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CVD risk factors and surrogate markers - Urban-rural differences

JOEL NUOTIO^{1,2} , LAURI VÄHÄMURTO¹, KATJA PAHKALA^{1,3},
 COSTAN G. MAGNUSSEN^{1,4}, NINA HUTRI-KÄHÖNEN⁵, MIKA KÄHÖNEN⁶,
 TOMI LAITINEN⁷, LEENA TAITTONEN⁸, PÄIVI TOSSAVAINEN⁹,
 TERHO LEHTIMÄKI¹⁰, EERO JOKINEN¹¹, JORMA S.A. VIIKARI¹², OLLI RAITAKARI¹³
 & MARKUS JUONALA^{1,12,14}

¹Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Finland, ²Heart Centre, Turku University Hospital and University of Turku, Finland, ³Paavo Nurmi Centre, Department of Physical Activity and Health, University of Turku, Finland, ⁴Menzies Research Institute Tasmania, University of Tasmania, Australia, ⁵Department of Paediatrics, University of Tampere and Tampere University Hospital, Finland, ⁶Department of Clinical Physiology, University of Tampere School of Medicine and Tampere University Hospital, Finland, ⁷Department of Clinical Physiology and Nuclear Medicine, University of Eastern Finland and Kuopio University Hospital, Finland, ⁸Vaasa Central Hospital, Finland, ⁹Department of Paediatrics, University of Oulu, Finland, ¹⁰Fimlab Laboratories and Finnish Cardiovascular Research Centre-Tampere, University of Tampere, Finland, ¹¹Department of Pediatric Cardiology, Hospital for Children and Adolescents, University of Helsinki, Finland, ¹²Department of Medicine, University of Turku, Finland, ¹³Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Finland, and ¹⁴Murdoch Children's Research Institute, Melbourne, Australia

Abstract

Aims: Disparity in cardiovascular disease (CVD) mortality and risk factor levels between urban and rural regions has been confirmed worldwide. The aim of this study was to examine how living in different community types (urban-rural) in childhood and adulthood are related to cardiovascular risk factors and surrogate markers of CVD such as carotid intima-media thickness (IMT) and left ventricular mass (LVM). **Methods:** The study population comprised 2903 participants (54.1% female, mean age 10.5 years in 1980) of the Cardiovascular Risk in Young Finns Study who had been clinically examined in 1980 (age 3–18 years) and had participated in at least one adult follow-up (2001–2011). **Results:** In adulthood, urban residents had lower systolic blood pressure (–1 mmHg), LDL-cholesterol (–0.05 mmol/l), lower body mass index (–1.0 kg/m²) and glycosylated haemoglobin levels (–0.05 mmol/mol), and lower prevalence of metabolic syndrome (19.9 v. 23.7%) than their rural counterparts. In addition, participants continuously living in urban areas had significantly lower IMT (–0.01 mm), LVM (1.59 g/m^{2.7}) and pulse wave velocity (–0.22 m/s) and higher carotid artery compliance (0.07%/10 mmHg) compared to persistently rural residents. The differences in surrogate markers of CVD were only partially attenuated when adjusted for cardiovascular risk factors. **Conclusions:** Participants living in urban communities had a more favourable cardiovascular risk factor profile than rural residents. Furthermore, participants continuously living in urban areas had less subclinical markers related to CVD compared with participants living in rural areas. Urban-rural differences in cardiovascular health might provide important opportunities for optimizing prevention by targeting areas of highest need.

Keywords: Atherosclerosis, risk factors, urban, rural, arterial stiffness, left ventricular mass

Correspondence: Joel Nuotio, Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Kiinamylynkatu 10, Turku, FIN-20520, Finland. E-mail: joel.nuotio@utu.fi

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Introduction

Cardiovascular diseases (CVDs) are one of the leading causes of death and disability globally [1]. In the 1960s, coronary heart disease incidence and mortality in Finland were the highest in the world [2]. Remarkable geographic differences were observed in the Seven Countries Study showing that Eastern Finns had markedly higher coronary heart disease mortality and risk factors than Western Finns. Mortality due to coronary heart disease has decreased ever since in Finland and the difference in cardiovascular risk factor levels between Eastern and Western regions has narrowed resulting from successful preventive actions [3]. Still, health inequalities across different regions remain and place of residence is an essential determinant of health [4,5].

Disparity in CVD mortality and risk factor levels between urban and rural regions has been confirmed worldwide [6–8]. Results from the Prospective Urban Rural Study have shown that the rates of cardiovascular events were higher in rural areas than in urban communities in middle-income and low-income countries, though the risk factors were higher in urban communities than in rural settings at the same time [6]. Nevertheless, no differences were observed in the rates of cardiovascular events between urban and rural communities in high-income countries including Sweden [6]. In addition, CVD mortality and risk factors were higher in rural areas than in urban communities in Iceland [9]. Furthermore, results from an earlier 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 [10]. However, the urban–rural differences in cardiovascular risk factor levels and subclinical markers of CVD among working-age population are unknown in Finland and have not been extensively explored in other populations either.

The aim of this study was to examine how living in different community types (urban–rural) is related to CVD factors and subclinical markers of CVD. We report results using data from the Cardiovascular Risk in Young Finns Study with 2903 participants having comprehensive data on CVD risk factors and ultrasonic markers of subclinical CVD.

Methods

Study population

The Cardiovascular Risk in Young Finns Study is a population-based follow-up study on cardiovascular risk factors in Finland [11]. The study has been performed in five Finnish university cities with medical

schools and nearby rural municipalities. The rural communities were chosen considering the following: their industrial structure corresponding to the average of rural communities in the province; the cohorts in the communities should be large enough; the distances should not be impractically long; and the sample should include an equal number of urban and rural population in each area. This study comprised 2903 participants (54.1% female) who had been seen in clinical examination in 1980 and at least once in adult follow-ups. Response rate compared to the baseline study was 73% in all participants (72 % in urban participants and 74% in rural participants according to the place of residence in childhood) in 2001, 62 % for all participants (64% in urban participants and 61 % in rural participants) in 2007, and 59% for all participants (60% in urban participants and 57 % in rural participants) in 2011. Data was primarily from the 2011 follow-up (71.5% of data), but in case of missing data from 2011, data from 2007 (13.8% of data) or 2001 (14.7% of data) were used. Written informed consent was obtained from participants or parents, and the study was approved by local ethics committees.

Place of residence

Living area of participants was classified as urban or rural. At baseline, participants living in university cities were classified as having an urban place of residence, and the municipalities in the vicinity of those cities were classified as rural. In adulthood, area of residence was defined according to questionnaire data: participants living in cities, suburbs or centre of a town were classified as urban and participants living outside a population centre were classified as rural. In sensitivity analyses, the corresponding classification was also used in childhood.

Anthropometry, blood pressure and laboratory measurements

Weight was measured to the nearest 0.1 kg and height to the nearest centimetre. Body mass index (BMI) was calculated as weight/height. Blood pressure was measured with a standard mercury sphygmomanometer in childhood and with a random-zero sphygmomanometer in adulthood. Fasting blood samples were analysed with standard enzymatic methods [11]. Metabolic syndrome was defined according to the Harmonized criteria [12]. The diagnosis of type 2 diabetes included participants with fasting glucose ≥ 7 mmol/l or glycosylated haemoglobin $\geq 6.5\%$ or self-reported diabetes or use of medication [13].

Health behaviours and socioeconomic status

Smoking, alcohol consumption, socioeconomic status (SES), physical activity and attention paid to health habits were assessed by questionnaires. Data on smoking was obtained from participants aged 12–18 years at baseline. Smoking was defined as positive if the participant smoked daily. Alcohol consumption was assessed as standard doses per week. Participants' SES (own/parental) was determined by the amount of school years. Physical activity index was calculated [14]. Attention paid to health habits was assessed on a five-point scale, lower values indicating more attention paid.

Subclinical markers of cardiovascular risk

Carotid artery intima-media thickness (IMT), carotid artery compliance (CAC), pulse wave velocity (PWV), brachial artery flow-mediated dilatation (FMD) and left ventricular mass (LVM) were measured as described earlier [15–17]. LVM was indexed according to height using the allometric power of 2.7 since this indexation has been shown to perform better for obese subjects [18].

Statistical methods

Differences between participants living in urban and rural areas were analysed using independent samples *t*-test for continuous variables. Continuous variables were standardized according to age and sex before analysis. Differences in categorical variables were analysed using Fisher's exact test in childhood and logistic regression models adjusted for age and sex in adulthood. Non-normally distributed variables were square root-transformed before the analyses. The association of SES and Eastern–Western origin with urban–rural differences in cardiovascular 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: (a) participants who had lived in rural areas as a child and had migrated to urban communities by adulthood ($n = 587$); (b) 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 ($n = 283$). Means adjusted for age and sex according to migration were calculated using analysis of covariance. Furthermore, analyses were additionally adjusted for risk factor levels at baseline (systolic blood pressure, total

cholesterol, LDL-cholesterol, triglycerides, parental SES, smoking and physical activity) and in adulthood (BMI, systolic blood pressure, diastolic blood pressure, LDL-cholesterol, glycosylated haemoglobin, SES, alcohol consumption, attention paid to health habits and physical activity) to test whether the association of migration with surrogate markers of CVD was mediated by risk factor levels.

All statistical tests were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) with statistical significance inferred at a 2-tailed *p*-value < 0.05 .

Results*Cardiovascular risk factors according to urban–rural residence in childhood (1980)*

In childhood, participants living in urban areas had significantly lower systolic blood pressure, total cholesterol, LDL-cholesterol and triglyceride levels, were more likely to smoke and were physically more active at the age of 9–18 years compared with their peers living in rural settings (Table I). In addition, urban residents had higher parental SES in childhood than their rural counterparts. No other significant urban–rural differences were observed at baseline in 1980.

Cardiovascular risk factors and subclinical markers CVD in adulthood according to urban–rural residence in childhood (1980)

Participants who had lived in urban communities as a child were significantly older, consumed more alcohol weekly and had higher SES as well as lower systolic blood pressure in adulthood compared to rural residents (Table II). Moreover, urban residents had lower LVM and higher CAC compared to participants with their rural counterparts. No other urban–rural differences were observed in adulthood according to place of residence in childhood.

Cardiovascular risk factors according to urban–rural residence in adulthood (2001–2011)

In adulthood, individuals living in urban settings were younger, had lower BMI, blood pressure, LDL-cholesterol, glycosylated haemoglobin and prevalence of metabolic syndrome than their rural counterparts (Table III). In addition, participants living in urban areas were physically more active, had higher SES and paid more attention to health habits than rural participants while their weekly consumption of alcohol was higher. Furthermore, urban participants also had lower carotid IMT, LVM and higher PWV than rural participants.

Table I. Cardiovascular risk factor levels in childhood (1980) according to urban–rural residence in childhood in participants of the Cardiovascular Risk in Young Finns Study.

	Urban residence		Rural residence		<i>p</i> for difference ^a	
<i>n</i>	1394		1509			
Female %	53.3		54.8		0.43	
Age (years)	10.7	± 5.0	10.3	± 5.0	0.09	
BMI (kg/m ²)	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	
Physical Activity	9–18 years (range 5–14)	9.2	± 1.9	8.9	± 1.7	0.01
	3–6 years (range 9–22)	16.0	± 2.3	16.1	± 2.6	0.18
Parental socioeconomic status (school years)	11.9	± 3.9	10.2	± 3.4	< 0.0001	
Smoking (%)	7.6		5.0		0.005	

Values are expressed as mean ± standard deviation or as proportions (%); *n* varied between 1192 and 1395 in participants living in urban areas and 1244 and 1509 in participants living in rural areas.

^aContinuous variables standardized according to age and sex before analyses; *t*-test used for continuous variables and Fisher's exact *t*-test for categorical variables. Insulin, triglycerides and physical activity (for 9–18 years old participants) were square root-transformed before analyses due to skewed distributions.

Sensitivity analyses

Because of urban–rural difference in SES, we additionally adjusted all prior analyses for parental SES in childhood or participant's own SES in adulthood. With adjustment for parental SES, childhood urban–rural differences (Table I) in systolic blood pressure ($p = 0.052$) and triglycerides ($p = 0.08$) diluted to borderline significant. With adjustment for participant's own adulthood SES, observed urban–rural differences (Table III) in diastolic blood pressure ($p = 0.20$), total cholesterol ($p = 0.18$), glycosylated haemoglobin ($p = 0.27$), weekly alcohol consumption ($p = 0.07$), physical activity ($p = 0.09$) and prevalence of metabolic syndrome ($p = 0.11$) were attenuated in adulthood.

Moreover, the classification of urban–rural residence differed between childhood and adulthood due to the original study design. When the classification of urban–rural residence in childhood (Tables I and II) was made similarly as in adulthood, the results remained unchanged.

Finally, because of the previously observed east–west differences in CVD risk factor levels [19], analyses reported in Tables II and III were adjusted for place of residence (Eastern–Western) at baseline. After the adjustment, results remained similar except for the difference in CAC which became borderline significant ($p = 0.059$) and attenuated differences in

glycosylated haemoglobin ($p = 0.09$) and alcohol consumption ($p = 0.29$).

Association of subclinical markers of CVD and urban–rural migration between childhood and adulthood

Associations of urban–rural migration between childhood and adulthood on subclinical markers of CVD are shown in Figure 1. Participants who had continuously lived in urban areas had significantly lower IMT and LVM compared to participants who had continuously lived in rural communities or who had migrated to rural areas by adulthood. Likewise, these participants had lower PWV and higher CAC compared to participants who had continuously lived in rural communities. In addition, participants continuously living in an urban setting had lower LVM than participants who had lived as a child in rural areas and had migrated to urban communities in adulthood. Furthermore, participants who had migrated to urban areas from rural areas by adulthood had significantly lower IMT and PWV than participants who had migrated to rural areas by adulthood. For PWV, participants who had migrated to urban areas by adulthood compared to participants continuously living in rural communities had significantly lower PWV. No significant differences between the groups were observed for FMD.

Table II. Levels of risk factors and surrogate markers for cardiovascular disease in adulthood according to urban-rural residence in childhood (1980) in participants of the Cardiovascular Risk in Young Finns Study.

	Urban residence		Rural residence		<i>p</i> for difference ^a
<i>n</i>	1394		1509		
Female (%)	53.3		54.8		0.41
Age (years)	39.9	± 6.2	39.2	± 6.6	0.001
BMI (kg/m ²)	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
LDL-cholesterol (mmol/l)	3.22	± 0.8	3.27	± 0.8	0.051
HDL-cholesterol (mmol/l)	1.33	± 0.3	1.32	± 0.3	0.55
Triglycerides (mmol/l)	1.37	± 1.0	1.35	± 1.3	0.26
Glucose (mmol/mol)	5.35	± 0.9	5.37	± 1.1	0.29
Glycosylated haemoglobin (mmol/mol)	36.7	± 5.4	36.8	± 5.2	0.43
Insulin (mU/l)	9.77	± 12.6	9.84	± 13.1	0.79
Socioeconomic status (school years)	15.4	± 3.6	14.7	± 3.5	< 0.0001
Alcohol consumption (drinks per week)	6.6	± 9.3	5.6	± 9.1	< 0.0001
Physical activity (Range 5–15)	9.0	± 1.9	8.9	± 1.8	0.33
Attention paid to health habits (range 1–5) ^b	2.5	± 1.0	2.5	± 1.0	0.39
Intima-media thickness (mm)	0.62	0.09	0.62	0.10	0.56
Left ventricular mass (g/m ^{2.7})	30.42	6.55	31.10	6.66	0.01
Pulse wave velocity (m/s)	10.53	2.04	10.45	1.96	1.00
Flow-mediated dilatation (%)	8.67	4.53	8.84	4.53	0.68
Carotid artery compliance (%/10 mmHg)	1.96	0.72	1.92	0.69	0.02
Smoking (%)	20.8		20.0		0.55
Metabolic Syndrome (%)	21.3		21.5		0.50
Type 2 Diabetes (%)	3.5		3.8		0.65

Values are expressed as mean ± standard deviation or as proportions (%); *n* varied between 1004 and 1395 in participants living in urban areas and 1018–1509 in participants living in rural areas.

^aContinuous variables standardized according to age and sex before analyses; *t*-test used for continuous variables and logistic regression adjusted for age and sex for categorical variables.

^bLower is better.

To examine whether the association of migration with subclinical markers of CVD was mediated by CVD risk factors, the analyses were adjusted for risk factor levels at baseline (Supplemental Figure 1). For IMT, the results were mainly 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. For LVM, the results remained mostly unchanged, although the difference between participants who had moved to urban areas and participants who had continuously lived in urban communities became borderline significant ($p = 0.06$). For PWV, the difference between participants who had continuously lived in urban or rural areas was attenuated ($p = 0.16$) while the difference between participants who had moved to urban areas and participants who had continuously lived in

urban communities became significant ($p = 0.01$). After the adjustments, the difference in CAC was diluted between participants who had continuously lived in urban or rural settings ($p = 0.16$).

Secondly, the analyses were adjusted for CVD risk factors in adulthood (Supplemental Figure 2). For IMT, the difference between participants who had moved to urban communities by adulthood and participants who had moved to rural areas by adulthood remained similar but differences between participants who had continuously lived in urban or rural areas ($p = 0.30$) or had moved to rural communities by adulthood ($p = 0.08$) were attenuated. For LVM, the results remained unchanged. For PWV, the difference between participants who had moved to urban areas by adulthood and participants who had moved to rural areas remained significant ($p = 0.02$) while the difference between participants who had moved to urban areas and participants who had continuously lived in urban communities became

Table III. Levels of risk factors and surrogate markers for cardiovascular disease in adulthood according to urban–rural residence in adulthood (2001–2011) in participants of the Cardiovascular Risk in Young Finns Study.

	Urban residence		Rural residence		<i>p</i> for difference ^a
<i>n</i>	1754		1149		
Female (%)	54.1		54.1		1.00
Age (years)	39.3	± 6.6	39.9	± 6.1	0.01
Body mass index (kg/m ²)	25.9	± 4.9	26.9	± 5.2	< 0.0001
Systolic blood pressure (mmHg)	119	± 14	121	± 14	< 0.0001
Diastolic blood pressure (mmHg)	75	± 11	76	± 11	0.04
Total cholesterol (mmol/l)	5.14	± 1.0	5.21	± 0.9	0.07
LDL-cholesterol (mmol/l)	3.21	± 0.8	3.30	± 0.8	0.005
HDL-cholesterol (mmol/l)	1.33	± 0.3	1.32	± 0.3	0.34
Triglycerides (mmol/l)	1.37	± 1.3	1.34	± 1.0	0.54
Glucose (mmol/mol)	5.33	± 0.8	5.41	± 1.2	0.053
Glycosylated haemoglobin (mmol/mol)	36.5	± 5.0	37.0	± 5.7	0.04
Insulin (mU/l)	9.52	± 11.8	10.24	± 14.3	0.07
Socioeconomic status (school years)	15.6	± 3.7	14.2	± 3.2	< 0.0001
Alcohol Consumption (drinks per week)	6.2	± 9.1	5.9	± 9.3	0.01
Physical Activity (Range 5–15)	9.0	± 1.9	8.8	± 1.8	0.001
Attention paid to health habits (range 1–5) ^b	2.4	± 0.9	2.6	± 1.0	< 0.0001
Intima-media thickness (mm)	0.61	0.09	0.63	0.10	0.0008
Left ventricular mass (g/m ^{2.7})	30.24	6.45	31.54	6.78	< 0.0001
Pulse wave velocity (m/s)	10.38	1.96	10.66	2.05	0.0002
Flow-mediated dilatation (%)	8.67	4.62	8.91	4.39	0.42
Carotid artery compliance (%/10 mmHg)	1.95	0.71	1.91	0.69	0.27
Smoking (%)	20.5		20.3		0.65
Metabolic Syndrome (%)	19.9		23.7		0.04
Type 2 Diabetes (%)	3.4		4.0		0.69

Values are expressed as mean ± standard deviation or as proportions (%); *n* varied between 1195 and 1754 in participants living in urban areas and 827–1509 in participants living in rural areas.

^aContinuous variables standardized according to age and sex before analyses; *t*-test used for continuous variables and logistic regression adjusted for age and sex for categorical variables.

^bLower is better.

significant ($p = 0.02$). Furthermore, there was no difference between participants who had continuously lived in urban or rural areas ($p = 0.84$) as well as the difference between those who had moved to urban areas by adulthood and participants who had moved to rural areas by adulthood became borderline significant ($p = 0.055$). For CAC, the difference between participants who had continuously lived in urban or rural settings was lost ($p = 0.83$).

Discussion

We observed that participants living in urban communities in childhood and adulthood had a more favourable CVD risk factor profile including lower blood pressure and cholesterol levels in comparison to individuals living in rural settings. Furthermore, we found that participants who had continuously lived in an urban setting had more favorable IMT, LVM, PWV and CAC, which have been shown to

predict future cardiovascular events [20–22], than participants who had continuously lived in rural areas. These differences were only partially attenuated when the analyses were adjusted for CVD risk factor levels in childhood and adulthood suggesting that urban–rural differences are not completely mediated by differences in CVD risk factors.

Our findings considering CVD risk factors are consistent with the PURE study, an extensive study of cardiac risk factors and cardiovascular events among adults ($n = 156,424$, mean age 50.7 years) in urban and rural communities on five continents, reporting that the mean INTERHEART Risk Score was higher in rural areas compared to urban communities in high income countries (Sweden, Canada and the United Arab Emirates) [6]. However, no significant urban–rural difference was observed for major cardiovascular events in the PURE study. In this study, significant urban–rural differences for subclinical markers of CVD that have been shown to

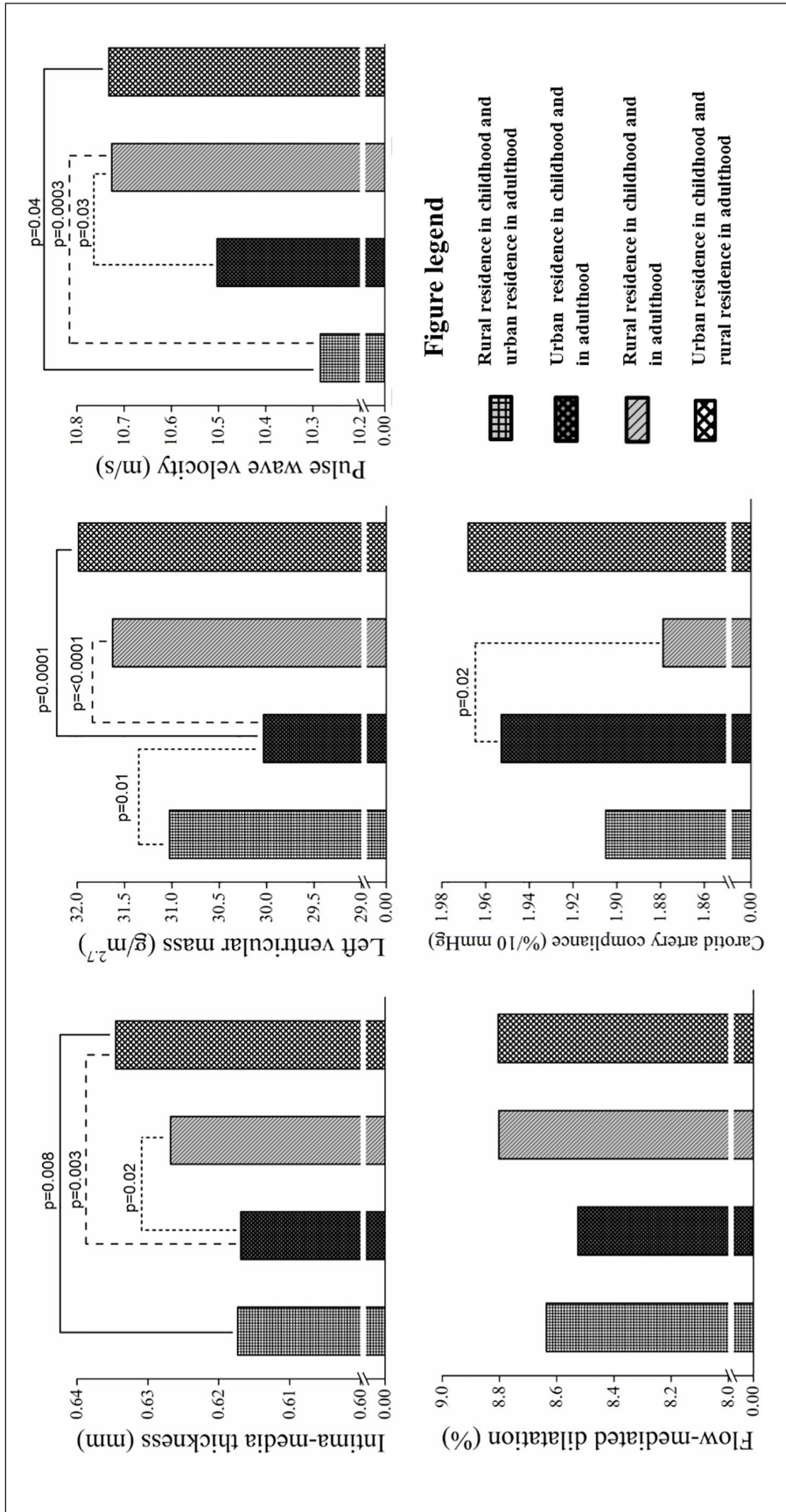


Figure 1. Effect of urban-rural migration on intima-media thickness, left ventricular mass, pulse wave velocity, flow-mediated dilatation and carotid artery compliance in adulthood in 1793-2599 participants of the Cardiovascular Risk in Young Finns Study. Values are presented as age and sex adjusted means. Significant differences between the groups are shown in the figure.

associate with future cardiovascular events were observed [20–23]. Furthermore, prior results from the GOAL cohort study, comprising 2815 elderly Finnish participants aged 52–76 years, showed significant urban–rural differences in serum cholesterol and BMI that were mainly explained by SES [10]. Our results are in line with these observations as higher cholesterol and BMI were observed among rural adult participants. In this study, urban–rural differences were partially attenuated when analyses were adjusted for SES. However, urban–rural differences in LDL-cholesterol and systolic blood pressure, both being major risk factors for CVD [24], remained significant in adulthood suggesting that the difference observed in cardiovascular risk is not fully captured by SES.

Differences observed in lipid and blood pressure levels may be partly attributed to several behavioural and dietary factors. In part, rural communities may have fewer healthy dietary choices available compared to urban areas and access to healthcare services might differ. The possible differential access to healthcare services could affect adherence to primary and secondary prevention of CVD. Furthermore, results from a National Dietary Survey demonstrated that individuals living in rural areas tend to consume less vegetables and use more butter than urban residents [25]. Moreover, it has been hypothesized that cultural aspects might also contribute to the cardiovascular health differences observed between urban and rural residents in Sweden as a more masculine lifestyle has been traditionally linked to living in rural communities [26]. Speculatively, cultural differences could have an unfavourable effect on adaptation to the health promotion efforts by other authorities also in Finland.

Our earlier reports and other studies have demonstrated that differences in cardiovascular risk factors between Eastern and Western Finland has been declining [19,27]. The results of this study remained almost unchanged after adjustment for place of residence (Eastern–Western). Hence, urban–rural differences observed in our study are not likely explained by the geographic origin of the participants. However, similarities between association of Eastern–Western and urban–rural migration with CVD risk factor levels can be observed. In this study, urban–rural differences in CVD risk factor levels in adulthood were more pronounced according to place of residence in adulthood compared to differences observed in adulthood according to living area in childhood. The same phenomenon was earlier found between Eastern and Western Finns, possibly suggesting that those with a lower risk profile may have been more prone to migrate by adulthood [19].

In this study, we observed that participants living in urban areas as a child had lower LVM and higher CAC compared to their rural counterparts. Furthermore, those who had lived persistently in urban areas had lower IMT, lower LVM and superior CAC than participants residing in rural communities. Likewise, participants who had migrated to urban communities by adulthood had lower IMT and PWV compared to participants living in rural areas. We have earlier shown that systolic blood pressure, LDL-cholesterol concentration, cigarette smoking and BMI are associated with IMT, a marker of structural atherosclerosis [28]. In addition, LVM is a marker of left ventricular remodelling often associated with arterial hypertension and obesity [20]. Furthermore, pathology of increased PWV normally includes a number of adverse functional and structural changes in vascular walls as exposure to cardiovascular risk factors such as arterial hypertension leads to, for example, a diminished quantities of elastin, an overproduction of collagen and elevated smooth muscle tone [29]. Together, these markers of subclinical CVD have been shown to independently predict cardiovascular events [20–23].

Differences observed in surrogate markers of atherosclerosis were partially attenuated after adjustment for risk factor levels in childhood and in adulthood. However, the urban–rural differences for LVM remained unchanged and were not fully attenuated for IMT and PWV after adjustments for risk factor levels in adulthood and childhood suggesting that the urban–rural differences are not entirely mediated by cardiovascular risk factor levels such as serum cholesterol, BMI, cigarette smoking and blood pressure. In a more clinical perspective, our results showed a difference of 0.15 mm in carotid IMT levels between participants living continuously in urban surroundings compared to participants who had migrated from urban areas to a rural environment by adulthood. Extending from the estimates of Lorenz et al. this difference could be converted to a 15–20% difference in myocardial infarction risk and a 20–25% difference in stroke risk later in life [23]. The mechanism underlying increased subclinical atherosclerosis among individuals living in rural areas remains unknown and requires further study. Prior studies on association of urban–rural migration with subclinical atherosclerosis are scarce. Woo et al. have earlier found that urban Chinese living in Hong Kong and Australia had higher IMT than Chinese living in rural areas ($n = 348$, mean age 42 years) [8]. The risk of atherosclerosis has been traditionally low in rural Chinese due to environmental factors and thus the results are not comparable to high income Western countries such as Finland where rural

lifestyle has become increasingly sedentary because of the mechanization of agricultural work.

Limitation in longitudinal studies is non-participation at follow-up which is inevitable. However, our study group has been dynamic, and thus probably representative of the original population [30]. Moreover, categorization of migration used was based on information of the participant's place of residence from childhood and adulthood. This categorization did not consider the possibility that individuals may have moved repeatedly between childhood and adulthood. Finally, we have no clinical end-points because the participants are still relatively young. However, data on surrogate markers of CVD were available that have been shown to predict the risk of future cardiovascular events and total mortality[20–23].

Conclusions

Participants living in urban communities had a more favourable CVD risk factor profile and less structural vascular and cardiac changes related to CVD compared with their rural counterparts. The differences in surrogate markers of CVD were only partially attenuated when adjusted for CVD risk factors. Our results suggest that enduring urban–rural differences in cardiovascular health might provide important opportunities for optimizing healthcare resources and improving prevention by targeting areas of highest need.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORCID iD

Joel Nuotio  <https://orcid.org/0000-0003-3890-7081>

Supplemental material

Supplemental material for this article is available online.

References

- [1] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380(9859): 2095–2128.
- [2] Keys A, Aravanis C, Blackburn HW, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40–59 in seven countries. *Acta Medica Scand* 1966; 460: 1–392.
- [3] Jousilahti P, Laatikainen T, Peltonen M, et al. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: population based observational study. *BMJ* 2016; 352: i721.
- [4] Hoffmann R, Borsboom G, Saez M, et al. Social differences in avoidable mortality between small areas of 15 European cities: an ecological study. *Int J Health Geogr* 2014; 13.
- [5] Anderson TJ, Saman DM, Lipsky MS, et al. A cross-sectional study on health differences between rural and non-rural US counties using the County Health Rankings. *BMC Health Serv Res* 2015; 15(1): 1–8.
- [6] Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014; 371(9): 818–827.
- [7] Vaughan AS, Quick H, Pathak EB, et al. Disparities in temporal and geographic patterns of declining heart disease mortality by race and sex in the United States, 1973–2010. *J Am Heart Assoc* 2015; 4(12): 1–12.
- [8] Woo KS, Chook P, Raitakari OT, et al. Westernization of Chinese adults and increased subclinical atherosclerosis. *Arter Thromb Vasc Biol* 1999; 19(10): 2487–2493.
- [9] Haraldsdottir S, Gudmundsson S, Thorgeirsson G, et al. Regional differences in mortality, hospital discharges and primary care contacts for cardiovascular disease. *Scand J Public Health* 2017; 5(3): 260–268.
- [10] Fogelholm M, Valve R, Kontinen R, et al. Rural–urban differences in health and health behaviour: a baseline description of a community health-promotion programme for the elderly. *Scand J Public Health* 2006; 34(6): 632–640.
- [11] Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: The Cardiovascular Risk in Young Finns Study. *Int J Epidemiol* 2008; 37(6): 1220–1226.
- [12] Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute;

- American Heart Association; World Heart Federation; International . *Circulation* 2009; 120(16): 1640–1645.
- [13] Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013; 36 (1): S67–74.
- [14] Telama R, Viikari J, Välimäki I, et al. Atherosclerosis precursors in Finnish children and adolescents. X. Leisure-time physical activity. *Acta Paediatr Scand* 1985; 318: 169–180.
- [15] Puolakka E, Pahkala K, Laitinen TT, et al. Childhood socioeconomic status and arterial stiffness in adulthood: The Cardiovascular Risk in Young Finns Study. *Hypertens (Dallas, Tex 1979)* 2017; 70(4): 729–735.
- [16] Juonala M, Kähönen M, Laitinen T, et al. Effect of age and sex on carotid intima-media thickness, elasticity and brachial endothelial function in healthy adults: The Cardiovascular Risk in Young Finns Study. *Eur Heart J* 2008; 29(9): 1198–1206.
- [17] Vähämurto L, Juonala M, Ruohonen S, et al. 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(6): 630–637.
- [18] de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in normotensive children and adults: assessment of allometric relations and impact of overweight. *J Am Coll Cardiol* 1992; 20(5): 1251–1260.
- [19] Vähämurto L, Pahkala K, Magnussen CG, et al. East–west differences and migration in Finland: association with cardiometabolic risk markers and IMT. The Cardiovascular Risk in Young Finns Study. *Scand J Public Health* 2016; 44: 402–410.
- [20] Armstrong AC, Jacobs DR, Gidding SS, et al. Framingham score and LV mass predict events in young adults: CARDIA study. *Int J Cardiol* 2014; 172(2): 350–355.
- [21] Yuan C, Wang J and Ying M. Predictive value of carotid distensibility coefficient for cardiovascular diseases and all-cause mortality: A meta-analysis. *PLoS One* 2016; 11(4): 1–15.
- [22] Vlachopoulos C, Aznaouridis K and Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 55(13): 1318–1327.
- [23] Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 2007; 115(4): 459–467.
- [24] Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129(25): S49–73.
- [25] Kaikkonen R, Murto J, Saarsalmi P, et al. Alueellisen terveys- ja hyvinvointitutkimuksen perustulokset kaupunkimaaseutu -luokittain 2013, www.thl.fi/ath(2013).
- [26] Lindroth M, Lundqvist R, Lilja M, et al. Cardiovascular risk factors differ between rural and urban Sweden: The 2009 Northern Sweden MONICA cohort. *BMC Public Health* 2014; 14(1): 1–8.
- [27] Vartiainen E, Laatikainen T, Peltonen M, et al. Thirty-five-year trends in cardiovascular risk factors in Finland. *Int J Epidemiol* 2010; 39(2): 504–518.
- [28] Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *Jama* 2003; 290(17): 2277–2283.
- [29] Cecelija M and Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: A systematic review. *Hypertension* 2009; 54(6): 1328–1336.
- [30] Nuotio J, Oikonen M, Magnussen CG, et al. Cardiovascular risk factors in 2011 and secular trends since 2007: The cardiovascular risk in Young Finns Study. *Scand J Public Health* 2014; 42(7): 563–571.