Prevalence and long-term prognostic implications of prolonged QRS duration in left ventricular hypertrophy: a population-based observational cohort study

Jani Rankinen, Petri Haataja, Leo-Pekka Lyytikäinen, Heini Huhtala, Terho Lehtimäki, Mika Kähönen, Markku Eskola, Suvi Tuohinen, Andrés Ricardo Pérez-Riera, Antti Jula, Harri Rissanen, Kjell Nikus, Jussi Hernesniemi

ABSTRACT

Objectives ECG left ventricular hypertrophy (ECG-LVH) has been associated with left ventricular dysfunction and adverse prognosis, but little is known about the prevalence and prognostic significance of different levels of QRS duration in the presence of ECG-LVH in a general population.


Participants Nationally representative random cluster of Finnish adult population.

Methods We assessed the prevalence and long-term (median 15.9 years) prognostic significance of QRS duration in ECG-LVH, and compared the risk to individuals without ECG-LVH in a predominantly middle-aged random sample of 6033 Finnish subjects aged over 30 years (mean age 52.2, SD 14.6 years), who participated in a health examination including a 12-lead ECG.

Main outcome measures Cardiovascular and all-cause mortality, incidence of heart failure (HF).

Results ECG-LVH was present in 1337 (22.2%) subjects; 403 of these (30.1%) had QRS duration ≥100 ms and 100 (7.5%) had >110 ms. The increased risk of mortality in ECG-LVH became evident after a QRS threshold of ≥100 ms. After controlling for known clinical risk factors, QRS 100–109 ms was associated with increased cardiovascular (HR 1.38, 95% CI 1.01 to 1.88, p=0.043) and QRS≥110 ms with cardiovascular (1.74, 95% CI 1.07 to 2.82, p=0.025) and all-cause mortality (1.52, 95% CI 1.02 to 2.25, p=0.039) in ECG-LVH. The risk of new-onset HF was two-fold in subjects with QRS 100–109 ms and three-fold in subjects with QRS ≥110 ms, even after adjustment for incident myocardial infarction within the follow-up. When the prognosis was compared with subjects without ECG-LVH, subjects with ECG-LVH but QRS duration <100 ms displayed similar mortality rates with or without ECG-LVH but higher rates of incident HF.

Conclusions In ECG-LVH, the risk of excess mortality and new-onset HF markedly increases with longer QRS duration, but even QRS duration within normal limits in ECG-LVH carried a risk of HF compared with the risk in individuals without ECG-LVH.

INTRODUCTION

Assessment of left ventricular hypertrophy (LVH) in the standard 12-lead ECG is recommended for every hypertensive individual and ECG-LVH is predictive of future cardiovascular (CV) events independently of echocardiography findings. The principal findings in ECG-LVH are increases of QRS amplitude and duration, and abnormalities of ST-segment with T-wave changes. While many previous studies have been dedicated to assess the prognostic relevance of different voltage criteria-based definitions for ECG-LVH, the prevalence and prognostic significance of QRS duration in ECG-LVH has not been well established in general.
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population. literature regarding the prognostic significance of QRS duration in a general population is also somewhat conflicting as a mild conduction delay (QRS duration 100–119 ms) was associated with increased risk of mortality even after adjustment for LVH in one study, but not after adjustment for known cardiac risk factors including LVH in another study.

Therefore, the aim of this study was to evaluate the prevalence and prognostic value of QRS duration in individuals with ECG-LVH in a nationally representative general population sample. In addition, we aimed at comparing the prognostic significance of different levels of QRS duration between individuals with and without ECG-LVH. We tested the hypothesis that QRS duration has prognostic relevance when associated with ECG-LVH, and that this easily recognised ECG finding could further stratify risk in patients with ECG-LVH and aid in screening for risk of CV mortality and for early identification of new-onset heart failure (HF).

methods

Study population
This study was conducted as part of the Health 2000 survey, which consists of a random sample of a predominantly Caucasian general population with applicable phenotype data collected at baseline and during 16.5 years of total follow-up. The survey was carried out in 2000–2001, and a representative stratified random cluster sample of the Finnish population was examined. The purpose of the survey was to provide up-to-date epidemiological data of major public health problems in Finland. The implementation of the survey was described in detail elsewhere. Sample comprised 8028 individuals (3637 men and 4391 women) aged 30 years or older, of whom 79% (6 354 individuals; 2876 men and 3 478 women) participated in the health examination. ECGs were obtained successfully in 6318 individuals (99 %). For this study, 19 subjects were excluded because of missing ECGs. We also excluded subjects with paced rhythm (n=13), left bundle branch block (n=47; defined by the Strauss definition), incomplete and complete right bundle branch block (n=136), left anterior fascicular block (n=69) and Wolff-Parkinson-White pattern (n=1) (figure 1). After these exclusions, the study population consisted of 6033 subjects: 3 320 women and 2713 men (mean age 52.2, SD 14.6 years).

Collection of clinical phenotype data
After a home interview, a comprehensive health examination including questionnaires, measurements and physician’s physical examination was performed. The National Care Register for Health Care and the national register on rights to reimbursements for medication costs were linked to the Health 2000 Survey data. The health examination included measurements of height, weight, body mass index (BMI). Blood pressure was measured two times with a mercury sphygmomanometer (Mercuro 300, Speidel & Keller, Jüningen, Germany) from the right arm. Hypertension was defined as a clinic average blood pressure ≥140/90 mm Hg or right to drug reimbursements for hypertension. Laboratory tests included measurements for serum glucose level and cholesterol levels. Diabetes mellitus was defined as a serum glucose level of 7.0 mmol/L or greater or a history of the use of oral hypoglycaemic agents or insulin therapy. Low-density
lipoprotein cholesterol was calculated with the Friedewald formula. Smoking was defined as daily use of tobacco products. Standard 12-lead ECGs were recorded in the resting supine position by MAC 5000 recorders (Marquette Hellige, Freiburg, Germany and Milwaukee, Wisconsin, USA) and stored as digital data on a Marquette MUSE CV 5B system (Marquette Hellige). All ECGs were read, and the computerised diagnoses and measurements corrected if needed, by a physician experienced with ECG before being stored in the database. The ECGs were recorded and printed using a paper speed of 50 mm/s. The maximal filter setting of the system (150 hertz) was used. Minnesota coding was performed at the Institute of Cardiology, Kaunas Medical Academy, Lithuania, by two investigators who were blinded to the clinical data of the patient. Abnormalities identified visually in the ECG strips were coded in accordance with the Minnesota coding scheme.12 ECG-LVH was identified with Cornell (SV3 + RV5 > 2.0 mV for women, >2.8 mV for men13) and/or Minnesota (code 3-1 which includes RV5 amplitude criterion: R5 >2.6 mV, or R, or RII or RIII or RaVF >2.0 mV, or RV5 >1.2 mV; and code 3-3 which includes the Sokolow-Lyon criteria: R1 >1.5 mV but ≤2.0 mV, or RV5 + Sv3 >3.5 mV, or RV5 + SV1 >3.5 mV15) voltage criteria. ECG-LVH was considered positive if any of the criteria was met, and negative if none of criteria was met.

Classification for coronary heart disease (CHD) required at least one of the following: diagnosis of myocardial infarction (MI) and/or angina pectoris during the field health examination by the examining physician, Q waves in the resting ECG, prior hospitalisation for CHD (International Classification of Diseases (ICD)-10 codes I20–I25), a history of coronary revascularisation procedure, the right to drug reimbursements for CHD, or the use of nitroglycerine and negative if none of criteria was met.

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Main exposure and outcome variables

The main exposure variable of this study was QRS duration in association with ECG-LVH. We also tested for the prognostic significance of QRS duration when unassociated with ECG-LVH. Main prognostic outcomes were CV mortality, all-cause mortality and new-onset HF during a follow-up starting from the baseline examination (between 2000 and 2001) until the end of 2015 (total follow-up time 16.5 years, median 15.9 years).

New-onset HF was defined as hospitalisation for HF from the Care Register for Healthcare, new right to drug reimbursements for HF, or HF as the primary underlying or immediate cause of death from the Causes of Death Register. For this particular endpoint, participants with prevalent HF or CHD or anginal symptoms at the baseline examination were excluded from the analysis when studying QRS duration as an independent risk factor for new-onset HF. The follow-up information was gathered by linking the personal identity code from the10 Survey database to the Care Register for Healthcare and the Causes of Death register, maintained by Statistic Finland, which records 100% of deaths of Finnish citizens in Finland. Diagnoses are registered in these registers by the treating physicians with codes defined in ICD-10. The Finnish Care Register for Healthcare has been shown to be valid in identifying major CHD events,14 and has been shown to be valid in identifying HF diagnoses with high positive and negative predictive values and can be reliably used for research purposes.15 The follow-up information was available for all subjects.

STATISTICAL ANALYSES

Proportions across groups were compared with the chi-square test or Fisher’s exact test. The distribution of QRS duration in the study population, was visualised by a density plot. The linearity of the association of QRS duration and mortality was checked in a spline model in subjects with ECG-LVH. This showed a clear deviation from linearity with the risk of death increasing clearly above QRS duration of 100 ms. In order to demonstrate the results in clinical context, the population was divided in three subgroups with different QRS durations:<100 ms, 100–109 ms and ≥110 ms. Prognostic implications of QRS duration were studied across these ECG-LVH groups and also further comparing the results to subjects without ECG-LVH. Unadjusted survival to each endpoint was assessed using the Kaplan-Meier method. Adjusted HRs were calculated by univariate and multivariable proportional Cox regression model analysis. Multivariable analysis included the following clinical parameters: age, sex, hypertension, diabetes mellitus, CHD, MI, HF, ST-depression lead V5, smoking, BMI and low-density lipoprotein cholesterol. Further adjustment for incident MI within the follow-up was included in the multivariable Cox regression analysis when studying the risk of new-onset HF. Death from non-CV causes was considered as a competing event to CV death. To take into account this competing risk, additional Fine and Gray subdistribution hazard modelling16 was applied to control for possible confounding due to censoring by competing events in the survival analysis when analysing the association between QRS time and CV mortality. There were no significant changes in the results, indicating that possible effect of exposure variables on the rate of competing events did not have significant effect on the observed risk estimates. We also tested for interaction between the QRS duration and sex by introducing their product as an interaction term. Interaction for QRS duration and prevalent CHD was also tested similarly. Interaction analyses showed no
interaction between QRS duration and sex associating with the risk of mortality or new-onset HF, or between QRS duration and CHD associating with the risk of mortality among subjects with ECG-LVH (p>0.1 for both). A p<0.05 was considered to be statistically significant.

Patient and public involvement
Patients and the public were not involved in the design, data provision, analysis or publication of the study.

RESULTS
Of the entire study population, 1337 subjects had ECG-LVH by any of the criteria (22.2%; 637 women and 700 men). Among subjects with LVH, men had longer QRS duration than women (mean 96 ms (SD 11 ms) vs 90 ms (SD 11 ms), p<0.001 for difference). The distribution of study subjects with ECG-LVH according to QRS duration is shown in figure 2.

At baseline (table 1), subjects with ECG-LVH were associated with every single CV risk factor and CV disease except for smoking as compared those without ECG-LVH (p<0.001). The majority (69.9%) of subjects with ECG-LVH had a QRS-duration of <100 ms, 22.7% had 100–109 ms and 7.5%≥110 ms. Those with QRS duration ≥110 ms were more often male and had a history of ischemic heart disease or prior MI. Clinical characteristics in a population matched by QRS duration is provided in online supplemental table 1.

Association between QRS duration in ECG-LVH and mortality
During the median 15.9 years’ follow-up, 19.5% of subjects died (n=1174/6033). Of these, 571 (48.6 % of all deaths) deaths were due to CV causes. Subjects with ECG-LVH met more often the primary endpoint than those without ECG-LVH (p<0.001). According to the unadjusted spline model (figure 3), the association between QRS duration in ECG-LVH and overall mortality seemed non-linear, with increased mortality rates after the threshold of 100 ms for QRS duration. Supporting this, adjusting for other clinical factors, subjects with ECG-LVH with QRS<100 ms showed no significant difference in all-cause or CV mortality when compared with subjects with no ECG-LVH and a normal QRS duration (<100 ms) in the general population (HR 1.11, 95% CI 0.89 to 1.38, p=0.350 for CV mortality and HR 0.96, 95% CI 0.83 to 1.11, p=0.599 for all-cause mortality). In other words, subjects with a
QRS duration <100 ms displayed similar mortality rates whether ECG-LVH was present or not.

When analysing only subjects with ECG-LVH (n=1 337) and using subjects with normal QRS duration (<100 ms) as a reference group (table 2), the risk of CV mortality was significantly higher among subjects with QRS 100–109 ms (HR 1.39, 95% CI 1.00 to 1.92, p=0.048) or with QRS ≥110 ms (HR 1.91, 95% CI 1.20 to 3.04, p=0.007). This same trend was also reflected in the increased risk for all-cause mortality in these groups (HR 1.38, 95% CI 1.01 to 1.88, p=0.045 for QRS 100–109 ms, and HR 1.74, 95% CI 1.07 to 2.82, p=0.025 for QRS ≥110 ms), respectively. While the visualisation of the unadjusted spline model suggested that the lower levels of QRS duration could associate with increased mortality (figure 3), this was not true after adjustment for age and clinical risk factors (HR 0.95, 95% CI 0.66 to 1.37, p=0.781 for QRS duration <80 ms as compared with QRS duration 80–99 ms).

**Figure 3** Unadjusted HRs for QRS duration and all-cause mortality in subjects with ECG left ventricular hypertrophy. Dotted lines are 95% confidence limits of the resulting HRs, the risk for mortality increases along with longer QRS duration

**Table 2** Adjusted Cox proportional hazard analysis for mortality and incident heart failure events in subjects with ECG left ventricular hypertrophy in three QRS duration subgroups

<table>
<thead>
<tr>
<th>No of deaths/incident HF (%)</th>
<th>Age and gender adjusted</th>
<th>Multivariable* adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Cardiovascular Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 ms</td>
<td>135 (14.5%)</td>
<td>1.39</td>
</tr>
<tr>
<td>100–109 ms</td>
<td>56 (18.5%)</td>
<td>1.91</td>
</tr>
<tr>
<td>≥110 ms</td>
<td>22 (22.0%)</td>
<td>1.54</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 ms</td>
<td>257 (27.5%)</td>
<td>1.17</td>
</tr>
<tr>
<td>100–109 ms</td>
<td>86 (28.4%)</td>
<td>1.54</td>
</tr>
<tr>
<td>≥110 ms</td>
<td>32 (32.0%)</td>
<td>1.54</td>
</tr>
<tr>
<td><strong>New-onset HF</strong></td>
<td></td>
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<tr>
<td>QRS duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 ms</td>
<td>87 (9.3%)</td>
<td>1.83</td>
</tr>
<tr>
<td>100–109 ms</td>
<td>38 (12.5%)</td>
<td>4.36</td>
</tr>
<tr>
<td>≥110 ms</td>
<td>23 (23.0%)</td>
<td>4.36</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, coronary heart disease, myocardial infarction, heart failure, hypertension, ST-depression in lead V5, diabetes mellitus, smoking, body mass index and low-density lipoprotein cholesterol.

HF, heart failure.

**Association between QRS duration in ECG-LVH and the risk of new-onset HF**

Among the 5904 subjects with no HF at baseline, 382 subjects (6.5 %) developed new-onset HF during the follow-up. Subjects with ECG-LVH developed more often incident HF (11.1 %) than those without ECG-LVH (5.0%; p<0.001). ECG-LVH was associated with an increased risk of new-onset HF in all the categories of QRS duration, even among subjects with a QRS <100 ms (HR 1.40, 95% CI 1.06 to 1.86, p=0.019), when compared with the subjects with no ECG-LVH and QRS <100 ms in the general population.

When analysing only subjects with ECG-LVH (n=1 337) and using subjects QRS duration <100 ms as a reference group (table 2), the risk of new-onset HF was significantly higher among subjects with QRS 100–109 ms (HR 2.18, 95% CI 1.32 to 3.61, p=0.003) and with QRS ≥110 ms (HR 3.39, 95% CI 1.60 to 7.17, p=0.001). Further adjustment for incident MI within the follow-up had no meaningful impact on results—the risk of HF was 1.83 (95% CI 1.12...
to 2.97, p=0.015) for QRS 100–109 ms, and 4.03 (95% CI 1.98 to 8.21, p<0.001) for QRS ≥110 ms.

Prognostic significance of QRS duration unassociated with ECG-LVH
Among 4696 subjects without meeting any of the predefined ECG-LVH criteria, 3785 subjects (80.6 %) had QRS duration <100 ms, 750 (16.0 %) had 100–109 ms, and 161 (3.4 %) had QRS duration ≥110 ms (online supplemental table 1). When none of the ECG-LVH criteria was met, subjects with QRS 100–109 ms or QRS ≥110 ms displayed no increased risk of mortality or HF as compared with those with QRS duration <100 ms (online supplemental tabel 2).

Supporting the impaired prognosis of prolonged QRS duration associated with ECG-LVH, when analysing subjects with QRS ≥110 ms in the population (n=261) and adjusting for clinical factors, subjects with ECG-LVH with QRS ≥110 ms had almost a two-fold risk of all-cause (HR 1.81, 95% CI 1.03 to 3.18, p=0.039) and CV mortality (HR 1.97, 95% CI 1.01 to 3.88, p=0.048) and over fivefold risk of incident HF (HR 5.23, 95% CI 1.62 to 16.94, p=0.006) when compared with subjects with QRS <100 ms but not meeting any of the predefined ECG-LVH criteria.

DISCUSSION
The main finding of this study is that among subjects with ECG-LVH, the risk of new-onset HF and mortality significantly increases with longer QRS duration. The higher mortality risk associated with QRS duration in ECG-LVH was driven by a strong association with CV mortality, and even subjects with ECG-LVH but normal QRS duration (<100 ms) had a significantly higher risk for new-onset HF when compared with subjects without ECG-LVH with normal QRS duration (<100 ms). Men have longer QRS duration when compared with women, but all observed associations were independent of sex and several known clinical risk factors.

A valid concern of the diagnostic accuracy of ECG-LVH pattern may arouse as 22.2% of the population met any of the predefined LVH criteria. In the Coronary Heart Disease study, the prevalence of ECG-LVH was 31.3 %, and in the Copenhagen City Heart Study voltage-only LVH was seen in 23.1 % of men. In addition, 19.6 % had LVH by any of predefined ECG criteria in the Atherosclerosis Risk in Communities Study, and the specificity of each ECG-LVH criterion used in the current study was ≥92% in reference to LVH defined by cardiac MRI in the Multi-Ethnic Study of Atherosclerosis cohort. Nevertheless the diagnostic accuracy of ECG-LVH, we have demonstrated in this study that QRS duration can be used as a risk marker in ECG-LVH as increased risk of mortality was only seen in subjects with prolonged QRS duration, and in fact ECG-LVH was related to an increased risk of incident HF irrespective of QRS duration.

As expected, the overall prevalence of a QRS duration ≥110 ms in ECG-LVH was lower (7.5 %) in the general population than what has been previously reported in selected patient cohorts; in a study dealing with hypertension and HF, the prevalence was 21.7 %. In line, the overall prevalence of a QRS duration ≥100 ms associated with ECG-LVH was lower in our study (30.1 %) than what was reported in an earlier report of veterans from the Palo Alto Veterans Administration Healthcare System. In that study, the prevalence of a QRS duration >100 ms in ECG-LVH was 43.8 % and the finding was linked to increased CV mortality, but the study sample consisted only of men.

Supporting our original hypothesis, when associated with ECG-LVH, prolonged QRS duration was a particularly strong risk factor for CV mortality and incident HF even after adjusting for relevant clinical risk factors including prevalent ischaemic heart disease. Association between QRS duration and increased risk of mortality was also observed in a prior study of hypertensive patients with ECG-LVH in a setting of aggressive hypertensive therapy, though the subjects in this study were clearly younger and predominantly middle-aged. In another report of the same cohort the risk of incident HF was observed only in subjects with ECG-LVH and QRS duration ≥110 ms during a mean follow-up of 4.7 years. Our study confirms the findings of the previous studies in a population-wide cohort with over 15 years of observation, and we are further reporting that subjects with ECG-LVH have increased risk of novel HF even when QRS duration is within normal limits (<100 ms), but the risk of incident HF and mortality strongly increases with longer QRS duration and even a mild conduction delay (QRS duration 100–109 ms) was associated with a twofold risk and QRS ≥110 ms with a threefold risk of new-onset HF in subjects with ECG-LVH, even after adjustment for incident MI.

Although the unadjusted spline model indicated the shorter QRS duration in ECG-LVH could be associated with increased mortality, this was not true after adjustment for clinical risk factors. The result is in line with a previous study that showed narrow QRS duration had no prognostic relevance in middle-aged men. The higher mortality risk associated with prolonged QRS duration in this study may be related to left ventricular structural remodelling as prolonged QRS has been shown to correlate with increased left ventricular mass, and previous study findings have established a linear relationship between left ventricular mass and CV mortality. In special patient cohorts, QRS duration may implicate other associated pathology as inverse relationship between QRS duration and left ventricular mass was found in a recent study investigating patients with hypertrophic cardiomyopathy. However, in an unscreened general population, QRS duration correlates with LVH, and at the population level the most important risk factor for LVH is hypertension. Possible pathophysiological mechanism for the relation of QRS duration and HF may also be related to increased left ventricular mass and structural remodelling. In previous studies, prolonged QRS duration was recognised as a specific indicator of
left ventricular dysfunction, and in the Cardiovascular Health Study increased left ventricular mass was independently associated with decreased left ventricular function within the follow-up in elderly subjects with normal left ventricular ejection fraction at baseline. In the Multi-Ethnic Study of Atherosclerosis, QRS duration ≥100 ms was associated with an increased incidence of HF, but the risk was attenuated to non-significance after adjustment for cardiac MRI measures of left ventricular structure, suggesting that prolonged QRS duration is a potentially useful marker to detect left ventricular remodelling that may predispose to HF.

Some study limitations need to be pointed out. First of all, even though the baseline health examination findings enabled the exclusion of subjects with either anginal symptoms or previously known or symptomatic HF and apparent ischaemic heart disease, absence of imaging data is a study limitation typical of a population study and thus the possibility of underlying silent cardiac conditions, such as reduced left ventricular function without symptomatic HF, could not be excluded. However, imaging data are not necessarily available in clinical practice when dealing with patients with prolonged QRS duration. The purpose of this study was to evaluate the prognostic implications of QRS duration using the information that is normally available in general practice in which the screening would normally take the place. We think that the large study population representing a wide age range from both genders, well-defined baseline characteristics, and long follow-up gives strength to our study findings.

CONCLUSIONS

In a nationally representative population study of predominantly middle-aged subjects with over 15 years of follow-up, prolonged QRS duration was associated with increased risk of mortality and with new-onset HF in subjects with ECG-LVH independently of several baseline variables. The risk was more pronounced with longer QRS duration.

This study may offer a couple of clinical implications. In the presence of even mildly prolonged QRS duration in the standard 12-lead ECG, ECG evidence of LVH ought to be carefully scrutinised as these patients were associated with impaired prognosis, and the presence of prolonged QRS duration in combination of ECG-LVH should alert physicians to perform careful cardiac evaluation even in absence of CV symptoms. Future studies should focus on whether clinical or imaging follow-up, such as a routine echocardiographic control, is prudent and cost-effective for early identification of asymptomatic heart disease in individuals with prolonged QRS duration with evidence of ECG-LVH.

Author affiliations

1Faculty of Medicine and Health Technology, Tampere University, and Finnish Cardiovascular Research Center, Tampere, Finland
2Department of Internal Medicine, Kanta-Häme Central Hospital, Hämeenlinna, Finland
3Heart Center, Department of Cardiology, Tampere University Hospital, Tampere, Finland
4Department of Clinical Chemistry, Tampere University Hospital, Tampere, Finland
5Faculty of Social Sciences, Tampere University, Tampere, Finland
6Department of Clinical Physiology, Tampere University Hospital, Tampere, Finland
7Heart and Lung Center, Helsinki University Central Hospital, Helsinki, Finland
8Design of Studies and Scientific Writing Laboratory, Faculdade de Medicina do ABC, Santo Andre, Sao Paulo, Brazil
9Finnish Institute for Health and Welfare, Helsinki/Turku, Finland

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Contributors JR conceived the original idea, performed the original analyses and wrote the original manuscript, HH provided the figures and helped with the statistics. AJ and HR provided the original Health 2000 Survey data and L-PL provided data curation. PH, TL, ME, ST and ARP-R helped supervise the project, MK supervised the project and helped to shape the final manuscript. KN and JH participated in writing and revising the manuscript and administered the project. As guarantor, JR accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

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Competing interests None.

Patient consent for publication Not applicable.

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ORCID iD

Jani Rankinen http://orcid.org/0000-0002-5796-6557

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