

1 **Cardiometabolic risk factors and subclinical markers of cardiovascular**  
2 **disease in urban and rural areas in Finland. The Cardiovascular Risk in**  
3 **Young Finns Study.**

4 Joel Nuotio<sup>1,2</sup>, Lauri Vähämurto<sup>1</sup>, Katja Pahkala<sup>1,3</sup>, Costan G. Magnussen<sup>1,4</sup>, Nina  
5 Hutri-Kähönen<sup>5</sup>, Mika Kähönen<sup>6</sup>, Tomi Laitinen<sup>7</sup>, Leena Taittonen<sup>8</sup>, Päivi  
6 Tossavainen<sup>9</sup>, Terho Lehtimäki<sup>10</sup>, Eero Jokinen<sup>11</sup>, Jorma S.A. Viikari<sup>12</sup>, Olli  
7 Raitakari<sup>13</sup>, and Markus Juonala<sup>1,12,14</sup>

8 <sup>1</sup>Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku,  
9 Turku, Finland; <sup>2</sup>Heart Center, Turku University Hospital and University of Turku, Turku,  
10 Finland; <sup>3</sup>Paavo Nurmi Centre, Sports and Exercise Medicine Unit, Department of Physical  
11 Activity and Health, University of Turku, Turku, Finland; <sup>4</sup>Menzies Research Institute  
12 Tasmania, University of Tasmania, Hobart, Tasmania, Australia; <sup>5</sup>Department of Pediatrics,  
13 University of Tampere and Tampere University Hospital, Tampere, Finland; <sup>6</sup>Department of  
14 Clinical Physiology, University of Tampere School of Medicine and Tampere University  
15 Hospital, Tampere, Finland; <sup>7</sup>Department of Clinical Physiology and Nuclear Medicine,  
16 University of Eastern Finland and Kuopio University Hospital, Kuopio, Finland; <sup>8</sup>Vaasa  
17 Central Hospital, Vaasa, Finland; <sup>9</sup>Department of Pediatrics, University of Oulu, Oulu,  
18 Finland; <sup>10</sup>Department of Clinical Chemistry, Fimlab Laboratories and Finnish Cardiovascular  
19 Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere;  
20 <sup>11</sup>Department of Pediatric Cardiology, Hospital for Children and Adolescents, University of  
21 Helsinki, Helsinki, Finland; <sup>12</sup>Department of Medicine, University of Turku and Division of  
22 Medicine, Turku University Hospital, Turku, Finland; <sup>13</sup>Department of Clinical Physiology and  
23 Nuclear Medicine, Turku University Hospital, Turku, Finland; and <sup>14</sup>Murdoch Childrens  
24 Research Institute, Melbourne, Victoria, Australia.

25 **Corresponding author and contact details:** Joel Nuotio, Research Centre of Applied and  
26 Preventive Cardiovascular Medicine, University of Turku, Kiinamylynkatu 10, FIN-20520  
27 Turku, Finland. E-mail [joel.nuotio@utu.fi](mailto:joel.nuotio@utu.fi)

1 **Abstract**

2 **Aims:** Disparity in cardiovascular disease (CVD) mortality and risk factor levels between  
3 urban and rural regions has been confirmed worldwide. The aim of this study was to examine  
4 how living in different community types (urban-rural) in childhood and adulthood are related  
5 to cardiovascular risk factors and surrogate markers of CVD such as carotid intima-media  
6 thickness (IMT) and left ventricular mass (LVM).

7 **Methods:** The study population comprised 2,903 participants (54.1% female, mean age 10.5  
8 years in 1980) of the Cardiovascular Risk in Young Finns Study who had been clinically  
9 examined in 1980 (age 3-18 years) and had participated in at least one adult follow-up (2001-  
10 2011).

11 **Results:** In adulthood, urban residents had lower systolic blood pressure (-1mmHg), LDL-  
12 cholesterol (-0.05mmol/l), lower BMI (-1.0kg/m<sup>2</sup>), and glycosylated hemoglobin levels (-  
13 0.05mmol/mol), and lower prevalence of metabolic syndrome (19.9% vs. 23.7%) than their  
14 rural counterparts. In addition, participants continuously living in urban areas had significantly  
15 lower IMT (-0.01mm), LVM (1.59 g/m<sup>2.7</sup>), and pulse wave velocity (-0.22m/s) and higher  
16 carotid artery compliance (0.07%/10 mmHg) compared to persistently rural residents. The  
17 differences in surrogate markers of CVD were only partially attenuated when adjusted for  
18 cardiovascular risk factors.

19 **Conclusions:** Participants living in urban communities had a more favorable cardiovascular  
20 risk factor profile than rural residents. Furthermore, participants continuously living in urban  
21 areas had less subclinical markers related to CVD compared with participants living in rural  
22 areas. Urban-rural differences in cardiovascular health might provide important opportunities  
23 for optimizing prevention by targeting areas of highest need.

24 **Key words:** atherosclerosis, risk factors, urban, rural, arterial stiffness, left ventricular mass

## 1 **Introduction**

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

10 Disparity in CVD mortality and risk factor levels between urban and rural regions has been  
11 confirmed worldwide.<sup>6-8</sup> Results from the Prospective Urban Rural Study have shown that the  
12 rates of cardiovascular events were higher in rural areas than in urban communities in middle-  
13 income and low-income countries, though the risk factors were higher in urban communities  
14 than in rural settings at the same time.<sup>6</sup> Nevertheless, no differences were observed in the rates  
15 of cardiovascular events between urban and rural communities in high-income countries  
16 including Sweden.<sup>6</sup> In addition, CVD mortality and risk factors were higher in rural areas than  
17 in urban communities in Iceland.<sup>9</sup> Furthermore, results from an earlier Finnish study suggest  
18 that elevated serum cholesterol levels and obesity are more prevalent in elderly citizens living  
19 in rural communities compared to individuals living in urban areas.<sup>10</sup> However, the urban-rural  
20 differences in cardiovascular risk factor levels and subclinical markers of CVD among  
21 working-age population are unknown in Finland and have not been extensively explored in  
22 other populations either.

23 The aim of this study was to examine how living in different community types (urban-rural) is  
24 related to CVD factors and subclinical markers of CVD. We report results using data from the

1 Cardiovascular Risk in Young Finns Study with 2,903 participants having comprehensive data  
2 on CVD risk factors and ultrasonic markers of subclinical CVD.

### 3 **Methods**

#### 4 *Study population*

5 The Cardiovascular Risk in Young Finns Study is a population-based follow-up study on  
6 cardiovascular risk factors in Finland.<sup>11</sup> The study has been performed in five Finnish  
7 university cities with medical schools and nearby rural municipalities. The rural communities  
8 were chosen followingly: their industrial structure corresponding to the average of rural  
9 communities in the province, the cohorts in the communities should be large enough, the  
10 distances should not be impractically long and sample should include an equal number of urban  
11 and rural population in each area. This study comprised 2,903 participants (54.1% female) who  
12 had been seen in clinical examination in 1980 and at least once in adult follow-ups. Response  
13 rate compared to the baseline study was 73% in all participants (72 % in urban participants and  
14 74% in rural participants according to place of residence in childhood) in 2001, 62 % for all  
15 participants (64% in urban participants and 61 % in rural participants) in 2007, and 59% for all  
16 participants (60% in urban participants and 57 % in rural participants) in 2011. Data was  
17 primarily from 2011 follow-up (71.5% of data), but in case of missing data from 2011, data  
18 from 2007 (13.8% of data) or 2001 (14.7% of data) were used. Written informed consent was  
19 obtained from participants or parents, and study was approved by local ethics committees.

#### 20 *Place of residence*

21 Living area of participants was classified as urban or rural. At baseline, participants living in  
22 university cities were classified as having an urban place of residence, and the municipalities  
23 in the vicinity of those cities were classified as rural. In adulthood, area of residence was  
24 defined followingly according to questionnaire data: participants living in cities, suburbs or  
25 center of a town were classified as urban and participants living outside a population center

1 were classified as rural. In sensitivity analyses, corresponding classification was also used in  
2 childhood.

### 3 *Anthropometry, blood pressure and laboratory measurements*

4 Weight was measured to the nearest 0.1 kg and height to the nearest centimeter. Body mass  
5 index (BMI) was calculated as weight/height. Blood pressure was measured with standard  
6 mercury sphygmomanometer in childhood and with random-zero sphygmomanometer in  
7 adulthood. Fasting blood samples analyzed with standard enzymatic methods.<sup>11</sup> Metabolic  
8 syndrome was defined according to the Harmonized criteria.<sup>12</sup> The diagnosis of type 2 diabetes  
9 included participants with fasting glucose  $\geq 7$ mmol/L or glycosylated hemoglobin  $\geq 6.5\%$  or  
10 self-reported diabetes or use of medication.<sup>13</sup>

11

### 12 *Health behaviors and socioeconomic status*

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

20

### 21 *Subclinical markers of cardiovascular risk*

22 Carotid artery intima-media thickness (IMT), carotid artery compliance (CAC), pulse wave  
23 velocity (PWV), brachial artery flow-mediated dilatation (FMD), and left ventricular mass  
24 (LVM) were measured as described earlier.<sup>15-17</sup> LVM was indexed according to height using

1 the allometric power of 2.7 since this indexation has been shown to perform better for obese  
2 subjects.<sup>18</sup>

3

#### 4 *Statistical methods*

5 Differences between participants living in urban and rural areas were analyzed using  
6 independent samples t-test for continuous variables. Continuous variables were standardized  
7 according to age and sex before analyses. Differences in categorical variables were analyzed  
8 using Fisher's exact test in childhood and logistic regression models adjusted for age and sex  
9 in adulthood. Non-normally distributed variables were square root-transformed before the  
10 analyses. The association of SES and eastern-western origin with urban-rural differences in  
11 cardiovascular risk factor levels was tested using analysis of covariance adjusted for age, sex,  
12 and additionally for SES or eastern-western origin. The association of urban-rural migration  
13 was examined by dividing participants into four groups: 1) participants who had lived in rural  
14 areas as a child and had migrated to urban communities by adulthood (n=587); 2) participants  
15 who had continuously lived in urban areas (n=991) 3) participants who lived in urban areas as  
16 a child and had migrated to rural settings by adulthood (n=738); 4) participants who  
17 continuously lived in rural communities (n=283). Means adjusted for age and sex according  
18 to migration were calculated using analysis of covariance. Furthermore, analyses were  
19 additionally adjusted for risk factor levels at baseline (systolic blood pressure, total cholesterol,  
20 LDL-cholesterol, triglycerides, parental SES, smoking, and physical activity) and in adulthood  
21 (BMI, systolic blood pressure, diastolic blood pressure, LDL-cholesterol, glycosylated  
22 hemoglobin, SES, alcohol consumption, attention paid to health habits, and physical activity)  
23 to test whether the association of migration with surrogate markers of CVD was mediated by  
24 risk factor levels.

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

3

#### 4 **Results**

##### 5 *Cardiovascular risk factors according to urban-rural residence in childhood (1980)*

6 In childhood, participants living in urban areas had significantly lower systolic blood pressure,  
7 total cholesterol, LDL-cholesterol and triglyceride levels, were more likely to smoke and were  
8 physically more active at the age of 9-18 years compared with their peers living in rural settings  
9 (Table 1). In addition, urban residents had higher parental SES in childhood than their rural  
10 counterparts. No other significant urban-rural differences were observed at baseline in 1980.

##### 11 *Cardiovascular risk factors and subclinical markers CVD in adulthood according to urban- 12 rural residence in childhood (1980)*

13 Participants who had lived in urban communities as a child were significantly older, consumed  
14 more alcohol weekly, and had higher SES as well as lower systolic blood pressure in adulthood  
15 compared to rural residents (Table 2). Moreover, urban residents had lower LVM and higher  
16 CAC compared to participants with their rural counterparts. No other urban-rural differences  
17 were observed in adulthood according to place of residence in childhood.

##### 18 *Cardiovascular risk factors according to urban-rural residence in adulthood (2001-2011)*

19 In adulthood, individuals living in urban settings were younger, had lower BMI, blood pressure,  
20 LDL-cholesterol, glycosylated hemoglobin and prevalence of metabolic syndrome than their  
21 rural counterparts (Table 3). In addition, participants living in urban areas were physically more  
22 active, had higher SES, and paid more attention to health habits than rural participants while  
23 their weekly consumption of alcohol was higher. Furthermore, urban participants also had  
24 lower carotid IMT, LVM and higher PWV than rural participants.

##### 25 *Sensitivity analyses*

1 Because of urban-rural difference in SES, we additionally adjusted all prior analyses for  
2 parental SES in childhood or participant's own SES in adulthood. With adjustment for parental  
3 SES, childhood urban-rural differences (Table 1) in systolic blood pressure ( $p=0.052$ ) and  
4 triglycerides ( $p=0.08$ ) diluted to borderline significant. With adjustment for participant's own  
5 adulthood SES, observed urban-rural differences (Table 3) in diastolic blood pressure ( $p=0.20$ ),  
6 total cholesterol ( $p=0.18$ ), glycosylated hemoglobin ( $p=0.27$ ), weekly alcohol consumption  
7 ( $p=0.07$ ), physical activity ( $p=0.09$ ), and prevalence of metabolic syndrome ( $p=0.11$ ) were  
8 attenuated in adulthood.

9 Moreover, the classification of urban-rural residence differed between childhood and adulthood  
10 due to the original study design. When the classification of urban-rural residence in childhood  
11 (Tables 1 and 2) was made similarly as in adulthood, the results remained mostly unchanged  
12 except for childhood (Table 1) urban-rural differences in systolic blood pressure and  
13 triglycerides that became significant.

14 Finally, because of the previously observed east-west differences in CVD risk factor levels<sup>19</sup>,  
15 analyses reported in Tables 2 and 3 were adjusted for place of residence (eastern – western) at  
16 baseline. After the adjustment, results remained similar except for the difference in CAC which  
17 became borderline significant ( $p=0.059$ ) and attenuated differences in glycosylated  
18 hemoglobin ( $p=0.09$ ) and alcohol consumption ( $p=0.29$ ).

#### 19 *Association of subclinical markers of CVD and urban-rural migration between childhood and* 20 *adulthood*

21 Associations of urban-rural migration between childhood and adulthood on subclinical markers  
22 of CVD are shown in Figure 1. Participants who had continuously lived in urban areas had  
23 significantly lower IMT and LVM compared to participants who had continuously lived in  
24 rural communities or who had migrated to rural areas by adulthood. Likewise, these  
25 participants had lower PWV and higher CAC compared to participants who had continuously



1 lived in rural communities. In addition, participants continuously living in urban setting had  
2 lower LVM than participants who had lived as a child in rural areas and had migrated to urban  
3 communities in adulthood. Furthermore, participants who had migrated to urban areas from  
4 rural areas by adulthood had significantly lower IMT and PWV than participants who had  
5 migrated to rural areas by adulthood. For PWV, participants who had migrated to urban areas  
6 by adulthood compared to participants continuously living in rural communities had  
7 significantly lower PVW. No significant differences between the groups were observed for  
8 FMD.

9 To examine whether the association of migration with subclinical markers of CVD was  
10 mediated by CVD risk factors, the analyses were adjusted for risk factor levels at baseline  
11 (Supplemental Figure 1). For IMT, the results were mainly similar, with the exception of lack  
12 of difference between participants who had continuously lived in urban or rural areas ( $p=0.42$ ),  
13 and the emerged difference ( $p=0.03$ ) between participants who had continuously lived in rural  
14 areas and those who had moved to rural areas by adulthood. For LVM, the results remained  
15 mostly unchanged, although the difference between participants who had moved to urban areas  
16 and participants who had continuously lived in urban communities became borderline-  
17 significant ( $p=0.06$ ). For PWV, the difference between participants who had continuously lived  
18 in urban or rural areas was attenuated ( $p=0.16$ ) while the difference between participants who  
19 had moved to urban areas and participants who had continuously lived in urban communities  
20 became significant ( $p=0.01$ ). After the adjustments, the difference in CAC was diluted between  
21 participants who had continuously lived in urban or rural settings ( $p=0.16$ ).

22 Secondly, the analyses were adjusted for CVD risk factors in adulthood (Supplemental Figure  
23 2). For IMT, the difference between participants who had moved to urban communities by  
24 adulthood and participants who had moved to rural areas by adulthood remained similar but  
25 differences between participants who had continuously lived in urban or rural areas ( $p=0.30$ )

1 or had moved to rural communities by adulthood ( $p=0.08$ ) were attenuated. For LVM, the  
2 results remained unchanged. For PWV, the difference between participants who had moved to  
3 urban areas by adulthood and participants who had moved to rural areas remained significant  
4 ( $p=0.02$ ) while the difference between participants who had moved to urban areas and  
5 participants who had continuously lived in urban communities became significant ( $p=0.02$ ).  
6 Furthermore, there was no difference between participants who had continuously lived in urban  
7 or rural areas ( $p=0.84$ ) as well as the difference between those who had moved to urban areas  
8 by adulthood and participants who had moved to rural areas by adulthood became borderline  
9 significant ( $p=0.055$ ). For CAC, the difference between participants who had continuously  
10 lived in urban or rural settings was lost ( $p=0.83$ ).

11

## 12 **Discussion**

13 We observed that participants living in urban communities in childhood and adulthood had a  
14 more favorable CVD risk factor profile including lower blood pressure and cholesterol levels  
15 in comparison to individuals living in rural settings. Furthermore, we found that participants  
16 who had continuously lived in an urban setting had more favorable IMT, LVM, PWV, and  
17 CAC, which have been shown to predict future cardiovascular events<sup>20-22</sup>, than participants  
18 who had continuously lived in rural areas. These differences were only partially attenuated  
19 when the analyses were adjusted for CVD risk factor levels in childhood and adulthood  
20 suggesting that urban-rural differences are not completely mediated by differences in CVD risk  
21 factors.

22 Our findings considering CVD risk factors are consistent with the PURE study, an extensive  
23 study of cardiac risk factors and cardiovascular events among adults ( $n=156,424$ , mean age  
24 50.7 years) in urban and rural communities on five continents, reporting that the mean  
25 INTERHEART Risk Score was higher in rural areas compared to urban communities in high

1 income countries (Sweden, Canada, and United Arab Emirates).<sup>6</sup> However, no significant  
2 urban-rural difference was observed for major cardiovascular events in the PURE study. In this  
3 study, significant urban-rural differences for subclinical markers of CVD that have been shown  
4 to associate with future cardiovascular events were observed.<sup>20-23</sup> Furthermore, prior results  
5 from the GOAL cohort study, comprising 2,815 elderly Finnish participants aged 52 to 76  
6 years, showed significant urban-rural differences in serum cholesterol and BMI that were  
7 mainly explained by SES.<sup>10</sup> Our results are in line with these observations as higher cholesterol  
8 and BMI was observed among rural adult participants. In this study, urban-rural differences  
9 were partially attenuated when analyses were adjusted for SES. However, urban-rural  
10 differences in LDL-cholesterol and systolic blood pressure, both being major risk factors for  
11 CVD<sup>24</sup>, remained significant in adulthood suggesting that the difference observed in  
12 cardiovascular risk is not fully captured by SES.

13 Differences observed in lipid and blood pressure levels may be partly attributed to several  
14 behavioral and dietary factors. In part of rural communities fewer healthy dietary choices may  
15 be available compared to urban areas and access to health care services might differ. The  
16 possible differential access to health care services could affect adherence to primary and  
17 secondary prevention of CVD. Furthermore, results from a National Dietary Survey  
18 demonstrated that individuals living in rural areas tend to consume less vegetables and use  
19 more butter than urban residents.<sup>25</sup> Moreover, it has been hypothesized that cultural aspects  
20 might also contribute to the cardiovascular health differences observed between urban and rural  
21 residents in Sweden as a more masculine lifestyle has been traditionally linked to the living in  
22 rural communities.<sup>26</sup> Speculatively, cultural differences could have an unfavorably effect on  
23 adaption to the health promotion efforts by authorities also in Finland.

24 Our earlier reports and other studies have demonstrated that difference in cardiovascular risk  
25 factors between eastern and western Finland has been declining<sup>19,27</sup>. The results of this study

1 remained almost unchanged after adjustment for place of residence (eastern-western). Hence,  
2 urban-rural differences observed in our study are not likely explained by the geographic origin  
3 of the participants. However, similarities between association of eastern-western and urban-  
4 rural migration with CVD risk factor levels can be observed. In this study, urban-rural  
5 differences in CVD risk factor levels in adulthood were more pronounced according to place  
6 of residence in adulthood compared to differences observed in adulthood according to living  
7 area in childhood. The same phenomenon was earlier found between eastern and western Finns,  
8 possibly suggesting that those with lower risk profile may have been more prone to migrate by  
9 adulthood.<sup>19</sup>

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

23 Differences observed in surrogate markers of atherosclerosis were partially attenuated after  
24 adjustment for risk factor levels in childhood and in adulthood. However, the urban-rural  
25 differences for LVM remained unchanged and were not fully attenuated for IMT and PWV

1 after adjustments for risk factor levels in adulthood and childhood suggesting that the urban-  
2 rural differences are not entirely mediated by cardiovascular risk factor levels such as serum  
3 cholesterol, BMI, cigarette smoking, and blood pressure. In a more clinical perspective, our  
4 results showed a difference of 0.15 mm in carotid IMT levels between participants living  
5 continuously in urban surroundings compared to participant who had migrated from urban  
6 areas to rural environment by adulthood. Extending from the estimates of Lorenz et al. this  
7 difference could be converted to a 15-20% difference in myocardial infarction risk and a 20-  
8 25% difference in stroke risk in later in life.<sup>23</sup> The mechanism underlying increased subclinical  
9 atherosclerosis among individuals living in rural areas remains unknown and requires further  
10 study. Prior studies on association of urban-rural migration with subclinical atherosclerosis are  
11 scarce. Woo et al. have earlier found that urban Chinese living in Hong Kong and Australia  
12 had higher IMT than Chinese living rural areas (n=348, mean age 42 years).<sup>8</sup> The risk of  
13 atherosclerosis has been traditionally low in rural Chinese due to environmental factors and  
14 thus the results are not comparable to high income Western country such as Finland where rural  
15 lifestyle has become increasingly sedentary because of mechanization of agricultural work.  
16 Limitation in longitudinal studies is non-participation at follow-up which is inevitable.  
17 However, our study group has been dynamic, and thus probably representative of the original  
18 population.<sup>30</sup> Moreover, categorization of migration used was based on information of  
19 participant's place of residence from childhood and adulthood. This categorization did not  
20 consider possibility that individuals may have moved repeatedly between childhood and  
21 adulthood. Finally, we have no clinical end-points because the participants are still relatively  
22 young. However, data on surrogate markers of CVD were available that have been shown to  
23 predict the risk of future cardiovascular events and total mortality.<sup>20-23</sup>

## 24 **Conclusions**

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

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8

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4 **Conflict of interest**

5 The authors report no relationships that could be construed as a conflict of interest.

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## 1 **References**

- 2 1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235  
3 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the  
4 Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2095-2128.  
5 doi:10.1016/S0140-6736(12)61728-0 [doi]
- 6 2. Keys A, Aravanis C, Blackburn HW, et al. Epidemiological studies related to coronary  
7 heart disease: characteristics of men aged 40-59 in seven countries. *Acta Medica*  
8 *Scand*. 1966;460:1-392.
- 9 3. Jousilahti P, Laatikainen T, Peltonen M, et al. Primary prevention and risk factor  
10 reduction in coronary heart disease mortality among working aged men and women in  
11 eastern Finland over 40 years: population based observational study. *BMJ*.  
12 2016;352:i721. doi:10.1136/bmj.i721 [doi]
- 13 4. Hoffmann R, Borsboom G, Saez M, et al. Social differences in avoidable mortality  
14 between small areas of 15 European cities: An ecological study. *Int J Health Geogr*.  
15 2014;13. doi:10.1186/1476-072X-13-8
- 16 5. Anderson TJ, Saman DM, Lipsky MS, Lutfiyya MN. A cross-sectional study on health  
17 differences between rural and non-rural U.S. counties using the County Health  
18 Rankings. *BMC Health Serv Res*. 2015;15(1):1-8. doi:10.1186/s12913-015-1053-3
- 19 6. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular Risk and Events in 17 Low-,  
20 Middle-, and High-Income Countries. *N Engl J Med*. 2014;371(9):818-827.  
21 doi:10.1056/NEJMoa1311890
- 22 7. Vaughan AS, Quick H, Pathak EB, Kramer MR, Casper M. Disparities in temporal and  
23 geographic patterns of declining heart disease mortality by race and sex in the United  
24 States, 1973-2010. *J Am Heart Assoc*. 2015;4(12):1-12.  
25 doi:10.1161/JAHA.115.002567



- 1 8. Woo KS, Chook P, Raitakari OT, McQuillan B, Feng JZ, Celermajer DS.  
2 Westernization of Chinese adults and increased subclinical atherosclerosis. *Arter*  
3 *Thromb Vasc Biol.* 1999;19(10):2487-2493. doi:10.1161/01.ATV.19.10.2487
- 4 9. Haraldsdottir S, Gudmundsson S, Thorgeirsson G, Lund SH, Valdimarsdottir UA.  
5 Regional differences in mortality, hospital discharges and primary care contacts for  
6 cardiovascular disease. *Scand J Public Health.* 2017;140349481668534.  
7 doi:10.1177/1403494816685341
- 8 10. Fogelholm M, Valve R, Kontinen R, et al. Rural—urban differences in health and  
9 health behaviour: A baseline description of a community health-promotion programme  
10 for the elderly. *Scand J Public Health.* 2006;34(6):632-640.  
11 doi:10.1080/14034940600616039
- 12 11. Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: The Cardiovascular Risk  
13 in Young Finns Study. *Int J Epidemiol.* 2008;37(6):1220-1226.  
14 doi:10.1093/ije/dym225; 10.1093/ije/dym225
- 15 12. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a  
16 joint interim statement of the International Diabetes Federation Task Force on  
17 Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American  
18 Heart Association; World Heart Federation; International . *Circulation.*  
19 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644;  
20 10.1161/CIRCULATIONAHA.109.192644
- 21 13. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes Care.*  
22 2013;36 Suppl 1:S67-74. doi:10.2337/dc13-S067; 10.2337/dc13-S067
- 23 14. Telama R, Viikari J, Välimäki I, et al. Atherosclerosis precursors in Finnish children  
24 and adolescents. X. Leisure-time physical activity. *Acta Paediatr Scand.*  
25 1985;318:169-180.

- 1 15. Puolakka E, Pahkala K, Laitinen TT, et al. Childhood Socioeconomic Status and  
2 Arterial Stiffness in Adulthood: The Cardiovascular Risk in Young Finns Study.  
3 *Hypertens (Dallas, Tex 1979)*. 2017;70(4):729-735.  
4 doi:10.1161/HYPERTENSIONAHA.117.09718
- 5 16. Juonala M, Kähönen M, Laitinen T, et al. Effect of age and sex on carotid intima-  
6 media thickness, elasticity and brachial endothelial function in healthy adults: The  
7 Cardiovascular Risk in Young Finns Study. *Eur Heart J*. 2008;29(9):1198-1206.  
8 doi:10.1093/eurheartj/ehm556
- 9 17. Vähämurto L, Juonala M, Ruohonen S, et al. Geographic origin as a determinant of left  
10 ventricular mass and diastolic function – the Cardiovascular Risk in Young Finns  
11 Study. *Scand J Public Health*. 2018;(December 2017):1-8.  
12 doi:10.1177/1403494818764782
- 13 18. de Simone G, Daniels SR, Devereux RB, et al. Left ventricular mass and body size in  
14 normotensive children and adults: Assessment of allometric relations and impact of  
15 overweight. *J Am Coll Cardiol*. 1992;20(5):1251-1260. doi:10.1016/0735-  
16 1097(92)90385-Z
- 17 19. Vähämurto L, Pahkala K, Magnussen CG, et al. East–west differences and migration  
18 in Finland: Association with cardiometabolic risk markers and IMT. The  
19 Cardiovascular Risk in Young Finns Study. *Scand J Public Health*. 2016;44:402-410.  
20 doi:10.1177/1403494815622859
- 21 20. Armstrong AC, Jacobs DR, Gidding SS, et al. Framingham score and LV mass predict  
22 events in young adults: CARDIA study. *Int J Cardiol*. 2014;172(2):350-355.  
23 doi:10.1016/j.ijcard.2014.01.003
- 24 21. Yuan C, Wang J, Ying M. Predictive value of carotid distensibility coefficient for  
25 cardiovascular diseases and all-cause mortality: A meta-analysis. *PLoS One*.

- 1 2016;11(4):1-15. doi:10.1371/journal.pone.0152799
- 2 22. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of Cardiovascular Events  
3 and All-Cause Mortality With Arterial Stiffness. A Systematic Review and Meta-  
4 Analysis. *J Am Coll Cardiol*. 2010;55(13):1318-1327. doi:10.1016/j.jacc.2009.10.061
- 5 23. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical  
6 cardiovascular events with carotid intima-media thickness: a systematic review and  
7 meta-analysis. *Circulation*. 2007;115(4):459-467.  
8 doi:10.1161/CIRCULATIONAHA.106.628875
- 9 24. Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the  
10 assessment of cardiovascular risk: a report of the American College of  
11 Cardiology/American Heart Association Task Force on Practice Guidelines.  
12 *Circulation*. 2014;129(25 Suppl 2):S49-73. doi:10.1161/01.cir.0000437741.48606.98  
13 [doi]
- 14 25. Kaikkonen R, Murto J, Saarsalmi P, et al. Alueellisen terveyst- ja  
15 hyvinvointitutkimuksen perustulokset kaupunki-maaseutu -luokittain 2013.  
16 www.thl.fi/ath.
- 17 26. Lindroth M, Lundqvist R, Lilja M, Eliasson M. Cardiovascular risk factors differ  
18 between rural and urban Sweden: The 2009 Northern Sweden MONICA cohort. *BMC*  
19 *Public Health*. 2014;14(1):1-8. doi:10.1186/1471-2458-14-825
- 20 27. Vartiainen E, Laatikainen T, Peltonen M, et al. Thirty-five-year trends in  
21 cardiovascular risk factors in Finland. *Int J Epidemiol*. 2010;39(2):504-518.  
22 doi:10.1093/ije/dyp330; 10.1093/ije/dyp330
- 23 28. Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood  
24 and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in  
25 Young Finns Study. *Jama*. 2003;290(17):2277-2283. doi:10.1001/jama.290.17.2277

1 [doi]

2 29. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk  
3 factors for cardiovascular disease other than hypertension: A systematic review.  
4 *Hypertension*. 2009;54(6):1328-1336.  
5 doi:10.1161/HYPERTENSIONAHA.109.137653

6 30. Nuotio J, Oikonen M, Magnussen CG, et al. Cardiovascular risk factors in 2011 and  
7 secular trends since 2007: The cardiovascular risk in Young Finns Study. *Scand J*  
8 *Public Health*. 2014;42(7):563-571.

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1 **Figure and Table legends.**

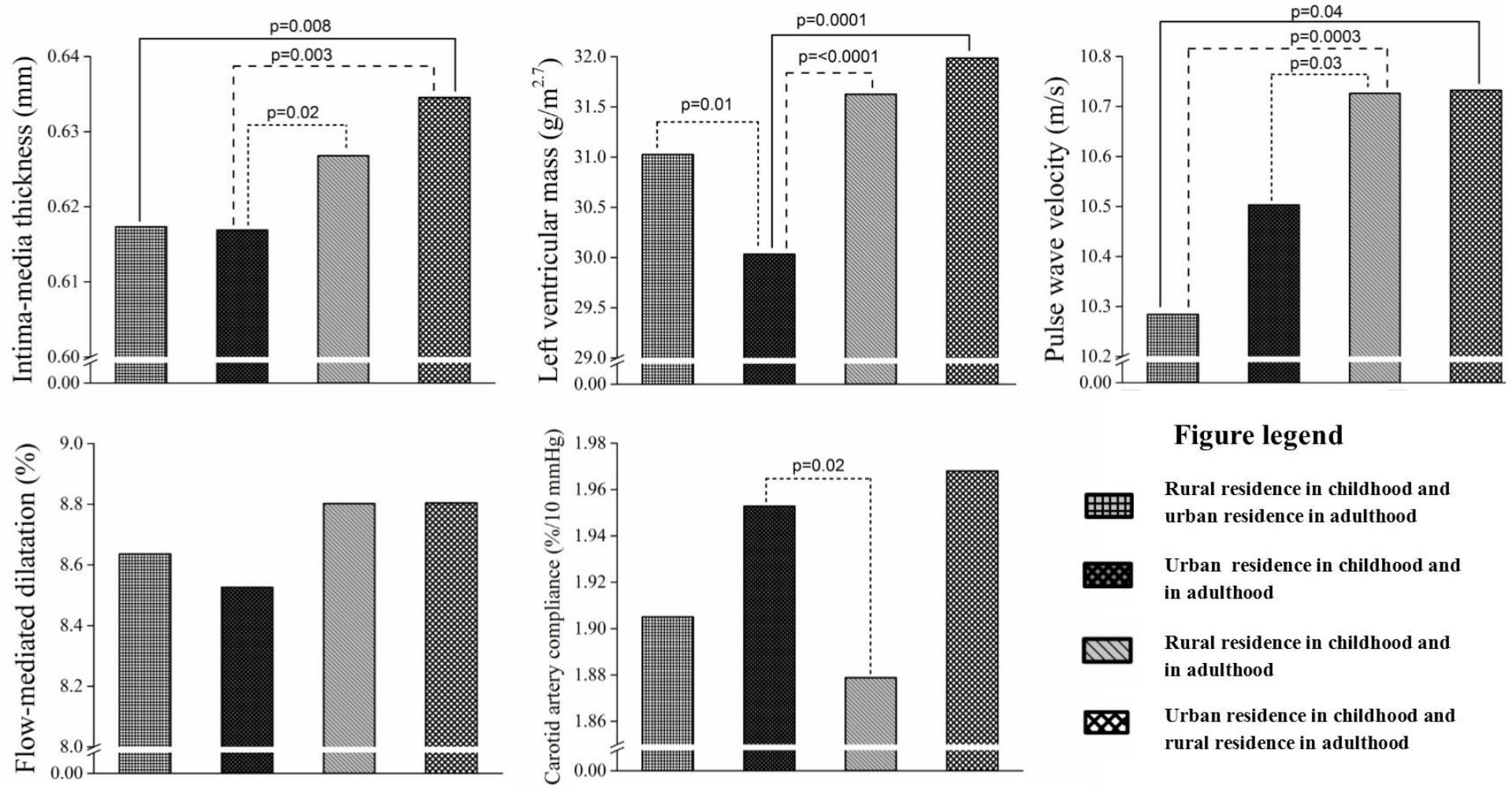
2 **Figure 1.** Association of urban-rural migration with intima-media thickness, left ventricular  
3 mass, pulse wave velocity, flow-mediated dilatation, and carotid artery compliance in  
4 adulthood in 2,599 participants of the Cardiovascular Risk in Young Finns Study. Values are  
5 presented as age and sex adjusted means. Significant differences observed between groups are  
6 shown in the figure.

7 **Table 1.** Cardiovascular risk factors according to urban-rural residence in childhood (1980).

8 **Table 2.** Cardiovascular risk factors and surrogate markers for cardiovascular disease in  
9 adulthood according to urban-rural residence in childhood (1980) in participants of the  
10 Cardiovascular Risk in Young Finns Study.

11 **Table 3.** Cardiovascular risk factors and surrogate markers for cardiovascular disease in  
12 adulthood according to urban-rural residence in adulthood (2001-2011) in participants of the  
13 Cardiovascular Risk in Young Finns Study.

**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 1,793 - 2,599 participants of the Cardiovascular Risk in Young Finns Study. Values are presented as age and sex adjusted means. Significant differences observed between the groups are shown in the figure.



**Table 1.** Cardiovascular risk factor levels in childhood (1980) according to urban-rural residence in childhood in participants of the Cardiovascular Risk in Young Finns Study.

		<b>Urban residence</b>		<b>Rural residence</b>		<b>P for difference<sup>a</sup></b>
<b>N</b>		1,394		1509		
<b>Female %</b>		53.3		54.8		0.43
<b>Age (years)</b>		10.7	±5.0	10.3	±5.0	0.09
<b>BMI (kg/m<sup>2</sup>)</b>		17.8	±3.0	17.8	±3.2	0.18
<b>Systolic blood pressure (mmHg)</b>		112	±12	113	±12	0.01
<b>Diastolic blood pressure (mmHg)</b>		69	±10	68	±10	0.15
<b>Total cholesterol (mmol/l)</b>		5.22	±0.9	5.40	±0.9	<0.0001
<b>LDL-cholesterol (mmol/l)</b>		3.36	±0.8	3.53	±0.9	<0.0001
<b>HDL-cholesterol (mmol/l)</b>		1.56	±0.3	1.56	±0.3	0.92
<b>Triglycerides (mmol/l)</b>		0.65	±0.3	0.68	±0.3	0.02
<b>Insulin (mU/l)</b>		9.60	±5.8	9.73	±6.1	0.10
<b>Physical Activity</b>	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
<b>Parental socioeconomic status (school years)</b>		11.9	±3.9	10.2	±3.4	<0.0001
<b>Smoking (%)</b>		7.6		5.0		0.005

Values are expressed as mean ± standard deviation or as proportions (%). N varied between 1,192 and 1,395 in participants living in urban areas and 1,244 and 1,509 in participants living in rural areas.

<sup>a</sup>Continuous 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.

**Table 2.** 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.

	<b>Urban residence</b>		<b>Rural residence</b>		<b>P for difference<sup>b</sup></b>
<b>n</b>	1,394		1,509		
<b>Female (%)</b>	53.3		54.8		0.41
<b>Age (years)</b>	39.9	±6.2	39.2	±6.6	0.001
<b>BMI (kg/m<sup>2</sup>)</b>	26.3	±4.9	26.4	±5.1	0.50
<b>Systolic blood pressure (mmHg)</b>	119	±14	120	±15	0.0004
<b>Diastolic blood pressure (mmHg)</b>	75	±11	75	±11	0.98
<b>Total cholesterol (mmol/l)</b>	5.15	±1.0	5.18	±1.0	0.26
<b>LDL-cholesterol (mmol/l)</b>	3.22	±0.8	3.27	±0.8	0.051
<b>HDL-cholesterol (mmol/l)</b>	1.33	±0.3	1.32	±0.3	0.55
<b>Triglycerides (mmol/l)</b>	1.37	±1.0	1.35	±1.3	0.26
<b>Glucose (mmol/mol)</b>	5.35	±0.9	5.37	±1.1	0.29
<b>Glycosylated hemoglobin (mmol/mol)</b>	36.7	±5.4	36.8	±5.2	0.43
<b>Insulin (mU/l)</b>	9.77	±12.6	9.84	±13.1	0.79
<b>Socioeconomic status (school years)</b>	15.4	±3.6	14.7	±3.5	<0.0001
<b>Alcohol Consumption (drinks per week)</b>	6.6	±9.3	5.6	±9.1	<0.0001
<b>Physical Activity (Range 5-15)</b>	9.0	±1.9	8.9	±1.8	0.33
<b>Attention paid to health habits (range 1-5)<sup>a</sup></b>	2.5	±1.0	2.5	±1.0	0.39
<b>Intima-media thickness (mm)</b>	0.62	0.09	0.62	0.10	0.56
<b>Left ventricular mass (g/m<sup>2.7</sup>)</b>	30.42	6.55	31.10	6.66	0.01
<b>Pulse wave velocity (m/s)</b>	10.53	2.04	10.45	1.96	1.00
<b>Flow-mediated dilatation (%)</b>	8.67	4.53	8.84	4.53	0.68
<b>Carotid artery compliance (%/10mmhg)</b>	1.96	0.72	1.92	0.69	0.02
<b>Smoking (%)</b>	20.8		20.0		0.55
<b>Metabolic Syndrome (%)</b>	21.3		21.5		0.50
<b>Type 2 Diabetes (%)</b>	3.5		3.8		0.65

Values are expressed as mean ± standard deviation or as proportions (%). N varied between 1,004 and 1,395 in participants living in urban areas and 1,018-1,509 in participants living in rural areas.

<sup>a</sup> Lower is better

<sup>b</sup>Continuous 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.



**Table 3.** 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.

	<b>Urban residence</b>		<b>Rural residence</b>		<b>P for difference<sup>b</sup></b>
<b>n</b>	1,754		1,149		
<b>Female (%)</b>	54.1		54.1		1.00
<b>Age (years)</b>	39.3	±6.6	39.9	±6.1	0.01
<b>Body mass index (kg/m<sup>2</sup>)</b>	25.9	±4.9	26.9	±5.2	<0.0001
<b>Systolic blood pressure (mmHg)</b>	119	±14	121	±14	<0.0001
<b>Diastolic blood pressure (mmHg)</b>	75	±11	76	±11	0.04
<b>Total cholesterol (mmol/l)</b>	5.14	±1.0	5.21	±0.9	0.07
<b>LDL-cholesterol (mmol/l)</b>	3.21	±0.8	3.30	±0.8	0.005
<b>HDL-cholesterol (mmol/l)</b>	1.33	±0.3	1.32	±0.3	0.34
<b>Triglycerides (mmol/l)</b>	1.37	±1.3	1.34	±1.0	0.54
<b>Glucose (mmol/mol)</b>	5.33	±0.8	5.41	±1.2	0.053
<b>Glycosylated hemoglobin (mmol/mol)</b>	36.5	±5.0	37.0	±5.7	0.04
<b>Insulin (mU/l)</b>	9.52	±11.8	10.24	±14.3	0.07
<b>Socioeconomic status (school years)</b>	15.6	±3.7	14.2	±3.2	<0.0001
<b>Alcohol Consumption (drinks per week)</b>	6.2	±9.1	5.9	±9.3	0.01
<b>Physical Activity (Range 5-15)</b>	9.0	±1.9	8.8	±1.8	0.001
<b>Attention paid to health habits (range 1-5)<sup>a</sup></b>	2.4	±0.9	2.6	±1.0	<0.0001
<b>Intima-media thickness (mm)</b>	0.61	0.09	0.63	0.10	0.0008
<b>Left ventricular mass (g/m<sup>2.7</sup>)</b>	30.24	6.45	31.54	6.78	<0.0001
<b>Pulse wave velocity (m/s)</b>	10.38	1.96	10.66	2.05	0.0002
<b>Flow-mediated dilatation (%)</b>	8.67	4.62	8.91	4.39	0.42
<b>Carotid artery compliance (%/10mmhg)</b>	1.95	0.71	1.91	0.69	0.27
<b>Smoking (%)</b>	20.5		20.3		0.65
<b>Metabolic Syndrome (%)</b>	19.9		23.7		0.04
<b>Type 2 Diabetes (%)</b>	3.4		4.0		0.69

Values are expressed as mean ± standard deviation or as proportions (%). N varied between 1,195 and 1,754 in participants living in urban areas and 827-1,509 in participants living in rural areas.

<sup>a</sup> Lower is better

<sup>b</sup> Continuous 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.