. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. Diabet Med. 1999;16:442–43.
28. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
29. Schillaci G, Pirro M, Vaudo G, Mannarino MR, Savarese G, Pucci G, et al. Metabolic syndrome is associated with aortic stiffness in untreated essential hypertension. Hypertension. 2005;45:1078–82.
30. Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein(a) are risk factors for major coronary events in middle-aged men. Am J Cardiol. 1996;77:1179–84.
31. Lind L, Hvarfner A, Pollare T, Lithell H, Ljunghall S. Fasting insulin, calcium metabolism and the electrocardiogram in hypertensive subjects. J Intern Med. 1992;232:335–9.
32. Sasson Z, Rasooly Y, Bhesania T, Rasooly I. Insulin resistance is an important determinant of left ventricular mass in the obese. Circulation. 1993;88:1431–6.
33. Palmieri V, Bella JN, Arnett DK, Liu JE, Oberman A, Schuck MY, et al. Effect of type 2 diabetes mellitus on left ventricular geometry and systolic function in hypertensive subjects: Hypertension Genetic Epidemiology Network (HyperGEN) study. Circulation. 2001;103:102–7.
34. Dahan M, Siohan P, Viron B, Michel C, Paillole C, Gourgon R, et al. Relationship between left ventricular hypertrophy, myocardial contractility, and load conditions in hemodialysis patients: an echocardiographic study. Am J Kidney Dis. 1997;30:780–5.
35. Grossman E, Oren S, Messerli FH. Left ventricular mass and cardiac function in patients with essential hypertension. J Hum Hypertens. 1994;8:417–21.
36. Hara-Nakamura N, Kohara K, Sumimoto T, Lin M, Hiwada K. Glucose intolerance exaggerates left ventricular hypertrophy and dysfunction in essential hypertension. Am J Hypertens. 1994;7:1110–4.
37. Wang TD, Lee CM, Wu CC, Lee TM, Chen WJ, Chen MF, et al. The effects of dyslipidemia on left ventricular systolic function in patients with stable angina pectoris. Atherosclerosis. 1999;146:117–24.
38. Rogowski O, Steinvil A, Berliner S, Cohen M, Saar N, Kliuk Ben-Bassat O, et al. Elevated resting heart rate is associated with the metabolic syndrome. Cardiovasc Diabetol. 2009;8:55.
39. Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. Lancet. 1993;342:707–9.
40. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Endothelial dysfunction in metabolic syndrome: Prevalence, pathogenesis and management. Nutr Metab Cardiovasc Dis. 2010;20:140–6.
41. Koskinen T, Kähönen M, Jula A, Mattsson N, Laitinen T, Keltikangas-Järvinen L, et al. Metabolic syndrome and

short-term heart rate variability in young adults. The Cardiovascular Risk in Young Finns study. Diabet Med. 2009;26: 354–61.
42. Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, et al. Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men. Angiology. 2009;60:351–7.
43. Mitchell GF, Dunlap ME, Warnica W, Ducharme A, Arnold JM, Tardif JC, et al. Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. Hypertension. 2007;49:1271–7.
44. Shinohara K, Shoji T, Kimoto E, Yokoyama H, Fujiwara S, Hatsuda S, et al. Effect of atorvastatin on regional arterial stiffness in patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2005;12:205–10.
45. Shargorodsky M, Wainstein J, Gavish D, Leibovitz E, Matas Z, Zimlichman R. Treatment with rosiglitazone reduces hyperinsulinemia and improves arterial elasticity in patients with type 2 diabetes mellitus. Am J Hypertens. 2003;16: 617–22.
46. Omvik P, Gerdts E, Myking OL, Lund-Johansen P. Long-term central hemodynamic effects at rest and during exercise of losartan in essential hypertension. Am Heart J. 2000;140:624–30.
47. Ferreira I, Henry RM, Twisk JW, van Mechelen W, Kemper HC, Stehouwer CD. The metabolic syndrome, cardiopulmonary fitness, and subcutaneous trunk fat as independent determinants of arterial stiffness: the Amsterdam Growth and Health Longitudinal Study. Arch Intern Med. 2005;165:875–82.
48. Simmons RK, Alberti KG, Gale EA, Colagiuri S, Tuomilehto J, Qiao Q, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. Diabetologia. 2010;53:600–5.
49. Borch-Johnsen K, Wareham N. The rise and fall of the metabolic syndrome. Diabetologia. 2010;53:597–9.

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Systemic hemodynamics in relation to glucose tolerance: the Health 2000 Survey

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Abstract

The influence of impaired glucose metabolism—that is, impaired fasting glucose, impaired glucose tolerance (IGT), and type 2 diabetes mellitus diabetes (DM2)—on systemic hemodynamics is largely unknown. Therefore, we investigated the associations of glucose metabolism disturbances with stroke index (SI), cardiac index, systemic vascular resistance index (SVRI), arterial pulse wave velocity (PWV), and heart rate among Finnish adults (N = 389; mean age, 58.3 ± 7.9 years) participating in the Health 2000 Survey. Systemic hemodynamic parameters were measured using the whole-body impedance cardiography device, and an oral glucose tolerance test (OGTT) was performed to evaluate glucose tolerance status. We found a decreasing trend for SI and increasing trends for SVRI and PWV according to the worsening of glucose tolerance (P for trend < .003 for all). In pairwise comparisons, SI was lower in the impaired fasting glucose group (P = .041) and the IGT group (P < .001) as compared with the normal glucose tolerance (NGT) group. Systemic vascular resistance index was higher in the IGT group (P = .045) and the DM2 group (P = .043) than in the NGT group. Subjects with IGT or DM2 had higher arterial PWV (10.7 ± 0.2 m/s, P < .001 and 11.7 ± 0.5 m/s, P = .001, respectively) than subjects with NGT (9.5 ± 0.1 m/s). Moreover, 2-hour glucose in OGTT was an independent determinant of SVRI and PWV (P < .001 and P = .005, respectively) in multivariable linear regression models. In conclusion, the present study demonstrates that glucose intolerance, even without DM2, associates with several adverse changes in systemic hemodynamics and that 2-hour glucose in OGTT is an independent determinant of SVRI and PWV. These findings support the systematic evaluation of glucose tolerance status in the estimation of cardiovascular risk among the middle-aged population.

1. Introduction

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM2) have been shown to associate with cardiovascular disease as well as increased all-cause and cardiovascular mortality [1-4]. The mechanisms of these associations are not fully understood but might involve increased sodium sensitivity in insulin-resistant states, which may lead to hypertension [5] and increased arterial stiffness [6,7] due to structural changes in the large arteries. Increased peripheral resistance, stiffening of large arteries, and higher venous tone [8] may, in turn, lead to concentric and/or eccentric left ventricular (LV) hypertrophy [9,10] and to decreased LV contractility [11,12]. Especially arterial pulse wave velocity (PWV), a commonly used marker of arterial stiffness, has been shown to be increased in subjects with IFG, IGT, or DM2 [13,14]; and increased PWV has been found to associate with cardiovascular disease and mortality in subjects with a glucose metabolism disorder [15]. In addition, echocardiography studies have suggested that the worsening of glucose tolerance has adverse cardiac effects, including decreased LV systolic and diastolic function [16-19].

More insight into systemic hemodynamics and cardiovascular function in subjects with a glucose metabolism disorder could be achieved by simultaneous evaluation of several systemic hemodynamic parameters—including

Institutional approval: The study was approved by local ethics committees.

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stroke volume (SV), a measure of cardiac function indicating the volume of blood pumped by the heart on every cardiac cycle; systemic vascular resistance (SVR), the force the LV must overcome to expel blood into arteries and a known determinant of blood pressure; and PWV. Previously, diabetes has been found to associate with decreased SV [20]; but the relation between SV and impaired glucose metabolism, that is, IFG or IGT, is less known. Moreover, associations between SVR and glucose metabolism disorders have not been described thoroughly.

To address the above-mentioned gaps in the literature, the present study was undertaken to evaluate systemic hemodynamics in adult Finnish individuals with normal glucose tolerance (NGT), IFG, IGT, or DM2 participating in the Health 2000 Survey.

2. Methods

2.1. Study population

The source of the study population was a large Finnish health examination survey (the Health 2000 Survey) carried out in 2000-2001 [21]. The overall study cohort was a 2-stage stratified cluster sample (8028 subjects) representing the entire Finnish population 30 years and older. To study cardiovascular disease and diabetes more thoroughly, a supplemental study (1867 subjects; participation rate, 82%) was carried out in the catchment areas of 5 Finnish university hospitals. Whole-body impedance cardiography (ICG_{WB}) monitoring and an oral glucose tolerance test (OGTT) were included in the study protocol in the catchment areas of Tampere and Turku University Hospitals (402 subjects, aged 46-76 years) to gain better insight into systemic hemodynamic alterations related to disturbances in glucose metabolism. Subjects with DM2 using insulin did not participate in the OGTT. Subjects with incomplete cardiovascular risk factor, OGTT, or systemic hemodynamics data (n = 11) and subjects with type 1 diabetes mellitus or undetermined diabetes (n = 2), were excluded. Therefore, a total of 389 subjects were included in the present analysis. In this study population, 4 subjects had self-reported cerebrovascular disease; and 10 subjects had self-reported ischemic heart disease.

2.2. Clinical characteristics

Venous blood samples were taken after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were determined enzymatically (Olympus System Reagent; Olympus, Hamburg, Germany, for total cholesterol and triglycerides; Roche Diagnostics, Mannheim, Germany, for HDL cholesterol) with a clinical chemistry analyzer (Olympus AU400). Low-density lipoprotein (LDL) cholesterol concentration was calculated using the Friedewald formula [22].

The OGTT was carried out after 10 to 12 hours of fasting. Subjects were given 75 g of glucose in a 10% solution. Venous blood samples for glucose and insulin determinations were taken before and 2 hours after the glucose load. Plasma glucose was determined by the glucose dehydrokinase method (Diagnostica Merck, Darmstadt, Germany) in a clinical chemistry analyzer (Konelab, Vantaa, Finland). In addition, plasma insulin was determined by the radio immunoanalysis method (Pharmacia, Uppsala, Sweden).

Height and weight were measured, and body mass index (BMI) was calculated. Continuous blood pressure was measured after 15 minutes of rest using a Finapres digital plethysmograph (Ohmeda, Engelwood, CO) placed on the middle finger of the left hand. An average blood pressure value of 30-second measurement was used. To verify the Finapres results, blood pressure was also measured from the upper arm using the automatic Omron M4 oscillometry manometer (Omron, Matsusaka, Japan, and Omron Healthcare Europe, Hoofddorp, the Netherlands). Smoking habits were ascertained with a questionnaire, defined as smoking on a daily basis. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

2.3. Glucose tolerance

We used the World Health Organization criteria for diabetes mellitus [23] in the classification of subjects with no previously diagnosed diabetes: (1) NGT—fasting venous plasma glucose less than 6.1 mmol/L and 2-hour venous plasma glucose less than 7.8 mmol/L in an OGTT; (2) IFG—fasting venous plasma glucose of 6.1 to 6.9 mmol/L and 2-hour venous plasma glucose less than 7.8 mmol/L; (3) IGT—fasting venous plasma glucose less than 7.0 mmol/L and 2-hour venous plasma glucose of 7.8 to 11.0 mmol/L; and (4) DM2—fasting venous plasma glucose of at least 7.0 mmol/L or 2-hour venous plasma glucose of at least 11.1 mmol/L. Subjects taking oral diabetes medication were considered as having DM2 regardless of their OGTT results.

2.4. Hemodynamic measurements

An ICG_{WB} device (CircMon B202; JR Medical, Tallinn, Estonia) was used to determine blood flow (SV and cardiac output [CO]), SVR, arterial stiffness (PWV), and heart rate (HR). A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest, Ölstykke, Denmark) was placed on the extremities just proximally to the wrists and the ankles. The outer electrodes feed current; and the inner electrodes measure the pulsatile changes in voltage that occur because of pulsatile changes in whole-body impedance as related to the change in the size of the aorta, reflecting SV. Cardiac output was estimated as HR ∗ SV; and SVR, as mean blood pressure (MBP) divided by CO. An additional pair of electrodes was placed on knee joint level and on the calf to measure PWV. The CircMon software measures the time difference between the onset of the decrease (“foot”) in impedance in the whole-body impedance signal and, subsequently, the popliteal artery signal. By means of this

time difference and the estimated distance between the electrodes, the software calculates the PWV. Stroke volume, CO, and SVR were indexed to body surface area to reduce the influence of body size on measurement results; and they were defined as follows: stroke index (SI) (SV/body surface area, in milliliters per square meter), cardiac index (CI) (CO/body surface area, in liters per minute per square meter), and systemic vascular resistance index (SVRI) (SVR/body surface area, dyne∗s/cm^{5}m^2). The procedure and evaluation as well as the good repeatability and reproducibility of the ICG_{WB} method have been described in more detail previously [24-26].

2.5. Statistics

Statistical analyses were performed using SPSS for Windows (version 16.0; SPSS, Chicago, IL). The skewed distribution of triglycerides was corrected logarithmically before statistical analyses. Analysis of variance was used in testing differences between unadjusted group means with Dunnett T3 post hoc test for multiple comparisons for continuous variables. χ^2 was used for categorical variables. Adjusted mean systemic hemodynamic parameters were analyzed using SPSS general linear models (analysis of covariance). Adjusted multivariable regression models were constructed to study independent effects of fasting glucose, 2-hour glucose in OGTT, fasting insulin, and 2-hour insulin in OGTT on systemic hemodynamic parameters. To limit the effects of collinearity and control the number of covariates, glucose and insulin measures were analyzed separately in multivariable models. There were no interactions between sex, glucose tolerance groups, and systemic hemodynamic parameters; and therefore, analyses were performed as sexes combined. All analyses were repeated after excluding subjects having self-reported cerebrovascular or ischemic heart disease (n = 14), with essentially similar results. A P value of < .05 was considered statistically significant.

3. Results

Table 1 shows the baseline characteristics of the study population according to glucose tolerance status. The prevalence of IFG, IGT, and DM2 was 9.3%, 19.5%, and 8.7%, respectively. Subjects with a glucose metabolism disorder had higher BMI, triglycerides, 2-hour glucose, and 2-hour insulin in OGTT as well as fasting glucose and fasting insulin values, than subjects with NGT. In comparison with the NGT group, systolic blood pressure (SBP) was higher in the IGT and DM2 groups; and MBP was higher in the DM2 group. Moreover, SBP was higher in subjects with DM2 than in those with IGT; and MBP was higher in subjects with IGT than in those with IFG. Compared with the NGT group, both the IFG and the IGT groups had lower HDL cholesterol values. Antihypertensive medication was more frequently used in the glucose metabolism disorder groups than the NGT group. Higher use of statin therapy was seen in subjects with DM2 than in those with NGT.

Independent associations of fasting glucose, fasting insulin, 2-hour glucose in OGTT, and 2-hour insulin in OGTT with systemic hemodynamic parameters are shown in Table 2. Multivariable regression models for SI and PWV included fasting glucose, fasting insulin, 2-hour glucose in OGTT or 2-hour insulin in OGTT, age, sex, HR, BMI, SBP, diastolic blood pressure (DBP), HDL cholesterol, LDL cholesterol, triglycerides, and smoking. For SVRI, similar

Table 1
Characteristics of the study population

	Glucose tolerance				
	NGT n = 243	IFG n = 36	IGT n = 76	DM2 n = 34	P for trend
Age (y)	57.5 ± 7.8	59.6 ± 7.3	59.0 ± 8.1	61.5 ± 8.0	.020
Men (%)	39.1	61.1*	48.7	44.1	.063
BMI (kg/m²)	26.1 ± 3.6	28.5 ± 4.9*	28.3 ± 4.4†	29.8 ± 5.4†	<.001
Smoking (%)	23.5	33.3	18.4	23.5	.386
Fasting glucose (mmol/L)	5.3 ± 0.4	6.3 ± 0.2‡	5.8 ± 0.5‡¶	7.3 ± 2.4‡‖	<.001
2-h glucose in OGTT (mmol/L)	5.5 ± 1.2	6.2 ± 1.1*	8.9 ± 0.8‡¶	14.1 ± 4.3‡¶	<.001
Fasting insulin (mmol/L)	7.0 ± 2.9	10.8 ± 4.9‡	10.2 ± 5.7‡	13.8 ± 10.4†	<.001
2-h insulin in OGTT (mmol/L)	37.1 ± 24.3	67.3 ± 52.7*	72.7 ± 38.7‡	82.7 ± 56.3‡	<.001
SBP (mm Hg)	126.2 ± 21.0	124.1 ± 18.5	134.0 ± 21.7*	146.7 ± 18.8‡§	<.001
DBP (mm Hg)	66.2 ± 13.0	64.1 ± 8.5	68.9 ± 12.0	71.4 ± 14.2	.035
MBP (mm Hg)	86.2 ± 14.5	84.1 ± 10.8	90.6 ± 14.0§	96.6 ± 14.0†	<.001
Antihypertensive medication (%)	19.3	36.1*	31.6*	67.6‡¶	<.001
Total cholesterol (mmol/L)	5.6 ± 0.9	5.9 ± 1.1	5.7 ± 1.0	5.4 ± 1.1	.053
LDL cholesterol (mmol/L)	3.4 ± 0.8	3.8 ± 1.0	3.5 ± 0.9	3.2 ± 1.0	.030
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.4 ± 0.4*	1.5 ± 0.4*	1.4 ± 0.5	<.001
Triglycerides (mmol/L)	1.1 (0.8-1.4)	1.5 (1.0-2.2)*	1.5 (1.1-2.0)‡	1.5 (1.1-2.2)‡	<.001
Statin medication (%)	7.0	11.1	10.5	23.5†	.021

Values are presented as unadjusted mean ± standard deviation or geometric mean (25th-75th percentiles) or percentages of subjects.
*P < .05, †P < .01, and ‡P < .001 in pairwise comparison with the NGT group.
§P < .05, ‖P < .01, and ¶P < .001 in pairwise comparison IGT vs IFG and DM2 vs IGT.

Table 2
Independent glucose/insulin effects on systemic hemodynamic parameters in multivariable regression models (N = 389)

	SI		SVRI		PWV	
	$\beta \pm$ SE	P	$\beta \pm$ SE	P	$\beta \pm$ SE	P
Fasting glucose (mmol/L)	−0.277 ± 0.381	.467	58.217 ± 36.654	.113	0.193 ± 0.091	.034
2-h glucose in OGTT (mmol/L)	−0.153 ± 0.127	.227	45.352 ± 11.717	<.001	0.085 ± 0.030	.005
Fasting insulin (mmol/L)	0.014 ± 0.078	.857	−2.026 ± 7.627	.791	0.033 ± 0.019	.075
2-h insulin in OGTT (mmol/L)	−0.012 ± 0.010	.223	2.666 ± 0.970	.006	0.002 ± 0.002	.331

Regression coefficients (β) are age, sex, HR, BMI, SBP and DBP (for SI and PWV only), HDL cholesterol, LDL cholesterol, triglycerides, and smoking adjusted.

multivariable regression models were constructed (with the exception that SBP and DBP were not included in the model because blood pressure was used in the calculation of SVRI). Two-hour glucose in OGTT ($P < .001$; adjusted model R^2, 12.9%) and 2-hour insulin in OGTT ($P = .006$; adjusted model R^2, 11.2%) were directly and independently associated with SVRI. Other risk factors associated with SVRI were sex and HR ($P < .02$ for both). In addition, fasting glucose ($P = .034$; adjusted R^2, 51.9%) and 2-hour glucose in OGTT ($P = .005$; adjusted model R^2, 52.3%) were directly and independently associated with PWV. Other risk factors associated with PWV were age, sex, HR, and SBP ($P < .02$ for all). High-density lipoprotein cholesterol ($P = .022$), HR ($P < .001$), BMI ($P = .039$), and DBP ($P = .032$) were independent predictors explaining 15.7% of the variation in SI; but glucose or insulin measures were not associated with SI.

Mean values of SI, SVRI, and PWV according to glucose tolerance status are shown in Fig. 1. Stroke index was observed to decrease (P for trend < .001) and SVRI and PWV to increase (P for trend = .002 and P for trend < .001, respectively) with the worsening of glucose tolerance. In pairwise comparisons, SI was lower in the IFG and IGT groups when compared with the NGT group ($P = .041$ and $P < .001$, respectively); but there was no statistically significant difference between the DM2 and NGT groups ($P = .221$). Systemic vascular resistance index and PWV were higher in the IGT and DM2 groups than in the NGT group (SVRI: IGT vs NGT, $P = .045$ and DM2 vs NGT, $P = .043$; PWV: IGT vs NGT, $P < .001$ and DM2 vs NGT, $P = .001$). The difference between the IFG and the NGT groups was not statistically significant. In addition, there was no statistically significant difference in CI or HR between the groups (data not shown). After adjusting for age, sex, HDL cholesterol, LDL cholesterol, triglycerides, smoking, SBP (for SI and PWV only), and DBP (for SI and PWV only), decreasing trend of SI and increasing trends of SVRI and PWV with the worsening of glucose tolerance remained statistically significant (analysis of covariance P for trend < .03 for all).

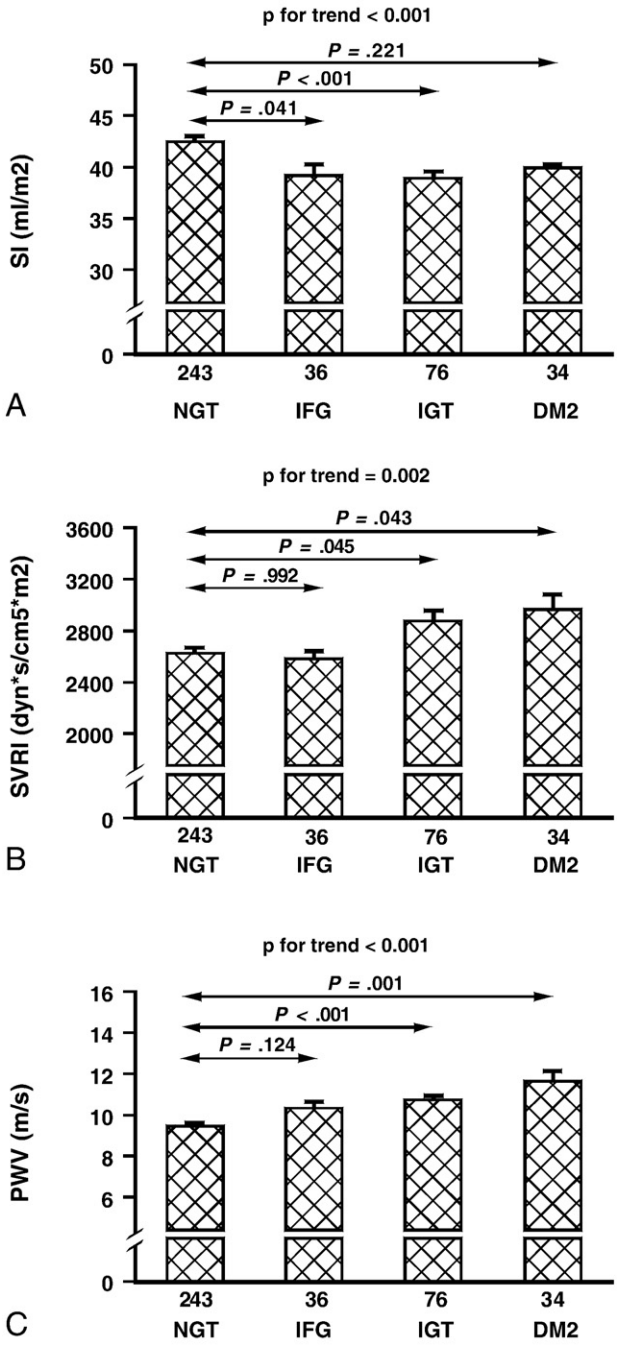

Fig. 1. Stroke index (A), SVRI (B), and PWV (C) means and standard errors according to glucose tolerance status.

4. Discussion

The aim of the present report was to study several systemic hemodynamic parameters simultaneously in

subjects with a different glucose tolerance status to achieve a deeper understanding of cardiovascular function in glucose metabolism disorders. We found that deteriorating glucose tolerance was associated with increased SVRI and PWV and with decreased SI. In addition, 2-hour glucose and insulin in OGTT were associated with SVRI independently of other cardiovascular risk factors; and fasting glucose and 2-hour glucose in OGTT were independent determinants of increased PWV.

We observed higher arterial stiffness, expressed as PWV, in subjects with DM2 [14,27,28] and IGT [13] compared with subjects with NGT, which is in line with previous reports. Previously, PWV has also been shown to be higher in subjects with IFG than in subjects with NGT [13,28]. In the present study, there was an increasing trend of PWV according to worsening of glucose tolerance, although in pairwise comparison, there was no statistically significant difference between IFG and NGT groups. Notably, the difference in PWV between subjects with IGT and those with NGT was 1.3 m/s; and that between subjects with DM2 and NGT was 2.2 m/s. This difference is worthy of mention because Blacher et al [29] observed an all-cause mortality odds ratio of 1.39 for each PWV increase of 1 m/s in patients with end-stage renal failure. In multivariable regression analysis, we found that sex, age, fasting glucose, 2-hour glucose in OGTT, SBP, and HR were determinants of PWV—a finding that is in agreement with previous studies [27,30]. Altogether, models including fasting glucose and 2-hour glucose in OGTT explained 51.9% and 52.3% of the variance in PWV, respectively. Thus, deteriorating glucose tolerance has unfavorable effects on arterial stiffness. Moreover, because PWV is a strong determinant of cardiovascular mortality and because fasting glucose and 2-hour glucose in OGTT remained as independent determinants of PWV in multivariable models, the current findings highlight the importance of glucose tolerance measurements in the risk evaluation of the middle-aged population.

The data available on the association between glucose metabolism disorders and cardiac function are limited and, to a degree, also controversial, particularly with reference to SV. Previous echocardiography studies suggest abnormalities in the cardiac structure and function of subjects with abnormal glucose tolerance [16-19,31], even without a difference in SI between the NGT, IGT, and DM2 groups [18]. However, Heckbert et al [20] found a decreased SV in subjects with diabetes as detected by cardiac magnetic resonance imaging. The present study shows a trend for decreasing cardiac function, measured by SI, with the deterioration of glucose tolerance. Decreased SI was found in both the IFG and the IGT groups as compared with the NGT group, but the difference between DM2 and NGT groups was not statistically significant. The mechanism of these adverse alterations in cardiac function is not completely understood; but it may involve myocardial cell injury and interstitial fibrosis [32], as well as slow coronary flow [33] and alterations in intracellular calcium homeostasis leading to depressed contractility [34]. On the other hand, in addition to a direct influence of deteriorating glucose tolerance on SI, increased arterial load caused by increased stiffness and SVR could be responsible for the lower SI in subjects with a glucose metabolism disorder. In concert with previous reports, [18,27], we observed no difference in HR, CO, or CI between study groups. Although many cardiovascular risk factors were univariately associated with SI, only HDL cholesterol, HR, BMI, and DBP were independent determinants of SI in multivariable models. Similar findings have been reported previously [20], but the mechanisms underlying these observations are less known and require further study.

Previous studies have shown higher mean levels of SVR and total peripheral resistance in subjects with IGT or DM2 as compared with healthy subjects, although these differences have not been statistically significant [18,35]. To the best of our knowledge, this is the first study to report a trend for increasing SVRI with the deterioration of glucose tolerance. In pairwise comparisons, SVRI was increased in subjects with IGT and DM2 when compared with subjects with NGT; but there was no statistically significant difference between subjects with IFG and NGT. Moreover, SVRI was higher in the IGT and DM2 groups than the IFG group. Previously, subjects with IGT have been shown to be more insulin resistant than subjects with IFG [36]; and this may also partially explain our findings. Interestingly, 2-hour glucose and insulin in OGTT were independently associated with SVRI, whereas fasting glucose and 2-hour glucose in OGTT were independent determinants of increased PWV. These findings highlight the fact that SVRI and PWV are clearly diverse vascular phenotypes with potentially different mechanisms behind elevation of them in glucose metabolism disorders. The pathophysiologic mechanism behind these observations is not clear based on the present findings. However, it is known that subjects with IFG, IGT, or DM2 have impaired endothelial function [37]; and this might have a role in increased SVR. In addition, it has been suggested that endothelial dysfunction causes decreased blood flow to skeletal muscles, which in turn could contribute to insulin resistance [38]. Furthermore, in hypertensive and obese subjects, impairment of insulin-mediated vasodilation may contribute to the increase in peripheral resistance [39]. It has been also shown that flow-mediated endothelium-dependent vasodilatation is rapidly reduced after glucose loading in subjects with DM2 and even in subjects with NGT or IGT whose fasting glucose levels are within normal limits [40]. Thus, it is tempting to speculate that prolonged and repeated exposure to postprandial hyperglycemia may play an important role in the development of atherosclerosis and alterations of systemic hemodynamics, even in those who have normal fasting plasma glucose levels, and that these pathophysiologic mechanisms may influence SVRI and PWV differentially. Clearly, the pathophysiologic bases underlying our observations, particularly whether there

are any alternative or additional factors responsible for increasing SVR in subjects with a glucose metabolism disorder, deserve further investigation.

In the present analysis, traditional cardiovascular risk factors explained only 15.7% of the variation in SI and 11.2% to 12.9% of the variation in SVRI. Previously, the proportion of the total variability of SV explained by the sociodemographic variables, height, and the cardiovascular risk factors (including also alcohol intake and exercise per week) has been shown to be roughly one third [20]. In addition, several other variables, such as genetic factors (heritable factors explaining 50%-60% of variance in systemic hemodynamics [41]) strongly explain variance in systemic hemodynamics. In the current study, we were not able to include all these potential explanators in the analysis; and this might lower the degree of explanation of variance in SI. One plausible factor explaining variance of SVRI could be HR variability because diabetic subjects have been shown to have higher sympathetic tone [42]. Therefore, associations of HR variability and SVRI on subjects with impaired glucose metabolism should be assessed in future studies.

There were some limitations in the present study. Our data were cross-sectional, and the causality of the observed associations could therefore not be assessed. Moreover, the study cohort was ethnically homogenous, limiting the generalization of the results to white Europeans only. The strengths of the present study include the fact that we used a population-based cohort and indexed hemodynamic parameters (SI, SVRI, and CI, which reduce the influence of body size to measurement results), improving the comparability of the present findings to those of previous studies and allowing a more direct evaluation of the associations of risk factors with systemic hemodynamics.

In conclusion, our results show that there is a trend for increasing SVR and arterial stiffness as well as decreasing cardiac pump function with the worsening of glucose tolerance status. Understanding the wide alterations in systemic hemodynamics and cardiovascular function caused by deteriorating glucose tolerance may lead to secondary preventive strategies to reduce cardiovascular disease and mortality.

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References

[1] de Vegt F, Dekker JM, Ruhé HG, Stehouwer CD, Nijpels G, Bouter LM, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia 1999;42:926-31.

[2] Jackson CA, Yudkin JS, Forrest RD. A comparison of the relationships of the glucose tolerance test and the glycated haemoglobin assay with diabetic vascular disease in the community. The Islington Diabetes Survey. Diabetes Res Clin Pract 1992;17:111-23.

[3] Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73-8.

[4] Gong W, Yang Z, Ye W, Du Y, Lu B, Wang M, et al. The association of dysglycaemia and cardiovascular disease in patients with metabolic syndrome. J Int Med Res 2009;37:1486-92.

[5] Rocchini AP, Katch V, Kveselis D, Moorehead C, Martin M, Lampman R, et al. Insulin and renal sodium retention in obese adolescents. Hypertension 1989;14:367-74.

[6] Schram MT, Henry RM, van Dijk RA, Kostense PJ, Dekker JM, Nijpels G, et al. Increased central artery stiffness in impaired glucose metabolism and type 2 diabetes: the Hoorn Study. Hypertension 2004; 43:176-81.

[7] Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, et al. Hoorn Study. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003;107:2089-95.

[8] Sullivan JM, Prewitt RL, Ratts TE, Josephs JA, Connor MJ. Hemodynamic characteristics of sodium-sensitive human subjects. Hypertension 1987;9:398-406.

[9] O'Rourke M, Frohlich ED. Pulse pressure: is this a clinically useful risk factor? Hypertension 1999;34:372-4.

[10] Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension. Emerging concepts. Hypertension 2010;55:9-14.

[11] Dahan M, Siohan P, Viron B, Michel C, Paillole C, Gourgon R, et al. Relationship between left ventricular hypertrophy, myocardial contractility, and load conditions in hemodialysis patients: an echocardiographic study. Am J Kidney Dis 1997;30:780-5.

[12] Grossman E, Oren S, Messerli FH. Left ventricular mass and cardiac function in patients with essential hypertension. J Hum Hypertens 1994;8:417-21.

[13] Xu L, Jiang CQ, Lam TH, Cheng KK, Yue XJ, Lin JM, et al. Impact of impaired fasting glucose and impaired glucose tolerance on arterial stiffness in an older Chinese population: the Guangzhou Biobank Cohort Study-CVD. Metabolism 2010;59:367-72.

[14] Taniwaki H, Kawagishi T, Emoto M, Shoji T, Kanda H, Maekawa K, et al. Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. Vessel wall properties in type 2 diabetes. Diabetes Care 1999;22: 1851-7.

[15] Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002;106:2085-90.

[16] Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, et al. Impact of diabetes on cardiac structure and function: the strong heart study. Circulation 2000;101:2271-6.

[17] Henry RM, Paulus WJ, Kamp O, Kostense PJ, Spijkerman AM, Dekker JM, et al. Deteriorating glucose tolerance status is associated with left ventricular dysfunction-the Hoorn Study. Neth J Med 2008; 66:110-7.

[18] Celentano A, Vaccaro O, Tammaro P, Galderisi M, Crivaro M, Oliviero M, et al. Early abnormalities of cardiac function in non-insulin-dependent diabetes mellitus and impaired glucose tolerance. Am J Cardiol 1995;76:1173-6.

[19] Annonu AK, Fattah AA, Mokhtar MS, Ghareeb S, Elhendy A. Left ventricular systolic and diastolic functional abnormalities in asymptomatic patients with non-insulin-dependent diabetes mellitus. J Am Soc Echocardiogr 2001;14:885-91.

[20] Heckbert SR, Post W, Pearson GD, Arnett DK, Gomes AS, Jerosch-Herold M, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: the Multiethnic Study of Atherosclerosis. J Am Coll Cardiol 2006;48:2285-92.

[21] Aromaa A, Koskinen S, editors. Health and functional capacity in Finland. Baseline results of the Health 2000 Health Examination Survey. Helsinki: Publications of the National Public Health Institute

B12/2004. 2004. p. 1-171. Available at: www.ktl.fi/health2000. Accessed October 15.
[22] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
[23] WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus. World Health Organization; 1999. Report No 99.2. 1-59. Available at: http://www.who.int/diabetes/currentpublications/en/.
[24] Kööbi T, Kaukinen S, Turjanmaa V, et al. Whole-body impedance cardiography in the measurement of cardiac output. Crit Care Med 1997;25:779-85.
[25] Kööbi T, Kähönen M, Iivainen T, et al. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics—a validation study. Clin Physiol Funct Imaging 2003;23:31-6.
[26] Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood. The Cardiovascular Risk in Young Finns Study. Hypertension 2010;55:806-11.
[27] Rahman S, Ismail AA, Ismail SB, Naing NN, Rahman AR. Early manifestation of macrovasculopathy in newly diagnosed never treated type II diabetic patients with no traditional CVD risk factors. Diabetes Res Clin Pract 2008;80:253-8.
[28] Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, et al. Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: the Tanno and Sobetsu study. Diabetes Care 2003;26:437-40.
[29] Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434-9.
[30] Webb DR, Khunti K, Silverman R, Gray LJ, Srinivasan B, Lacy PS, et al. Impact of metabolic indices on central artery stiffness: independent association of insulin resistance and glucose with aortic pulse wave velocity. Diabetologia 2010;53:1190-8.
[31] Rutter MK, Parise H, Benjamin EJ, Levy D, Larson MG, Meigs JB, et al. Impact of glucose intolerance and insulin resistance on cardiac structure and function: sex-related differences in the Framingham Heart Study. Circulation 2003;107:448-54.
[32] Kawaguchi M, Techigawara M, Ishihata T, Asakura T, Saito F, Maehara K, et al. A comparison of ultrastructural changes on endomyocardial biopsy specimens obtained from patients with diabetes mellitus with and without hypertension. Heart Vessels 1997;12:267-74.
[33] Binak E, Gunduz H, Sahin M, Kurtoglu N, Dindar I. The relation between impaired glucose tolerance and slow coronary flow. Int J Cardiol 2006;111:142-6.
[34] Lopaschuk GD. Metabolic abnormalities in the diabetic heart. Heart Fail Rev 2002;7:149-59.
[35] Reitblat T, Polishchuk I, Zamir D, Isakov I, Oren S. Arterial compliance: is it reduced in antiphospholipid syndrome? J Hum Hypertens 2006;20:504-9.
[36] Festa A, D'Agostino Jr R, Hanley AJ, Karter AJ, Saad MF, Haffner SM. Differences in insulin resistance in nondiabetic subjects with isolated impaired glucose tolerance or isolated impaired fasting glucose. Diabetes 2004;53:1549-55.
[37] Su Y, Liu XM, Sun YM, Wang YY, Luan Y, Wu Y. Endothelial dysfunction in impaired fasting glycemia, impaired glucose tolerance, and type 2 diabetes mellitus. Am J Cardiol 2008;102:497-8.
[38] Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113:1888-904.
[39] Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. Lancet 1993;342:707-9.
[40] Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. J Am Coll Cardiol 1999;34:146-54.
[41] Snieder H, Harshfield GA, Treiber FA. Heritability of blood pressure and hemodynamics in African- and European-American youth. Hypertension 2003;41:1196-201.
[42] Singh JP, Larson MG, O'Donnell CJ, Wilson PF, Tsuji H, Lloyd-Jones DM, et al. Association of hyperglycemia with reduced heart rate variability (The Framingham Heart Study). Am J Cardiol 2000;86:309-12.

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ORIGINAL ARTICLE

Metabolic syndrome in childhood and increased arterial stiffness in adulthood — The Cardiovascular Risk in Young Finns Study

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Abstract

Objective. We conducted the present study to examine the associations of two different paediatric metabolic syndrome (MetS) definitions and recovery from childhood MetS with arterial pulse wave velocity (PWV), an index of arterial stiffness, measured in adulthood.

Methods. A total of 945 subjects participated in the base-line study in 1986 (then aged 9–18 years) and the adult follow-up in 2007 (then aged 30–39 years). Cardiovascular risk factor data were available at both base-line and follow-up. In the follow-up study, arterial PWV was measured using a whole-body impedance cardiography device.

Results. Subjects suffering from MetS in childhood (prevalence 11.1%–14.1%) had higher arterial PWV after 21-year follow-up when compared with those not afflicted by the syndrome in childhood ($P < 0.007$). An increasing number of the MetS components in childhood were associated with increased PWV in adulthood (P for trend = 0.005). Subjects who recovered from the MetS during the 21-year follow-up period had lower PWV than those with persistent MetS ($P < 0.001$).

Conclusion. MetS in childhood predicted increased arterial stiffness in adulthood, and recovery from childhood MetS was associated with decreased arterial PWV in adulthood. The current results emphasize the importance of the prevention and controlling of MetS risk factors both in childhood and adulthood.

Key words: *Arterial stiffness, epidemiology, metabolic syndrome*

Introduction

Metabolic syndrome (MetS) is a constellation of several cardiovascular risk factors, including hypertension, obesity, glucose intolerance, and dyslipidaemia. MetS has been associated with an increased risk for cardiovascular disease (CVD) and type 2 diabetes mellitus (1). Previous studies have also shown that MetS in childhood predicts CVD in adulthood (2) and increases the risk of adult MetS (3).

High pulse wave velocity (PWV), as an index for arterial stiffness, has proven an independent predictor of all-cause and cardiovascular mortality for several patient groups (4–6). High PWV has also been associated with cardiovascular mortality and coronary heart disease among generally healthy older adults (7). In addition, PWV has been found to be increased in young adults with MetS and an increasing number of MetS components (8). Moreover, it

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Key messages

- Childhood metabolic syndrome predicted increased arterial pulse wave velocity, a measure of increased arterial stiffness, in adulthood.
- Recovery from childhood metabolic syndrome was associated with decreased arterial stiffness in adulthood.

Abbreviations

BMI	body mass index
CVD	cardiovascular disease
HDL	high-density lipoprotein
IMT	carotid intima-media thickness
LDL	low-density lipoprotein
MetS	metabolic syndrome
NCEP	National Cholesterol Education Program Adult Treatment Panel III guideline
Ped1MetS	the first paediatric metabolic syndrome definition
Ped2MetS	the second paediatric metabolic syndrome definition
PWV	pulse wave velocity

has been previously shown that the increase in PWV with age is greater in middle-aged subjects with MetS than in those without MetS (9,10), and that subjects with persistent MetS have higher PWV rates than those without MetS or a regression of MetS (11). Although the relationships between MetS and PWV have been widely studied in adult population samples, limited data are available concerning the associations between childhood MetS, its components, and arterial stiffness (12). Iannuzzi et al. (13) showed in a cross-sectional setting that obese children with MetS have increased arterial stiffness, and Whincup et al. (14) reported a strong inverse association between the number of metabolic syndrome components and arterial distensibility in apparently healthy adolescents. In addition, we have shown with the present adult population that carotid artery elasticity decreases and PWV increases with the increase in the number of cardiovascular risk factors measured in childhood (15,16). However, the relationship between childhood MetS and adulthood PWV is, to the best of our knowledge, unknown.

Therefore, the present study was undertaken to examine the relationships between childhood MetS and adulthood arterial PWV among 945 subjects participating in the Cardiovascular Risk in Young Finns Study. We also determined whether recovery from childhood MetS over a 21-year follow-up has favourable effects on arterial stiffness in adulthood.

Materials and methods

Subjects

The first cross-sectional survey was conducted in 1980 and included 3,596 participants (aged 3–18 years) who were randomly selected from the national (population) register (17). Thereafter, several follow-up studies have been conducted. The study cohort for the present analysis included those subjects who participated in the 1986 survey at the ages of 9, 12, 15, or 18 years as well as the adult follow-up in 2007 (then aged 30–39 years), and for whom complete risk factor data were available in 1986, in addition to risk factor and pulse wave velocity data in 2007 ($n = 959$). After excluding those female participants who were pregnant at the time of the follow-up ($n = 14$), a total of 945 subjects were included in the present analysis. Subjects participating in the 1986 survey were selected to comprise the base-line study sample in the present analysis, since fasting glucose was not measured in the 1980 survey. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

Biochemical analyses and clinical characteristics

Venous blood samples were collected after a 12-hour fast. Standard methods were used for high-density lipoprotein (HDL) cholesterol, triglycerides, insulin, and plasma glucose concentration measurements. Details of all of the methods have been described previously (15,18,19). Waist circumference (only in 2007), height, and weight were measured, and body mass index (BMI; kg/m^2) was calculated. Blood pressure was measured from the brachial artery with standard methods, as described previously (15). The mean of three measurements was used in the analysis.

Definition of metabolic syndrome

According to the updated National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) definition, adult subjects were categorized as having MetS (in 2007) if they met at least three of the following conditions (20): waist circumference $\geq$ 102 cm for men and $\geq$ 88 cm for women; triglycerides $\geq$ 1.7 mmol/L or relevant drug treatment; HDL cholesterol $<$ 1.03 mmol/L for men and $<$ 1.3 mmol/L for women, or relevant drug treatment; systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg, or relevant drug treatment; fasting glucose $\geq$ 5.6 mmol/L or relevant drug treatment.

Because there is no universally accepted definition for paediatric MetS (12), we created two paediatric

MetS definitions similar to the previous study by Lambert et al. (21). Values of age- and sex-specific cut-off points used to define risk factors were estimated from the study population. Overweight was defined as BMI ≥ 85th percentile (22). High triglycerides, high systolic blood pressure, hyperinsulinaemia, and low HDL cholesterol were defined as values in the respective extreme quartiles (triglycerides ≥ 75th percentile, systolic blood pressure ≥ 75th percentile, fasting insulin ≥ 75th percentile, HDL cholesterol ≤ 25th percentile). These cut-off points are also similar to those used in the Bogalusa Heart Study (23). Hyperglycaemia was defined as fasting blood glucose ≥ 6.1 mmol/L (24). The first paediatric MetS (Ped1MetS) definition required the presence of any three of these six risk factors. The second paediatric MetS (Ped2MetS) definition required the presence of hyperinsulinaemia and any two of the other five risk factors.

The study population was classified further into four different groups according to MetS status in 1986 and 2007: control group (no MetS in 1986 or 2007), recovery group (MetS in 1986 but not in 2007), incident group (no MetS in 1986 but MetS in 2007), and the persistent group (MetS in both 1986 and 2007). These groups were comprised separately for the two paediatric MetS definitions (Ped1MetS and Ped2MetS).

Arterial pulse wave velocity measurement

PWV was determined by using a commercially available whole-body impedance cardiography monitor, the CircMon B202 (CircMon™; JR Medical Ltd, Tallinn, Estonia). A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest A/S, Ölstykke, Denmark) were placed on the distal parts of the extremities just proximal to the wrists and the ankles. Voltage electrodes were placed proximal to the current electrodes, with a distance of 5 cm between the centres of the electrodes. The distal impedance plethysmogram 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 about 20 cm. Alternating electrical current was applied to current electrodes and change in whole-body impedance was measured from voltage electrodes. The whole-body impedance decreases when the pulse pressure enters the aortic arch and changes the diameter of the aorta. The CircMon software measures the time difference between the onset of the decrease in impedance in the whole-body impedance signal caused by pulse wave in the aortic arch and, subsequently, in the popliteal artery signal. The PWV can be determined from the distance and the time difference between the two recording sites. A more detailed description of the method (16,25) and the validation study (25) has been published previously.

Statistical analyses

All statistical analyses were performed with SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). Comparison of base-line and follow-up characteristics between subjects with and without MetS was performed using the *t* test for continuous variables and the chi-square for sex as a categorical variable. The skewed distributions of triglycerides and insulin were corrected logarithmically before statistical analyses. The univariate relationships between PWV and MetS components were studied by means of regression analysis. Multivariable regression models, including age and sex, were constructed to examine the independent effects of the MetS components on PWV. In regression analysis we used heart rate-specific *z* scores for PWV because heart rate may be a confounding factor (26). Variation in risk variables during the 21-year follow-up was studied by subtracting the base-line value from the follow-up value. Age- and sex-adjusted differences in risk variable changes, as well as heart rate-, sex-, and age-adjusted mean PWV values, were analysed using general linear models. There were no interactions between sex, MetS, and PWV, and analyses were therefore performed with the sexes combined. Statistical significance was determined as two-tailed $P < 0.05$.

Results

Base-line and follow-up characteristics of the study subjects are shown in Table I. The prevalences of MetS in the base-line paediatric population (ages 9–18 years in 1986) were 14.1% for the Ped1MetS definition and 11.1% for the Ped2MetS definition. Furthermore, the prevalence of MetS in the follow-up adult population (ages 30–39 years in 2007) was 18.1%. Subjects with MetS were older (in the adult population) and had a higher body mass index, systolic and diastolic blood pressure, triglycerides, fasting glucose, fasting insulin, and waist circumference (only in the adult population), as well as lower HDL cholesterol, when compared with subjects without MetS ($P < 0.05$ for all).

In univariate regression analysis, hyperinsulinaemia ($P = 0.005$) and hypertension ($P < 0.024$) as individual components of paediatric MetS were directly associated with PWV measured in adulthood (Table II). In multivariable regression analysis, age ($P < 0.001$), sex ($P < 0.001$), and hyperinsulinaemia ($P = 0.021$) were directly and independently

Table I. Base-line and follow-up characteristics of study subjects.

Variable	1986			2007	
	No MetS	Ped1MetS	Ped2MetS	No MetS	Adult MetS
Number of subjects	812	133	105	774	171
Age (years)	13.6 ± 3.3	13.5 ± 3.4	13.5 ± 3.3	34.4 ± 3.3	35.3 ± 3.4[b]
Sex (%, females)	55.5	48.9	51.4	56.8	44.4[a]
Body mass index (kg/m^2)	18.9 ± 2.7	22.2 ± 3.6[b]	22.4 ± 3.8[b]	24.5 ± 3.7	31.2 ± 4.3[b]
Systolic blood pressure (mmHg)	110.0 ± 11.4	119.7 ± 12.4[b]	118.9 ± 12.8[b]	117.6 ± 12.7	127.5 ± 15.0[b]
Diastolic blood pressure (mmHg)	62.5 ± 9.2	65.3 ± 10.3[a]	64.9 ± 10.1[a]	72.8 ± 10.4	81.5 ± 11.6[b]
HDL cholesterol (mmol/L)	1.6 ± 0.3	1.3 ± 0.2[b]	1.3 ± 0.2[b]	1.4 ± 0.3	1.1 ± 0.3[b]
Triglycerides (mmol/L)	0.8 (0.6–1.0)	1.3 (1.0–1.5)[b]	1.2 (1.0–1.5)[b]	1.0 (0.8–1.4)	2.0 (1.7–2.7)[b]
Insulin (mmol/L)	8.4 (6.5–12.0)	14.3 (11.0–18.0)[b]	16.5 (13.0–19.3)[b]	5.7 (3.9–8.8)	13.2 (9.4–18.1)[b]
Glucose (mmol/L)	4.7 ± 0.5	4.9 ± 0.5[b]	4.9 ± 0.5[b]	5.2 ± 0.4	5.7 ± 0.9[b]
Waist circumference (cm)	–	–	–	84.3 ± 10.8	103.0 ± 11.3[b]

MetS = metabolic syndrome; Ped1MetS = the first paediatric MetS definition; Ped2MetS = the second paediatric MetS definition; 1986 No MetS = no MetS according to Ped1MetS or Ped2MetS.
Values are presented as unadjusted mean ± standard deviation or geometric mean (25th–75th percentile) or percentages of subjects. Waist circumference was not measured in 1986.
[a]$P < 0.05$; [b]$P < 0.001$ in pairwise comparison No MetS versus MetS.

associated with PWV in adulthood (Table II). In univariate regression analysis for the adult population, hypertension (β ± SE 0.631 ± 0.068), obesity (0.361 ± 0.071), high triglycerides (0.502 ± 0.077), and hyperglycaemia (0.407 ± 0.078) as individual components of adult MetS were directly associated with PWV ($P < 0.001$ for all). In multivariable regression analysis for the adult population, age (0.050 ± 0.009; $P < 0.001$), sex (0.515 ± 0.061; $P < 0.001$), hypertension (0.406 ± 0.067; $P < 0.001$), obesity (0.277 ± 0.070; $P < 0.001$), and high triglycerides (0.169 ± 0.078; $P = 0.031$) as individual components of adult MetS were independently associated with PWV. When using continuous paediatric risk variables in multivariable regression analysis, sex, age, systolic blood pressure, and triglycerides were directly and independently associated with PWV in adulthood ($P < 0.02$ for all) (data not shown).

Adulthood PWV adjusted for age, sex, and heart rate was higher in subjects with paediatric MetS ($P < 0.007$ for both paediatric MetS definitions) and adult MetS ($P < 0.001$) than in those not suffering from MetS in childhood or adulthood (Figure 1A). There was also an increasing trend for adult PWV with the increase in the number of paediatric MetS components (P for trend = 0.005) (Figure 1B). Subjects who had persistent MetS over the 21-year follow-up had higher PWV than those without MetS at base-line and follow-up ($P < 0.001$) (Figure 1C). In addition, subjects who recovered from MetS during the 21-year follow-up had lower PWV than those with persistent MetS ($P < 0.001$) (Figure 1C). Furthermore, we observed increasing trends (age- and sex-adjusted) for BMI ($P < 0.001$), systolic blood pressure ($P < 0.002$), diastolic blood pressure ($P < 0.05$), triglycerides ($P < 0.001$), fasting insulin ($P < 0.001$), and fasting glucose ($P < 0.001$), as well as a decreasing trend for HDL cholesterol ($P < 0.003$), over the 21-year follow-up in the MetS persistent group when compared to the MetS recovery group, with both paediatric MetS definitions.

All analyses were repeated after excluding subjects on antihypertensive ($n = 46$), lipid-lowering ($n = 11$), or antidiabetic ($n = 6$) medications, with essentially similar results. In addition, all analyses were repeated using a recently published harmonized MetS definition in adulthood (27), with

Table II. Univariate and multivariable relationships between components of paediatric MetS (ages 9–18 years in 1986) and adult PWV (in 2007) ($n = 945$).

	PWV	
	β ± SE	P
Univariate relations		
Hyperinsulinaemia	0.203 ± 0.071	0.005
Hypertension	0.165 ± 0.073	0.024
Overweight	0.149 ± 0.090	0.099
Low HDL cholesterol	0.022 ± 0.074	0.764
High triglycerides	0.117 ± 0.073	0.110
Hyperglycaemia	0.002 ± 0.564	0.998
Multivariable relations		
Age	0.059 ± 0.009	< 0.001
Sex	0.608 ± 0.060	< 0.001
Hyperinsulinaemia	0.164 ± 0.071	0.021
Hypertension	0.126 ± 0.069	0.068
Overweight	0.039 ± 0.089	0.661
Low HDL cholesterol	–0.036 ± 0.072	0.613
High triglycerides	0.082 ± 0.073	0.260
Hyperglycaemia	–0.200 ± 0.526	0.703

PWV = pulse wave velocity; MetS = metabolic syndrome; β = regression coefficient; SE = standard error.
Heart rate-specific z scores were used for PWV.

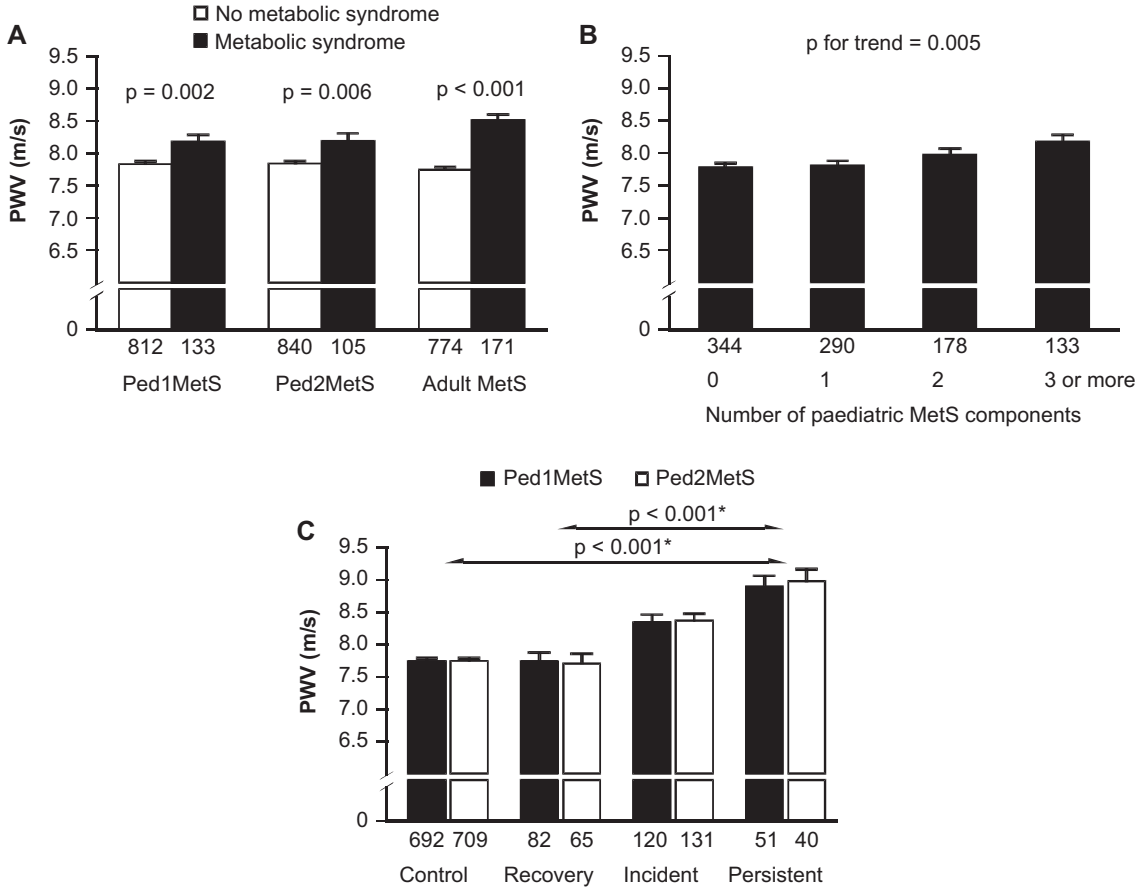

Figure 1. A: Comparison of adult PWV between subjects with and without MetS according to the paediatric MetS definitions (Ped1MetS and Ped2MetS) (ages 9–18 years in 1986) and the adult MetS definition (ages 30–39 years in 2007). B: Adult PWV by the number of paediatric MetS components (ages 9–18 years in 1986). C: Comparison of adult PWV between the 21-year changes in MetS status. PWV values are age-, sex-, and heart rate-adjusted means and standard errors. Values under columns indicate the number of subjects in each group. *For both paediatric MetS definitions (Ped1MetS and Ped2MetS). (PWV = pulse wave velocity; MetS = metabolic syndrome; Ped1MetS = the first paediatric MetS definition requiring any three of six risk factors (hyperinsulinaemia, high triglycerides, high systolic blood pressure, overweight, hyperglycaemia, low HDL cholesterol); Ped2MetS = the second paediatric MetS definition requiring the presence of hyperinsulinaemia and any two of the other five risk factors; Control = no MetS at 1986 according to Ped1MetS or Ped2MetS and no MetS at 2007 according to the adult MetS definition; Recovery = MetS at 1986 according to Ped1MetS or Ped2MetS but not at 2007 according to the adult MetS definition; Incident = no MetS at 1986 according to Ped1MetS or Ped2MetS but MetS at 2007 according to the adult MetS definition; Persistent = MetS both at 1986 according to Ped1MetS or Ped2MetS and 2007 according the adult MetS definition.)

essentially similar results. Moreover, all analyses were repeated without heart rate correction for PWV, with essentially similar findings (data not shown).

Discussion

The present study shows that MetS and the accumulation of the number of MetS components in childhood have an adverse effect on arterial stiffness in adulthood. Children and adolescents with MetS at base-line had higher PWV after a 21-year follow-up in adulthood, when compared to their peers who did not suffer from MetS at base-line. In addition, persistent MetS over the 21-year follow-up associated with increased arterial stiffness. Subjects with persistent MetS had higher PWV than those who recovered or were free from of MetS during the 21-year follow-up.

To the best of our knowledge, this is the first study to report an association between increased adult PWV in subjects with MetS and increasing number of MetS components in childhood. Previously, elevated cardiovascular risk levels in childhood have been shown to predict increased carotid intima-media thickness (IMT), a marker of early atherosclerosis, in adulthood (28). In addition, decreased carotid artery elasticity and increased PWV have been found in adults with increasing number of cardiovascular risk factors measured in childhood (15,16). However, childhood MetS and arterial stiffness have received little academic interest to date. Iannuzzi et al. (13) reported in a cross-sectional

setting that arterial stiffness was increased in obese children with MetS, and Whincup et al. (14) found the arterial distensibility in adolescents to decrease with the increase in the number of MetS components.

In our cohort, hyperinsulinaemia and hypertension as individual components of paediatric MetS were associated with adult PWV in the univariate regression analysis, and childhood hyperinsulinaemia was an independent predictor of increased PWV in adulthood in the multivariable analysis. Furthermore, we found a border-line significant association ($P = 0.068$) between childhood hypertension and adulthood PWV in the multivariable model. These findings are consistent with the notion that childhood systolic blood pressure is directly associated with PWV in young adulthood (16,29). In addition, blood pressure measured in childhood and adolescence has been found to predict decreased carotid artery elasticity in adulthood (15). Furthermore, insulin levels in childhood have been shown to correlate inversely with carotid artery compliance and directly with Young's elastic modulus in adulthood (15). Taken together, the current findings provide further insight into the associations of childhood MetS, the components of childhood MetS, and adulthood arterial stiffness.

Our findings supported the view that PWV is increased in young adults with MetS when compared to subjects not afflicted by the syndrome (8). Previously, hypertension and obesity as individual components of MetS have been found to be independent predictors of PWV, and triglyceride concentration has shown a direct association with PWV (30). In line with this, we found the independent adult determinants of increased PWV to be hypertension, obesity, and high triglycerides as individual components of adult MetS. Therefore, our observations regarding adult MetS and PWV fall in line with the previous studies.

Tomiyama et al. (11) have previously shown with a middle-aged Japanese male population that the annual rate of increase in PWV is higher in subjects with persistent MetS than in those with a regression of or no MetS. In addition, Nakanishi et al. (9) and Safar et al. (10) have reported with middle-aged populations that the increase in PWV escalates with age in subjects with MetS, as compared with those without the condition. In line with these studies, we found that subjects who had persistent MetS over the 21-year follow-up had a 1.2–1.3 m/s (depending on the paediatric MetS definition used) higher PWV than subjects who recovered from MetS, and a 1.2 m/s higher PWV compared to subjects without MetS over the 21-year follow-up. This difference in PWV is noteworthy, since Vlachopoulos et al. reported a 14%–15% increase in cardiovascular events, cardiovascular mortality, and all-cause mortality for each 1 m/s increase in aortic PWV (31).

One plausible explanation for the increased PWV in the MetS persistent group as compared to the MetS recovery group could be provided by the increasing trends for BMI, systolic and diastolic blood pressure, triglycerides, fasting insulin, and fasting glucose, as well as the decreasing trend for HDL cholesterol, in subjects with persistent MetS when compared to those who recovered from MetS over the 21-year follow-up. This is in accordance with previous studies that have demonstrated a decrease in carotid-femoral PWV after weight reduction in middle-aged men (32), a reduction in carotid-femoral PWV after long-term trandolapril treatment in older adults (33), and a decrease in femoral-ankle PWV after atorvastatin treatment in patients with type 2 diabetes mellitus (34). We have also recently shown that recovery from MetS in young adults during a 6-year follow-up period was associated with the reversibility of IMT progression and with a decreased rate of carotid artery distensibility regression, suggesting that arterial structure and function may be restored in young adults with MetS by improving the metabolic risk factor profile and by weight reduction (35). However, as reviewed by Zieman et al. (36) and Stehouwer et al. (37), the mechanism by which arterial stiffness increases in subjects with MetS is a complex and partly unknown process. Nevertheless, it has been suggested that chronic hyperglycaemia and hyperinsulinaemia increase the local activity of the renin-angiotensin-aldosterone system and the expression of angiotensin type 1 receptor in vascular tissue, promoting the development of wall hypertrophy and fibrosis. Furthermore, impaired glucose tolerance enhances the glycation of proteins with the cross-linking of collagen, which may lead to the loss of collagen elasticity. In addition, endothelial dysfunction caused by high low-density lipoprotein (LDL) cholesterol, free fatty acids, endothelin-1, inadequate vasodilatory effects of insulin, or decreased adiponectin may explain, at least in part, the increased arterial stiffness (36,37). Further studies are clearly needed on the pathophysiological mechanisms behind the adverse effects of MetS on arterial stiffness and those affecting the arteries when recovering from MetS.

A potential limitation of the present study is the whole-body impedance cardiography method, which is not yet widely used in epidemiology settings to measure PWV, apparently limiting comparability of the present findings with the observations from other cohorts. However, PWV values measured between the aortic arch and popliteal artery using

the CircMon are highly comparable to those measured by Doppler ultrasound method (25). In addition, reference values (38), as well as good repeatability and reproducibility indexes (99% and 87%, respectively) for PWV measured by CircMon have been published previously (39). Moreover, the whole-body impedance cardiography is a handy and reliable tool in epidemiological studies, because the method is operator-independent and inexpensive, and the observed variability of PWV is mainly physiological (25,39).

Our study has some other limitations. Firstly, cut-off point-based definitions of MetS in children and adolescents have been shown to have marked short-term instability (40,41). Secondly, MetS was defined at base-line and at follow-up, but PWV was measured only at follow-up. Therefore, the current study does not allow the evaluation of longitudinal changes in PWV in relation to MetS status. Thirdly, overweight at base-line was determined by using age- and sex-specific cut-off points for BMI, which might be a less sensitive method to estimate adiposity. However, in determining MetS, BMI is considered an alternative if waist circumference data are not available (42). Finally, lack of a standard paediatric MetS definition and the ethnically homogeneous study sample may limit the generalizability of the present results. A potential strength of the current study is the use of age- and sex-specific cut-off points for risk variables at base-line, which may help to avoid misclassification due to age and gender differences in risk factor levels in childhood and adolescence.

In conclusion, findings in the present study suggest that MetS in childhood is associated with subclinical vascular damage in adulthood, and that recovery from childhood MetS during a 21-year follow-up period might have positive effects on arterial stiffness. Since MetS and increased PWV have been shown to be strong predictors of CVD, the current results emphasize the importance of the prevention and controlling of MetS risk factors both in childhood and adulthood.

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References

1. Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation. 2005;112: 3066–72.
2. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics. 2007;120:340–5.
3. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr. 2008;152:201–6.
4. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37:1236–41.
5. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999;99:2434–9.
6. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation. 2002;106: 2085–90.
7. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation. 2005;111:3384–90.
8. Li S, Chen W, Srinivasan SR, Berenson GS. Influence of metabolic syndrome on arterial stiffness and its age-related change in young adults: the Bogalusa Heart Study. Atherosclerosis. 2005;180:349–54.
9. Nakanishi N, Suzuki K, Tatara K. Clustered features of the metabolic syndrome and the risk for increased aortic pulse wave velocity in middle-aged Japanese men. Angiology. 2003; 54:551–9.
10. Safar ME, Thomas F, Blacher J, Nzietchueng R, Bureau JM, Pannier B, et al. Metabolic syndrome and age-related progression of aortic stiffness. J Am Coll Cardiol. 2006;47: 72–5.
11. Tomiyama H, Hirayama Y, Hashimoto H, Yambe M, Yamada J, Koji Y, et al. The effects of changes in the metabolic syndrome detection status on arterial stiffening: a prospective study. Hypertens Res. 2006;29:673–8.
12. Steinberger J, Daniels SR, Eckel RH, Hayman L, Lustig RH, McCrindle B, et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2009;119:628–47.
13. Iannuzzi A, Licenziati MR, Acampora C, Renis M, Agrusta M, Romano L, et al. Carotid artery stiffness in obese children with the metabolic syndrome. Am J Cardiol. 2006;97: 528–31.
14. Whincup PH, Gilg JA, Donald AE, Katterhorn M, Oliver C, Cook DG, et al. Arterial distensibility in adolescents: the influence of adiposity, the metabolic syndrome, and classic risk factors. Circulation. 2005;112:1789–97.
15. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the

Cardiovascular Risk in Young Finns Study. Circulation. 2005;112:1486–93.
16. Aatola H, Hutri-Kähönen N, Juonala M, Viikari JS, Hulkkonen J, Laitinen T, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood. The Cardiovascular Risk in Young Finns Study. Hypertension. 2010;55:806–11.
17. Raitakari OT, Juonala M, Rönnemaa T, Keltikangas-Järvinen L, Räsänen L, Pietikäinen M, et al. Cohort profile: the Cardiovascular Risk in Young Finns Study. Int J Epidemiol. 2008;37:1220–6.
18. Raiko JR, Viikari JS, Ilmanen A, Hutri-Kähönen N, Taittonen L, Jokinen E, et al. Follow-ups of the Cardiovascular Risk in Young Finns Study in 2001 and 2007: Levels and 6-year changes in risk factors. J Intern Med. 2010;267: 370–84.
19. Porkka KV, Raitakari OT, Leino A, Laitinen S, Räsänen L, Rönnemaa T, et al. Trends in serum lipid levels during 1980–1992 in children and young adults. The Cardiovascular Risk in Young Finns Study. Am J Epidemiol. 1997;146:64–77.
20. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112:2735–52.
21. Lambert M, Paradis G, O'Loughlin J, Delvin EE, Hanley JA, Levy E. Insulin resistance syndrome in a representative sample of children and adolescents from Quebec, Canada. Int J Obes Relat Metab Disord. 2004;28:833–41.
22. Himes JH, Dietz WH. Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. Am J Clin Nutr. 1994;59:307–16.
23. Chen W, Srinivasan SR, Elkasabany A, Berenson GS. Cardiovascular risk factors clustering features of insulin resistance syndrome (Syndrome X) in a biracial (Black-White) population of children, adolescents, and young adults: the Bogalusa Heart Study. Am J Epidemiol. 1999; 150:667–74.
24. Fagot-Campagna A, Saaddine JB, Flegal KM, Beckles GL. Diabetes, impaired fasting glucose, and elevated HbA1c in U.S. adolescents: the Third National Health and Nutrition Examination Survey. Diabetes Care. 2001;24:834–7.
25. Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics—a validation study. Clin Physiol Funct Imaging. 2003;23:31–6.
26. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. Hypertension. 2002;39:1083–7.
27. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
28. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA. 2003;290:2277–83.
29. Li S, Chen W, Srinivasan SR, Berenson GS. Childhood blood pressure as a predictor of arterial stiffness in young adults: the Bogalusa heart study. Hypertension. 2004;43:541–6.
30. Schillaci G, Pirro M, Vaudo G, Mannarino MR, Savarese G, Pucci G, et al. Metabolic syndrome is associated with aortic stiffness in untreated essential hypertension. Hypertension. 2005;45:1078–82.
31. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;55:1318–27.
32. Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, et al. Effect of weight reduction with dietary intervention on arterial distensibility and endothelial function in obese men. Angiology. 2009;60:351–7.
33. Mitchell GF, Dunlap ME, Warnica W, Ducharme A, Arnold JM, Tardif JC, et al. Long-term trandolapril treatment is associated with reduced aortic stiffness: the prevention of events with angiotensin-converting enzyme inhibition hemodynamic substudy. Hypertension. 2007;49:1271–7.
34. Shinohara K, Shoji T, Kimoto E, Yokoyama H, Fujiwara S, Hatsuda S, et al. Effect of atorvastatin on regional arterial stiffness in patients with type 2 diabetes mellitus. J Atheroscler Thromb. 2005;12:205–10.
35. Koskinen J, Magnussen CG, Taittonen L, Räsänen L, Mikkilä V, Laitinen T, et al. Arterial structure and function after recovery from the metabolic syndrome. The Cardiovascular Risk in Young Finns Study. Circulation. 2010;121:392–400.
36. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25:932–43.
37. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia. 2008;51:527–39.
38. Koivistoinen T, Kööbi T, Jula A, Hutri-Kähönen N, Raitakari OT, Majahalme S, et al. Pulse wave velocity reference values in healthy adults aged 26–75 years. Clin Physiol Funct Imaging. 2007;27:191–6.
39. Tahvanainen A, Koskela J, Tikkakoski A, Lahtela J, Leskinen M, Kähönen M, et al. Analysis of cardiovascular responses to passive head-up tilt using continuous pulse wave analysis and impedance cardiography. Scand J Clin Lab Invest. 2009;69:128–37.
40. Goodman E, Daniels SR, Meigs JB, Dolan LM. Instability in the diagnosis of metabolic syndrome in adolescents. Circulation. 2007;115:2316–22.
41. Gustafson JK, Yanoff LB, Easter BD, Brady SM, Keil MF, Roberts MD, et al. The stability of metabolic syndrome in children and adolescents. J Clin Endocrinol Metab. 2009;94: 4828–34.
42. Eisenmann JC. On the use of a continuous metabolic syndrome score in pediatric research. Cardiovasc Diabetol. 2008;7:17.

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Apolipoprotein B is related to arterial pulse wave velocity in young adults: The Cardiovascular Risk in Young Finns Study

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ABSTRACT

Objective: Limited data are available regarding the relationship of apolipoproteins B (ApoB) and A-1 (ApoA-1) with arterial stiffness. We conducted the present study to determine whether adulthood ApoB and ApoA-1 are related to arterial pulse wave velocity (PWV). Moreover, we examined whether ApoB and ApoA-1 measured in young adulthood are predictive of PWV assessed 6 years later.
Methods: The study population consisted of 1618 apparently healthy Finnish young adults (aged 30–45 years, 44.9% males) whose apolipoproteins, other cardiovascular risk factors and PWV were measured in 2007. In a sub-sample population, apolipoproteins and other cardiovascular risk factors had also been measured in 2001 ($n = 1264$). PWV measurements were performed using a whole-body impedance cardiography device.
Results: ApoB ($p < 0.001$) and the ApoB/ApoA-1 ratio ($p < 0.001$) were directly associated with PWV. ApoB and the ApoB/ApoA-1 ratio measured in young adulthood were also predictive of PWV measured 6 later ($p < 0.001$ for both). These relations remained significant ($p < 0.006$) in models adjusted for non-lipid risk factors. The areas under the receiver-operating characteristic (ROC) curves (AUC) were similar for ApoB and non-HDL cholesterol (2001: p for AUC comparison = 0.15; 2007: p for AUC comparison = 0.07) in detecting subjects with increased PWV (PWV ≥ 90th percentile).
Conclusion: The present study suggests that elevation of ApoB or non-HDL cholesterol is associated with increased arterial stiffness in young adults.

1. Introduction

Dyslipidemia is a strong predictor of atherosclerosis and coronary heart disease [1]. Elevated low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels are mainly used in clinical risk evaluation, although accumulating evidence suggests that apolipoproteins B (ApoB) and A-1 (ApoA-1) could be better markers of cardiovascular risk [2–5].

Pulse wave velocity (PWV), a measure of arterial stiffness, is a strong predictor of cardiovascular events and all-cause mortality [6]. PWV has been shown to associate with age, sex, heart rate, and several traditional cardiovascular risk factors [7–10]. However, previous data on the relation between apolipoproteins and arterial stiffness are available only for a few relatively small study populations. In the study by Amar et al. [11], a positive association was found between PWV and ApoB in patients treated for cardiovascular risk factors ($n = 247$). In addition, Schmidt-Trucksäss et al. [12] reported an independent association between ApoB and local ultrasonographically determined carotid arterial stiffness ($n = 51$). To our knowledge, there is a paucity of information concerning the role of ApoB and ApoA-1 as determinants of PWV at the population level.

In the present study, we therefore set out to examine whether ApoB and ApoA-1, additionally to other cardiovascular risk factors, are associated with PWV among 1618 young adults participating in the Cardiovascular Risk in Young Finns Study. In addition, we studied whether young adulthood ApoB and ApoA-1 are predictive of PWV measured 6 years later ($n = 1264$).

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2. Methods

2.1. Subjects

The Cardiovascular Risk in Young Finns Study is an on-going multicentre study of atherosclerosis risk factors in Finnish children and young adults. The first cross-sectional survey was conducted in 1980 including 3596 randomly selected participants (ages 3, 6, 9, 12, 15 and 18 years) [13]. Thereafter, several follow-up studies have been performed. The latest study was conducted in 2007, with 1872 subjects (aged 30–45 years) participating in whole-body impedance cardiography (ICGWB) monitoring. Subjects with incomplete cardiovascular risk factor data ($n = 82$), those with type 1 or type 2 diabetes ($n = 12$), pregnant women ($n = 19$) and subjects using antihypertensive ($n = 120$) or cholesterol-lowering medication ($n = 21$) were excluded. Therefore, a total of 1618 subjects were included in the present analysis to study the associations between cardiovascular risk factors and PWV in 2007.

We also formed a sub-sample group to study whether ApoB and ApoA-1 measured in young adulthood are predictive of PWV assessed 6 years later. The sub-group was comprised of those 1264 adult subjects for whom complete cardiovascular risk factor data (after above-mentioned exclusions) was available in 2001 and whose PWV was measured in 2007.

2.2. Clinical characteristics

Venous blood samples were collected after an overnight fast. Standard methods were used for serum total cholesterol, HDL cholesterol, triglycerides, C-reactive protein (CRP), insulin and glucose concentration measurements. LDL cholesterol concentration was calculated with the Friedewald formula, and non-HDL cholesterol concentration was calculated by subtracting the HDL cholesterol from the total cholesterol. ApoB and ApoA-1 were determined immunoturbidometrically (Orion Diagnostica, Espoo, Finland). Details of the methods have been described previously [14–18].

Height and weight were measured and body mass index (BMI, kg/m^2) calculated. Blood pressure was measured from the brachial artery with standard methods, as described previously [15]. The mean of 3 measurements was used in the analysis. Smoking habits were ascertained with a questionnaire, and smokers were defined as those smoking on a daily basis. Informed written consent was obtained from all subjects, and the study was approved by local ethics committees.

2.3. Arterial PWV studies

An ICGWB device (CircMon B202, JR Medical Ltd., Tallinn, Estonia) was used to determine PWV. A pair of electrically connected current electrodes (Blue Sensor type R-00-S; Medicotest A/S, Ölstykke, Denmark) was placed on the distal parts of the extremities just proximal to the wrists and the ankles. Voltage electrodes were placed proximal to the current electrodes, with a distance of 5 cm between the centres of the electrodes. The distal impedance plethysmogram 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 about 20 cm. Alternating electrical current (30 kHz) was applied to current electrodes and change in whole-body impedance was measured from voltage electrodes. When pulse pressure wave enters to aortic arch and aorta's diameter increases, 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 caused by pulse wave in the aortic arch and, subsequently, the popliteal artery signal. By means of this time difference and distance between 2 recording sites, the software calculates the PWV. A more detailed procedure of the ICGWB method [7,19] and the validation study [19] has been published previously.

2.4. Statistics

The statistical comparison of the receiver-operating characteristic (ROC) curves was carried out with a Statistical Analysis System (SAS, Cary, NC) macro. Other statistical analyses were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA). The skewed distributions of triglycerides, CRP and insulin were corrected logarithmically before statistical analyses. The univariate relationships between PWV and cardiovascular risk factors were studied by means of regression analysis. Multivariable linear regression models, including variables that had a statistically significant ($p < 0.05$) or borderline significant ($p < 0.10$) association with PWV in univariate regression models, were constructed to study the independent effects of cardiovascular risk factors on PWV. Because there were strong bivariate correlations for LDL (Pearson correlation coefficient $r < 0.837$–0.843, $p < 0.001$), triglycerides ($r < 0.673$–0.708, $p < 0.001$) and non-HDL cholesterol ($r = 0.942$–0.959, $p < 0.001$) with ApoB, the regression models were assessed for multicollinearity before the analysis. Variance inflation factors for ApoB, LDL cholesterol, triglycerides and non-HDL cholesterol in the present models ranged from 12.0 to 191.7 (tolerances ranging from 0.006 to 0.083), and lipid measures were therefore analysed separately in multivariable models. In the regression analysis, we used heart rate-specific z-scores for PWV [20]. To analyse heart rate-, age- and sex-adjusted mean PWV values across the ApoB tertiles, we used the SPSS general linear model. Fisher's least significant difference test was used to evaluate differences in PWV between the ApoB tertiles groups. ROC analyses – including areas under curves (AUC) – were generated to study the utility of ApoB and non-HDL cholesterol in order to detect subjects with ≥90th percentile adulthood PWV. There were no interactions between sex, cardiovascular risk factors and PWV, and the analyses were therefore performed with the sexes combined. A p value of <0.05 was considered statistically significant.

3. Results

The characteristics of the study subjects in 2001 and 2007 are shown in Table 1. PWV (unadjusted mean ± standard deviation) was 8.1 ± 1.5 m/s in the population of 1618 young adults with com-

Table 1
Clinical characteristics of study subjects.

	Characteristics in 2001	Characteristics in 2007
Number of subjects	1264	1618
Male subjects (%)	45.6	44.9
Age (years)	31.7 ± 5.0	37.4 ± 5.0
Smoking (%)	24.0	19.2
Body mass index (kg/m^2)	24.6 ± 4.0	25.6 ± 4.4
Systolic blood pressure (mmHg)	114.9 ± 12.0	119.7 ± 14.1
Apolipoprotein A-I (g/L)	1.5 ± 0.2	1.6 ± 0.3
Apolipoprotein B (g/L)	1.0 ± 0.2	1.0± 0.3
Total cholesterol (mmol/L)	5.1 ± 0.9	5.0 ± 0.9
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3
LDL cholesterol (mmol/L)	3.2 ± 0.8	3.1 ± 0.8
Triglycerides (mmol/L)	1.1 (0.8–1.5)	1.1 (0.9–1.6)
C-reactive protein (mg/L)	0.8 (0.3–1.7)	0.9 (0.4–1.7)
Insulin (mU/L)	6.3 (4.3–9.0)	6.4 (4.2–10.2)
Fasting glucose (mmol/L)	5.0 ± 0.5	5.3 ± 0.5

Values are presented as unadjusted mean ± standard deviation or geometric mean (25th–75th percentiles) or percentage of subjects. Smoking was defined as smoking on daily basis.

Table 2
Univariate relations between risk factors and PWV.

	Risk variables measured in 2001 and PWV in 2007		Risk variables and PWV measured in 2007	
	β (SE)	p	β (SE)	p
ApoA-I (g/L)	−0.259 (0.112)	0.022	−0.166 (0.099)	0.094
ApoB (g/L)	0.969 (0.110)	<0.001	1.154 (0.093)	<0.001
ApoB/ApoA-1 ratio	1.069 (0.123)	<0.001	1.285 (0.115)	<0.001
HDL cholesterol (mmol/L)	−0.414 (0.090)	<0.001	−0.385 (0.076)	<0.001
LDL cholesterol (mmol/L)	0.195 (0.033)	<0.001	0.241 (0.030)	<0.001
Non-HDL cholesterol (mmol/L)	0.213 (0.030)	<0.001	0.274 (0.026)	<0.001
LDL/HDL ratio	0.185 (0.024)	<0.001	0.235 (0.024)	<0.001
Triglycerides (mmol/L)	0.896 (0.143)	<0.001	1.291 (0.119)	<0.001
Systolic blood pressure (mmHg)	0.031 (0.002)	<0.001	0.032 (0.002)	<0.001
Body mass index (kg/m2)	0.040 (0.007)	<0.001	0.039 (0.005)	<0.001
Insulin (mU/L)	0.486 (0.122)	<0.001	0.520 (0.075)	<0.001
Fasting glucose (mmol/L)	0.520 (0.064)	<0.001	0.521 (0.048)	<0.001
C-reactive protein (mg/L)	0.070 (0.053)	0.187	0.207 (0.052)	<0.001
Smoking	−0.025 (0.065)	0.696	−0.082 (0.062)	0.186

Heart rate-specific z-scores were used for PWV. PWV, pulse wave velocity; β, regression coefficient; SE, standard error; Apo, apolipoprotein.

plete data on cardiovascular risk variables in 2007, as well as in the sub-group with cardiovascular risk factor data available in 2001 (n = 1264).

In the univariate regression analysis, all risk factors measured in 2007, except for ApoA-1 and smoking, were associated with PWV (p < 0.001 for all) (Table 2). Similar results were observed between risk factors measured in 2001 and PWV assessed in 2007, with the exception that ApoA-1 was inversely associated with PWV (p = 0.022) and CRP was not associated with PWV. In the multivariable analyses, ApoB (2001: p = 0.005; 2007: p = 0.003), the ApoB/ApoA-1 ratio (2001: p = 0.002; 2007: p = 0.004) and the LDL/HDL ratio (2001: p = 0.012; 2007: p = 0.008) were associated with PWV independently of other risk factors (Table 3). In addition, triglycerides and non-HDL cholesterol measured in 2007 were directly associated with PWV (p = 0.004 and 0.025, respectively). The non-lipid risk factors independently related with PWV were sex (p < 0.001), age (p < 0.001), fasting insulin (p < 0.006), systolic blood pressure (p < 0.001) and fasting glucose (only in 2007, p = 0.041). A graphic evaluation supported a linear association between ApoB measured in 2001 and PWV assessed in 2007 (Fig. 1A), as well as between ApoB and PWV measured in 2007 (Fig. 1B).

Table 3
Multivariable relations between risk factors and PWV.

	Risk variables measured in 2001 and PWV in 2007		Risk variables and PWV measured in 2007	
	β (SE)	p	β (SE)	p
ApoA-1[a] (g/L)	−0.110 (0.106)	0.301	0.034 (0.090)	0.704
ApoB[a] (g/L)	0.310 (0.111)	0.005	0.292 (0.098)	0.003
Sex	0.374 (0.059)	<0.001	0.323 (0.050)	<0.001
Insulin (mU/L)	0.385 (0.130)	0.003	0.229 (0.082)	0.005
Fasting glucose (mmol/L)	0.005 (0.065)	0.943	0.099 (0.048)	0.041
Age (years)	0.053 (0.005)	<0.001	0.045 (0.004)	<0.001
Body mass index (kg/m^2)	−0.013 (0.007)	0.090	−0.011 (0.006)	0.079
C-reactive protein (mg/L)			0.094 (0.049)	0.058
Systolic blood pressure (mmHg)	0.024 (0.002)	<0.001	0.024 (0.002)	<0.001

Heart rate-specific z-scores were used for PWV.

[a] When ApoA-1 and ApoB were replaced with their ratio, or with HDL and LDL cholesterol, the LDL/HDL ratio, the non-HDL cholesterol, or triglycerides, an independent association was found between the 2001 ApoB/ApoA-1 ratio (β [SE] = 0.397 [0.128], p = 0.002), the 2001 LDL/HDL ratio (0.061 [0.024], p = 0.012), the 2007 ApoB/ApoA-1 ratio (0.353 [0.123], p = 0.004), the 2007 LDL/HDL ratio (0.064 [0.024], p = 0.008), the 2007 triglycerides (0.369 [0.128], p = 0.004), the 2007 non-HDL cholesterol (0.057 [0.025], p = 0.025), and PWV assessed in 2007. Abbreviations as in Table 2.

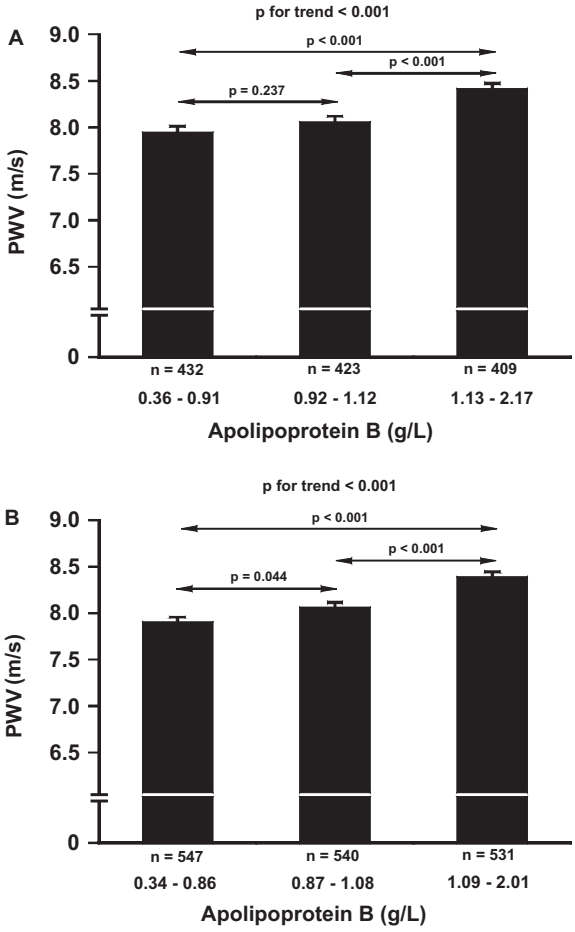

Fig. 1. (A) Heart rate-, age- and sex-adjusted PWV means and standard errors (measured in 2007) across apolipoprotein B tertiles measured in 2001 (n = 1264, subjects aged 24–39 years). (B) Heart rate-, age- and sex-adjusted PWV means and standard errors (measured in 2007) across apolipoprotein B tertiles measured in 2007 (n = 1618, subjects aged 30–45 years). PWV, pulse wave velocity.

The AUC for ApoB (measured in 2001) was higher than for non-HDL cholesterol in predicting ≥90th percentile PWV when the model additionally included only heart rate (0.673 vs. 0.654, respectively, p = 0.008), but this difference was diluted after adding age and sex in the model (p = 0.10) (data not shown). The AUC for ApoB (measured in 2007) was higher than for non-HDL cholesterol in detecting PWV ≥ 90th percentile when heart rate, age and sex were included in the model (0.756 vs. 0.749, respectively, p = 0.025), but after adding all non-lipid factors independently associating with PWV in the model, this difference was diluted (p = 0.067) (data not shown).

4. Discussion

In this cohort of apparently healthy young Finnish adults, we found three main results. Firstly, the present study showed that ApoB was independently associated with PWV. Secondly, ApoB in young adulthood was an independent predictor of PWV measured 6

years later. Thirdly, findings of the present study suggest that ApoB is not superior to non-HDL cholesterol in detecting subjects with increased PWV.

PWV is widely used as a non-invasive modality for evaluating vascular health, and it has been shown to relate to several cardiovascular risk factors [7–9], but previous data on the association of LDL and HDL cholesterol with PWV is, to a degree, controversial [8–10]. A recently published systematic review of the independent association of carotid-femoral PWV with cardiovascular risk factors found a significant association between HDL cholesterol and PWV only in 4 (11%) out of 37 studies, and between LDL cholesterol and PWV only in 1 (5%) out of 21 studies [9]. In line with most previous reports [7,9], HDL or LDL cholesterol were also not associated with PWV in the present study. Furthermore, HDL and LDL cholesterol measured in 2001 were not related to PWV measured 6 years later. Interestingly, the LDL/HDL ratio was an independent determinant, as well as independent predictor, of PWV, which, to our knowledge, is novel information. Moreover, as also previously shown in young [7] and middle-aged adults [21], triglycerides were independently associated with PWV. However, triglycerides measured in 2001 did not predict PWV as assessed 6 years later. Secular trends of lipid and non-lipid risk factors in the present study were as expected, and these trends have been discussed in detail previously [18].

Previously, a limited number of studies have addressed the relation between ApoB and arterial PWV. In relatively small study populations, using multiple linear regression models, an independent positive association has been found between ApoB and PWV in patients treated for cardiovascular risk factors ($n = 247$) [11], and between ApoB and local ultrasonographically determined carotid arterial stiffness measured by Young's modulus ($n = 51$) [12]. Moreover, in women but not in men, ApoB has been shown to correlate negatively with arterial compliance (univariate correlation, $n = 223$) [22]. In line with these reports, our findings clearly suggest a direct association of ApoB and the ApoB/ApoA-1 ratio with PWV in a population of 1618 apparently healthy young adults. In addition, ApoB and the ApoB/ApoA-1 ratio were found to predict PWV assessed 6 years later. Furthermore, in the present analysis, ApoA-1 was not related to PWV, as also shown previously in a population of 429 healthy middle-aged women [23]. Taken together, the current findings suggest that ApoB is associated with arterial stiffness in young adults, and that ApoB may be a better dyslipidemia risk marker of increased arterial stiffness than LDL cholesterol. Potential explanatory factors and pathophysiological bases behind the superiority of ApoB have been discussed in detail elsewhere [24,25]. In brief, ApoB levels reflect the total number of atherogenic particles (very low-density lipoprotein [VLDL], VLDL remnants, LDL, lipoprotein [a]), and therefore ApoB dosage is more representative of the atherogenic burden than each of these fractions [25–27], especially in subjects with elevated triglycerides [24].

Whether non-HDL cholesterol, a content of the cholesterol in atherogenic ApoB-containing lipoproteins, could be used as a surrogate measure for ApoB in predicting cardiovascular risk is a widely debated question [27–32]. Nevertheless, to the best of our knowledge, data comparing the utility of non-HDL cholesterol and ApoB in detecting increased arterial stiffness is lacking. Moreover, relationship between non-HDL cholesterol and arterial stiffness has not been extensively studied. In the present study, non-HDL cholesterol was cross-sectionally associated with arterial stiffness, a finding which is in consistent with earlier reports in renal failure patients [33] and older women [22]. Although non-HDL cholesterol measured in 2001 was not an independent predictor of PWV assessed 6 years later, the ROC analysis demonstrated that there were no differences between non-HDL cholesterol and ApoB in identifying increased PWV. Thus, our findings suggest that ApoB is not superior to non-HDL cholesterol in detecting increased arterial stiffness in young adults.

ICGWB is not widely used method to measure PWV, apparently limiting comparability of the present findings with the observations from other cohorts. However, PWV measured between the aortic arch and popliteal artery using the ICGWB has shown to be well in agreement with the Doppler ultrasound method [19]. Moreover, ICGWB provides handy and reliable means of evaluating arterial stiffness on the basis of PWV in large-scale epidemiologic studies, since the method is inexpensive, fast, operator independent and highly repeatable and reproducible [19]. Another potential limitation in the present study was the different sample size of the two populations. In addition, the study cohort was ethnically homogenous, limiting the generalizability of our results to white European subjects. The strengths of the present study include the use of a large population-based cohort of apparently healthy young adults with a very low prevalence of potentially confounding morbidities and medications.

In conclusion, the present study suggests that elevation of ApoB or non-HDL cholesterol is associated with increased arterial stiffness in young adults. It is interesting and valid to note that the six years of dyslipidemia may influence the arterial stiffening in young adults, and therefore the current findings reinforce the focus on primary prevention and the possibility of modulating the arterial aging process.

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References

[1] Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[2] Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet 2001;358:2026–33.
[3] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 2004;364:937–52.
[4] Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec cardiovascular study. Circulation 1996;94:273–8.
[5] Sniderman AD, Furberg CD, Keech A, et al. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. Lancet 2003;361:777–80.
[6] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–27.
[7] Aatola H, Hutri-Kähönen N, Juonala M, et al. Lifetime risk factors and arterial pulse wave velocity in adulthood, The Cardiovascular Risk in Young Finns Study. Hypertension 2010;55:806–11.
[8] Benetos A, Waeber B, Izzo J, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. Am J Hypertens 2002;15:1101–8.
[9] Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 2009;54:1328–36.
[10] Li S, Chen W, Srinivasan SR, Berenson GS. Childhood blood pressure as a predictor of arterial stiffness in young adults: the Bogalusa heart study. Hypertension 2004;43:541–6.
[11] Amar J, Ruidavets JB, Chamontin B, Drouet L, Ferrières J. Arterial stiffness and cardiovascular risk factors in a population-based study. J Hypertens 2001;19:381–7.

[12] Schmidt-Trucksäss AS, Grathwohl D, Frey I, et al. Relation of leisure-time physical activity to structural and functional arterial properties of the common carotid artery in male subjects. Atherosclerosis 1999;145:107–14.
[13] Åkerblom HK, Viikari J, Uhari M, et al. Atherosclerosis precursors in Finnish children and adolescents. I. General description of the cross-sectional study of 1980, and an account of the children's and families' state of health. Acta Paediatr Scand, Suppl 1985;318:49–63.
[14] Juonala M, Viikari JS, Kähönen M, et al. Childhood levels of serum apolipoproteins B and A-I predict carotid intima-media thickness and brachial endothelial function in adulthood: the cardiovascular risk in young Finns study. J Am Coll Cardiol 2008;52:293–9.
[15] Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood: the Cardiovascular Risk in Young Finns Study. Circulation 2005;112:1486–93.
[16] Juonala M, Viikari JS, Hutri-Kähönen N, et al. The 21-year follow-up of the Cardiovascular Risk in Young Finns Study: risk factor levels, secular trends and east-west difference. J Intern Med 2004;255:457–68.
[17] Juonala M, Viikari JS, Rönnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2006;26:1883–8.
[18] Raiko JR, Viikari JS, Ilmanen A, et al. Follow-ups of the cardiovascular risk in Young Finns Study in 2001 and 2007: levels and 6-year changes in risk factors. J Intern Med 2010;267:370–84.
[19] Kööbi T, Kähönen M, Iivainen T, Turjanmaa V. Simultaneous non-invasive assessment of arterial stiffness and haemodynamics—a validation study. Clin Physiol Funct Imaging 2003;23:31–6.
[20] Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. Hypertension 2002;39: 1083–7.
[21] Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004;43:1239–45.
[22] Le NA, Brown WV, Davis WW, et al. Comparison of the relation of triglyceride-rich lipoproteins and muscular artery compliance in healthy women versus healthy men. Am J Cardiol 2005;95:1049–54.
[23] Taquet A, Bonithon-Kopp C, Simon A, et al. Relations of cardiovascular risk factors to aortic pulse wave velocity in asymptomatic middle-aged women. Eur J Epidemiol 1993;9:298–306.
[24] Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein AI and apolipoprotein B plasma levels. J Intern Med 2006;259:437–46.
[25] Sniderman AD, Scantlebury T, Cianflone K. Hypertriglyceridemic hyperapob: the unappreciated atherogenic dyslipoproteinemia in type 2 diabetes mellitus. Ann Intern Med 2001;135:447–59.
[26] Rasouli M, Kiasari AM, Mokhberi V. The ratio of apoB/apoAI, apoB and lipoprotein(a) are the best predictors of stable coronary artery disease. Clin Chem Lab Med 2006;44:1015–21.
[27] Simon A, Chironi G, Gariepy J, Del Pino M, Levenson J. Differences between markers of atherogenic lipoproteins in predicting high cardiovascular risk and subclinical atherosclerosis in asymptomatic men. Atherosclerosis 2005;179:339–44.
[28] Schulze MB, Shai I, Manson JE, et al. Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. Diabetologia 2004;47:2129–36.
[29] Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation 2008;117:3002–9.
[30] Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. Circulation 2005;112:3375–83.
[31] Chan DC, Watts GF. Apolipoproteins as markers and managers of coronary risk. QJM 2006;99:277–87.
[32] Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
[33] Shinohara K, Shoji T, Tsujimoto Y, et al. Arterial stiffness in predialysis patients with uremia. Kidney Int 2004;65:936–43.