Association of lifelong occupation and educational level with subclinical atherosclerosis in different European regions. Results from the IMPROVE study

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ABSTRACT

Background and aims: We aimed to examine the association between socioeconomic status (SES) and subclinical atherosclerosis, as assessed by carotid intima-media-thickness (C-IMT) and to investigate whether the effect of social inequality on C-IMT is mediated by cardiovascular (CV) risk factors and whether it is dissimilar in men and women, and in different European countries.

Methods: We assessed the association of lifelong occupation and educational level with C-IMT in the IMPROVE study cohort including 3,703 subjects (median age 64.4 years; 48% men) from Southern (Italy), Western (France and the Netherlands) and Northern Europe (Finland and Sweden). Three summary measures of C-IMT (IMTmean, IMTmax, IMTmean-max), obtained from four segments of both carotids, were considered.

Results: After adjusting for conventional CV risk factors, current employment status and diet, C-IMT was higher in manual workers than in white collars (+7.7%, +5.3%, +4.6% for IMTmax, IMTmean-max and IMTmean, respectively; all p<0.0001). Similar results were obtained by stratification for educational level. The effect of occupation on C-IMT was comparable in men and women and in different age groups, and was only partially mediated by differences in CV risk factors. Of note, the association of C-IMT with occupation was significant in Western and Northern Europe but not in Italy, with a significant statistical interaction (p=0.0005).

Conclusions: Low SES was associated with subclinical atherosclerosis in subjects with at least three CV risk factors. Such association was stronger in Northern and Western Europe than in Italy. This difference was not completely explained by inequalities in CV risk factors and behavioural variables.

Keywords: Atherosclerosis, socioeconomic status, European countries, geographical variations, vascular risk factors.

Abbreviations: C-IMT, carotid Intima-media-thickness; CV, cardiovascular; CVD, cardiovascular disease; SES, socioeconomic status; IMTmean, mean of all local mean measures; IMTmax, maximum of all local maximal measures; IMTmean-max, mean of all local maximal measures; hs-CRP, high sensitive C reactive protein; BMI, body mass index; RRs, risk ratios; MI, myocardial infarction.

1. INTRODUCTION

In the last decades, numerous Public Health action plans have been implemented worldwide to reduce the burden of modifiable cardiovascular (CV) risk factors, with a remarkable impact on CV mortality. However, cardiovascular disease (CVD) remains the main cause of death in western countries in spite of the actions undertaken, and many contributors, both known or unknown, are likely to be involved.
A low socioeconomic-status (SES) has long been recognized as a modifiable risk factor for CVD, though the specific mechanisms leading to health inequalities are not completely understood. In addition, several studies documented a significant association between SES and carotid intima-media thickness (C-IMT), an established surrogate marker of subclinical atherosclerosis that is strongly associated with most CV risk factors and predictive of future cardiovascular events. Nevertheless, some issues related to the association between SES and C-IMT need to be clarified. For example, it is unknown a) whether the effect of SES on C-IMT is completely or partially mediated by CV risk factors; b) whether the association is present in both men and women, or is only present in one gender, with a significant gender × SES interaction reported in some studies; and c) whether the association between SES and C-IMT is modified by geography, in analogy with the results of Mackenbach et al. on the relation between SES and cardiovascular mortality.

Here, we investigated the association of SES, as indexed by type of lifelong occupation and education (years of study), with single-point C-IMT measures in IMPROVE, a large European study of individuals at moderate to high risk for CVD. As it was recruited in five European countries, the IMPROVE cohort provides a unique opportunity to analyse the effects of SES on subclinical atherosclerosis in geographical areas with different latitude, culture and social and economic characteristics.

2. Patients and methods

2.1. Subjects

Methods for patient selection, laboratory analyses and C-IMT measurements in IMPROVE have been published. Briefly, the IMPROVE study enrolled 3,703 subjects (1,774 Men and 1,929 women) aged 55 to 79 years, with at least three vascular risk factors but free from previous cardiovascular and cerebrovascular events, to assess the relations between C-IMT and C-IMT progression and the risk to develop future CV events. Participants were recruited in Kuopio (Finland, 2 centres), Stockholm (Sweden), Groningen (the Netherlands), Paris (France), Milano and Perugia (Italy). About 47% of the subjects were recruited from the general population (all the Stockholm cohort, about 85% of the subjects in Kuopio and 60% of the subjects in Groningen). The remaining subjects were recruited from lipid or hypertension clinics.

2.2. Ultrasound measurements

Sonographers and readers were centrally trained and certified. The far walls of left and right common carotid arteries, carotid bifurcations, and internal carotid arteries were visualized in three angles and recorded on sVHS videotapes. Intima–media thickness measurements were performed in a centralized laboratory (Department of Pharmacological and
Biomolecular Sciences, University of Milan, Italy) using a dedicated software (M’Ath, Metris SRL France). All measures were performed in at least three different frames.

Mean and maximal local (segment-specific) C-IMT values were computed. The ultrasonic variables selected for the present study were three summary measures: IMT\text{mean} (the mean of all local mean measures), IMT\text{max} (the maximum of all local maximal measures) and IMT\text{mean-max} (the mean of all local maximal measures). The mean±SD intra-observer absolute differences between duplicate scans were 0.038±0.06, 0.164±0.23 and 0.096±0.11 mm for IMT\text{mean}, IMT\text{max} and IMT\text{mean-max} respectively; the mean±SD inter-observer absolute differences between duplicate scans were 0.054±0.095, 0.239±0.238 and 0.134±0.145 mm for IMT\text{mean}, IMT\text{max} and IMT\text{mean-max} respectively.

2.3. Assessment of socioeconomic status

Two indicators of SES were employed: type of lifelong occupation and level of education (number of years at school). Data about these variables were obtained by a self-administered questionnaire. Occupations were classified using a scale of three main categories, with higher values indicating lower SES: 1) white collars, including office workers, managers and professionals; 2) service workers, an intermediate category including professions such as policemen, taxi and bus drivers, plumbers etc.; and 3) manual workers, including blue collars and farmers. The occupational status at enrolment, categorized as presently employed versus unemployed or retired, was also evaluated as a covariate. Educational level was categorized in tertiles. As recommended by Karvanen et al., tertiles were computed within gender, city of recruitment and age classes (below or above median=64.4 years). A total of 311 subjects were excluded from the analyses: 204 because of lacking information about the main lifelong occupation and 107 women who referred their occupation as ‘housewife’ were excluded since their position in the SES scale was thus uncertain. Thus, a total of 3396 participants were included in the main analysis.

2.4. Biochemical and behavioural variables

Serum concentrations of total, HDL and LDL cholesterol (computed by the Friedewald formula), high sensitive C-reactive protein (hs-CRP) and triglycerides were measured in a centralized laboratory with the use of LX Beckman instruments. Clinical variables, such as body mass index (BMI), systolic, diastolic and pulse blood pressure, and pharmacological treatments were also recorded.

Leisure-time physical activity was categorized as low (brisk walk for ten minutes less than once a week), medium (brisk walk for ten minutes from one to three times a week) or high (brisk walk for ten minutes more than three times a week). Smoking habits were quantified by smoking duration, calculated as the difference between the years when smoking began and ended (for former smokers), and by the average number of cigarettes smoked per day; pack-years were
computed as average number of cigarettes / 20 × years of smoking. Dietary habits were recorded as frequency of consumption (times a week) of the following seven foods: fish, fruit, milk, meat, eggs, wine. The type of fat (olive oil, seed oil, butter margarine or lard) most frequently used was also recorded.

2.6. Ethical considerations

The IMPROVE study was approved by the Ethics Committees of all participating institutions. The study also complies with the Declaration of Helsinki. All subjects signed the informed consent.

2.5. Statistical analysis

Descriptive statistics were reported as mean ± standard deviation for continuous variables, and as frequency and percentage for categorical variables. Due to their skewed distributions, C-IMT variables and levels of triglycerides and hs-CRP were log-transformed before analysis, and presented as median with interquartile range. Trends across occupational category were adjusted for age, gender and country.

The associations of C-IMT with occupation and educational classes were evaluated by multivariable linear regression analysis, with incremental models adjusted for different sets of covariates: model 1, adjusted for age and gender; model 2, as model 1 plus latitude, serum lipids, BMI, pulse pressure, pharmacological treatments, hs-CRP, triglycerides, pack-years, current employment status and leisure-time physical activity; model 3, as model 2 plus diet; model 4, in which the two SES indices were adjusted reciprocally, together with the covariates of model 3.

In order to test the impact of C-IMT measurement variability on the estimated occupation effect, a sensitivity analysis was carried out by artificially increasing the variability of IMT\textsubscript{max} by adding a simulated random error with the same distribution as the IMT\textsubscript{max} inter-observer variability (mean absolute difference = 0.239±0.238). Then we re-run model 3 using the IMT\textsubscript{max} with the simulated error as dependent variable.

The effects of occupation and education versus C-IMT variables were reported as percent change with respect to the category referring to the highest social status. Linear trends across categories of occupation or education were also evaluated. The attenuation effect, representing the proportion of the relation between occupation/education and C-IMT attributable to CV risk factors disparities, was evaluated as the beta coefficient in each incremental model divided by the beta coefficient in model 1, minus 1 × 100, as described by Kershaw et al.\textsuperscript{24}

Subgroup analyses were performed after stratification by geography, gender and age classes (below or above 64 yrs.). Geographical variations were evaluated by comparing the effects of lifelong occupation/education in the six cities of recruitment. The cities were also combined into three main regions: Southern Europe (Perugia and Milano), Western Europe (Groningen and Paris) and Northern Europe (Stockholm and Kuopio). A two-region stratification was also
performed by comparing Italy versus the rest of Europe. Statistical interactions region × occupation and region × education were also computed. All subgroup analyses were adjusted for covariates in model 3. The analyses stratified by region were also adjusted for city within region. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Occupation and C-IMT

Subjects characteristics, stratified according to the occupational scale, are shown in Table 1. Individuals with less remunerative professions were more likely men, less educated and heavier smokers, had higher BMI - in spite of higher leisure-time physical activity - and consumed less olive oil, fish and wine, and more milk. Pharmacological treatments also differed among professions, with more prevalent hypoglycaemic and antihypertensive treatments and fewer statin prescriptions in the less remunerative professions. Such professions were also associated with many CV risk factors, i.e. diabetes, high blood glucose, systolic and pulse blood-pressure and low HDL-cholesterol.

In univariable analysis, all C-IMT measures exhibited a significant positive trend \((p<0.0001)\) from white collars to manual workers (Table 1). The effect of occupation on C-IMT, adjusted with incremental models (Models 1, 2, 3 and 4), was consistently significant for all C-IMT measures (Table 2). In model 4, the percent increase in C-IMT for one increase in occupation category was larger for \(\text{IMT}_{\text{max}}\) (3.5%) compared to \(\text{IMT}_{\text{mean-max}}\) (2.2%) or \(\text{IMT}_{\text{mean}}\) (1.9%). The attenuation of the relationship between occupation and C-IMT, due to CV risk factors, lifestyle and diet is depicted in Fig. 1A. After adjustment for all covariates of the model 3, the attenuation reached \(-20\%\) for \(\text{IMT}_{\text{max}}\), \(-29\%\) for \(\text{IMT}_{\text{mean-max}}\) and \(-30\%\) for \(\text{IMT}_{\text{mean}}\).

Fig. 2A shows the absolute log-\(\text{IMT}_{\text{max}}\) increase for one increase in occupation category after stratification for geographical, gender and age subgroups. Heterogeneous effects were observed across cities \((p\text{-interaction}=0.02)\). The interaction was even more marked across the three regions (Southern Europe, Western Europe, Northern Europe, \(p\text{-interaction}=0.0026)\) and between Italy and the rest of Europe \((p\text{-interaction}=0.006)\). This analysis depicts a nearly null association between occupation and \(\text{IMT}_{\text{max}}\) in Italy and a significant effect in the rest of Europe. Similar results were observed for \(\text{IMT}_{\text{mean}}\) and \(\text{IMT}_{\text{mean-max}}\) \((p\text{-interaction Italy vs. rest of Europe }0.02\text{ and }0.01,\text{ respectively, even after full adjustment for CV risk factors and diet.}\)
After stratification for gender, the association of occupation with $IMT_{\text{max}}$ was moderately stronger in men than in women, but the gender × occupation interaction did not reach statistical significance ($p=0.16$). Stratification by age indicated a non-significant slightly stronger effect for subjects >64 yrs. ($p$-interaction = 0.11).

3.2. Inequality of factors associated with cardiovascular disease

Table 3 reports the inequality of several factors associated with cardiovascular disease, comparing Italy and the rest of Europe. The inequality is expressed as percent difference between manual and office workers. The main differences observed in the two regions regard smoking habits, spirits intake and olive oil consumption.

3.3. Sensitivity analysis

In the sensitivity analysis carried out with the simulated $IMT_{\text{max}}$ with artificially increased error in model 3, the estimated difference between manual workers and white collars was 8.0% (95% C.I. 4.6%, 11.5%), a figure which is very close to that obtained with the original data (Table 2).

3.4. Education and C-IMT

Supplementary Table 1 shows the subjects’ characteristics stratified by tertiles of educational level. As expected, there was a strong direct association between tertiles of education and occupational categories. Other results were in line with those obtained with stratification by occupation, although the differences between the tertiles were generally weaker, because the confounding effects of age, gender and geography were already adjusted for by the stratification method.

The multivariable association between educational level and C-IMT was similar to that observed with lifelong occupation (Supplementary Table 2). The linear trend was statistically significant for all C-IMT variables, in models 1 to 3, although less marked than that observed considering lifelong occupation. The effect was slightly greater for $IMT_{\text{max}}$ (1.6%) compared to $IMT_{\text{mean-max}}$ (1.5%) or $IMT_{\text{mean}}$ (1.1%).

The attenuation of the association between education and C-IMT by CV risk factors and diet was less marked than that observed considering occupation, i.e. $-0\%$ for $IMT_{\text{max}}$, $-6\%$ for $IMT_{\text{mean-max}}$ and $-15\%$ for $IMT_{\text{mean}}$ (Fig. 1B).

Subgroups stratification by geography, gender and age class is depicted in Fig.2B. The geographical pattern of the education–log-$IMT_{\text{max}}$ association was similar to that observed considering occupation, but the interactions were not significant. Conversely, a significant sex × education interaction was observed for $IMT_{\text{max}}$ ($p=0.04$), $IMT_{\text{mean}}$ ($p=0.005$) and $IMT_{\text{mean-max}}$ ($p=0.04$).

3.5. Analysis with mutual adjustment
When considering a multiple linear regression analysis including both lifelong occupation and educational level, together with all covariates of model 3, the effect of occupation versus C-IMT was only minimally attenuated by additional adjustment for educational level (a further −2%; −9% and −7% for the linear trend of IMT$_{\text{max}}$, IMT$_{\text{mean-max}}$ and IMT$_{\text{mean}}$, respectively) and remained fully significant for all C-IMT variables (model 4 of Table 2 and Fig.1A). In contrast, the effect of educational level was strongly attenuated by additional adjustment for occupation (−65%, −38% and −46% for the linear trend of IMT$_{\text{max}}$, IMT$_{\text{mean-max}}$ and IMT$_{\text{mean}}$, respectively) and completely lost statistical significance (model 4 of Supplementary Table 2 and Fig. 1B).

4. Discussion

In this study, carried out in five European countries, we showed that social class is an important independent determinant of C-IMT. After adjusting for age and gender, the estimated difference in C-IMT$_{\text{max}}$ between the lowest and the highest occupational category was 8.7% and even after adjustment for the major CV risk factors, which are strongly associated with a low social class, this difference remained at 7.8%.

It is still debated whether the effect of SES on C-IMT is completely due to the difference in conventional CV risk factors and behavioural variables across different social classes. To address this issue, most studies use a criterion based on the significance of the associations persisting or disappearing after adjustment, with some studies reporting a persisting association$^5, 8, 13, 17$ and others reporting a disappearing association$^4, 7, 11$ after adjustment. More properly, Kershaw et al.$^{24}$ provided a quantitative estimate (56%) of the attenuating effect of CVD risk factors on the association between SES and incident CHD. Similarly, Veronesi et al.$^{25}$ reported a 36% mediation by CVD risk factors on social class inequalities in CHD incidence. In our study, the attenuation of the occupation vs. C-IMT association, due to full adjustment for CVD risk factors, including lifestyle and diet, ranged from 20% to 30%, according to the C-IMT endpoint used. This indicates that a substantial proportion of the effect of SES on C-IMT is not explained by conventional CV risk factors, including smoking habits, obesity, physical activity and diet. One explanation might be that the measures of CV risk factors may be imprecise, and that, in addition, cross-sectional measures fail to reflect a potential prolonged effect over an individual’s lifetime. Alternatively, other unmeasured factors, such as environmental and psychosocial factors, depression, job strain, and chronic stress, may be involved. Inequalities in access to medical care may also contribute, although their effect on subclinical atherosclerosis is expected to be less important than on clinical endpoints, which often occur after a prolonged interaction of the individual with medical facilities.
The mutual adjustment for education and occupation deserves special attention. In fact, while the effect of education is strongly attenuated by adjustment for occupation, the effect of occupation is only minimally mediated by education. This is in line with a model in which higher education leads to a more profitable employment; therefore, occupation is expected to be more closely associated with SES than education, and, as such, to be a stronger independent predictor of the unhealthy effects of low social status.

In the present study, the association of C-IMT with occupational level was comparable in men and women. In contrast, the association with education was observed in men only, with a significant education × gender interaction. In the literature, the results concerning the heterogeneity of the SES effect on C-IMT in men and women are rather contrasting, with some studies in line with our results, others observing a stronger effect in women and one observing a stronger association for occupation in women and for education in men. Among the explanations for this gender heterogeneity, besides insufficient sample size in one of the two strata, Grimaud et al. suggested that women may be more susceptible than men to psychosocial stress deriving from their neighbourhood, and from familial and professional environments. Our results are in accordance with Grimaud et al. concerning the effect of education on C-IMT, but, in contrast with most of the reported results, we showed a comparable effect of occupation in men and women.

To the best of our knowledge, this is the first study comparing the effect of SES on subclinical atherosclerosis in different European countries. The effect of social class (particularly of the occupational level) on C-IMT was stronger in non-Mediterranean countries than in Italy, with a significant statistical interaction. Concerning the educational level, the pattern of the effect on C-IMT was similar to the one of occupational level, but the interaction with geographical region did not reach statistical significance. This might be due to the fact that educational classes were computed using country-specific tertiles, thus reducing geographical differences.

Mackenbach et al. documented a stronger effect of occupational class on total mortality or CVD mortality in the North than in the South of Europe, with risk ratios (RRs) of CVD mortality for manual vs. non-manual occupations of about 1.55 in Finland and England, compared with RRs of about 1.15 in Spain and Italy, and 1.0 in Portugal. The authors suggested that inter-regional differences may be partially explained by disparities in the social patterning of health-related behaviour, with larger inequalities in harmful behaviours like cigarette smoking and excessive alcohol consumption in Northern than in Southern countries. However, this was only partially true in our population, where the distribution of inequalities of harmful or protective factors across occupational categories exhibited a complex pattern when Italy was compared with the rest of Europe (Table 3). Indeed, in accordance with Mackenbach et al., smoking burden and spirits consumption were lower in manual than in office workers in Italy, and higher in the rest of Europe; however, the opposite was found for low physical activity, and the inequality of other factors was very similar in the
two geographical regions. Another important SES inequality, with a greater impact in the North, is related to diet. In Italy the intake of fruit and olive oil was similar in manual workers as compared to office workers, whereas in the rest of Europe a lower intake in manual workers than in office workers was found. This may reflect the well-known fact that in Northern Europe fruit and vegetables are less affordable for lower classes, and their everyday consumption is not supported by a long-standing cultural tradition, as in Mediterranean countries. In summary, taking into account that the North-South interaction persisted after adjusting for all conventional CV risk factors and diet, it appears that geographical differences in the effect of occupation are not completely explained by differential distribution of conventional risk factors or dietary habits; needless to say, other, still unmeasured discrepancies in lifestyle, environment and cultural pattern may play an important role.

Concerning the potential clinical impact expected from the effect of SES on C-IMT, some guidance can be obtained from the estimate provided by Lorenz et al.\textsuperscript{31} that a 0.1 mm increment in mean IMT of internal carotid arteries corresponds to a 7% excess incidence for MI and a 8% excess incidence for stroke. When we analysed the same segments in our study, we found, in non-Mediterranean European countries, an age- and gender-adjusted difference of 0.14 mm between manual and office workers, thus resulting in an expected excess incidence of 9.5% for MI and of 11% for stroke.

The present study has several strengths. In IMPROVE, carotid image acquisition and measurement of C-IMT were standardized across centres and all scans were analysed centrally; therefore, it is unlikely that the geographical differences evidenced in our study are due to a bias in the C-IMT measurements. Another strength derives from the use of subclinical atherosclerosis in place of a clinical endpoint, which allows us to detect the effects of SES at a relatively early, and often silent, stage of the disease, when the differential access to health structures contributes minimally to the inequality among SES classes.

There are also potential limitations: firstly, more than 50% of the study participants were selected from lipid/hypertension clinics and this may have generated some unknown bias; thus, our findings should be extrapolated with caution to the general population or to subjects with fewer than three VRFs. Nevertheless, our results are in accordance with those of other large studies performed on general populations.

A second limitation is the lack of some indicators interconnected with education or occupation, such as income, job strain and job control, and other indices measured at distinct stages of life, often employed in epidemiological studies.

Finally, a third potential limitation may lie in the use of C-IMT as surrogate end-point, in view of the methodological problems inherent to C-IMT reproducibility. However, in a sensitivity analysis carried out by artificially increasing the $\text{IMT}_{\text{max}}$ measurement error, we have shown that the estimated occupation effect remains almost identical to that
obtained with the original data. Therefore, we believe that it is unlikely that measurement variability may have substantially affected the results here presented.

In conclusion, our study documents a greater subclinical atherosclerosis burden in both men and women of lower social classes. Such difference is not fully explained by disparities in the prevalence of CVD risk factors or modifiable risky behaviours. Moreover, the effect of social inequalities appeared to be stronger in the countries of Northern Europe than in Italy; this result warrants further studies aimed at investigating the underlying reasons for these disparities.

Conflict of interest
The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Substantial contributions to the acquisition, analysis, or interpretation of data for the work: Tedesco, Veglia, Amato, Bonomi, Ravani, Frigerio, Castelnuovo, Sansaro, Baldassarre.

Drafting of the manuscript: Tedesco, Veglia, Baldassarre.

Critical revision of the manuscript for important intellectual content: Tedesco, Veglia, de Faire, Kurl, Smit , Rauramaa, Giral, Amato, Bonomi, Ravani, Frigerio, Castelnuovo, Sansaro, Mannarino, Humphries, Hamsten, Tremoli, Baldassarre.

Final approval of the manuscript submitted: Tedesco, Veglia, de Faire, Kurl, Smit , Rauramaa, Giral, Amato, Bonomi , Ravani, Frigerio, Castelnuovo, Sansaro, Mannarino, Humphries, Hamsten, Tremoli, Baldassarre.
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Figure captions

**Figure 1.** Attenuation of the occupation effect by incremental adjustment for vascular risk factors.
Percent residual effect of socio-economic status on C-IMT after incremental models adjustment, with respect to the reference model 1 adjusted for age and gender (100%). Model 2: as model-1 plus latitude, blood lipids, body mass index, pulse pressure, pharmacological treatments (statin, hypoglycaemic and antihypertensive) Hs-C-Reactive Protein, triglycerides, pack-years, current employment status, leisure-time physical activity; model 3: as model 2 plus dietary items; model 4: as model 3 plus educational level. (A) Effects of occupation. (B) Effects of education. CV, cardiovascular.

**Figure 2.** Subgroup analysis of the relation of socio-economic status and log IMT\(_{\text{max}}\) stratified by geography, gender and age classes.
(A) Effects of occupation. (B) Effects of education. Beta values are adjusted for covariates used in model 3. The analyses stratified by region were also adjusted for city within region.
References


### Table 1. Characteristics of patients stratified according to occupation categories.

<table>
<thead>
<tr>
<th>Variables</th>
<th>White collars (n=1379)</th>
<th>Service workers (n=1138)</th>
<th>Manual workers (n=879)</th>
<th>p trend</th>
<th>p trend adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.2±5.4</td>
<td>64.2±5.3</td>
<td>64.1±5.5</td>
<td>0.63</td>
<td>0.3</td>
</tr>
<tr>
<td>Gender (n, % males)</td>
<td>736 (53.4)</td>
<td>448 (39.4)</td>
<td>559 (63.6)</td>
<td>0.0006</td>
<td>0.005</td>
</tr>
<tr>
<td>Country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>401 (29)</td>
<td>259 (22.7)</td>
<td>304 (34.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>313 (22.7)</td>
<td>102 (9)</td>
<td>37 (4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>106 (7.7)</td>
<td>178 (15.6)</td>
<td>125 (14.2)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sweden</td>
<td>255 (18.5)</td>
<td>186 (16.3)</td>
<td>86 (9.8)</td>
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</tr>
<tr>
<td>Finland</td>
<td>304 (22)</td>
<td>413 (36.3)</td>
<td>327 (37.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>139.5±18.7</td>
<td>144.5±18.5</td>
<td>143.4±18</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81±10.1</td>
<td>82.6±9.7</td>
<td>83±9.4</td>
<td>&lt;.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>58.5±13.8</td>
<td>61.9±14.4</td>
<td>60.4±14.1</td>
<td>0.0002</td>
<td>0.002</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>138±39</td>
<td>134±39</td>
<td>137±38</td>
<td>0.32</td>
<td>0.58</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>49.1±13.9</td>
<td>47.9±14.6</td>
<td>46.3±12.6</td>
<td>&lt;.0001</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hs-CRP (mg)</td>
<td>1.6 (0.7, 3.4)</td>
<td>1.9 (0.8, 3.6)</td>
<td>2 (0.9, 3.6)</td>
<td>0.002</td>
<td>0.0003</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>114 (83, 166)</td>
<td>112 (79, 163)</td>
<td>119 (84, 170)</td>
<td>0.82</td>
<td>0.7</td>
</tr>
<tr>
<td>Physical activity and BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive n (%)</td>
<td>450 (32.7)</td>
<td>466 (41)</td>
<td>336 (38.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium n (%)</td>
<td>647 (47)</td>
<td>479 (42.1)</td>
<td>374 (42.7)</td>
<td>0.0004</td>
<td>0.15</td>
</tr>
<tr>
<td>Low n (%)</td>
<td>279 (20.3)</td>
<td>192 (16.9)</td>
<td>166 (18.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (Kg/m²)</td>
<td>26.7±4</td>
<td>27.5±4.3</td>
<td>27.8±4.3</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Socioeconomic variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current worker</td>
<td>430 (31.6)</td>
<td>295 (26.6)</td>
<td>203 (23.7)</td>
<td>0.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Educational level (Study years)</td>
<td>12.1±3.6</td>
<td>10.9±4.1</td>
<td>7.9±2.6</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years (smokers only)</td>
<td>21.1±17.4</td>
<td>20.2±20</td>
<td>24.6±18.7</td>
<td>0.005</td>
<td>0.009</td>
</tr>
<tr>
<td>Never smokers n (%)</td>
<td>651 (47.2)</td>
<td>553 (48.6)</td>
<td>393 (44.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smokers n (%)</td>
<td>538 (39)</td>
<td>423 (37.2)</td>
<td>329 (37.4)</td>
<td>0.06</td>
<td>0.4</td>
</tr>
<tr>
<td>Current smokers n (%)</td>
<td>190 (13.8)</td>
<td>162 (14.2)</td>
<td>157 (17.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary habits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olive oil consumers n (%)</td>
<td>708 (51)</td>
<td>447 (39)</td>
<td>378 (43)</td>
<td>&lt;.0001</td>
<td>0.15</td>
</tr>
<tr>
<td>Fish consumption (times a week)</td>
<td>2±1.3</td>
<td>1.7±1.1</td>
<td>1.6±1</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Wine consumption (dL/day)</td>
<td>1.4±2.2</td>
<td>0.8±1.6</td>
<td>0.9±1.7</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fruit consumption (times a week)</td>
<td>2.3±1.4</td>
<td>2.15±1.3</td>
<td>2.2±1.5</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>Milk consumption (dL/day)</td>
<td>2.4±2.4</td>
<td>2.9±2.7</td>
<td>2.9±2.7</td>
<td>&lt;.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Eggs consumption (times a week)</td>
<td>1.3±1.2</td>
<td>1.4±1.4</td>
<td>1.4±1.25</td>
<td>0.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Meat consumption (times a week)</td>
<td>3.7±1.8</td>
<td>3.5±1.75</td>
<td>3.8±1.75</td>
<td>0.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Spirits consumption (dL/day)</td>
<td>0.06±0.2</td>
<td>0.07±0.27</td>
<td>0.09±0.32</td>
<td>0.001</td>
<td>0.1</td>
</tr>
<tr>
<td>Pharmacological treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin use n (%)</td>
<td>589 (42.7)</td>
<td>454 (39.9)</td>
<td>310 (35.3)</td>
<td>0.0005</td>
<td>0.001</td>
</tr>
<tr>
<td>Antihypertensive use n (%)</td>
<td>727 (52.7)</td>
<td>667 (58.6)</td>
<td>532 (60.5)</td>
<td>0.0001</td>
<td>0.0004</td>
</tr>
<tr>
<td>Hypoglycaenic use n (%)</td>
<td>187 (13.8)</td>
<td>214 (19.1)</td>
<td>182 (21.1)</td>
<td>&lt;.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>C-IMT variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Column 1</td>
<td>Column 2</td>
<td>Column 3</td>
<td>Column 4</td>
<td>Column 5</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>IMT$_{\text{mean}}$ (mm)</strong></td>
<td>0.84 (0.73, 0.96)</td>
<td>0.85 (0.74, 0.99)</td>
<td>0.89 (0.78, 1.06)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>IMT$_{\text{max}}$ (mm)</strong></td>
<td>1.76 (1.39, 2.4)</td>
<td>1.93 (1.45, 2.5)</td>
<td>2.04 (1.55, 2.68)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>IMT$_{\text{mean-max}}$ (mm)</strong></td>
<td>1.31 (1.11, 1.59)</td>
<td>1.35 (1.11, 1.64)</td>
<td>1.44 (1.18, 1.74)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation for continuous variable, median and interquartile range for variables with non-normal distribution, frequency and percentages for categorical variables.

* Adjusted for age, gender and country. Except for age: adjusted for gender and country; gender: adjusted for age and country; country: adjusted for age and gender.
Table 2. Association between occupation categories and C-IMT.

<table>
<thead>
<tr>
<th></th>
<th>IMT&lt;sub&gt;max&lt;/sub&gt; mean (%)</th>
<th>IMT&lt;sub&gt;mean-max&lt;/sub&gt; mean (%)</th>
<th>IMT&lt;sub&gt;mean&lt;/sub&gt; mean (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% change (C.I.)</td>
<td>p value</td>
<td>% change (C.I.)</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>8.7 (5.4, 12.2)</td>
<td>&lt;0.0001</td>
<td>6.9 (4.7, 9.2)</td>
</tr>
<tr>
<td>Service</td>
<td>6 (3.0, 9.1)</td>
<td>&lt;0.0001</td>
<td>4.4 (2.3, 6.5)</td>
</tr>
<tr>
<td>White collars Ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear trend</td>
<td>4.5 (3.1, 6.0)</td>
<td>&lt;0.0001</td>
<td>3.5 (2.5, 4.5)</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>7.7 (4.4, 11.1)</td>
<td>&lt;0.0001</td>
<td>5.3 (3.1, 7.5)</td>
</tr>
<tr>
<td>Service</td>
<td>2.5 (-0.4, 5.6)</td>
<td>0.09</td>
<td>1.6 (-0.4, 3.6)</td>
</tr>
<tr>
<td>White collars Ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear trend</td>
<td>3.5 (2.0, 5.0)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.4, 3.5)</td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>7.8 (4.5, 11.3)</td>
<td>&lt;0.0001</td>
<td>5.3 (3.1, 7.6)</td>
</tr>
<tr>
<td>Service</td>
<td>2.7 (-0.3, 5.7)</td>
<td>0.0772</td>
<td>1.6 (-0.4, 3.6)</td>
</tr>
<tr>
<td>White collars Ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear trend</td>
<td>3.6 (2.1, 5.1)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.5, 3.5)</td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>7.5 (3.9, 11.4)</td>
<td>&lt;0.0001</td>
<td>4.7 (2.3, 7.2)</td>
</tr>
<tr>
<td>Service</td>
<td>2.5 (-0.5, 5.6)</td>
<td>0.10</td>
<td>1.4 (-0.6, 3.4)</td>
</tr>
<tr>
<td>White collars Ref.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear trend</td>
<td>3.5 (1.8, 5.1)</td>
<td>&lt;0.0001</td>
<td>2.2 (1.0, 3.3)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for age and gender.
<sup>b</sup>As model-1 plus latitude, blood lipids, body mass index, pulse pressure, pharmacological treatments (statin, hypoglycaemic and antihypertensive) Hs-C-Reactive Protein, triglycerides, pack-years, current employment status, leisure-time physical activity.
<sup>c</sup>As model 2 plus dietary items.
<sup>d</sup>As model 3 plus educational level.
C.I., 95% confidence interval; linear trend, estimated percent change in C-IMT for one class step.
Table 3. Distribution of the inequality of some factors associated with cardiovascular disease in Italy and in the rest of Europe.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Italy</th>
<th>Rest of Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoke (pack-years)</td>
<td>− 11.0%</td>
<td>+ 28.0%</td>
</tr>
<tr>
<td>BMI</td>
<td>+ 5.1%</td>
<td>+ 4.7%</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>+ 1.6%</td>
<td>− 2.8%</td>
</tr>
<tr>
<td>Pulse blood pressure</td>
<td>+ 1.6%</td>
<td>+ 6.3%</td>
</tr>
<tr>
<td>Meat consumption</td>
<td>+ 9.8%</td>
<td>− 0.8%</td>
</tr>
<tr>
<td>Spirits intake</td>
<td>− 70.6%</td>
<td>+ 34.4%</td>
</tr>
<tr>
<td>Low physical activity</td>
<td>+ 8.0%</td>
<td>− 25.0%</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>− 3.2%</td>
<td>− 3.6%</td>
</tr>
<tr>
<td>Fish consumption</td>
<td>− 16.2%</td>
<td>− 20.9%</td>
</tr>
<tr>
<td>Fruit consumption</td>
<td>+ 0.2%</td>
<td>− 8.5%</td>
</tr>
<tr>
<td>Olive oil consumption</td>
<td>+ 0.4%</td>
<td>− 53.9%</td>
</tr>
</tbody>
</table>

Data are reported as mean percent difference between manual and office workers.
BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
(A) Adjusted beta effect of occupation on log(\(MT_{\text{rel}}\))

- Geography:
  - Perugia: 0.02
  - Milano: 0.0026
  - Paris: 0.006
  - Groeningen: 0.16
  - Stockholm: 0.47
  - Kuopio: 0.1

- Gender:
  - Male: 0.16
  - Female: 0.04

- Age:
  - <64: 0.11
  - \(\geq 64\): 0.40

(B) Adjusted beta effect of education on log(\(MT_{\text{rel}}\))

- Geography:
  - Italy: 0.16
  - Western Eu: 0.16
  - North Eu: 0.16
  - Italy Rest of Eu: 0.16
  - Perugia: 0.16
  - Milano: 0.16
  - Paris: 0.16
  - Groeningen: 0.16
  - Stockholm: 0.16
  - Kuopio: 0.16

- Gender:
  - Male: 0.16
  - Female: 0.16

- Age:
  - <64: 0.16
  - \(\geq 64\): 0.16
• Socioeconomic status is a major determinant of intima-media thickness (IMT).
• This social inequality of IMT is more marked in northern Europe than in Italy.
• The effect of social class on IMT is not only due to difference in CV risk factors.