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The Cardiovascular Risk in Young Finns Study

Lauri Vähämurto

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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University of Turku

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To my family

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ABSTRACT

Background: Since the 1940's, coronary heart disease (CHD) has been recognized as a major cause of death in the developed countries. Men born in eastern Finland were found to have internationally high CHD mortality in the late 1960's. As a result, the "North Karelia Project" was launched, aiming to decrease CHD risk factors especially in the high risk areas. Since then, CHD mortality rates have decreased significantly in Finland with over two thirds of the decline explained by favourable changes in modifiable risk factors. Despite the overall reduction, regional differences in the rates are still seen. Although regularly studied, the current regional differences in Finland in CHD risk factors and surrogate markers subclinical atherosclerosis are thoroughly investigated.

Aims: This thesis aimed to investigate current and 31-year longitudinal CHD risk factors between eastern and western Finns, to examine east-west differences in subclinical atherosclerosis measured by carotid intima-media thickness (IMT) and in cardiac left ventricular (LV) structure and function, to explore CHD risk factors, carotid IMT and left ventricular structure and function between urban and rural Finns, and to study the association of migration with CHD risk factors and carotid IMT.

Participants and methods: This thesis uses data from the Cardiovascular Risk in Young Finns Study which is a prospective multicentre cohort launched in 1980. CHD risk factors have been measured from the participants repeatedly since the baseline study. Carotid IMT was first measured in 2001 from the participants and echocardiography was included in 2011, when over 57% of the original study population participated in the latest follow-up study at the age of 34–49.

Results: In 2011 CHD risk factor profile between participants with eastern or western baseline origin was essentially similar. However, eastern participants have excessive risk in longitudinal risk factor analyses and they have higher carotid IMT, LV mass and worse LV diastolic function than western participants. Participants with urban baseline origin have lower CHD risk factor levels and LVM compared to rural participants. Participants who migrated from east-to-west or rural-to-urban have currently lower CHD risk factor levels and carotid IMT compared to participants who stayed in east/rural areas, respectively.

Conclusions: Differences between eastern and western Finns in CHD risk factor levels are levelling off but can still be found in carotid IMT, LV mass and diastolic function, and in longitudinal CHD risk factor analyses. Urban Finns have lower CHD risk factor levels compared to rural Finns. Migration from areas characterised by higher CHD risk factor levels is associated with improvements in cardiovascular health.

KEYWORDS: Atherosclerosis, geographic differences, coronary heart disease, carotid intima-media-thickness, left ventricular mass

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kardiologia ja kardiovaskulaarilääketiede
LAURI VÄHÄMURTO: Maantieteelliset erot sepelvaltimotaudin riskiprofiilissa – Lasten Sepelvaltimotaudin Riskitekijät (LASERI) -tutkimus
Väitöskirja, 124 s.
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TIIVISTELMÄ

Tausta: Sepelvaltimotauti on maailman johtavia kuolinsyitä ja siihen alettiin kiinnittää huomiota länsimaissa 1940-luvulla. 1960-luvulla tutkijat osoittivat, että itäsuomalaisilla miehillä on kansainvälisesti verrattuna korkea sepelvaltimotautikuolleisuus. Tähän reagoitiin aloittamalla Pohjois-Karjala-projekti, joka pyrki alentamaan sepelvaltimotaudin riskitekijöitä erityisesti korkeimman riskin alueilla. Sepelvaltimotautikuolleisuus laski Suomessa 1972–2012 yli 80 %. Yli kaksi kolmasosaa tästä laskusta on selitettävissä muutoksilla riskitekijöissä. Tämänhetkisiä maantieteellisiä eroja sepelvaltimotaudin riskitekijöissä ja varhaisissa valtimomuutoksissa ei täysin tiedetä, vaikka aihetta on Suomessa tutkittu säännöllisesti.

Tavoitteet: Tämän väitöskirjatutkimuksen tavoitteena oli itä- ja länsisuomalaisten välinen vertailu sepelvaltimotaudin riskitekijöissä nykyisin ja 31-vuotisen seurannan aikana. Lisäksi työssä tutkittiin itä- ja länsisuomalaisten eroja kaulavaltimon intima-media-kerroksen paksuudessa (IMT) sekä sydämen vasemman kammion rakenteessa ja toiminnassa. Tutkimuksen kohteena oli myös selvittää kaupungissa ja maaseudulla asuvien eroja sepelvaltimotaudin riskitekijöissä ja varhaisissa valtimoiden ja sydämen muutoksissa.

Aineisto ja menetelmät: Tämän tutkimuksen aineisto on LASERI (Lasten Sepelvaltimotaudin Riskitekijät) -tutkimuksesta, joka on vuonna 1980 aloitettu prospektiivinen monikeskustutkimus. Sepelvaltimotaudin riskitekijöitä on mitattu osallistujilta säännöllisesti, heidän kaulavaltimon IMT on tutkittu ensimmäisen kerran vuoden 2001 ja sydämen ultraäänikuvaus toteutettu vuoden 2011 seurantatutkimuksessa.

Tulokset: Vuonna 2011 sepelvaltimotaudin riskitekijöissä ei itä- ja länsisuomalaisten välillä ollut eroja. Itä-Suomessa lapsuudessa asuneilla havaittiin korkeammat riskitekijätasot 31 vuoden pitkittäisanalyyseissä ja aikuisuudessa suurempi kaulavaltimon IMT, sydämen vasemman kammion massa sekä heikompi diastolinen toiminta kuin länsisuomalaisilla. Kaupungissa kasvaneilla todettiin alhaisemmat sepelvaltimotaudin riskitekijätasot ja sydämen vasemman kammion massa kuin maaseudulla lapsuutensa asuneilla. Itä-Suomesta Länsi-Suomeen tai kaupungista maaseudulle muuttaneilla sepelvaltimotaudin riskitekijätasot ja kaulavaltimon IMT olivat alhaisemmat kuin heillä, jotka asuivat jatkuvasti Itä-Suomessa tai maaseudulla.

Johtopäätökset: Itä- ja länsisuomalaisten väliset erot sepelvaltimotaudin riskitekijöissä ovat tasaantumassa. Eroja on yhä nähtävissä riskitekijöiden pitkän ajan kertymässä sekä varhaisissa valtimo- ja sydänmuutoksissa. Kaupunkilaisilla on matalammat sepelvaltimotaudin riskitekijätasot kuin maaseudulla asuvilla. Matalamman sepelvaltimotaudin riskitekijätason alueelle muuttajilla havaittiin matalammat riskitekijätasot kuin heillä jotka jäivät korkeamman riskin alueelle.

AVAINSANAT: ateroskleroosi, maantieteelliset erot, sepelvaltimotauti, sisemmän kaulavaltimon paksuus, vasemman kammion massa

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Abbreviations

ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
BMI	body mass index
CHD	coronary heart disease
CV	cardiovascular
CVD	cardiovascular disease
DBP	diastolic blood pressure
HDL	high-density lipoprotein
IMT	intima-media thickness
LDL	low-density lipoprotein
LV	left ventricular
LVM	left ventricular mass
SD	standard deviation
SE	standard error
SBP	systolic blood pressure
SES	socioeconomic status
YFS	Young Finns Study, Cardiovascular Risk in Young Finns Study

List of Original Publications

This thesis is based on the following original publications, referred to by Roman numerals I–IV. Additionally, unpublished data are also presented.

I Vähämurto L, Pahkala K, Magnussen CG, Mikkilä V, Hutri-Kähönen N, Kähönen M, Laitinen T, Taittonen L, Tossavainen P, Lehtimäki T, Jokinen E, Telama R, Rönnemaa T, Viikari J, Juonala M, Raitakari O. East-west differences and migration in Finland. Association with cardiometablic risk markers and IMT. The Cardiovascular Risk in Young Finns Study. *Scand J Public Health* 2016;44:402–10.

II Vähämurto L, Juonala M, Ruohonen S, Hutri-Kähönen N, Kähönen M, Laitinen T, Tossavainen P, Jokinen E, Viikari J, Raitakari OT, Pahkala K: Geographic origin as a determinant of left ventricular mass and diastolic function – the Cardiovascular Risk in Young Finns Study. *Scand J Public Health* 2018;46:630–637.

III Vähämurto L, Pahkala K, Magnussen CG, Hutri-Kähönen N, Kähönen M, Laitinen T, Taittonen L, Tossavainen P, Lehtimäki T, Jokinen E, Telama R, Rönnemaa T, Viikari J, Juonala M, Raitakari OT: Coronary heart disease risk factor levels in eastern and western Finland from 1980 to 2011 in the Cardiovascular Risk in Young Finns Study. *Atherosclerosis* 2018;280:92–98

IV Nuotio J, Vähämurto L Pahkala K, Magnussen CG, Hutri-Kähönen N, Kähönen M, Laitinen T, Taittonen L, Tossavainen P, Lehtimäki T, Jokinen E, Viikari JSA, Raitakari O, Juonala M: CVD risk factors and surrogate markers – Urban-rural differences. *Scand J Public Health.* 2019 Aug 29:1403494819869816 [Epub ahead of print]

1 Introduction

Since the 1940's, coronary heart disease (CHD) has been recognized as a major cause of death in the developed countries. The Seven Countries Study investigated the international CHD mortality in the 1960's and found high CHD mortality in Finland compared to other countries (1), in particular among men born in eastern Finland.

The geographical difference in CHD mortality in Finland, namely excess risk in eastern Finns compared with western Finns was considered a consequence of higher CHD risk factors, mainly hypercholesterolemia, hypertension, and smoking. To tackle the observed east-west difference and overall high CHD mortality in Finland, a national program called the North Karelia project was launched in the 1970s aiming to affect health behaviour and decrease CHD risk factor levels and morbidity, especially in eastern Finland (2).

Following the launch of North Karelia Project, age-adjusted CHD mortality in working-age men decreased by 82% and among working-age women by 84% in eastern Finland between 1972 and 2012 (3). The decrease in serum total cholesterol in men, and the decrease in systolic blood pressure (SBP) and serum total cholesterol in women, explained most of the decline in CHD mortality (3). CHD mortality also decreased in western Finland, but not as dramatically as was observed in eastern Finland. Currently, both men and women residing in eastern Finland have about 20% higher CHD mortality compared to those residing in western Finland (National Institute for Health and Welfare; 2016).

In addition to geographical east-west differences in CHD risk factors and mortality in Finland, disparity between urban and rural regions in cardiovascular diseases (CVD) risk factors and mortality has been confirmed worldwide (4–6). In Finland, elevated serum cholesterol levels and obesity are suggested to be more pronounced in elderly citizens living in rural than in urban communities (7). CHD mortality differences between urban and rural Finns are currently unknown.

The Cardiovascular Risk in Young Finns Study (YFS) is a national, longitudinal multicentre study of Finnish children and adolescents that was launched in 1980 to examine precursors of atherosclerosis (8). Studying the differences in CHD risk factors between eastern and western Finland and in urban vs. rural Finland was one

of the key purposes since the design of the study. The YFS participants residing in eastern Finland in childhood have been shown to have higher childhood total cholesterol concentrations (9). As adults eastern participants have been shown to have higher blood pressure, total cholesterol (10) as well as higher carotid IMT and lower brachial flow-mediated dilatation, both markers of subclinical atherosclerosis(11), compared to those residing in western Finland in childhood. However, longitudinal differences from childhood to adulthood in CHD risk factors between eastern and western have not been investigated. Moreover, current differences in carotid IMT, and cardiac left ventricular (LV) structure and function between eastern and western Finns are not known. Urban-rural differences in CHD risk factors, carotid IMT and LV structure and function are also unknown in Finland and have not been extensively explored in other populations either. Moreover, the association of east-west migration as well as urban-rural migration with CHD risk factors and carotid IMT is unknown.

2 Review of the Literature

2.1 Cardiovascular diseases (CVDs) and coronary heart disease (CHD) as an international public health problem with special reference to Finland

Since the improvements in hygiene, immunization, infrastructure and introduction of antibiotics, the average life expectancy in the western world increased significantly in the 19th and early 20th century. Due to changes in lifestyle and increased life expectancy, CVDs, including hypertension, CHD, myocardial infarction and stroke became a health concern. By the 1940's, half of the deaths in the United States were CVD-related (12). The threat posed by the CVDs caught attention in the early 1940's when the president of the United States, Mr Theodor Roosevelt, was diagnosed with hypertension and heart failure, and later in 1945 died prematurely of hypertension induced cerebral haemorrhage (13). In 1948, one of the first long-term epidemiologic studies investigating the causes of CVDs and especially CHD was launched in Framingham, Massachusetts (United States) (13). The baseline survey in 1948-1952 included over 5,000 participants aged 28 to 62 years, 55% of which women. The first major results were presented in 1957 declaring hypertension as a risk factor for CHD (14).

Following the Framingham Heart Study, several large studies on CHD were launched. The first multinational study on CHD, the Seven Countries Study, was conducted in 1957 (1). The study includes cohorts from the United States, Finland, Netherlands, Italy, Yugoslavia, Greece, and Japan with a total of 12,763 male participants, 40 to 59 years of age. At the baseline survey, the lowest CHD mortality rate was found in Japan and in southern European cohorts whereas the highest rate was found in Finland, particularly in eastern Finland (1). In the 15-year follow-up study, similar trends were still found (15).

In 1974,researchers found that age-adjusted CHD mortality in the United States had been declining since the 1960's (16). In 1978, the first Bethesda Conference concluded that CHD mortality had started declining in the United States. However, the causes behind the decline were somewhat unclear. Beneficial changes in diet, smoking habits, and other CHD risk factors, as well as improvements in medical care

were all considered as contributors. Following the Bethesda Conference, several population-based studies in different countries were started in the 1980's, including the Atherosclerosis Risk in Communities Study (ARIC) (17), the Princeton Study (18,19), the Muscatine Study (20), the Bogalusa Heart Study (21) and the YFS (22). An international study called the MONICA (monitoring trends and determinants in cardiovascular disease) was designed by the World Health Organization to monitor CHD mortality and events (23). During the 10-year follow-up of the MONICA study, the highest total CHD mortality rate among men was found in eastern Finland and among women in Glasgow, United Kingdom, whereas the lowest rates in men were found in Beijing, China, and in women in Catalonia, Spain (24). The greatest decline in coronary event rates among men during 10 years was found in North Karelia, Finland (1983-1992 in Finnish cohorts).

After a significant decrease in the CHD mortality in the developed countries in the 1970's, the decline started deceleration in countries such as the United States and Australia (25) (26). In eastern Europe countries like Poland and Hungary, CHD mortality increased until 1990's and first then started declining (27). Since the collapse of Soviet Union, the age-adjusted CHD mortality rates increased in Russia and between 1992-1994 the life expectancy at birth dropped by 6.1 years for men and by 3.3 years for women (28,29).

Overall, CHD mortality rates decreased over 40% from 1980 to 2000 in the United States (30). Declining CHD risk factors accounted for approximately 44% of this mortality decrease, including reductions in total cholesterol concentration (24%), systolic blood pressure (SBP) (20%), smoking prevalence (12%), and physical inactivity (5%). The reductions in risk factors were, however, partially diluted by increasing body mass index (BMI) and prevalence of diabetes. Simultaneously, from 1985-1989 to 2000-2004, the age-specific CHD mortality in the European Union fell by a third in men and by over a quarter in women (31). In Sweden, the age-specific CHD mortality rates decreased by over 50% from 1986 to 2002, and 55% of the falling-off in CHD mortality was projected to derive from declining CHD risk factor levels (32). In the Seven Countries study, the 40-year results showed that CHD annual conditional risk of death had declined in the United States, Finnish, Dutch and Japanese cohorts, moderately increased in Italy and exponentially increased in cohorts of Serbia and Greece (33).

In the developing countries, the epidemic of CVDs, such as CHD, hypertension and stroke, has mounted first in the most recent decades. In China, CHD mortality among men amplified by 50% between 1984 and 1999. It has been estimated that about 75% of this increase has been contributed by the increase in total cholesterol concentration (34). A profound report from the Global Burden of Disease study concluded that premature morbidity due to CHD and other CVDs increased over the past 20 years most rapidly in East, South, and Southeast Asia, and parts of Latin

America, although the prevalence is still low in these parts of the world when compared to the developed countries (35) (36). According to the same report, the probability of premature death (age 30-70) attributable to CVD was the highest for men in Eastern Europe and for women in Oceania, and the lowest for both sexes in the high-income Asia-Pacific region. Globally, CHD is nowadays the leading cause of death (37). The prevalence of CHD and other CVDs is predicted to surge in the future in the developing countries (38).

Finally, the new millennium has witnessed the stagnation of decades-long decrease in CHD mortality in the United States. This phenomenon is evident especially in the younger population (39) and is largely due to emerging obesity and type 2 diabetes. Also, the racial and geographical variation in CHD mortality has become an alarming problem (40). A decline in CHD mortality in the developed countries is not inevitable in the future. In Finland, however, CHD mortality declined continuously between 1972 and 2012 altogether astonishingly 82% (from 643 to 118 per 100,000) among 35-64-year-old men and 84% (from 114 to 17 per 100,000) among 35-64-year-old women (3). According to the latest report from the National Institute for Health and Welfare, serum total cholesterol concentration is currently decreasing in Finland after a temporary increase between 2007 and 2012 (41).Increasing obesity among the working-aged and persistent hypertension are current obstacles in cardiovascular (CV) health (42).

2.2 Geographic differences in CVDs

2.2.1 Eastern and western Finland division

Finland can be divided into eastern and western parts with different borders according to the context (Figure 1). Finland became under the influence of Sweden in the 13th century and large parts of the country were under the Swedish monarchy until 1809, but recurring wars between Sweden and Russia moved the Swedish-Russian border within Finland several times. After the Nöteborg Peace Treaty in 1323, eastern parts of today's Finland were separated from western parts of Finland until the end of 16th century as western parts were part of Sweden and eastern parts were part of Russia. Until the 20th century, (south) western Finland was one of the most developed region in the country and had closest contact with Sweden. Northeastern Finland instead was less developed for centuries and has had close contacts to outside world mainly via Russia.

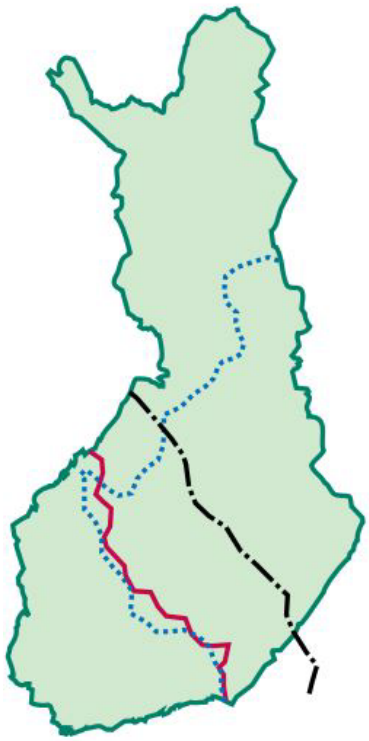


Figure 1. East-west- division in Finland. Continuous line is the anthropological line, dashed line is the Nöteborg Peace Treaty borderline, and dotted line is the dialect border line.

2.2.2 East-west- differences in CHD epidemiology in Finland

Increased CHD mortality in eastern Finland compared to western Finland was recognized before the Second World War (43). Especially eastern men were found to have higher CHD and overall mortality than western Finns. In the ground-breaking Seven Countries Study, a notorious reputation for having the highest CHD mortality was linked especially to eastern Finland (1). This excess of risk was explained by higher levels of CHD risk factors; middle-aged men in eastern Finland had higher blood pressure, serum total cholesterol levels and prevalence of smoking than those in southwestern Finland or in any other area included in the Seven Countries study.

In order to lower the CHD risk factors levels through dietary and other lifestyle changes, a pilot project, the North Karelia project was launched in 1972 (2). Between 1972 and 1982, age-adjusted CHD mortality rate in Finland fell over 40% (44). In the FINRISK study in 1982, eastern men still had a higher total cholesterol concentration and SBP, and eastern women higher SBP than the western counterparts (45). In the baseline study of YFS in 1980, eastern participants (aged 3-18 years) had higher total and low-density lipoprotein (LDL) cholesterol

concentrations than the western participants. From 1982 to 1987, CHD mortality in Finland fell over 50%, of which over half was estimated to be the consequence of a decline in CHD risk factor levels (46). During the same time period, CHD event risk was found to be 40% higher among men in eastern Finland than in western Finland and 40% of this excess of risk could be explained by higher rates of CHD risk factors (47).

In 2001, YFS participants with eastern baseline origin had a higher total and LDL cholesterol concentration, and SBP and DBP than those originating from western Finland (10). In the FINRISK study in 2007, eastern women had higher total cholesterol, SBP and BMI compared to western women whereas among men these risk factor levels appeared to be similar (48). Carotid artery intima-media-thickness (IMT) has also been found to be higher in eastern Finns compared to western Finns. Researchers have shown that carotid IMT correlates with CHD risk factors (49) (8) and associates with future CVD's (50). Among Finnish-born twins (men) living in Sweden, higher IMT was found in those originating from eastern Finland compared to those originating from western Finland (51). In a previous study of the YFS, participants originating from eastern Finland were shown to have higher carotid IMT than western participants in 2001 (11). Higher carotid IMT was also found in participants with eastern grandparents compared to participants with western grandparents, and in participants currently living in eastern Finland compared to participants currently living in western Finland. Similarly, flow-mediated dilation of brachial artery was lower in participants that originated from eastern Finland compared to participants with baseline origin in western Finland.

In 2012 the difference in CHD mortality between eastern and western Finns was less than 20% in both sexes (3). According to the most recent data from the National Institute for Health and Welfare, CHD mortality in 2016 among 35-84-year-old Finns was 21% higher in eastern men and 19% higher in eastern women than among western men/women, respectively (National Institute for Health and Welfare; 2016).

Besides the traditional risk factors such as blood pressure, serum total cholesterol and blood glucose levels and smoking, also other reasons have been suggested to explain differences in CHD mortality between eastern and western Finns. Eastern Finns are on average shorter than western Finns and it has been suggested that a 10 cm shorter height associates with a 19% increased CHD risk (52). Therefore, the height difference could partly explain the higher CHD risk found among eastern Finns. Other studies suggest, however, that there is no evident correlation of height and CHD risk (53,54). A Finnish study on socioeconomic status (SES) and CHD mortality found between 1959-1974 an excessive CHD mortality in east, especially in the group with lowest SES (landless participants) (2,19 times the risk of western participants with low SES) (55). Association of higher SES with lower CHD risk factor levels has been shown earlier in the YFS population (56). Higher SES is also

associated with lower CHD mortality (57) and CVD prevalence (58). These findings suggest that east-west- differences in CHD mortality in Finland could associate with east-west differences in SES.

Genetic differences between eastern and western Finns are relatively large, even larger than between some nations in Europe and it has been suggested that Finland was settled from two directions (59). Finnish maternal mitochondrial DNA is essentially similar to other European populations (60) (61), while paternal DNA from Y-chromosome shows two distinct lines; one western European and one deriving from east (59) (62). Finnish Y-chromosomes also have less haplotypes (less variation) than other European populations. This indicates that Finnish gene population has undergone several bottle neck -occasions and genetic drifting.

Family history of CHD and several genetic markers have been acknowledged to associate with CHD risk (63,64). Nevertheless, the role of hereditary factors is unclear in the prediction of CHD (65). In Finland, previous studies emphasize the role of birthplace or early life environment on CHD risk. In the coronary arteries of newborns thicker inner vascular layers were found in eastern Finland compared to western newborns (66), which could indicate either for the role of differences in genetics or pre-birth conditions between eastern and western Finns. In the Helsinki Sudden Death Study, men under 54 years of age residing in the west but born in the east had higher risk for sudden cardiac death than western-born men (67). Previous studies have shown that the parental history of premature CHD is an independent risk factor for myocardial infarction and explains part of the disease's risk difference between eastern and western Finland (68) (63). The differences in genetic factors cannot, however, explain the major decrease in CHD mortality difference between eastern and western Finland as the genetic differences in a population cannot vanish in just decades. Finally, CHD mortality in Sweden is similar or lower than that in southwestern Finland (69), while in the Karelian Republic of Russia, CHD mortality is similar to or higher than that in eastern Finland (70). However, population of the Karelian Republic nowadays originates from many parts of the former Soviet Union. The findings of CHD mortality differences on both sides of the borders can support both environmental and/or genetic factors in explaining the CHD mortality differences between eastern and western Finland.

2.2.3 Urban-rural differences in CHD and other CVDs in Finland and worldwide

The disparity in CVD mortality and risk factor levels between urban and rural regions was first recognized in the United States in the early 1970's (71). The increasing geographic, especially urban-rural, differences in CV health became one of the major concerns in the United States in the 2000's as improvements in overall

CV health started slowing down (Gillum et al., 2012). Nowadays urban-rural disparities in CV health have been confirmed worldwide. Results from the Prospective Urban Rural Study have shown that the rates of major CVDs, namely CV-related deaths, nonfatal stroke, myocardial infarction, and heart failure were higher in rural areas than in urban communities in middle-income and low-income countries even though the CHD risk factor levels, e.g. INTERHEART Risk Score, were higher in urban communities than in rural settings (6). However, in high-income countries no urban-rural differences were observed in the rates of major CVDs (6).

In a recent study in Iceland, CVD mortality and risk factor levels were found to be higher in the rural areas than in the urban communities (72). In a Chinese population, urban citizens living in Hong Kong and Australia were found to have higher carotid IMT's than Chinese living rural areas (5). These results are, however, not directly comparable to a high income Western country such as Finland where rural lifestyle has become increasingly sedentary. Finally, earlier results from a Finnish study suggest that elevated serum cholesterol levels and obesity are more prevalent in elderly citizens living in rural communities compared to individuals living in urban areas (7). The urban-rural differences among working-age population in CHD risk factor levels, carotid IMT and LV structure and function are unknown in Finland and have not been extensively explored in other populations either.

The themes urban-rural and eastern-western are closely linked in the Finnish population. The largest cities in Finland (Helsinki Metropolitan area, Tampere and Turku) are considered western according to YFS and previous studies as these areas have had close connections to west and especially to Sweden during the history. The massive migration since the 1950's from rural to urban areas can mostly be described as migration from east to west, most specifically to the Helsinki Metropolitan area.

2.2.4 Migration in Finland and association with CVDs

Migration within and emigration from Finland has been considerable during the last 100 years. More than one million Finns have moved abroad, of which almost 500,000 before and over 700,000 after Second World War. The majority of the emigration was directed to North America before and to Sweden after the war. The emigration was mainly motivated by seeking for better work and higher standards of living. After Since the 1980s, emigration due to the economic reasons has decreased noticeably as the Finnish economy has become more robust (73).

In the Second World War Finland lost most of the Karelian Province to the Soviet Union and following 400 000 Finnish Karelians were migrated all over other parts of Finland. Since then, migration within Finland has mostly been driven by employment-seeking. At first, migration targeted regional centres where industry

needed labour. In the last decades, the migration has shifted towards few cities and regions characterized by the presence of universities and mostly located in western Finland (74). Between 1970 and 2014, only six provinces in Finland have been net-winners of the migration and Uusimaa-province with the Helsinki Metropolitan -area has gained over two thirds of the surplus. Current migraters in Finland are characterized by high education and this has increased the regional differences concerning income and employment rate.

The association of migration with regional and individual health and CV health in particular, has not been studied to a large extent in Finland. Studies from other countries have examples of migration having either positive or negative association with individual's CV health (75)(76).

2.3 Atherosclerosis as an etiologic factor for CVDs

Atherosclerosis is the most common underlying cause of CHD, carotid artery disease, and peripheral arterial disease. CVDs with atherosclerotic are the leading causes of death in developing and developed countries (37). Although these disease manifestations occur in middle age or later in life, the vascular atherosclerosis leading to these diseases begins often in early life and remains asymptomatic for decades. Young male soldiers were shown to have high prevalence of coronary atherosclerotic lesions in the Korean and Vietnam War casualties' autopsy studies (77) (78). Autopsies on 2-39 year olds after premature death have shown an association of atherosclerotic changes in coronary arteries and aorta with several CHD risk factors, e.g. BMI, SBP, DBP, serum total, LDL and HDL cholesterol, serum triglycerides and smoking in the Bogalusa Heart Study (79). Since the 1970s, large prospective studies have been launched to study further the pathogenesis of atherosclerosis. These studies including the Muscatine Study (20), the YFS (22), the Coronary Artery Disease Risk Development in Young Adults (CARDIA) (80), the Childhood Determinants of Adult Health (81) (CDAH), and the Special Turku Coronary Risk Factor Intervention Project (82) have shown the influence of childhood risk factors and lifestyle in the development of atherosclerosis. For instance, these prospective studies have shown an association of elevated blood pressure in children and adolescents with post-mortem fatty streaks, increased carotid IMT, decreased carotid elasticity and impaired endothelial function (79,83–87) and the association of childhood cholesterol levels with adult carotid IMT and coronary artery calcification (49,83,85,87,88). Currently it is largely recognized that progression of atherosclerosis begins in childhood and the risk of subclinical atherosclerosis in adulthood is associated with childhood CHD risk factors (89).

2.3.1 Development of atherosclerotic lesions

Atherosclerosis is commonly considered as a state of chronic inflammation (90). The accumulation of cholesteryl esters in the sub-endothelial space of artery is thought to initiate this progression. A fatty streak is the first visible lesion and is rich of foam cells that contain cholesteryl esters (91). Particles containing ApoB, such as very low-density lipoprotein, LDL and intermediate-density lipoprotein particles, contribute to cholesterol plaques. The retained lipoproteins trigger an inflammatory response, which gathers monocytes inside the arterial wall and leads to the formation of the atherosclerotic lesions (91). LDL-cholesterol has a major role in plaque initiation and progression (92). The development of plaque in the arterial wall is a process marked by intimal inflammation, necrosis, fibrosis and calcification (93).

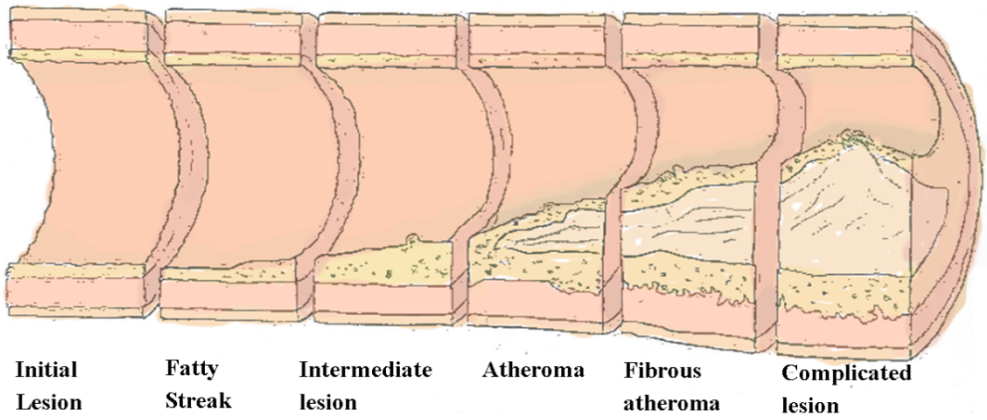


Figure 2. Development of atherosclerosis. Blocks indicate decades of life. The initial lesions contain atherogenic lipoproteins that provoke an increase in macrophages in the arterial wall causing adaptative intimal thickening. Later on, fatty streaks can be found. Finally, atheromas and fibroatheromas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

2.3.2 Risk factors for atherosclerosis and CVDs

2.3.2.1 Serum lipids

LDL particles are the main carriers of cholesterol to peripheral tissues. Accumulation of LDL and other ApoB containing particles in the subendothelial matrix is a primary event in atherosclerosis (94). LDL is modified by oxidation, glycation, aggregation, association with proteoglycans, or incorporation to immune complexes. These modified LDL particles cause severe injury to the endothelium and underlying smooth muscle (95). Raised levels of circulating LDL lead to greater accumulation in the arterial wall.

LDL-cholesterol levels correlate with atherosclerosis risk and treatments that lower LDL- cholesterol decrease CVD morbidity and mortality (96). Familial hypercholesterolemia with significantly elevated LDL-cholesterol concentration is the most severe human model of atherosclerosis. Elevated LDL-cholesterol associates with increased risk of myocardial infarction and vascular death in epidemiological studies (97). A 1 mmol/l lower lifetime LDL-cholesterol concentration has been estimated to associate with a 54% reduction in CHD morbidity(92) .

HDL particles are a heterogeneous group of molecules characterized by high density and smaller size than other lipoproteins (98). Their one hypothesized function is to transport cholesterol from peripheral cells to the liver for excretion into bile (99). The hypothesis has been reinforced by several animal studies (99,100).The Framingham Heart Study established the inverse association of HDL-cholesterol and CHD (100). In the last decades large prospective studies have found low HDL-cholesterol to be an independent predictor of myocardial infarction and ischemic stroke, also among those already diagnosed with CVD (101,102). In some of the more recent studies, a drug-induced increase in HDL-cholesterol concentrations did not convey any reduction in CVD morbidity (103)(104,105) and HDL- cholesterol was not associated causally with CHD risk (106).

Triglycerides are produced and secreted by liver as chylomicrons in a small extent but majority of the blood triglycerides are absorbed from the small intestine. Lipoproteins carrying triglycerides deliver free fatty acids to tissues to be used as source of energy or to be stored in adipose tissue (107). Elevated serum triglyceride concentrations indicate elevated concentrations of very low density lipoprotein. These very low density lipoproteins are later transformed into LDLs that contribute to foam cell and plaque formation (108). Hypertriglyceridemia is often a part of the metabolic syndrome comprising low HDL cholesterol and elevated LDL cholesterol concentration as well as obesity and insulin resistance, but eminent triglyceride levels alone also associate with higher CHD risk (109). In a meta-analysis with data from over 300,000 individuals, triglyceride concentrations over 2.8 mmol/l and 2.2 mmol/l indicate an increased risk of CHD and ischemic stroke, respectively (110). In individuals with baseline triglycerides over 2 mmol/l, a 1 mmol/l reduction in triglycerides induced by fibrates reduced coronary events by 43% (111,112). Recent Mendelian Randomization studies have found a causal association between triglyceride concentration and CHD risk with 1.62 odds ratio for unrestricted allele score (113).

2.3.2.2 Blood pressure

Hypertension has several mechanisms that induce atherogenesis (114) (115). The risk of CHD has been estimated to double with each increment of 20/10 mmHg

beginning from 115/75 mmHg (116). Hypertension is characterized by vascular remodelling and stiffness, and it results in endothelial dysfunction with activation of renin-angiotensin-aldosterone systems (117). Elevated childhood blood pressure has been shown to predict higher incidence of fibrous lesions, increased carotid IMT, coronary calcification and decreased arterial elasticity (79) (49) (118). An estimated 24% of adult men (≥18 years of age) and 21% of adult women have elevated BP wordlwide (defined as ≥140/90 mm Hg) (119).

2.3.2.3 Obesity

Obesity is nowadays a global epidemic and its prevalence and severity are predicted to increase. In 2016, more than 1.9 billion adults were overweight (BMI 25-30 kg/m2), and 650 million were obese (BMI ≥30 kg/m2) comprising 13% of the world's adult population (120). Obesity is associated with numerous comorbidities such as type 2 diabetes, atherosclerosis, CHD and cancer. The YFS has contributed to this literature particularly by linking childhood obesity to later cardiometabolic health outcomes (121–123). Obesity arises from a combination of genetic and environmental factors that interact to promote the phenotype(124).

2.3.2.4 Serum glucose and insulin, diabetes

Diabetes is a well-recognized risk factor for early CVDs and it is described by elevated blood glucose due to unbalanced glucose-insulin-homeostasis (125). Slightly elevated levels of blood glucose and insulin can forecast erupting diabetes and hence they may be considered as early CVD risk factors (126). Insulin is the key stimulator of glucose uptake in cells from the liver and other glycogen storages. In type 1 diabetes, hyperglycaemia is caused by insufficient insulin production following autoimmune destruction of pancreatic beta cells. Type 2 diabetes is preceded by peripheral insulin resistance combined with beta cell exhaustion that leads to jeopardized glucose tolerance and hyperglycaemia. Type 2 diabetes often occurs with metabolic syndrome and has become an ever-growing international epidemic. It leads to estimated two to three times higher CVD risk compared to the non-diabetic population, and to a worse survival prognosis for CVD (127,128).

2.3.2.5 Low-level inflammation

Atherosclerosis is considered as a form of chronic vascular inflammation that happens mostly in the endothelium (129).Especially high-sensitivity C-reactive protein is a promising marker for vascular inflammation and together with Framingham score it achieves better predictive accuracy for atherosclerosis than

Framingham score alone (130).High-sensitivity C-reactive protein has however poor specificity for atherosclerosis as it also associates with old age, hypertension and diabetes, for instance.

Low- level inflammation is associated with poor oral health, for instance. Studies have shown that poor oral health increases CVD mortality(131). Especially appearance of periodontal diseases seems to have an adverse on CV health (132).

2.3.2.6 Health behaviours

2.3.2.6.1 Diet

Diet impacts several components of CVD risk profile, including obesity, blood pressure, lipoprotein profile, glucose-insulin homeostasis, hepatic function, cardiac function, inflammation and oxidative stress (133,134). Ideal diet for CV health comprises energy balance and dietary quality (135). An ideal diet for CV health is rich in vegetables and fruits, fish and whole grains and consist only small amount of sodium and sugar- sweetened beverages (136).

2.3.2.6.2 Alcohol use

Association of alcohol with CV health is debated. Excessive use of alcohol has a negative impact on CV health and increases the risk for stroke (137,138). Epidemiologic and clinical evidence suggests, however, that moderate consumption of alcohol associates with a reduced risk for developing CHD and ischemic stroke (139), possibly by means of reducing cardiac responsiveness during mental stress (140).

2.3.2.6.3 Physical activity

Lack of physical activity and low fitness are known to elevate the risk for CVDs (141). Due to its strong association with CVD mortality, low fitness could be considered as an established CVD risk factor besides the traditional risk factors, such as blood pressure, serum total cholesterol, blood glucose and smoking (142). The association of physical activity with increased CVD mortality is evident regardless of ethnicity, body weight and traditional CVD risk factors (143,144). Physical inactivity is estimated to cause 6% of the CHD morbidity and account for 9% or over 5 million of the premature deaths worldwide (145). Physical activity is nowadays recognized as a fourth type of risk exposure in non-communicable diseases (146).

2.3.2.6.4 Smoking

Cigarette smoking is a major risk factor contributing to premature mortality and CVD morbidity internationally (147). Smoking was estimated to cause 6.4 million deaths worldwide in 2015 and the second-leading risk factor for attributable mortality among both sexes after hypertension(148).

Exposure to cigarette smoke induces multiple pathological effects on the endothelium (149). Smoking also activates the whole coagulation cascade and the increases the risk of thrombotic cardiovascular events (150).

Epidemiologic studies have shown that cigarette smoking increases the incidence of CHD and myocardial infarction (151–153). Depending on the study, active smokers have been estimated to have 80% increase and those exposed to passive smoking 30% increased risk for fatal CHD (154,155) and smoking men a two-three-fold death-rate-ratio in the middle-age compared to non-smoking men (156)

2.3.2.7 Socioeconomic status

The converse association of SES with CDH mortality (157), myocardial infarction (158) and CVD/CHD risk factor levels in adulthood (159) and childhood (19) has been shown before. Besides the higher CHD morbidity and risk factor levels, lower SES is associated with poorer access to treatment of CHD (160). In Finland in the 1980's relative risk of CHD was especially high in subjects from eastern Finland with low SES even when compared to western peers with low SES (55). Overall and CVD mortality has been earlier found higher in participants with low SES also in the FINRISK-study (161). Association of SES with some of CHD risk factors (BMI, SBP, triglyceride, glucose and insulin levels, cigarette smoking and physical inactivity) and carotid IMT has been shown earlier in the YFS (56). Also the association of SES with arterial stiffness (162) and LV mass and diastolic function (163) have been shown in the YFS. An association of SES with rural residency is a worldwide phenomenon (164,165).

Mechanisms underlying the association of SES with CHD and other CVDs are numerous. For example, overweight in childhood associates with parental SES and predicts obesity also in adulthood (166). Diet, for example consumption of fruits and vegetables, is associated with SES (167,168). Low SES associates also with higher alcohol consumption in low and middle-income countries (168), and with more alcohol-caused problems in high-income countries (169). Lower SES is also associated with psychosocial stress. Alcohol intake, smoking and comfort eating are common coping methods for psychosocial stress (166). For instance, dramatic overall and CVD mortality increase in the post-Soviet Russia in the 1990's was shown to be linked with psychosocial stress and increased alcohol consumption (170).

2.4 Surrogate markers of CVDs

2.4.1 Subclinical markers of atherosclerosis

Although the atherosclerotic process begins in early life, clinical symptoms and events usually take place at the earliest in middle age. Subclinical changes in the structure and function of the vessels can be reliably measured noninvasively. Established methods include ultrasound-based assessments of carotid IMT (87), carotid artery elasticity (171), endothelial function measured by brachial artery flow-mediated dilation (172), and coronary artery calcification assessed by computed tomography (173). In the present thesis, carotid IMT was used to estimate subclinical atherosclerosis.

The reported association between aortic IMT estimated using ultrasonography and by light microscopy in using *in vitro* samples (174) marked the beginning of ultrasound arterial IMT measurement as a tool to estimate subclinical atherosclerosis. Carotid IMT has become the method of choice due to its size and accessible anatomy, and it is nowadays recognized as a subclinical marker of atherosclerosis (175). The measurements are taken between the leading edges of the lumen-intima and media-adventitia ultrasound interfaces. Increased carotid IMT correlates with CVD/CHD risk factors (49) (8), and the grade of coronary artery disease (176) as well as predicts future CVDs (50). In a meta-analysis, a 0.1 mm increase in carotid IMT was shown to raise the future risk of myocardial stroke/infarction? by 15% and the risk of stroke by 18% (177).

2.4.2 Left ventricular mass and function

Increased LVM is a predictor of future CVDs (178) (179). The relation between LVM and CVDs rate in the general population (180) was first reported in the Framingham Heart Study. Persistent hypertension contributes to elevated left LVM due to increased afterload, as shown in several populations (181–183). In the YFS study, it has been shown that childhood ideal CV health associates inversely with higher LV mass and impaired diastolic function (184). In the Finnish STRIP- study (Special Turku Coronary Risk factor Intervention Project), higher BMI was found to associate with increased LVM and septal thicknesses in adolescence (185).

LV ejection fraction associates with LVM. A pathological increase in LVM often occurs simultaneously with decreased ejection fraction and for diagnosis of patients with heart failure, ejection fraction was earlier a standard parameter in clinical practice (186). Ejection fraction has several limitations, however. The estimation of ejection fraction is assessed on linear or two-dimensional measurements, it can change significantly based on loading conditions and it is only moderately

reproducible (172). It is nowadays widely recognized that heart failure often occurs with normal ejection fraction and may be categorized as heart failure with preserved, mid-range or reduced ejection fraction (188).

Heart failure with preserved ejection fraction is sometimes referred to as LV diastolic dysfunction. It is recognized as a common clinical manifestation with high morbidity and mortality (28). Elevated LVM may contribute to the development of diastolic dysfunction (189) although normal LVM can also been found in patients with impaired diastolic function (190).

The ratio of transmitral blood flow velocity during the early filling of the LV (E) by mitral annular early diastolic velocity towards left atrium (e'), so called E/e'-ratio is a well-established non-invasive indicator of increased LV end-diastolic pressure (188). E/e'-ratio is considered as an estimate of LV end-diastolic pressure regarding diastolic dysfunction (191,192) and the most extensively studied parameter for estimation of LV filling pressure (193).

The use of E/e′ to estimate LV filling pressures is, however, controversial as it does not correlate with invasive measurements in various clinical situations (194). When assessing the diastolic function of LV in individual patient with E/e'-ratio it is important to acknowledge the subject's age, possibly underlying CVD and other abnormalities found in the echocardiography (195). At a population level, E/e′ has been shown to predict all-cause and CVD mortality and heart failure hospitalizations in several disease states, including acute myocardial infarction, cardiomyopathy, and heart failure with preserved and reduced ejection fraction (194,196,197). In addition to E/e'-ratio, LV diastolic function is related to LV end-diastolic volume (198) and E/A-ratio (188). E/A is calculated as dividing transmitral blood flow velocity in the early filling of the LV by the transmitral blood flow velocity in the late filling of the LV.

3 Aims of the Study

This thesis aims to study the association of geographic origin with CHD risk factor profile, carotid IMT, and LV structure and function in the Young Finns Study. In specific, it aims to:

1. Report the CHD risk factor differences between the eastern and western participants in adulthood (2011) and during the 31-year follow-up
2. Investigate differences in carotid IMT and LV mass and function between eastern and western participants in adulthood
3. Explore the CHD risk factor, carotid IMT and LVM differences between urban and rural Finns in adulthood (2007, 2011)
4. Study the association of migration with CHD risk factors and carotid IMT in adulthood (2007, 2011)

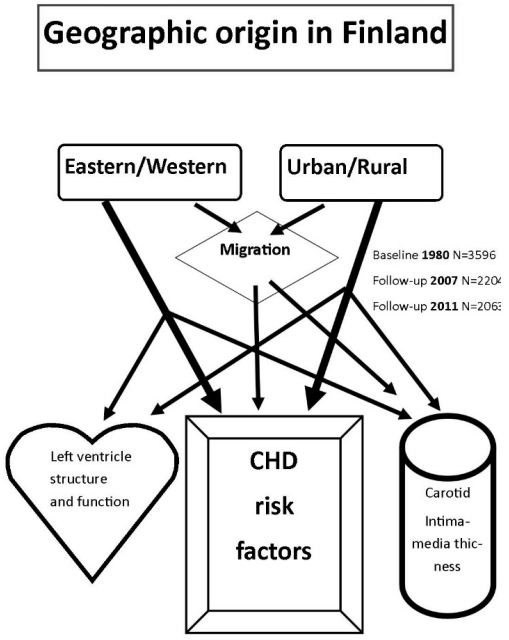


Figure 3. Aims of the thesis. Arrows indicate, which associations were studied in this thesis.

4 Participants and Methods

4.1 Cardiovascular Risk in Young Finns Study

YFS is an ongoing multicentre follow-up study to investigate atherosclerotic risk factors from early childhood to adulthood (199) (8). The study areas are five university hospital cities (Helsinki, Turku, Tampere, Kuopio and Oulu) with their rural surroundings. Kuopio had a double size sample to able assessment of equal number of participants from east and west. The participants were randomly chosen from the national register in order to produce a representative sample of Finnish children and adolescents. Two pilot studies were conducted in 1978 and 1979. The main study was launched in 1980 including 3596 participants aged 3,6,9,12,15 and 18 years. The follow-up studies have mainly been performed at 3-year intervals. The 27-year follow-up in 2007 comprised of 2204 subjects and the latest follow-up in 2011-12 of 2063 participants. The design of YFS and participation rates in the follow-ups are shown in Figure 4. YFS has been approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital and has been conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants or their parents.

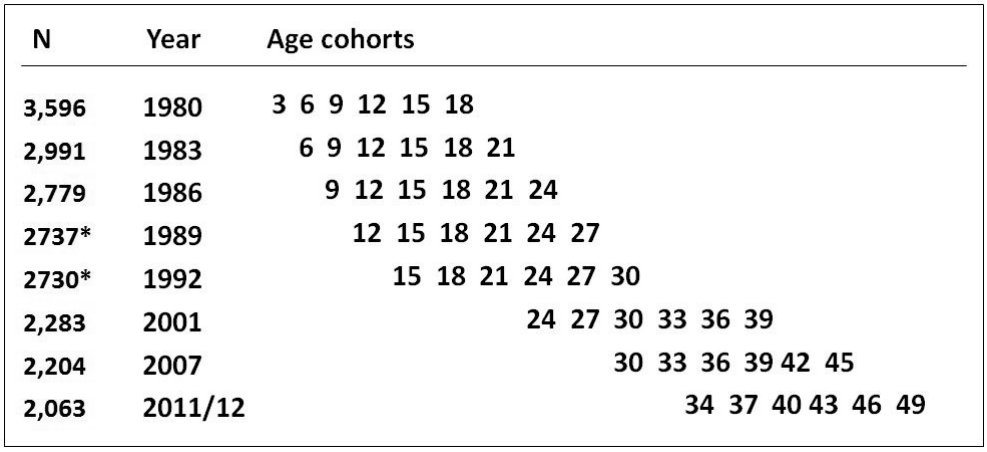


Figure 4. The design and follow-ups of the YFS

4.1.1 Definition of geographic origin

Participants of this Caucasian population were compared according to their baseline origin (1980), current residency (2011) or family origin. Participants were determined according to their study centre either as eastern (Kuopio and Oulu) or western (Helsinki, Turku and Tampere) (11). Geographically more correct terms would be north-eastern and southwestern Finns, but the terms eastern and western are commonly used due to historical and simplicity reasons. Family origin was assessed by the subjects' grandparents' place of birth and was considered eastern if all four grandparents were born in eastern Finland (37%) and western if three or four grandparents were born in western Finland (20%). Data of grandparents' birthplace was incomplete in 26% of subjects and they were excluded from family origin categorization. Proportions of men and women were similar between groups with eastern (48,7 % men) and western (49,4% men) baseline origin.

The living area of participants was also classified as urban or rural. At baseline, the participants living in the university cities (Helsinki, Turku, Tampere, Kuopio and Oulu) were classified as having an urban place of residence, and the municipalities in the vicinity of those cities were classified as rural (Nurmijärvi, Vihti, Loimaa, Mynämäki, Orivesi, Ruovesi, Ilomantsi, Juuka, Lapinlahti, Nilsiä, Haapavesi, Pudasjärvi). In adulthood, the area of residence was defined on the basis of a question on the subject's current place of residence. Participants living in cities, suburbs or center of a town/village were classified as having an urban place of residence and participants living outside a population center were classified as having a rural place of residence.

4.2 Data acquisition in the Young Finns Study

4.2.1 Physical examination

Weight was measured with weighing scales to the nearest 0.1 kg and height with statiometer to the nearest centimetre. BMI was calculated as weight(kg)/height(m)^2. Waist circumference was measured using an anthropometric tape at the midpoint between the iliac crest and the lowest rib to the nearest 0.1 cm. The average of two measurements was used. Blood pressure was measured from the right brachial artery with a standard mercury sphygmomanometer in 1980 and 1983, and with a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK) in 1986, 2001, 2007 and 2011. The measurement was done in a sitting position after a 5-minute rest. The Korotkoff first phase was used as the sign SBP, DBP was determined from the fifth phase. Readings were performed to the nearest two of millimeters of mercury 3 times on each participant and the average of 3 measurements was used in the analysis. From participants 3 years old at baseline, only SBP was collected by using an ultrasound device.

4.2.2 Biochemical analyses

In 1980, 1983 and 1986, venous blood samples were drawn after a 12-hour fast and stored at -20°C until thawed for the first time for the analyses. In 1980, triglyceride concentrations were measured using a fully enzymatic CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany) with OLLI 3000 and Kone CD analyzers (Kone Co., Espoo, Finland) and determined by using a fully enzymatic method (Boehringer Mannheim). Serum HDL-cholesterol concentrations were measured from the supernatant after precipitation of very low density lipoprotein cholesterol and LDL-cholesterol with dextran sulphate 500 000 (Pharmacia, Uppsala, Sweden) (200) in 1980. The concentration of LDL-cholesterol was calculated using the Friedewald formula (201).

From 2001 onwards, venous blood samples were drawn after an overnight fast and serum was separated, aliquoted and stored at -70°C until analysis. The assays were performed on an AU400 instrument (Olympus, Japan) and the same methods were used both in 2007 and 2011. Triglyceride concentration was determined using the enzymatic glycerol kinase–glycerol phosphate oxidase method (Triglyceride reagent, Beckman Coulter Biomedical, Ireland). Total cholesterol levels were measured by the enzymatic cholesterol esterase–cholesterol oxidase method (Cholesterol reagent, Beckman Coulter Biomedical). The same reagent was used for estimating HDL-cholesterol levels after precipitation of LDL- cholesterol with dextran sulfate- Mg^{2+} (200). LDL-cholesterol was calculated by the Friedewald formula in participants with triglyceride levels <4.0 mmol/L (201). The analysis methods for total cholesterol and triglycerides have been accredited by the Finnish Accreditation Service according to standard ISO/IEC17025.

Serum glucose concentration was determined with the enzymatic hexokinase method (Glucose reagent, Beckman Coulter Biomedical). Due to changes in methods or reagents from 2001 to 2007, glucose levels were corrected by using the following correction factor equation: Glucose = [glucose (year 2007) – 0.0235]/0.9471. The concentration of HbA1c was assayed with an immunoturbidimetric method (Hemoglobin A1c assay, Abbott, USA) on an Architect ci8200 analyzer (Abbott) in 2011.

4.2.3 Definition of hypertension, metabolic syndrome and type 2 diabetes in adulthood

Hypertension was defined as blood pressure at or above 140/90 mmHg, use of reimbursed antihypertensive medication, or the self-reported use of antihypertensive medication (202). The metabolic syndrome was defined according to the Harmonized criteria (203). The definition included the following criteria; waist circumference ≥102 cm in men and ≥88 cm in women, serum fasting glucose ≥5.6

mmol/L) or treatment, hypertriglyceridemia ≥1.7 mmol/L) and HDL-cholesterol ≤1.0 mmol/L) in men and ≤1.3 in women and SBP ≥130mmHg or DBP ≥85 mmHg or the use of antihypertensive medication. A diagnosis required that any 3 of the 5 criteria to be present. Pregnant women were excluded from analyses involving the metabolic syndrome (in 2007, n = 37 and in 2011, n = 13). The diagnosis of type 2 diabetes included participants with fasting serum glucose ≥7 mmol/L) or HbA1c ≥6.5% or self-reported diabetes or use of medication (204).

4.2.4 Ultrasound imaging of carotid IMT

A high-resolution ultrasound system (Sequoia 512, Acuson, CA, USA) with 13.0 MHz linear array transducer was used to perform carotid ultrasound studies in 2007. Ultrasound studies were performed for 2,197 participants in 2007. All studies were performed simultaneously by physicians/ultrasound technicians in the five cities of the study. Carotid artery IMT was measured approximately 10 mm proximal to the bifurcation on the left common carotid artery focusing the image on the posterior wall and recording images from the angle showing the greatest distance between the lumen-intima interface and the media-adventitia interface. At least four measurements were taken at each scan of the common carotid artery incident with the R-wave of the continuously monitored ECG to derive mean carotid IMT. One reader analysed the scans and was blinded to participants' details.

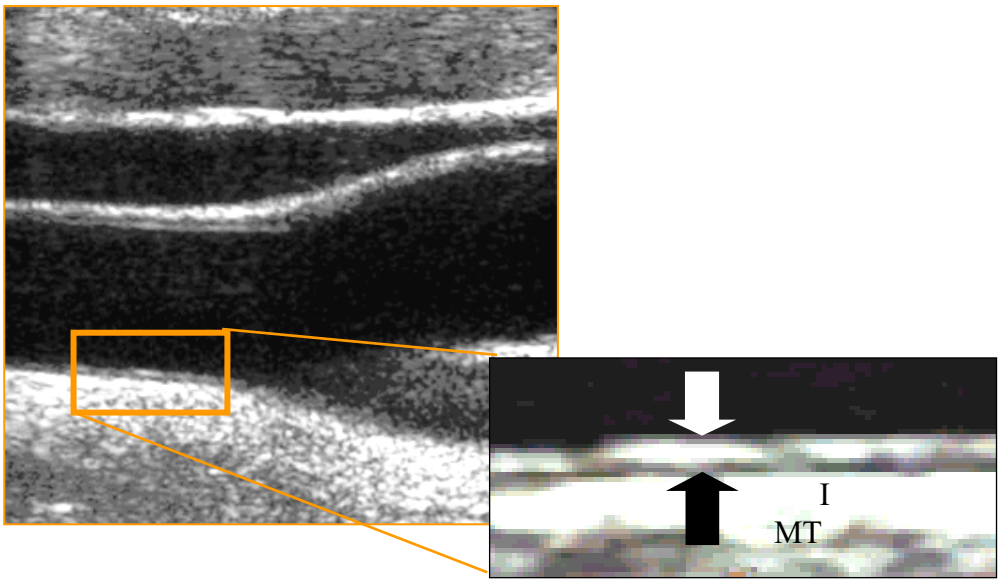


Figure 5. Carotid IMT. The layers between the black (media-adventitia interface) and the white (lumen-intima interface) arrow represent the intima-media layers in the ultrasound image.

4.2.5 Echocardiography

Measurement of LVM and diastolic function with echocardiography was introduced to YFS in the latest follow-up in 2011. Echocardiographic measurements and analysis were performed according to the European Association of Echocardiography/ American Society of Echocardiography guidelines (188,205,206). The sonographers in all study locations were trained by a cardiac imaging specialist. Transthoracic echocardiography was performed with Acuson Sequoia 512 (Acuson, Mountain View, CA, USA) ultrasonography, using 3.5 MHz scanning frequency phased-array transducer. Analysis of the echo images was carried out by one observer using ComPACS 10.7.8 (MediMatic Solutions, Genova, Italy) analysis program. Both the sonographer and the observer were blinded to the subjects' details.

LVM was calculated as follows: (0.8[1.04((LV end-diastolic diameter + posterior wall thickness + interventricular septum thickness)^3–LV end-diastolic diameter)^3] + 0.6 g (206). LVM was indexed according to subject's height using the allometric power of 2.7 (indexed LVM =LVM/height$^{2.7}$) since this indexation performs better for overweight/obesity (207).

Continuous and pulse-wave Doppler were used to measure transmitral flow and tissue velocities and using this data, LV diastolic performance index, E/e'-ratio, was defined as described earlier (205). E wave describes the mitral blood flow during the early filling of the LV, and é measures mitral annular early diastolic velocity towards left atrium (LA). In this study E/é ratio was calculated using the average of lateral and septal values of é velocity. Lower ratio of E/é indicates better LV diastolic function (205).

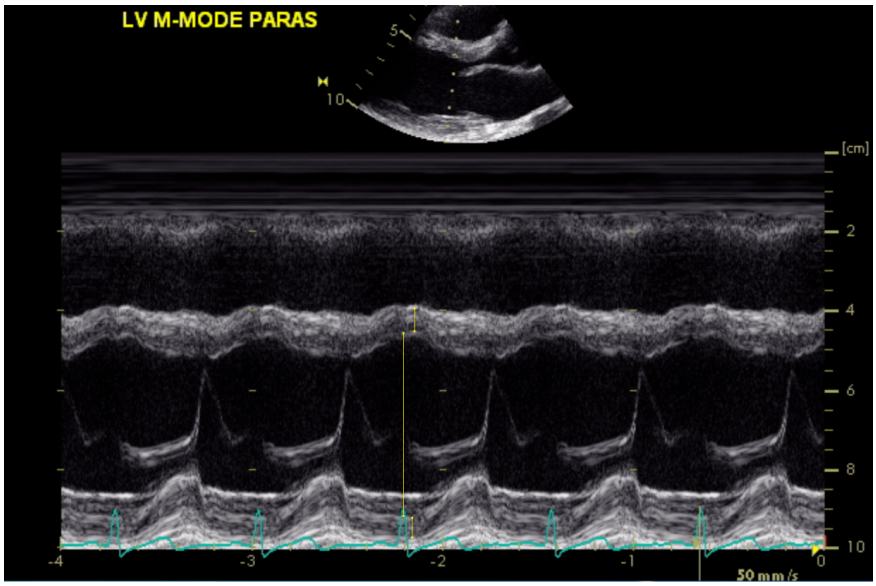


Figure 6. M-mode ultrasound image obtained during measurement of cardiac LVM.

4.2.6 Health behaviours, SES and medication questionnaires

Self-report questionnaires were used to assess physical activity, smoking, alcohol consumption, SES and use of lipid-lowering and antihypertensive medication in adulthood. Participants answered the questions themselves, with parents' assistance if necessary. The following variables were included in the physical activity questionnaire and applied in this study: intensity of physical activity, frequency of moderate or vigorous activity, and hours spent on moderate or vigorous activity per week (208). Information on cigarette smoking was collected using a questionnaire. In childhood, smoking was assessed by a questionnaire in subjects aged ≥12 years. Alcohol consumption was determined as standard doses per week. A healthy diet score (range 0–27, higher is better) was calculated as a combination of daily consumed portions of “healthy” and “unhealthy” foods assessed from a food frequency questionnaire (209). In the score, whole grains, fish, fruits, vegetables and nuts/seeds are designated as healthy foods, whereas red and processed meats, sweets, sugar-sweetened beverages, and fried potatoes were designated as unhealthy.

4.3 Statistical methods

Continuous variables are presented as means (±standard deviation, SD or standard error, SE) for normally distributed variables or medians (interquartile range) for variables with a skewed distribution. Categorical variables are presented as proportions. P-values for continuous variables were analysed using independent samples t-test when comparing two groups without adjustments. Non-normally distributed risk factors were first log-transformed. Categorical risk factors were analysed using the chi-square test. Statistical significance was considered as a p-value <0.05. The analyses were performed with SAS version 9.3 (SAS institute, Inc, Cary, NC).

4.3.1.1 Study I

In CHD risk factors that showed a significant east–west difference in t-test, an analysis of covariance was performed with separate adjustment for age and SES. Participants who had moved from east-to-west were compared to the other groups for their CHD risk factors in 2007 and 1980 with an age- and sex-adjusted analysis of covariance using Dunnett’s multiple comparison correction. Categorical risk markers were analysed with a Poisson regression model with a robust error variance. P-values were calculated with adjustments for sex, and a further adjustment for age, sex, and SES was also made. Sex*east-west migration interactions were studied and if significant interactions were found the analyses were done separately for men and women. Similar analyses were performed to study the association of east–west

migration with IMT. In addition to adjustment for age and sex, the analyses were further adjusted for risk factors that showed difference between the groups in 1980 or 2007.

4.3.1.2 Study II

Association of LVM, E/e′-ratio, EF, LV end- diastolic volume and LA end-systolic volume with eastern/western baseline origin (also with current residency and family origin for LV mass and E/e′) were analysed with an age- and sex-adjusted analysis of covariance. Mean, SE and p-values were calculated with adjustment for age, sex and area of examination in 2011, and for LVM and E/e′ additionally baseline and current CHD risk factors were used as covariates. Birthweight, BMI, SBP, total cholesterol, parental SES and physical activity at baseline and BMI, SBP, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity at the time of the echocardiography (2011) were chosen as the covariates since these risk factors are known to associate with LVM and we have previously found an east–west difference in these risk factors in our data.

4.3.1.3 Study III

For longitudinal analyses, Z-scores (males and females combined, mean 0, SD 1) were generated for continuous risk factor variables; BMI, SBP, DBP, total, LDL- and HDL-cholesterol, triglycerides, ApoA1, ApoB, insulin and glucose to investigate the east-west differences, but not the secular trends, at each follow-up year from 1980 to 2011. The longitudinal differences between participants with eastern or western baseline residency were analysed with repeated measures linear mixed models. At this point, adjustment was made for age and sex, and the year of study using an unstructured covariance structure. As there were no sex*east-west baseline residency interactions, data for males and females were analysed together. The longitudinal differences in CHD risk factors were further analysed with adjustment for parental SES (school years and income status) at baseline as it was different between participants with eastern or western baseline residency and is known to associate with traditional CHD risk factors.

4.3.1.4 Study IV

Continuous variables are presented as means (±standard deviation, SD or standard error, SE) for normally distributed variables or as medians (interquartile range) for variables with a skewed distribution. Continuous childhood and adulthood variables were Z-scored (mean 0, SD 1, standardized for age and sex) for the analyses.

Differences in categorical variables were analysed using Fisher's exact test in childhood and logistic regression models adjusted for age and sex in adulthood. The association of SES and eastern-western origin with urban-rural differences in CV risk factor levels was tested using analysis of covariance adjusted for age, sex, and additionally for SES or eastern-western origin. The association of urban-rural migration was examined by dividing participants into four groups: 1) participants who had lived in rural areas as a child and had migrated to urban communities by adulthood (n=587); 2) participants who had continuously lived in urban areas (n=991) 3) participants who lived in urban areas as a child and had migrated to rural settings by adulthood (n=738); 4) participants who continuously lived in rural communities (n=283). Least-square means according to migration classification adjusted for age and sex were calculated using analysis of covariance.

5 Results

5.1 Characteristics of the participants (Study III, Study IV)

Clinical and biochemical characteristics of the study population at baseline (1980) are presented in Tables 1–2. In this thesis the population was studied for geographic differences with special reference to eastern/western differences and urban-rural differences, hence we present the baseline characteristic with east-west-division (Table 1) and urban-rural-division (Table 2).

At baseline, participants living in western Finland had significantly lower SBP, DBP, total cholesterol, LDL-cholesterol, triglycerides and higher parental SES compared with their eastern counterparts (Table 1).

Those living in urban areas had lower SBP, total cholesterol, LDL-cholesterol, triglycerides and higher parental SES compared with rural participants at baseline (Table 2).

Table 1. Baseline (1980) characteristics of the participants with data of CHD risk factors in adulthood (2007) according to eastern/western baseline origin. Mean±SD or median [interquartile range]* or proportions (%).

	Eastern		**Western**		
	Mean	±SD	Mean	±SD	**P for difference**
N range	829–961		924–1084		
Males (%)	45.2		45.8		**0.78**
Age (years)	11.0	±5.0	10.7	±5.0	**0.20**
Body mass index (kg/m²)	18.0	±2.9	18.0	±3.3	**0.93**
Systolic blood pressure (mmHg)	114	±12	112	±12	**<0.0001**
Diastolic blood pressure (mmHg)	70	±9	67	±10	**<0.0001**
Total cholesterol (mmol/l)	5.36	±0.98	5.24	±0.89	**0.002**
LDL-cholesterol (mmol/l)	3.49	±0.91	3.38	±0.79	**0.003**
HDL-cholesterol (mmol/l)	1.56	±0.30	1.56	±0.32	**0.82**
Triglycerides (mmol/l)	0.68	±0.32	0.65	±0.31	**0.06**
Insulin (mU/l)*	9.91	[5.90]	9.78	[6.08]	**0.61**
Parental SES (school years)	10.6	±3.7	11.3	±3.8	**<0.0001**

Table 2. Baseline (1980) characteristics of the participants with data from the 2011, 2007 or 2001 follow-up in adulthood according to urban/rural baseline origin. mean±SD or median [interquartile range]* or proportions (%).

	Urban		Rural		
	Mean	±SD	Mean	±SD	**P for difference**
N range	1192–1394		1244–1509		
Males (%)	46.7		45.2		**0.43**
Age (years)	10.7	±5.0	10.3	±5.0	**0.09**
Body mass index (kg/m²)	17.8	±3.0	17.8	±3.2	**0.18**
Systolic blood pressure (mmHg)	112	±12	113	±12	**0.01**
Diastolic blood pressure (mmHg)	69	±10	68	±10	**0.15**
Total cholesterol (mmol/l)	5.22	±0.9	5.40	±0.9	**<0.0001**
LDL-cholesterol (mmol/l)	3.36	±0.8	3.53	±0.9	**<0.0001**
HDL-cholesterol (mmol/l)	1.56	±0.3	1.56	±0.3	**0.92**
Triglycerides (mmol/l)	0.65	±0.3	0.68	±0.3	**0.02**
Insulin (mU/l)*	9.60	[5.8]	9.73	[6.1]	**0.10**
Parental SES (school years)	11.9	±3.9	10.2	±3.4	**<0.0001**

5.2 CHD risk factors in 2011 according to eastern/western baseline origin (Study III)

Men and women were equally divided in the east-west groups (p=0.78) and the mean age between the groups was similar (Table 3). Participants with eastern baseline origin were, on average, shorter than those with western baseline origin. There were no differences in traditional CHD risk factors in 2011 between participants originating from eastern or western Finland. The prevalence of type 2 diabetes and hypertension were also similar between participants with eastern/western baseline origin.

Table 3. CHD risk factors in 2011 (mean±SD or median [interquartile range]*) according to eastern/western baseline origin.

	Eastern	**Western**	
	Mean±SD	Mean±SD	**P for difference**
N range	809-961	972-1084	
Males (%)	45.2	45.8	**0.78**
Age (years)	42.0±5.0	41.4±5.0	**0.94**
Height (cm)	172 ±9	173±9	**0.0005**
Body mass index (kg/m²)	26.5 ±4.9	26.6±5.2	**0.76**
Waist (cm)	91.4 14.2	92.3±14.2	**0.13**
Systolic blood pressure (mmHg)	119±13.4	119±14	**0.61**
Diastolic blood pressure (mmHg)	75±10.4	75±11	**0.73**
Hypertension (%)	19.9	18.9	**0.58**
Total cholesterol (mmol/l)	5.20±0.95	5.17±0.96	**0.47**
HDL-cholesterol (mmol/l)	1.32±0.32	1.21±0.31	**0.71**
LDL-cholesterol (mmol/l)	3.29±0.83	3.25±0.83	**0.29**
ApoA1 (g/l)	1.60±0.24	1.58±0.24	**0.27**
ApoB (g/l)	1.06±0.28	1.06±0.29	**0.62**
Triglycerides (mmol/l)*	1.05[0.81]	1.05[0.81]	**0.87**
Insulin (mU/l)*	7.41[7.05]	7.26]7.20]	**0.91**
Glucose (mmol/l)*	5.25[0.63]	5.25[0.74]	**0.31**
Metabolic syndrome (%)	20.5	22.4	**0.36**
Type 2 diabetes (%)	3.8	4.1	**0.73**
Smoking (%)	13.4	12.5	**0.16**
Physical activity index (range 5-15)	9.0±1.9	9.0±1.9	**0.65**
SES (school years)	15.3±3.4	15.3±3.7	**0.74**
Alcohol consumption (doses per week)*	3±5	3±7	**0.20**

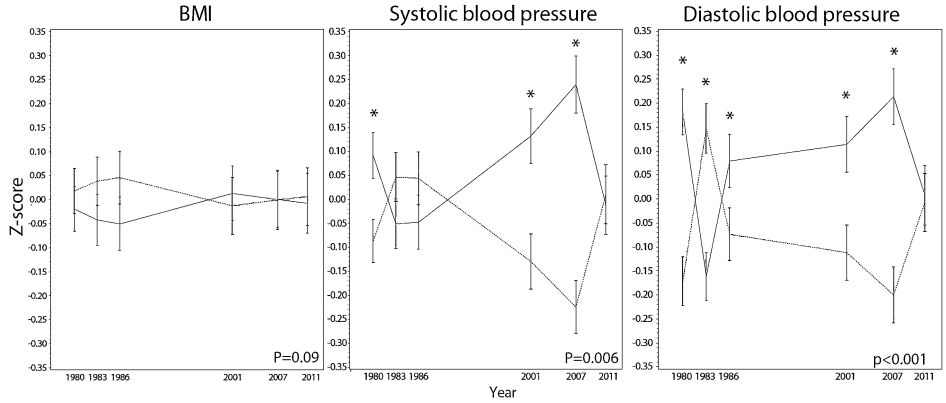
5.3 CHD risk factors in 1980–2011 according to eastern/western baseline origin (Study III)

In 1980-2011 BMI was similar between those resident in eastern or western Finland at baseline. Eastern participants had significantly higher SBP and DBP from 1980 to 2011 compared with western participants. As indicated by the 95% confidence intervals, eastern participants had higher SBP in 1980, 2001, and 2007 and higher DBP in 1980, 1986, 2001 and 2007 compared to western peers. East-west differences in SBP and DBP were largest in 2007 but not apparent in 2011.

Participants with eastern baseline origin had higher total and LDL- cholesterol, triglycerides and ApoB concentrations compared with western participants during the 31-year-follow-up. At single follow-up years, the concentrations were higher for eastern participants in 1980, 1983, and in 1986 only for triglycerides. From 1980 to 2011, no east-west differences were observed for HDL-cholesterol and ApoA1. At single follow-up years, an east-west difference in ApoA1 was found in 1983.

Participants with baseline origin in east had on average higher glucose but similar insulin concentrations compared with those with western baseline residency in 1980-2011. At single follow-up years, glucose was higher in 1986 and serum insulin in 1983 among the eastern participants.

The longitudinal analyses investigating differences in CHD risk factors were also adjusted for baseline parental SES (school years and income class). Except for triglycerides, the observed east-west differences in the risk factors remained statistically significant.



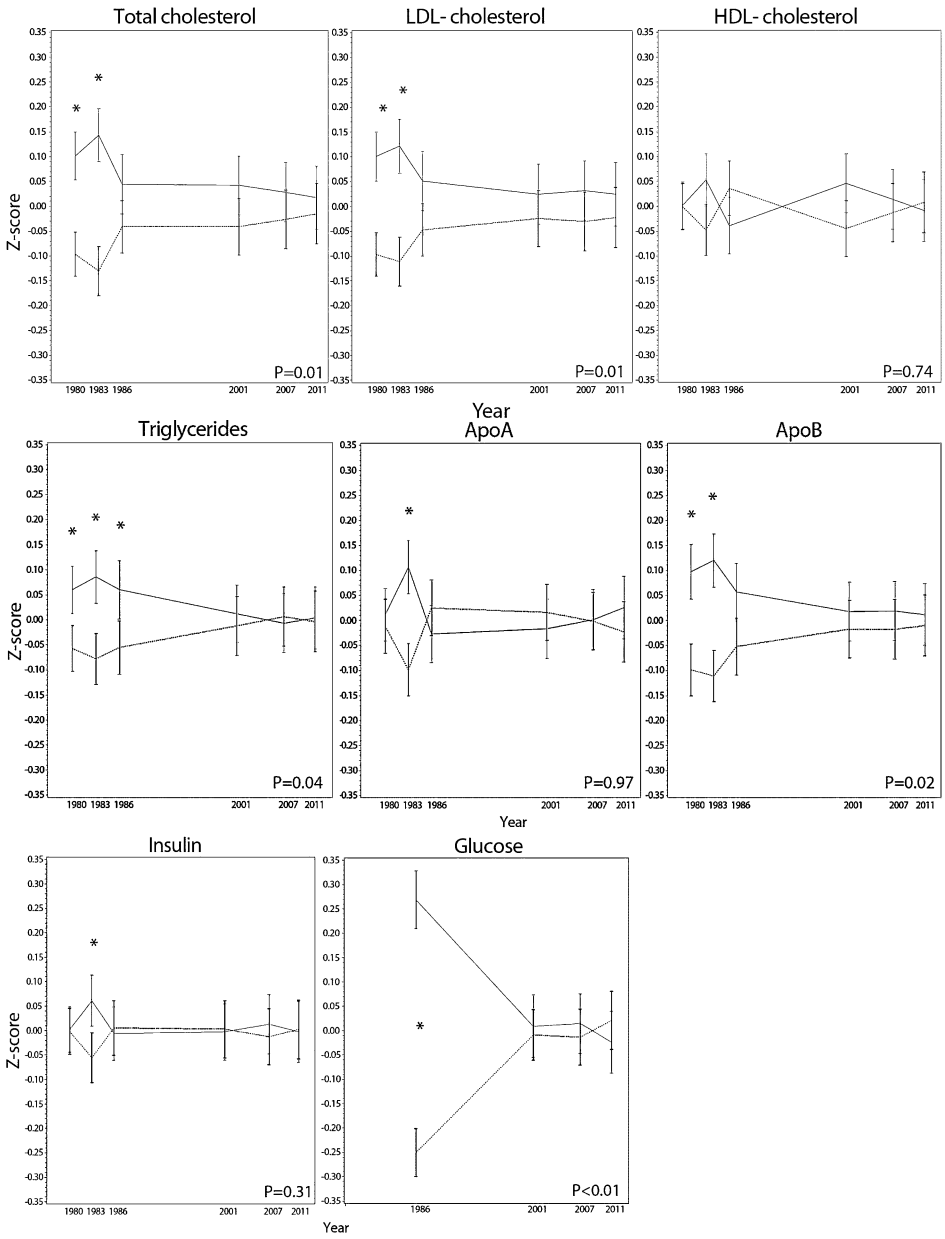


Figure 7. ◄▲Longitudinal analyses of coronary heart disease risk factors from 1980 to 2011. N is given as number of participants with data from at least one of the follow-ups between 1980 and 2011. P value is for the longitudinal analyses. Z score is given as mean and 95% confidence intervals. * P value <0.05 for east–west difference at a single follow-up year. Y-axis displays mean Z-score with 95% confidence intervals (eastern, continuous line, N 1726-1750; western, dash line, N=1808-1842). 1 standard deviation equals 12.2 (1980)–14.1 (2011) mmHg for systolic blood pressure and 9.6 (1980)–10.5 (2011) mmHg for diastolic blood pressure, 0.92 (1980)–0.95 (2011) mmol/l for total cholesterol, 0.83 (1980)–0.83 (2011) mmol/l for LDL-cholesterol, 0.31 (1980)–0.33 (2011) mmol/l for HDL-cholesterol, 0.22 (1980)–0.24 (2011) g/l for ApoA1 and 0.18 (1980)–0.29 (2011) g/l for ApoB.

5.4 Carotid IMT in adulthood (2007) according to eastern/western baseline origin (Study I)

IMT was higher in participants with eastern baseline origin compared to those with western baseline origin. There was no sex*baseline origin interaction indicating that the results were similar in both sexes. The IMT difference remained significant after adjustment for SES.

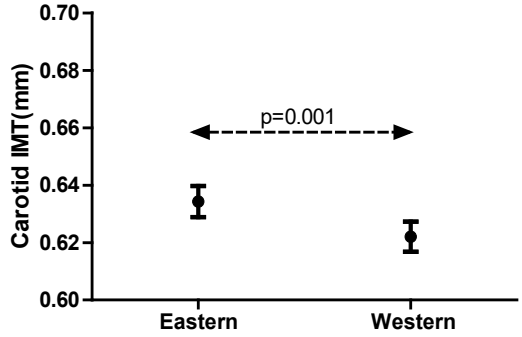


Figure 8. Carotid IMT in 2007 according to eastern/western baseline origin (mean and 95% confidence intervals), adjusted for age and sex.

5.5 LV mass and diastolic function according to eastern/western baseline origin (Study II)

Participants with eastern baseline origin had greater LVM, indexed LVM and lower ejection fraction than subjects with western origin. Concerning LV diastolic function, subjects with baseline origin in east had higher E/e'-ratio and LV end-diastolic volume but no difference in left atrial end-systolic volume or E/A- ratio.

Table 4. Echocardiography measurements according to eastern/western baseline origin. Mean ± SE and p-value; adjusted for age, sex and area of examination in 2011.

	Eastern	**Western**	
	Mean ± SE	Mean ± SE	**P for difference**
N range	902-941	1005-1022	
LV mass, g	139± 1.0	135± 1.0	**0.006**
LV mass, indexed, g/m$^{2.7}$	31.5± 0.2	30.4± 0.2	**0.0008**
Ejection fraction, %	58.1± 0.1	58.4± 0.1	**0.04**
Left atrium end-systolic volume, ml	43.4± 0.5	44.0± 0.5	**0.45**
LV end-diastolic volume, ml	135± 0.9	131± 0.9	**0.001**
E/e'- ratio	4.86± 0.03	4.74± 0.03	**0.02**
E/A- ratio	1.55± 0.01	1.55±0.01	**0.57**

The mean±SE for LVM in men was 158±33 g and with allometric index 32.5±6.9 g/m$^{2.7}$ (N=862). In women, the mean±SE for LVM and indexed LVM were 115±33 g and 29.4±6.1 g/m$^{2.7}$, respectively (N=1045). Indexed LVM according to eastern/western baseline origin, current residency and family origin is shown in Figure 9a (adjusted for age, sex and area of examination in 2011). In all comparisons, the eastern participants had higher indexed LVM compared to their western peers. The most pronounced east-west difference in LVM was found when the participants were studied according their current place of residency. There was no sex*geographic origin interaction, indicating that the results were similar for men and women. When the analyses were adjusted additionally for CHD risk factors at baseline and currently, the east-west differences in indexed LVM persisted (Figure 9b).

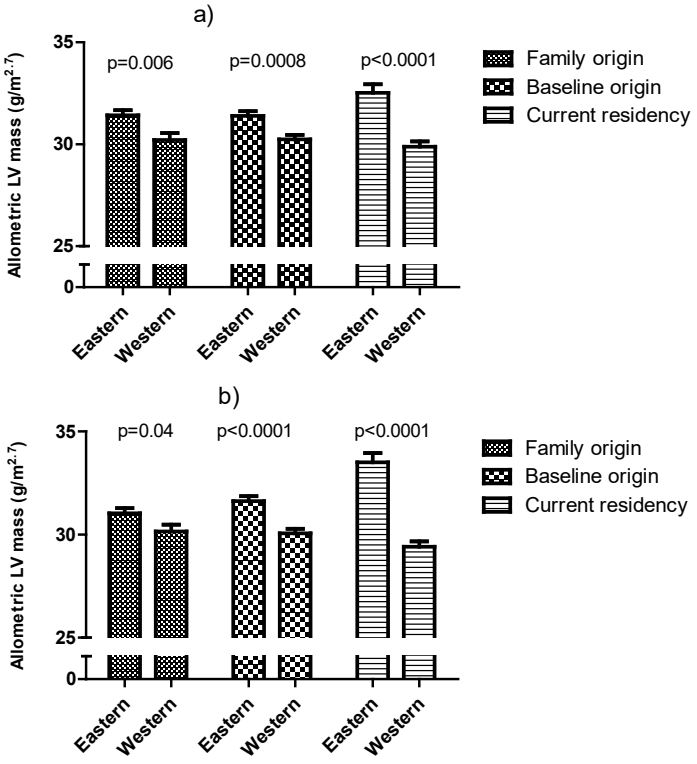


Figure 9. LV mass (allometric index, mean and SE). **a)** for participants with baseline origin in east (N=902) / west (N=1005), current residency in east (N=653) / west (N=1254), family origin in east (N=672) / west (N=401); adjusted for age, sex and area of examination in 2011. **b)** for participants with baseline origin in east (N=645) / west (N=745), current residency in east (N=465) / west (N=925), family origin in east (N=499) / west (N=309); adjusted for age, sex, examination area in 2011, risk factors at baseline (BMI, systolic blood pressure, total cholesterol, birthweight, parental SES, physical activity) and currently (BMI, systolic blood pressure, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity)

The average E/e'-ratio was 4.6±1.0 in men (N=887) and 5.0±1.0 in women (N=1051). The E/e'-ratio according to eastern/western baseline origin, current residency or family origin is shown in Figure 10a. The western participants had better diastolic function than eastern peers according to baseline origin, current residency and family origin. There was no sex*geographic origin interaction indicating that the results were similar for men and women. To examine the independent association between geographic origin and E/e'-ratio, CHD risk factors at baseline and currently were included in the analyses (Figure 10b). When adjusted additionally for the CHD risk factors, the east-west difference in E/e'-ratio according to family origin was no longer significant but persisted for differences according to baseline origin or current residency.

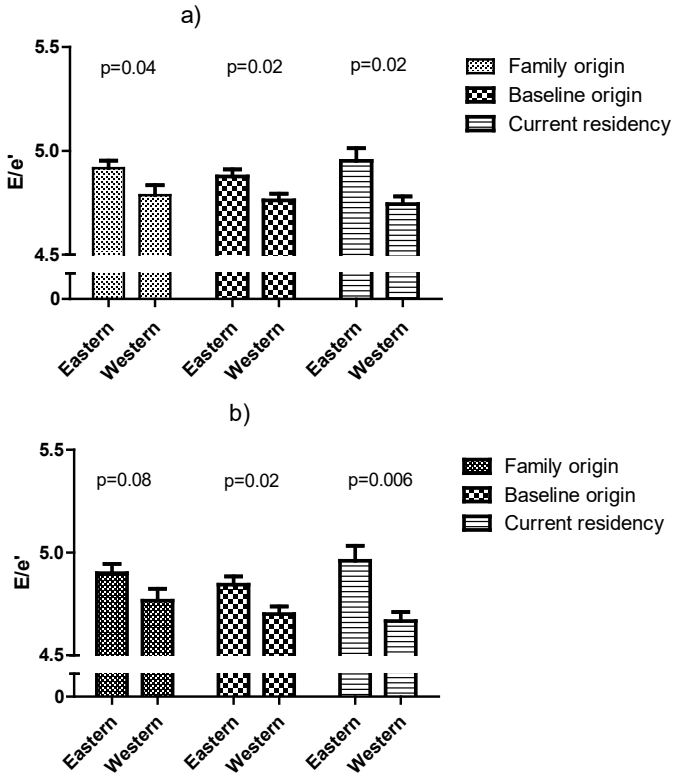


Figure 10. E/e' - ratio (Mean and SE). **a)** for participants with baseline origin in east (N=920) / west (N=1017), current residency in east (N=680)/ west (N=1257), family origin in east (N=684) / west (N=407), adjusted for age, sex and area of examination in 2011. **b)** for participants with baseline origin in east (N=655) / west (N=752), current residency in east (N=484) / west (N=923), family origin in east (N=505) / west (N=312), adjusted for age, sex, examination area in 2011, risk factors at baseline (BMI, SBP, total cholesterol, birthweight, parental SES, physical activity) and currently(BMI, SBP, total cholesterol, plasma glucose, prevalence of smoking, own SES and physical activity).

5.6 Urban-rural differences in CHD risk factors, carotid IMT and LVM (Study IV)

Men and women were equally divided into urban and rural groups (Table 5). Participants from urban baseline residency were, on average, older than those with rural baseline origin. Urban baseline origin was associated with lower SBP, higher alcohol consumption and SES, and a tendency for lower LDL-cholesterol. Carotid IMT was similar between the groups but urban baseline origin was associated with lower LVM compared to rural baseline origin.

Table 5. CHD risk factors, carotid IMT and LVM in adulthood according to urban-rural baseline origin. Values are expressed as mean ± SD or median [interquartile range]*. Data is primarily from the 2011 follow-up (71.5% of the adult data), but in case of missing data from 2011, data from 2007 (13.8 of the adult data) or 2001 (14.7% of the adult data) were used.

	Urban		Rural		
	Mean	±SD	Mean	±SD	P for difference
N range	1004–1394		1395–1509		
Males (%)	46.7		45.2		**0.41**
Age (years)	39.9	±6.2	39.2	±6.6	**0.001**
Body mass index (kg/m²)	26.3	±4.9	26.4	±5.1	**0.50**
Systolic blood pressure (mmHg)	119	±14	120	±15	**0.0004**
Diastolic blood pressure (mmHg)	75	±11	75	±11	**0.98**
Total cholesterol (mmol/l)	5.15	±1.0	5.18	±1.0	**0.26**
HDL-cholesterol (mmol/l)	1.33	±0.3	1.32	±0.3	**0.55**
LDL-cholesterol (mmol/l)	3.22	±0.8	3.27	±0.8	**0.051**
Triglycerides (mmol/l)*	1.05	[0.81]	1.05	[0.71]	**0.26**
Insulin (mU/l)*	7.57	[7.21]	7.18	[7.04]	**0.41**
Glucose (mmol/l)*	5.25	[0.74]	5.25	[0.63]	**0.79**
Metabolic syndrome (%)	21.3		21.5		**0.50**
Type 2 diabetes (%)	3.5		3.8		**0.65**
Smoking (%)	20.8		20.0		**0.55**
Physical activity index (range 5-15)	9.0	±1.9	8.9	±1.8	**0.33**
SES (school years)	15.4	±3.6	14.7	±3.5	**<0.0001**
Alcohol consumption (doses per week)*	3.5	[7.0}	3.0	[5.0]	**0.0003**
Carotid IMT (in 2007, mm)	0.62	0.09	0.62	0.10	**0.56**
LV mass (g/m$^{2.7}$)	30.42	6.55	31.10	6.66	**0.01**

5.7 Association of migration with CHD risk factors and carotid IMT

5.7.1 Details of east-to-west and urban-rural migration (Studies I, IV)

Most of those who moved east-to-west lived in the Helsinki area in 2007 (n=231, 79%). Majority (n=223, 77%) of those that moved east-to-west had done so by 2001, while 23 (8%) migrated later and 45 (15%) lacked data of place of residence in 2001. When analyzing for the association of east-west-migration with rural-urban-migration, we noticed that 37% of east-to-west migraters also moved from rural to urban areas and 43% stayed in urban areas while moving from east-to-west. Thus 80% of those who migrated from eastern to western Finland lived in urban communities in 2011.

Table 6. Directions of east-to-west-migration and association with urban-rural residency.

Participants who moved from eastern Finland to western Finland between 1980 and 2007 (n=291)				
Area of residence in 1980	**Area of residence in 2007**			
	Helsinki area	**Turku area**	**Tampere area**	**Total**
Kuopio area	180	7	29	216
Oulu area	51	9	15	75
Total	**231**	16	44	291
	Place of residence in 2001			
	Eastern	**Western**	**No data**	
	23	223	45	
Association with urban/rural residency (N=288)				
	Rural 1980 Urban 2011	**Urban 1980 Urban 2011**	**Rural 1980 Rural 2011**	**Urban 1980 Rural 2011**
	106 / 37%	124/ 43%	31/ 11%	27/ 9%

5.7.2 East-west migration and CHD risk factors (Study I)

In 2007, participants that moved east-to-west between 1980 and 2007 had, on average, lower BMI, waist circumference, SBP, DBP, serum insulin and glucose, prevalence of hypertension, metabolic syndrome and prevalence of smoking as well as higher diet score and SES than participants who lived in east both in 1980 and 2007 (Table 7). Compared to those who lived in west both 1980 and 2007, participants who migrated east-to-west had lower BMI and waist circumference but

higher SBP and DBP. The east-to-west-migraters had a higher diet score, SES and physical activity than those who continuously lived in west.

Because of the significant difference in SES between the groups, we made further adjustment to the prior analyses for adulthood SES. After the adjustment, smoking and physical activity between the groups was similar. Difference in the diet score between east-to-west-migraters and those who continuously lived in west also became non-significant (data not shown for the analyses adjusted with SES).

Table 7. CHD risk factors (mean±SD or median [interquartile range]*) in 2007 according to east-west migration. The probability values show significance compared to the East 1980 West 2007 group, adjusted for sex and age.

	Eastern 1980 Western 2007	**Eastern 1980 Eastern 2007**		**Western 1980 Western 2007**	
	Mean ±SD	Mean ±SD	**P1**	Mean ±SD	**P2**
N range	239–291	652–771		952–1106	
Males (%)	45	45	**0.86**	46	**0.89**
Age (years)	37.6±5.0	37.9±4.9	**0.36**	37.5±5.1	**0.99**
Body mass index (kg/m²)	25.3±4.3	26.2±4.5	**0.02**	26.1±5.0	**0.04**
Waist (cm)	85.7±12.8	88.6±12.8	**0.001**	89.4±14.0	**<0.0001**
Systolic blood pressure (mmHg)	120±15	127±15	**<0.0001**	118±14	**0.02**
Diastolic blood pressure (mmHg)	77±12	80±12	**<0.0001**	74±12	**0.0003**
Total cholesterol (mmol/l)	5.03±0.96	5.09±0.88	**0.77**	5.02±0.91	**1.00**
HDL-cholesterol (mmol/l)	1.36±0.34	1.34±0.32	**0.57**	1.33±0.33	**0.51**
LDL-cholesterol (mmol/l)	3.06±0.85	3.14±0.76	**0.49**	3.07±0.79	**1.00**
ApoA1 (g/l)	1.60±0.26	1.60±0.26	**0.94**	1.60±0.25	**0.97**
ApoB (g/l)	1.01±0.28	1.04±0.26	**0.28**	1.02±0.27	**0.88**
Triglycerides (mmol/l)*	1.05[0.81]	1.15[0.81]	**0.67**	1.05[0.92]	**0.84**
Insulin (mU/l)*	6.05[5.87]	7.48[6.30]	**0.0007**	5.77[5.86]	**0.10**
Glucose (mmol/l)*	5.15[0.64]	5.25[0.53]	**0.004**	5.25[0.63]	**0.08**
Metabolic syndrome (%)	13	21	**0.01**	18	**0.08**
Type 2 diabetes (%)	1.7	1.2	**0.45**	1.7	**1.00**
Diet score (range 0-27)	14.4±4.0	13.3±4.0	**<0.0001**	13.6±4.1	**0.02**
Smoking (%)	14	21	**0.01**	18	**0.14**
Physical activity index (range 5-15)	9.1± 1.7	8.8±1.8	**0.08**	8.8±1.9	**0.01**
SES (school years)	16.6±3.3	15.0±3.3	**<0.0001**	15.3±3.6	**<0.0001**
Alcohol consumption (doses per week)*	3[8]	4[8]	**0.17**	4[9]	**0.99**

We found a significant sex*east-west-migration interaction in total, HDL- and LDL-cholesterol, ApoB, triglycerides and insulin suggesting that the associations between the groups in these outcomes were different in males and females. Thus, these variables were analyzed separately for the sexes (data not shown). In men, these variables were found similar between the east-west groups. In women, those who moved east-to-west had lower total and LDL-cholesterol, ApoB, triglycerides and insulin, and higher HDL-cholesterol concentration than those who stayed in east. Compared to women who continuously lived in west, those who moved east-to-west had lower insulin and ApoB, and higher HDL-cholesterol.

5.7.3 East-west migration and carotid IMT (Study I)

East-to-west-migraters had lower IMT than those who continuously lived in east but the IMT was similar to those who continuously lived in west (Figure 11a). The results remained similar when the analyses were adjusted for the CHD risk factors that showed difference between the groups in 2007 (Figure 11b), and also in 1980 (Figure 11c).

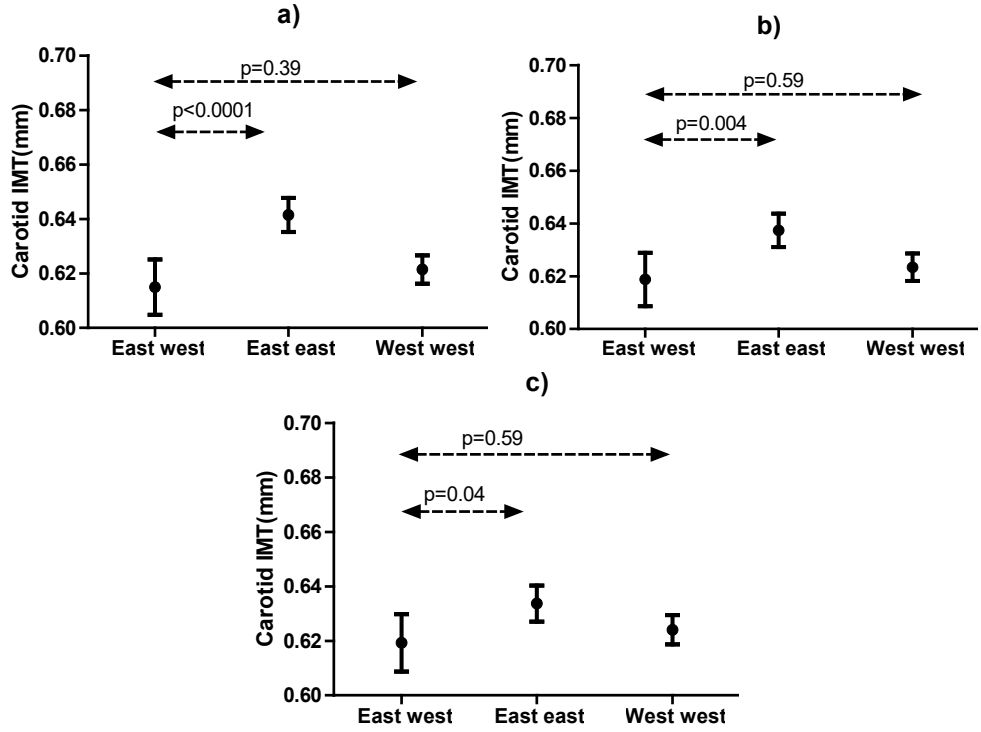


Figure 11. Association of east-west migration with carotid IMT (mean and 95% confidence intervals). The East1980-West2007 (n=243) group is compared to East1980-East2007 (n=626) and West1980-West2007 (n=923) groups. a) Adjusted for age and sex. b) Additionally to a), adjusted for risk markers that differed between the groups in 2007. c) Additionally to a), adjusted for risk markers that differed between the groups in 1980 and 2007.

5.7.4 Urban-rural migration and CHD risk factors (Study IV)

In 2011 those who had moved from rural surroundings to urban areas between 1980 and 2011 were younger but had essentially similar CHD risk factor profile than those who continuously lived in urban areas. Compared to participants who continuously lived in rural areas, rural-to-urban migraters were younger, had lower BMI and waist circumference, and higher SES. Compared to those who migrated from urban-to-rural surroundings between 1980 and 2011, rural-to-urban migraters had lower BMI, waist circumference and DBP, lower prevalence of smoking and higher SES.

Table 8. CHD risk factors (mean±SD or median [interquartile range]*) in 2011. The probability values show significance of the difference between the Rural 1980 Urban 2011 group and the Urban 1980 Urban 2011 group (P1), Rural 1980 Rural 2011 group (P2) and Urban 1980 Rural 2011 group (P3), adjusted for sex and age.

	Rural 1980 Urban2011		**Urban 1980 Urban 2011**			**Rural 1980 Rural 2011**			**Urban 1980 Rural 2011**		
	Mean	±SD	Mean	±SD	**P1**	Mean	±SD	**P2**	Mean	±SD	**P3**
N range	406–432		727–775			550–597			223–234		
Men (%)	44.5		46.8		**0.34**	46.1		**0.54**	46.3		**0.60**
Age (years)	41.0	±5.2	41.6	±5.0	**0.02**	41.7	±4.9	**0.02**	41.7	±4.9	**0.06**
Body mass index (kg/m²)	25.9	±4.8	26.3	±5.0	**0.43**	27.1	±5.4	**0.004**	27.1	±4.6	**0.007**
Waist (cm)	89.6	±13.2	91.6	±14.2	**0.06**	93.3	±15.4	**0.001**	93.0	±13.0	**0.01**
Systolic blood pressure (mmHg)	119	±14	117	±14	**0.28**	121	±15	**0.09**	120	±12	**0.77**
Diastolic blood pressure (mmHg)	74	±11	74	±10	**0.93**	75	±11	**0.10**	76	±9	**0.03**
Total cholesterol (mmol/l)	5.15	±0.97	5.17	±0.97	**0.99**	5.22	±0.92	**0.57**	5.22	±0.97	**0.75**
HDL-cholesterol (mmol/l)	1.34	±0.35	1.33	±0.34	**0.95**	1.31	±0.32	**0.32**	1.32	±0.31	**0.88**
LDL-cholesterol (mmol/l)	3.25	±0.81	3.23	±0.84	**0.96**	3.33	±0.83	**0.36**	3.31	±0.85	**0.70**
ApoA1 (g/l)	1.60	±0.25	1.59	±0.25	**0.99**	1.58	±0.22	**0.71**	1.59	±0.24	**0.99**
ApoB (g/l)	1.04	±0.28	1.06	±0.30	**0.63**	1.07	±0.28	**0.20**	1.07	±0.28	**0.51**
Triglycerides (mmol/l)*	0.95	[0.71[	1.05	[0.81]	**0.23**	1.05	[0.81]	**0.29**	1.05	[0.61]	**0.51**
Insulin (mU/l)*	6.79	[6.80]	7.41	[7.36]	**0.39**	7.26	[7.51]	**0.28**	7.57	[6.41]	**0.98**
Glucose (mmol/l)*	5.25	[0.63]	5.25	[0.74]	**0.99**	5.25	[0.63]	**0.77**	5.25	[0.74]	**0.96**
Metabolic syndrome (%)	18.5		21.1		**0.45**	24.4		**0.06**	21.1		**0.51**
Type 2 diabetes (%)	3.6		3.7		**0.94**	4.3		**0.64**	3.4		**0.79**
Smoking (%)	14.4		16.4		**0.38**	12.5		**0.38**	20.6		**0.04**
Physical activity index (range 5-15)	9.1	±1.9	9.1	±2.0	**1.00**	8.9	±1.8	**0.44**	8.9	±1.8	**0.27**
SES (school years)	16.0	±3.6	15.9	±3.8	**0.95**	14.5	±3.3	**<0.0001**	14.6	±3.1	**<0.001**
Alcohol consumption (drinks per week)*	3.0	[5.0]	3.5	[7.3]	**0.91**	2.0	[5.7]	**0.35**	3.3	[8.0]	**0.69**

5.7.5 Urban-rural migration and carotid IMT (Study IV)

Participants who had migrated from rural to urban areas by adulthood had significantly lower IMT than participants who had migrated from urban to rural areas (Figure 12). Participants who had continuously lived in urban areas had significantly lower IMT compared to participants who had continuously lived in rural communities or who had migrated to rural areas as adults. To examine if the association of migration with IMT was mediated by CHD risk factors, the analyses were adjusted for risk factor levels at baseline. The results remained similar with the exception of lack of difference between participants who had continuously lived in urban or rural areas (p=0.42), and the emerged difference (p=0.03) between participants who had continuously lived in rural areas and those who had moved to rural areas by adulthood.

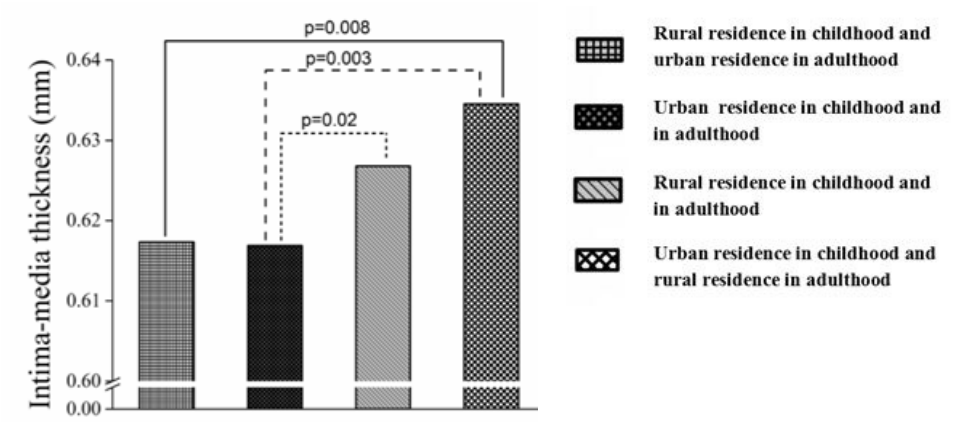


Figure 12. Carotid IMT (mean) in 2007 in the rural-urban migration.

6 Discussion

6.1 Participants

This study comprised of participants in YFS which is an on-going epidemiological study of CVD risk factors and surrogate markers (Raitakari et al. 2008). Individuals aged 3, 6, 9, 12, 15 and 18 years in 1980 were invited (n=4,320) to a cross-sectional baseline survey and 3,596 took part (83.2% of those invited). The sampling frame was designed to establish a cohort that reliably represented Finnish children and adolescents. The participants were equally from both sexes and from urban and rural areas. Replies obtained from the non-participating families revealed no systematic reason for non-participation. Thus, the final sample in 1980 was concluded to be representative of the total random sample (Raitakari et al., 2008).

Of the original study cohort in 1980, a total of 2,204 individuals (61.3%) participated in the 2007 follow-up and 2,063 individuals in the 2011 follow-up (57.4%). Non-participation at follow-up is a common limitation in longitudinal studies, particularly when non-participation is differential. However, participation of this study group in the follow-up studies has been dynamic, with few exceptions. In the 1980's the loss-to-follow-ups were more often men, smokers and older (210) and in 2001, loss-to-follow-ups were more often men and younger than follow-ups (Juonala et al., 2004). However, there were no differences in men or women between participants and loss-to-follow-ups in terms of total cholesterol, blood pressure, BMI or physical activity (10).

To summarise, the sample size of this study had sufficient power for the statistical analyses, and the randomly selected study population represented the original study population. Hence, the results in this study can be generalized to Caucasian populations consisting of apparently healthy individuals.

6.2 Methods

Since the methods for laboratory measurements including lipid levels are well standardized, the results are reliable. All assays were performed in the Laboratory for Population Research of the National Institute for Health and Welfare (Turku, Finland) and the following methods of the laboratory are also accredited by the

Finnish Accreditation Service according to standard ISO / IEC17025: total cholesterol, HDL cholesterol and triglycerides, glucose. Due to changes in methods or reagents between follow-ups, values were adjusted using correction factors determined from linear regression analysis using standardized principal component adjustments. In addition, lack of systematic changes in the lipid and glucose levels during follow-up lend support to the stability of these essential laboratory methods.

BMI and blood pressure measurements have remained uniform throughout the study and therefore can be compared from time-point to time-point, although blood pressure differences between study areas should be interpreted with caution (211). Self-reported questionnaire measures of physical activity and smoking may constitute a potential limitation due to recall or reporting bias. Nevertheless, they are widely accepted and affordable instruments for evaluating health behaviours, and have been consistently measured through follow-ups.

For estimating LVM, we used echocardiographic measurement although cardiac magnetic resonance has become the gold standard (212). Echocardiographic measurement of LVM is based on the assumption that the LV has an ellipsoid shape with a symmetric hypertrophic distribution. As linear measures are cubed, even small measurement errors have an impact on accuracy. Nonetheless, the echocardiographic measurement is still a widely-used method in clinical practice due to its accuracy, low cost, good accessibility and fastness (213), especially in large study populations (206).

In our study, echocardiography has been performed only at one time point, thus longitudinal estimation of change in cardiac shape cannot be made. To model diastolic function, a strain-analysis would have been even more accurate than the measurements available in this study (214). Ejection fraction was calculated from measurements made in a single plane. It is also unknown whether any baseline differences in LV structure and function existed. Despite the east-west differences in LV mass and E/e'-ratio was the majority of our study population well within the normal values and thus it is too early to say whether east-west differences in prevalence of actual LV hypertrophy and diastolic dysfunction will be seen.

Echocardiography was performed with same methods and devices but by different sonographer in each five centres. This might contribute to the results between different areas and thus east-west differences in echocardiographic measurements. The echo images were, however, interpreted by the same observer. Both the sonographer and the observer were blinded to the subjects' details.

Measuring the far wall of the common carotid artery, as done in the YFS, has been shown be the most reliable method for assessing carotid IMT (215). Meta-analyses conclude, however, that common carotid artery IMT alone improves only scarcely predictive influence beyond traditional risk factors, whereas including the carotid bulb and interior carotid artery IMT improves prediction of both cardiac risk

and stroke risk (216). Far wall measurements of the common carotid artery alone have been favored in population studies because the common carotid artery is easily assessable, reproducible and perpendicular to the ultrasound beam (174,217).

6.3 Results

6.3.1 East-west differences in CHD risk factors at baseline (1980), longitudinally 1980-2011 and currently (2011)

The excess CHD mortality among eastern Finns in the 1960s was accompanied by higher prevalence of hypertension, smoking and hypercholesterolemia compared with individuals from other nations and those from western Finland (1). In the nationwide FINRISK-study in 1982, total cholesterol levels among men and SBP levels in both men and women in eastern Finland remained higher than among men/women from western Finland (Turku/Loimaa). YFS participants (aged 3-18 years) with baseline eastern origin had higher SBP and DBP, total and LDL-cholesterol than western participants at baseline in 1980.

In prior publications of YFS, eastern participants had higher total and LDL-cholesterol levels at baseline (1980) (218), and in 2001 higher total cholesterol and blood pressure levels (10) than the western participants. In this study, those with eastern baseline origin had higher average blood pressure, total and LDL-cholesterol, triglycerides, ApoB, and glucose levels than western participants when longitudinal data from 1980 to 2011 was applied. Currently (2011) there were no differences in traditional CHD risk factors between participants with eastern or western baseline origin in this study. Our findings on the longitudinal data indicate that despite similar CHD risk factor levels currently in the eastern and western Finns, there remains a residual burden or legacy effect of higher CHD risk factors from past decades in the east, as has also been suggested earlier (3) (51).

In the FINRISK-study the regional differences in total cholesterol have been constant in both sexes except for men in 2007. The highest levels have been measured at each follow-up in one of the eastern areas (North Karelia, Northern Savo or Northern Ostrobothnia/Kainuu) and the lowest levels in either one of the western areas (Turku/Loimaa or Helsinki/Vantaa) (219). In SBP, regional differences have been present in both men and women from 1982 to 2012 with highest levels constantly in one of the eastern and lowest levels in one of the western areas. In DBP, regional differences have been mostly present since 1982 but continuous and systematic east-west difference could not be found. The researchers of the FINRISK-study have not reported specific east-west-differences of the CHD risk factor levels but rather analysed whether there existed any differences between several study

areas. Therefore, differences in CHD risk factors between eastern and western Finns cannot be exclusively studied in the FINRISK-study.

The association of health behaviours with the CHD risk factors in relation to the observed east-west differences would be a very interesting topic but cannot be fully studied in YFS. The FINRISK/FINDIET-study reported the effect of dietary changes corresponding to 0.3-0.5 mmol/l change in serum total cholesterol in their study between 1982-2012 (220). Analyses for the effect of dietary changes on total cholesterol differences specifically between eastern and western Finns have nevertheless not been reported. The FINDIET-study (221) also found that salt intake among Finns reduced from 13 g/day to 8–9 g/day in men and from11 g/day to 7 g/d in women between 1979 and 2007. As YFS participants are representative of the Finnish population we suspect that their dietary choices and nutritional intakes are in accordance with the FINRISK/FINDIET-studies.

Currently there were no differences in smoking, physical activity or alcohol consumption between participants with eastern or western baseline origin. Earlier publications in the YFS study have reported that in 2001 smoking was more frequent among participants living in eastern Finland (10), which could associate with their higher LDL-cholesterol in longitudinal analyses (222) and increase in their CVD risk (147).

In the last years (from 2011 to 2017) the prevalence of active smoking and serum total cholesterol have decreased in the Finnish population according to the FINRISK-study. The amount of overweight instead increased in the FINRISK- study from 2011 to 2017 (42)

6.3.2 CHD mortality in relation to east-west differences in CHD risk factors

The narrowing of east-west differences in CHD risk factors observed in this study has occurred in conjunction with an overall decline in CHD risk factor levels and CHD mortality in Finland. In Finland the CHD mortality fell by over 80% among working-age men and women from 1972 to 2012 (3). In impact analyses of the FINRISK-cohort, the diminishing CHD risk factor levels in the population accounted for over 95% of the reduction in CHD mortality in the 1970s (46) and two thirds of the CHD mortality reduction from 2002 to 2012. The remaining last third of the decline in CHD mortality in the latest decade was due to changes in other primary risk factors such as diet and physical activity, and secondary prevention with medication and the treatment of acute cardiac events (3).

In the latest FINRISK-study, the CHD mortality in 35-74 year-old Finns was 17% lower in western men and 15% lower among western women than in eastern Finland (3). According to the National Institute for Health and Welfare's data from

2016, eastern men continued to have 21% higher and eastern women 19% higher CHD mortality than western men/women, respectively. The higher CHD mortality still found in eastern Finns compared with western Finns supports the legacy effect of an earlier, higher risk CHD profile. This kind of legacy effect is known earlier from cholesterol-lowering drugs for instance: the WOSCOPS-study found that treatment with pravastatin for 5-years reducing CV mortality and hospitalizations over a 20-year period (223).

Finland was settled from two directions (59) and genetic differences between eastern and western Finns are larger than between some nations in Europe. It has also been suggested (224) that being born in East Finland is a more important CHD risk factor than is living there. This might be due to genetics, epigenetics or inherited health behaviours.

Earlier studies have suggested that genetic differences within Finland could contribute to the observed east-west difference in CHD risk factor levels (9) and CHD risk (47). Twin studies suggested an association of genetics with CHD (51,63) (225,226). Family history of CHD (64,227) and several genetic factors (228) have been found to associate with CHD risk. The genetic factors cannot, however, explain the remarkable decline in CHD mortality especially in eastern Finland as the population has remained seemingly stable within the last decades.

6.3.3 Carotid IMT, LV mass and diastolic function according to eastern/western baseline origin

Participants with eastern baseline origin had higher adult carotid IMT than participants with baseline origin in western Finland, independently of CDH risk factors. Higher IMT among participants currently living in eastern Finland compared to western participants was also observed in 2001 (11). In a Finnish-based population living in Sweden higher IMT was found in men originating from Eastern Finland compared to men originating from western Finland (51).

Participants with baseline origin or current residency in east Finland also had higher LVM and higher E/e'-ratio, indicating subtle differences in diastolic function, in 2011 compared to their western peers. These associations were independent of childhood and adulthood CHD risk factors. Of note, most of our middle-aged population was well within the normal limits for LVM and E/e'. LV hypertrophy pathogenesis initiates usually with essential arterial hypertension, reversibly reduction in blood pressure is marked with regression of LV hypertrophy (179). As the results in this study show, eastern participants have had higher SBP in the 31-year analyses, which probably contributes to the higher LVM. Nevertheless, LVM in east was higher than in west independently of baseline and current risk factors, including blood pressure. Higher LVM, E/e'- ratio and carotid IMT support the

hypothesis of a persisting increased risk for CVDs in eastern Finns compared to western Finns also in the future despite that the risk factor levels are currently evening out.

LV diastolic function is associated to LV end-diastolic volume and E/A-ratio besides E/e'- function (198). In this study, both E/e' and LV end-diastolic volume were higher among subjects with eastern baseline origin compared to western subjects, thus indicating less effective diastolic function among eastern Finns. A well-established marker of diastolic function, E/A-ratio, showed no east-west difference in the study. E/A- ratio typically declines in grade I diastolic dysfunction and then increases in more severe stages (194). This narrows its usefulness in study populations although it is an excellent tool in the clinical practice when individual age and echocardiography are taken into account. Another marker of LV diastolic dysfunction, the volume of LA, also remained unchanged in this study. This is probably explained by the young age of the study group when considering CVDs. The volume change of the LA needs longer exposure time to develop than a change in the E/e'-ratio (229,230).

Eastern family origin, i.e. the number of eastern grandparents, associated with higher LV mass and diastolic function, in line with previously reported higher carotid IMT and lower brachial flow-mediated dilation in subjects with eastern family origin when compared to peers with western family origin (11). The effect of family origin might be a result of genetics, inherited health behaviour differences, epigenetics or a result of all these. In this study, the subject's current residency was not controlled in the analyses of family origin and may thus affect the association of the family origin with LV mass and diastolic function. This study also suggests that migration has contributed to east-west differences in LV structure and function as the observed differences in LV mass and E/e' were greater according to current residency than according to baseline origin.

Findings on geographical differences in LV mass and diastolic function are limited. Geographic difference in LVM has been found earlier in Germany, where north-eastern individuals had higher LVM than south-western individuals (231). A systematic review of 33 studies from different countries showed that normal values for LVM differ essentially between different nations and ethnicities (232).

6.3.4 Urban-rural differences in CHD risk factors, carotid IMT and LVM

In childhood, participants of this study living in urban communities had better levels in several CHD risk factors than those living in rural areas. Notable was also the higher SES among urban children's parents compared to rural children's parents. In adulthood, the differences had mostly levelled off. In 2011, participants with

baseline origin in urban communities had lower SBP than those with baseline origin in rural areas, but otherwise the CHD risk profile was similar. The findings are not as evident as in the PURE study, a broad study of cardiac risk factors and CVDs among adults (n=156,424, mean age 50.7 years) in urban and rural communities on five continents, which reported higher INTERHEART Risk Score in rural areas compared to urban ones in high income countries (Sweden, Canada, and United Arab Emirates) (6). In the PURE-study, no significant urban-rural difference was observed for major CVDs. In this study, significant urban-rural differences were shown for LVM. The differences were not fully attenuated with adjustment for CHD risk factors in childhood and adulthood.

Prior results from the GOAL cohort study, comprising 2,815 elderly Finnish men and women aged 52 to 76 years, showed significant urban-rural differences in serum total cholesterol and BMI that could be mainly explained by SES (education) (7). Our results are not as pronounced as the GOAL-cohort's observations. As rural-urban-migration is associated with improvement in CHD risk profile, the urban-rural-differences would be more pronounced if we compared participants according to their current urban/rural place of residence. In the FINRISK-study, urban-rural perspective is not comprehensively studied. Eastern areas in the FINRISK-study can be considered also rural whereas western areas as urban (219) even if the study is not designed for comparison of urban and rural areas.

Behavioural and dietary factors may contribute to the differences observed in lipids and blood pressure. In the rural communities, fewer healthy dietary choices may be available compared to modern urban areas and access to public health care can vary. Prior results from a national dietary survey by the National Institute for Health and Welfare revealed that rural individuals consume less vegetable and use more butter than urban residents on average (233).

Urban areas of Finland locate nowadays mostly in western Finland whereas eastern Finland can be considered mostly rural. The results of the present study remained almost unchanged with the adjustment for eastern/western baseline origin, however. Hence, the observed urban-rural differences in our study are presumably not explained by the eastern/western origin of the participants.

6.3.5 Migration, CHD risk factors and carotid IMT

Of those who lived in eastern Finland in 1980, 27% had moved to west by 2007, thus migration in our study population has been substantial. Those who moved east-to-west had lower CHD risk factors than participants who continuously lived in east with lower BMI, blood pressure, serum insulin and glucose, for instance. Compared to those who lived in west both 1980 and 2007, participants who migrated east-to-west had no systemically better or worse CHD risk factor profile as their BMI and

waist circumference were lower but SBP and DBP higher. In 2001 lower SBP and DBP were found among east-to-west migraters compared to those who stayed in east in YFS population (10).

Participants who migrated from east-to-west between 1980 and 2007 had lower carotid IMT in 2007 than participants who stayed in east but no difference to those who continuously lived in west. The difference in IMT between east-to-west migraters and those who stayed in east remained independent of CHD risk factors, suggesting that other mediators likely exist. Previously in YFS has been shown that carotid IMT increases 0.0057±0.0004 mm/year (234). Applying the vascular age concept (235), the IMT difference between participants who moved east-to-west and those who stayed in east corresponds to a difference of 4.7 years in vascular age, which is even more than the difference between eastern and western Finns (0.0216 mm corresponding to 3.8 years). The differences in CHD morbidity could not been studied because of the young study population. In an earlier study on of middle-aged men living in the Helsinki metropolitan area (western Finland), those born in the Eastern Finland had higher risk for sudden cardiac death than men born in Western Finland (67)

Participants who had migrated from rural to urban communities by adulthood had similar CHD risk factor profile and carotid IMT in adulthood than those who continuously lived in urban areas. Rural-to-urban- migraters had instead lower BMI and waist circumference than those moved from urban to rural areas between 1980-2011 and lower BMI, waist circumference, carotid IMT and prevalence of smoking than those who continuously lived in rural areas. Migrating from rural-to-urban was thus associated with improvements in CV health similarly to east-to-west-migration. Improvements seemed to be clearer in east-to-west-migration, however. Earlier studies on association of urban-rural migration with subclinical atherosclerosis are limited. Urban Chinese living in Hong Kong and Australia were found to have higher IMT than Chinese living rural areas (5). These results are, however, not comparable to high income Western country such as Finland where rural lifestyle has become increasingly sedentary because of mechanization of agricultural work whereas in China the risk of atherosclerosis has been traditionally very low in rural areas due to environmental factors.

Participants who moved east-to-west had higher SES than participants continuously living in east or west. They also smoked less than those who continuously lived in east and were physically more active than those who continuously lived in west, but adjustment with SES diluted these differences. This suggests that the higher SES among participants who moved east-to-west contributed to their healthier CV lifestyle. Participants who moved from rural to urban areas had higher SES than participants who continuously lived in rural areas or moved urban-to-rural and also smoked less than those who moved urban-to-rural. Higher SES

among those who moved east-to-west or rural-to-urban likely contributed to better health awareness and cardiometabolic risk markers as other studies (157) and YFS previous publications have observed (56). This study cannot provide data whether migration was a cause or a consequence of higher SES. The data and our knowledge on migration in Finland mainly supports that both those who already are highly educated and those targeting for high education are prone to move from east to west, or from rural to urban areas.

Similar studies of SES's association with migration and its influence on CV health are not easily found in other populations. In Germany lower CVD mortality rates were observed among ethnic Germans who had moved from the former Soviet Union to Germany compared to a general German population (236). The researchers found higher perceived SES as a possible explanation to this phenomenon.

Superior CV health in those who migrate from A to B compared to those who stay in place A has been earlier found in the Great Britain, where middle-aged men who moved from other parts of the country to South Britain had lower CVD mortality than men in the rest of the country (75). Controversial results were found in Hawaii where men with Japanese ancestry have an excessive CHD risk compared with men living in Japan and higher CHD risk factor levels were suggested as an explanation (76). Indian Gujaratis living in the Great Britain / United Kingdom were also found to have excessive CHD risk factors compared with their Indian contemporaries (237).

6.4 Strengths and limitations

The prospective study design, follow-up time extending 30 years, detailed phenotyping of YFS participants and standardized laboratory methods are the main strengths of this study. Of the original 3,596 participants at baseline (1980), over 57% (2063) participated in the latest follow-up over 30 years later, in 2011. Even if CHD and other CVDs are still somewhat rare in the middle-aged population, ultrasonography measurements of carotid IMT and echocardiography contribute to the clinical implications of the study.

In longitudinal studies an inevitable limitation is non-participation at follow-up. In this study, baseline CHD risk factors were similar among participants and non-participants, and the study group has been dynamic as discussed previously. Therefore, the present study population was likely representative of the original population. However, loss to follow-up was greater in cigarette smokers who also had higher SBP and DBP in the 2007 and 2011 follow-ups, which might have differentially affected secular trend analyses in blood pressure levels and the prevalence of smoking and the metabolic syndrome.

Diagnosis of type 2 diabetes using fasting glucose and HbA1c should be based on repeated measurements to rule out the laboratory error, which was not possible in this study. The established diagnostic thresholds for diabetes have been developed for plasma glucose (American Diabetes Association 2013) but were determined from serum samples in this study. The differences between these two methods are minimal, however. Blood pressure was measured using random-zero sphygmomanometers which may have resulted in a downward bias in the blood pressure levels (Yang et al. 2008). Therefore, the prevalence of hypertension and the metabolic syndrome may be lower in this study than in similar studies. Blood pressure was measured by a different study nurse in each study center and therefore the regional/east-west-differences in blood pressure must be interpreted with caution (211).

Our classification of participants as those who migrated or not (east-to-west, west-to-east, rural-to-urban or urban-to-rural) is based on information of their place of residence from only a few time points (1980 and 2007 for east-west migration, 1980 and 2011 for urban-rural migration) and does not consider the possibility that some participants may have moved several times between these time-points, nor does it consider at which time the migration occurred.

The methods used to assess diet, e.g. salt intake, have changed during the 30 years of follow-up, beginning since the participants were children at the baseline. Also the questionnaires assessing physical activity habits have been modified during the follow-up to capture as well as possible the behaviour in the given age group.

A further limitation is that questionnaires were used to assess data on lifestyles and e.g. consumption of alcohol. Studies have shown that there is a tendency for under-reporting of own alcohol consumption in questionnaires (238,239).

6.5 Clinical implications

Eastern Finns were shown to have higher CHD mortality and risk factor profile in the Seven Countries Study for over 50 years ago (1) The phenomenon has been followed ever since and east-west differences in both CHD mortality and risk factor levels have been narrowing until nowadays simultaneously with the decline in total CHD mortality (3). This study gives support to the diminishing of CHD risk factors between Finns originating from eastern or western Finland. Our study highlights the success of the North Karelia Project, launched in the 1970's aiming to improve CV health especially in eastern Finland (2), and other health promotion projects in Finland.

However, we found eastern participants having higher burden of CHD risk factors than western participants in longitudinal analyses from childhood to adulthood. In addition, carotid IMT, LV mass and diastolic function, all surrogate

markers of CVDs, were higher among participants with eastern baseline origin. These findings propose that we might find a higher prevalence of CVDs in eastern Finns still in the future. This motivates why eastern Finns should still be a special target in CV health promotion, secondary prevention and regional health care units.

Due to similar risk factor profile observed today, the excess CHD mortality amongst eastern Finns may also vanish in the future. Migration could compromise this improvement, however. Over a quarter of baseline's eastern population had moved to western Finland by 2007. These east-to-west migraters had better CHD risk profile and higher SES and physical activity than those who stayed in east. Higher income, employment rate and SES among east-to-west migraters have also been noticed before (74). These findings support the idea that migration from eastern to western Finland increases the regional differences in the country.

Participants with baseline origin in urban communities had a slightly more favorable CHD risk factor profile and lower LVM compared to individuals originating from rural settings, in line with previous results from Finland (7). It is remarkable that urban-rural and eastern/western terms are associated as most urban citizens are western in the Finnish population. Rural participants had lower SES than their urban peers in this study, which is known to associate with poorer CV and overall health. Our findings suggest that, national focus should be targeted on rural surroundings and promoting CV health should be emphasized to individuals with low SES.

6.6 Future research directions

This thesis did not study genetic differences and their possible impact on CHD risk profile differences between eastern and western Finns. Several studies from the times of Seven Countries Study until the 2010's have suggested that genetic factors might explain the CHD risk factor level differences and mortality differences between east and west (240). This thesis supports that the east-west differences in CHD risk factors have been more associated with diet and lifestyle than genetics.

The YFS is a dynamic, on-going study that has followed the participants since their childhood. As the study population passes middle-age in the near-future, prevalence of CHD and other CVDs increases and possible geographic differences become apparent. As the risk profile of the participants has been followed since childhood, the role of risk factors and health behaviour in explaining the geographic differences of CVDs and the pathophysiology of these diseases should become more evident in the future.

This study reports the CHD risk profile differences between individuals who migrated from eastern to western Finland compared to those who stayed in the east. These differences and reasons underlying should be studied in other study

populations also and future follow-ups of the YFS, with special emphasis on socioeconomic dispersion. Influence of migration on total east-west-differences should also be investigated properly.

Studies on urban-rural differences in CV health are, although worldwide numerous, in Finland only scarce. Socioeconomic disparity seems to contribute to these differences and CV health should be studied also in relation to SES.

7 Summary and Conclusions

Firstly, CHD risk factor profile is currently similar between participants with eastern/western baseline origin in the Young Finns Study (**Study III**). In longitudinal analyses from 1980 to 2011, participants with eastern baseline origin had higher levels in several CHD risk factors, including SBP, total cholesterol and serum glucose. These findings support the view that east-west differences in the CHD mortality will be seen also in the future but the differences are narrowing.

Secondly, geographic origin in eastern Finland associated with higher LVM and E/e' (a marker of LV diastolic function) compared with geographic origin in western Finland (**Study II**). Most echocardiographic results of the participants were, however, well within the normal limits in these variables. These findings suggest that participants with eastern baseline origin might have higher prevalence of LV hypertrophy, diastolic dysfunction and other cardiac diseases in the future compared to participants with western baseline origin.

Thirdly, higher carotid IMT was found in eastern participants compared to western participants (**Study I**). Participants who moved from east to west from 1980 to 2007 had lower carotid IMT, BMI, SBP, serum insulin levels, prevalence of metabolic syndrome and higher SES than those who lived continuously in east. The study could not explain the causality of migration's association with improvements in CV health.

Fourthly, participants living in urban areas had a more favorable CHD risk factor profile and lower LVM than their rural peers (**Study IV**). Migration from rural to urban areas was associated with improvements in CV health when compared to participants who continuously lived in rural areas. Urban-rural differences in CV health could offer opportunities for optimizing prevention by targeting subjects in areas of the highest need.

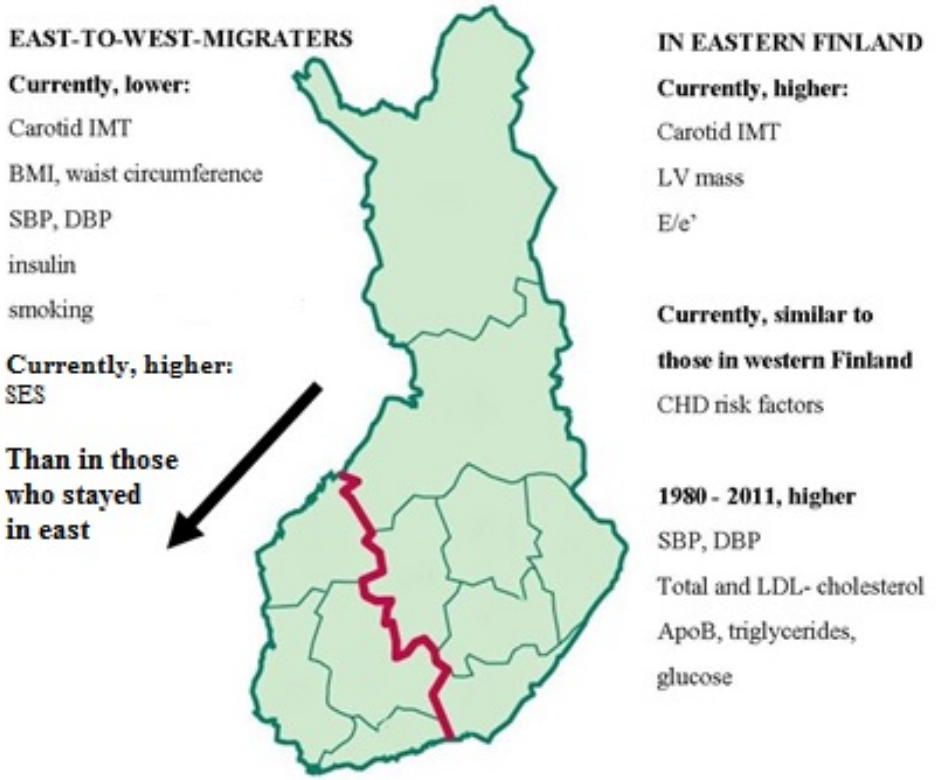


Figure 13. Conclusions of the study. Refers to the conclusions on the page 61.

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Lauri Vähämurto

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