Association of lifelong occupation and educational level with subclinical atherosclerosis is stronger in north Europe, independently of conventional risk factors and dietary habits.

Results from the IMPROVE study

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Short running head: Social class and subclinical atherosclerosis in Europe

Abstract.

The association between socioeconomic status (SES) and subclinical atherosclerosis, as assessed by carotid intima-media-thickness (C-IMT), has been widely documented, but whether the effect of social inequality on C-IMT is mediated by cardiovascular (CV) risk factors, and whether it is dissimilar in males and females, or in different European countries, is still debated.

We investigated the association of 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 (IMT_{mean}, IMT_{max}, $IMT_{mean\text{-}max}$), obtained from four segments of both carotids, were considered.

After adjusting for conventional CV risk factors, current employment status and diet, C-IMT was higher in manual workers vs. white collars (+7.7%, +5.3%, +4.6% for IMT_{max}, $IMT_{mean\text{-}max}$ and IMT_{mean}, 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 explained by CV risk factors. Of interest, the association of C-IMT with occupation was significant in western and northern Europe but not in Italy, with a significant occupation × region interaction (p=0.0005).

In conclusion, low SES was associated with subclinical atherosclerosis in a European cohort; the association of occupation was nearly null in Italy, but very marked in the rest of Europe, and this difference was not explained by cardiovascular 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

IMT_{mean} = mean of all local mean measures

IMT_{max} = maximum of all local maximal measures

$IMT_{mean\text{-}max}$ = mean of all local maximal measures

hs-CRP = high sensitive C reactive protein

BMI = body mass index

RRs = risk ratios

MI= myocardial infarction

Introduction

In the last decades, numerous Public Health action plans has been undertaken worldwide in order to reduce the burden of modifiable cardiovascular (CV) risk factors, with a remarkable impact on CV mortality [1]. 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 factors for CVD [2], though the specific mechanisms leading to health inequalities are not completely understood [3]. In addition, several studies [4-17] documented a significant association between SES and carotid intima-media thickness (C-IMT), an established surrogate marker of subclinical atherosclerosis, strongly associated with most cardiovascular risk factors and predictive of future cardiovascular events[18-21]. Nevertheless, some issues on 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 [4, 7, 11] or partially [5, 8, 9, 13, 14, 17] mediated by cardiovascular risk factors; b) whether the association is present in both men and women [4, 6-8, 10, 12, 13, 15], or is only present in one gender, with a significant gender × SES interaction reprted in some studies [9, 11, 13, 15, 16]; c) whether the association between SES and C-IMT is modified by geography, in analogy with the results of Mackenbach et al. [22] on the relation between SES and cardiovascular mortality.

Here we investigated the association of SES, as indexed by type of lifelong profession and education (years of study), with single-point C-IMT measures in the cohort of IMPROVE, a large European study of individuals at moderate tohigh risk for CVD. Being recruited in five different 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.

Methods

Subjects

Methods for patient selection, laboratory analyses and C-IMT measurements in IMPROVE have been previously published [19]. 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 relation between C-IMT and C-IMT progression and the risk to develop future CV events. Participants were recruited in in Kuopio (Finland, 2 centres), Stockholm (Sweden), Groningen (the Netherlands), Paris (France), Milano and Perugia

(Italy). The left and right common carotid arteries, carotid bifurcations, and internal carotid arteries were visualized in three angles. Mean and maximal local (segment-specific) C-IMT values were computed. The ultrasonic variables selected for the present study were three summary measures: IMT_{mean} (the mean of all local mean measures), IMT_{max} (the maximum of all local maximal measures) and $IMT_{mean\text{-}max}$ (the mean of all local maximal measures).

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 in 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., [23] tertiles were computed within gender, city of recruitment and age classes (below or above median=64.4 years). Three hundred and eleven 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' and their position in the SES scale was thus uncertain. From 3703 a total of 3392 participants were included in the main analysis.

Covariates

Serum concentrations of total, HDL and LDL cholesterol (computed by 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, 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 two-three times a week) or high (brisk walk for ten minutes more than two-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.

Statistical analysis

Descriptive statistics were reported as mean ± standard deviation for continuous variables, and 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.

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. 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. [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 rest of Europe. Statistical interactions region × occupation and region × education were also computed. Statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

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 univariate analysis all C-IMT measures differed among occupational classes, with a significant positive trend ($p<0.0001$) from white collar to manual workers (Table 1). The effect of occupation on C-IMT, adjusted with incremental models, was consistently significant for all IMT measures (Table 2). In model 4, the percent increase in C-IMT for one increase in occupation category was stronger for IMT_{max} (3.5%) compared to $IMT_{mean-max}$ (2.2%) or IMT_{mean} (1.9%). The attenuation of the relationship between occupation and C-IMT, due to CV risk factors, lifestyle and diet is depicted in Figure 1 (Panel A). After full adjustment, the attenuation reached –20% for IMT_{max}, –29% for $IMT_{mean-max}$ and –30% for IMT_{mean}.

Figure 2 (panel A) shows the absolute log-IMT_{max} increase for one increase in occupation category after stratification for geographical, gender and age subgroups. Heterogeneous effects were observed between cities (P-interaction=0.02). The interaction was even more marked between the three regions (Southern Europe, Western Europe, Northern Europe, p-interaction=0.0005) and between Italy and the rest of Europe (p-interaction=0.0002). This analysis depicts a nearly null association between occupation and IMT_{max} in Italy and a significant effect in the rest of Europe. Similar results were observed for IMT_{mean} and $IMT_{mean-max}$ (p-interaction Italy vs. rest of Europe <.0001 and =0.0005, respectively, even after full adjustment for CV risk factors and diet.

After stratification for gender, the association of occupation with IMT_{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 = 0.XX).

Education and C-IMT

Table 3 shows the subjects' characteristics stratified by tertiles of educational level. Data on age, gender and geography are not reported, as the tertiles were computed within age class, gender and city. 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 corrected by the stratification method.

The multivariable association between educational level and C-IMT was similar to that observed with lifelong occupation (Table 4). 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_{max} (1.6%) compared to $IMT_{mean-max}$ (1.5%) or IMT_{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_{max}, –6% for $IMT_{mean-max}$ and –15% for IMT_{mean} (Figure 1, panel B).

Subgroups stratification by geography, gender and age class is depicted in figure 2 (panel B). The geographical pattern of the education–log-IMT_{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_{max} (p=0.04), IMT_{mean} (p=0.005) and $IMT_{mean\text{-}max}$ (p=0.04).

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_{max}, $IMT_{mean\text{-}max}$ and IMT_{mean}, respectively) and remained fully significant for all C-IMT variables (model 4 of Table 2 and Figure 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_{max}, $IMT_{mean\text{-}max}$ and IMT_{mean}, respectively) and completely lost statistical significance (model 4 of Table 4 and Figure 1B).

Discussion

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

Mediating role of CVD risk factors

It is still debated whether the effect of SES on C-IMT is completely due to the difference in conventional cardiovascular risk factors and behavioural variables among 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 [26, 27], and, as such, to be a stronger independent predictor of the unhealthy effects of low social status.

Gender effect

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 [4, 6-8], others observing a stronger effect in women [11, 13, 15, 16] and one observing a stronger association for occupation in women and for education in men [9]. Among the explanations for this gender heterogeneity, besides insufficient sample size in one of the two strata, Grimaud et al. [9] suggested that women may be more susceptible than men to psychosocial stress deriving from their neighbourhood, and from familial and professional environments [28]. Our results are in accordance with Grimaud concerning the effect of education on C-IMT, but, in contrast with most of the reported results, we also showed a comparable and even stronger effect of occupation in men. This may be due to the inclusion of a Mediterranean population in our cohort. In fact, when the data are stratified by region and sex (supplemental figure 1), they suggest a complete lack of effect of occupation in women in the South, in contrast to the women in the North. However, in the absence of significant statistical interactions, these results need to be confirmed in further studies.

Geographical difference

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 the 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 [22, 29]. The authors suggest 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 5). 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. As reported in Table 5, 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 [30].In summary, taking into account that the North-South interaction persisted after adjusting for all conventional CV risk factors and diet, it appears that the geographical differences in the effect of occupation are not completely explained by differential distribution of conventional risk factors or dietary habits; 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, we can consider the estimate provided by Lorenz et al. [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.

Strengths and limitations

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 may be due to a bias in the C-IMT measurements. Another strength derives from the use of subclinical atherosclerosis in place of clinical endpoint, which allows us to detect the effects of SES in a relatively early, and often unnoticed, stage of the disease, when the differential access to health structures contributes minimally to the inequality among SES classes.

There are also potential limitations: our findings should be extrapolated with caution to the general European population or to subjects with fewer than three VRFs. However, our results are in great accordance with those of other large studies performed on general populations. Another limitation is the lack of other indicators interconnected with education or occupation; such as income, job strain and job control, and other indices measured in distinct stages of life, often employed in epidemiological studies.

Conclusions

Our study shows that in the 21^{st} century both men and women of lower social classes are still penalized in term of subclinical atherosclerosis burden and that this inequality is not fully explained by differences in the prevalence of CVD risk factors or known modifiable risky behaviours. Moreover, the social inequality appeared stronger in North European countries than in Italy, and this prompts to specific investigations and interventions in order to discover the reasons of these inequalities and to reduce their impact in public health.

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

Variable	White collars (n=1379)	Service workers (n=1138)	Manual workers (n=879)	P trend
Age (years)	64.2±5.4	64.2±5.3	64.1±5.5	0.63
Gender (n, % males)	736(53.4)	448(39.4)	559(63.6)	0.0006
Italy	401(29)	259(22.7)	304(34.6)	
France	313 (22.7)	102 (9)	37 (4.2)	
The Netherlands	106 (7.7)	178 (15.6)	125 (14.2)	<.0001
Sweden	255 (18.5)	186 (16.3)	86 (9.8)	
Finland	304 (22)	413 (36.3)	327 (37.2)	
Biological variables				
Systolic blood pressure (mmHg)	139.5±18.7	144.5±18.5	143.4±18	<.0001
Diastolic blood pressure (mmHg)	81±10.1	82.6±9.7	83±9.4	<.0001
Pulse pressure (mmHg)	58.5±13.8	61.9±14.4	60.4±14.1	0.0002
LDL cholesterol (mg/dL)	138±39	134±39	137±38	0.32
HDL cholesterol (mg/dL)	49.1±13.9	49.7±14.6	46.3±12.6	<.0001
Hs-CRP (mg)	1.6 (0.7, 3.4)	1.9 (0.8, 3.6)	2 (0.9, 3.6)	0.002
Triglycerides (mg/dL)	114 (83, 166)	112 (79, 163)	119 (84, 170)	0.82
Physical Activity and BMI				
Intensive n (%)	450 (32.7)	466 (41)	336 (38.4)	
Medium n (%)	647 (47)	479 (42.1)	374 (42.7)	0.0004
Low n (%)	279 (20.3)	192 (16.9)	166 (18.9)	
Body Mass Index (Kg/m^2)	26.7±4	27.5±4.3	27.8±4.3	<.0001
Socioeconomic variables				
Current worker	430 (31.6)	295 (26.6)	203 (23.7)	0.0001
Educational level (Study Years)	12.1±3.6	10.9±4.1	7.9±2.6	<.0001
Smoking habits				
Pack-years (smokers only)	21.1±17.4	20.2±20	24.6±18.7	0.005
Never smokers n (%)	651 (47.2)	553 (48.6)	393 (44.7)	
Former smokers n (%)	538 (39)	423 (37.2)	329 (37.4)	0.06
Current smokers n (%)	190 (13.8)	162 (14.2)	157 (17.9)	
Dietary habits				
Olive oil consumers n (%)	708 (51)	447 (39)	378 (43)	<.0001
Fish consumption (times a week)	2±1.3	1.7±1.1	1.6±1	<.0001
Wine consumption (dL/day)	1.4±2.2	0.8±1.6	0.87±1.7	<.0001
Fruit consumption (times a week)	2.3±1.43	2.15±1.3	2.2±1.5	0.28
Milk consumption (dL/day)	2.4±2.4	2.9±2.7	2.9±2.7	<.0001
Eggs consumption (times a week)	1.3±1.21	1.44±1.39	1.38±1.25	0.1
Meat consumption (times a week)	3.7±1.8	3.5±1.75	3.8±1.75	0.2
Pharmacological treatment				
Statin use n (%)	589 (42.7)	454 (39.9)	310 (35.3)	0.0005
Antihypertensive use n (%)	727 (52.7)	667 (58.6)	532 (60.5)	0.0001
Hypoglycaemic use n (%)	187 (13.8)	214 (19.1)	182 (21.1)	<.0001
IMT variables				
IMT_{mean} (mm)	0.84 (0.73, 0.96)	0.85 (0.74, 0.99)	0.89 (0.78, 1.06)	<.0001
IMT_{max} (mm)	1.76 (1.39, 2.4)	1.93 (1.45, 2.5)	2.04 (1.55, 2.68)	<.0001

IMT$_{mean-max}$ (mm)	1.31 (1.11, 1.59)	1.35 (1.11, 1.64)	1.44 (1.18, 1.74)	<.0001

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

TABLE 2. Association between occupation categories and C-IMT.

		IMT_{max}		$IMT_{mean\text{-}max}$		IMT_{mean}	
		% change (C.I.)	p-value	% change (C.I.)	p-value	% change (C.I.)	p-value
Model 1							
	Manual	8.7 (5.4, 12.2)	<.0001	6.9 (4.7, 9.2)	<.0001	6 (4.2, 7.8)	<.0001
	Service	6 (3.0, 9.1)	<.0001	4.4 (2.3, 6.5)	<.0001	3.6 (2, 5.2)	<.0001
	White collars	Ref.		Ref.		Ref.	
	Linear trend[a]	4.5 (3.1, 6.0)	<.0001	3.5 (2.5, 4.5)	<.0001	3 (2.2, 3.8)	<.0001
Model 2							
	Manual	7.7 (4.4, 11.1)	<.0001	5.3 (3.1, 7.5)	<.0001	4.6 (2.9, 6.3)	<.0001
	Service	2.5 (-0.4, 5.6)	0.09	1.6 (-0.4, 3.6)	0.12	1.4 (-0.2, 2.9)	0.08
	White collars	Ref.		Ref.		Ref.	
	Linear trend	3.5 (2.0, 5.0)	<.0001	2.5 (1.4, 3.5)	<.0001	2.1 (1.3, 2.9)	<.0001
Model 3							
	Manual	7.8 (4.5, 11.3)	<.0001	5.3 (3.1, 7.6)	<.0001	4.5 (2.8, 6.2)	<.0001
	Service	2.7 (-0.3, 5.7)	0.0772	1.6 (-0.4, 3.6)	0.1122	1.3 (-0.2, 2.9)	0.0863
	White collars	Ref.		Ref.		Ref.	
	Linear trend	3.6 (2.1, 5.1)	<.0001	2.5 (1.5, 3.5)	<.0001	2.1 (1.3, 2.9)	<.0001
Model 4							
	Manual	7.5 (3.9, 11.4)	<.0001	4.7 (2.3, 7.2)	0.0001	4.2 (2.3, 6.1)	<.0001
	Service	2.5 (-0.5, 5.6)	0.10	1.4 (-0.6, 3.4)	0.1766	1.2 (-0.4, 2.7)	0.1427
	White collars	Ref.		Ref.		Ref.	
	Linear trend	3.5 (1.8, 5.1)	<.0001	2.2 (1.0, 3.3)	0.0002	1.9 (1.1, 2.8)	<.0001

[a]Linear trend: estimated percent change in C-IMT for one class step.

Model 1: adjusted for age and gender. Model 2: as moldel-1 plus latitude, blood lipids, body mass index, pulse pressure, pharmacological treatments (statin, hypoglycaemic and antihypertensive) Hs-CRP, 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.

Table 3. Characteristics of patients stratified according to tertiles of years at school.

TOTAL GROUP	3rd tertile (n=1185)	2nd tertile (n=1287)	1st tertile (n=1188)	P trend
Biological variables				
Systolic blood pressure (mmHg)	141.3±18.1	142.7±19.3	142.1±18	0.27
Diastolic blood pressure (mmHg)	81.7±9.8	82.7±10.1	81.7±9.3	0.85
Pulse blood pressure (mmHg)	59.6±13.7	60.1±14.6	60.4±13.9	0.19
LDL cholesterol (mg/dL)	136.2±39.2	135.7±38.4	137.9±39	0.3
HDL cholesterol (mg/dL)	49.7±14.3	48.5±14	48.2±13.6	0.01
Hs-CRP (mg)	1.7 (0.7, 3.4)	1.8 (0.8, 3.5)	2 (0.9, 3.9)	<.0001
Triglycerides (mg/dL)	109.8 (80, 159)	116.9 (82, 173)	116.9 (83, 166)	0.11
Physical Activity and BMI				
Intensive n (%)	449 (37.9)	465 (36.2)	393 (33.2)	
Medium n (%)	533 (45)	576 (44.8)	516 (43.5)	0.37
Low n (%)	202 (17.1)	245 (19.1)	276 (23.3)	
Body mass index	26.7±4.1	27.3±4.4	27.8±4.3	<.0001
Socioeconomic variables				
Employment status (current worker)	426 (36.9)	410 (32.4)	310 (26.8)	<.0001
Manual workers	47 (4.2)	299 (25.3)	519 (49)	
Service workers	424 (37.7)	367 (31.1)	341 (32.2)	<.0001
White collars	654 (58.1)	515 (43.6)	199 (18.8)	
Smoking habits				
Pack-years (smokers only)	19.6±17.3	21.3±16.5	23.4±21.3	0.0003
Never smokers n (%)	567 (47.8)	605 (47)	590 (49.7)	
Former smokers n (%)	456 (38.5)	482 (37.5)	420 (35.4)	0.86
Current smokers n (%)	162 (13.7)	200 (15.5)	178 (15)	
Dietary habits				
Olive oil consumers n (%)	598 (50)	563 (43)	535 (45)	0.008
Fish consumption (times a week)	1.9±1.26	1.7±1.2	1.6±1.1	<.0001
Wine consumption (dl/day)	1.2±1.89	1±1.8	0.89±1.9	0.0001
Fruit consumption (times a week)	2.4±1.4	2.15±1.4	2.2±1.4	0.0001
Milk consumption (dL/day)	2.62±2.3	2.68±2.8	2.6±2.5	0.7
Eggs consumption (times a week)	1.4±1.3	1.41±1.3	1.34±1.2	0.46
Meat consumption (times a week)	3.7±1.8	3.7±1.7	3.7±1.8	0.61
Pharmacological treatment				
Statin use n (%)	509 (43)	504 (39.2)	451 (38)	0.01
Antihypertensive use n (%)	648 (54.7)	732 (56.9)	710 (59.8)	0.01
Hypoglycaemic use n (%)	181 (15.5)	230 (18.2)	220 (18.8)	0.04
IMT variables				
IMT_{mean} (mm)	0.86(0.75,1.02)	0.85(0.75,1)	0.84(0.73,0.98)	0.0005
IMT_{max} (mm)	1.85(1.45,2.51)	1.85(1.39,2.5)	1.84(1.39,2.41)	0.02
$IMT_{mean-max}$ (mm)	1.35(1.14,1.67)	1.34(1.12,1.64)	1.32(1.1,1.6)	0.0008

Data are mean ± standard deviation for continuous variable, median and interquartile range for variables with non-normal distribution, frequency and percentages for categorical variables. Data about age, gender and geographical distributions are not reported because the education tertiles were age, gender and country specific.

TABLE 4. Association between education categories and C-IMT.

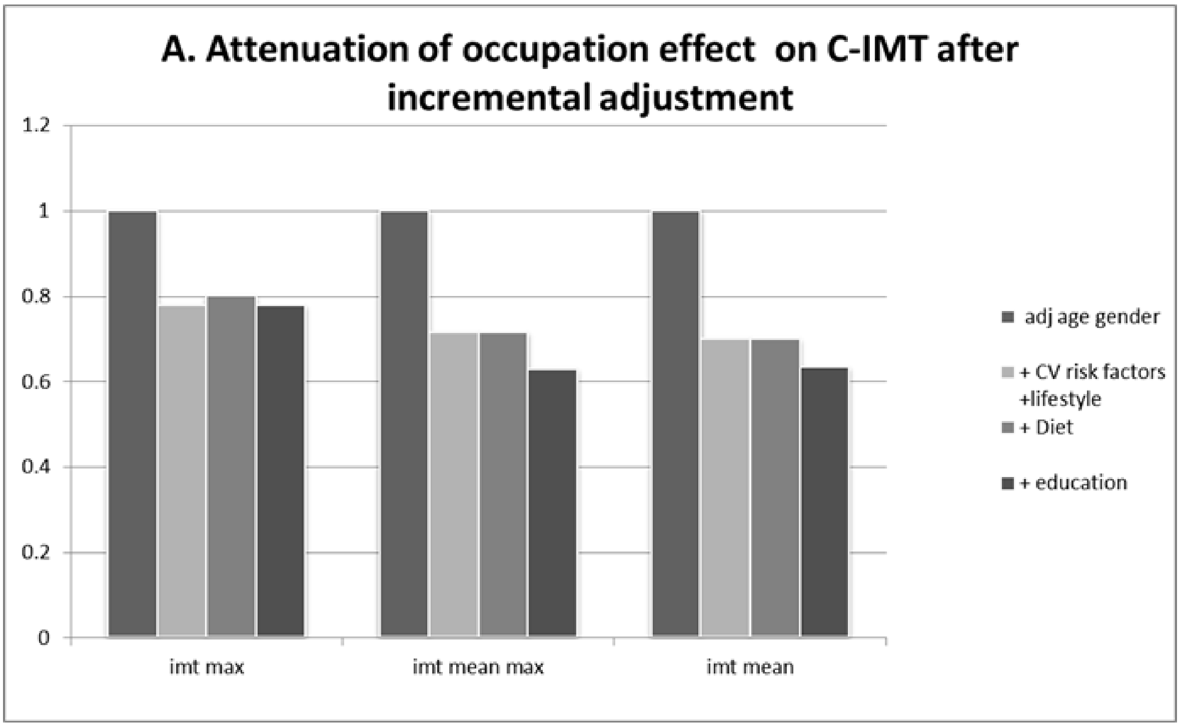
		IMT_{max}		$IMT_{mean-max}$		IMT_{mean}	
		% change (C.I.)	p-value	% change (C.I.)	p-value	% change (C.I.)	p-value
Model 1							
	Low	3.3 (0.3, 6.4)	0.03	3.3 (1.2, 5.4)	0.002	2.7 (1.1, 4.3)	0.001
	Medium	2.1 (-0.8, 5.1)	0.16	2.4 (0.3, 4.4)	0.02	2.1 (0.5, 3.7)	0.008
	High	Ref.		Ref.		Ref.	
	Linear trend	1.6 (0.1, 3.0)	0.03	1.6 (0.6, 2.6)	0.002	1.3 (0.5, 2.0)	0.001
Model 2							
	Low	3.5 (0.5, 6.7)	0.02	3.2 (1.1, 5.2)	0.002	2.3 (0.7, 3.9)	0.005
	Medium	1.5 (-1.4, 4.5)	0.30	1.8 (-0.2, 3.8)	0.08	1.5 (0, 3)	0.06
	High	Ref.		Ref.		Ref.	
	Linear trend	1.7 (0.3, 3.2)	0.02	1.5 (0.6, 2.5)	0.002	1.1 (0.3, 1.9)	0.005
Model 3							
	Low	3.3 (0.2, 6.4)	0.03	3 (1.0, 5.1)	0.004	2.2 (0.6, 3.8)	0.007
	Medium	1.4 (-1.5, 4.4)	0.35	1.7 (-0.2, 3.7)	0.09	1.4 (-0.1, 3)	0.06
	High	Ref.		Ref.		Ref.	
	Linear trend	1.6 (0.1, 3.1)	0.03	1.5 (0.5, 2.5)	0.004	1.1 (0.3, 1.8)	0.007
Model 4							
	Low	1.2 (-2.2, 4.7)	0.49	1.9 (-0.4, 4.2)	0.11	1.1 (-0.7, 2.9)	0.24
	Medium	0.7 (-2.3, 3.8)	0.65	1.2 (-0.9, 3.3)	0.26	0.9 (-0.7, 2.5)	0.28
	High	Ref.		Ref.		Ref.	
	Linear trend	0.6 (-1.1, 2.3)	0.48	0.9 (-0.2, 2)	0.11	0.5 (-0.3, 1.4)	0.23

[a]Linear trend: estimated percent change in C-IMT for one class step.

Model 1 adjusted for age and gender. Model 2 as moldel-1 plus latitude, blood lipids, body mass index, pulse pressure, pharmacological treatments (statin, hypoglycaemic and antihypertensive), Hs-CRP, triglycerides, pack-years, current employment status, leisure-time physical activity. Model 3 as model 2 plus dietary items. Model 4 as model 3 plus lifelong occupation.

Table 5 Distribution of inequality of CV risk and protective factors in Italy and in the rest of Europe

	Mean % difference of manual vs. office workers	
	Italy	Rest of Europe
Risk factors		
Smoke (pack-years)	-11.0%	28.0%
BMI	5.1%	4.7%
LDL-Cholesterol	1.6%	-2.8%
Pulse blood pressure	1.6%	6.3%
Meat	9.8%	-0.8%
Spirits	-70.6%	34.4%
Low physical activity	8.0%	-25.0%
HDL- Cholesterol	-3.2%	-3.6%
Fish	-16.2%	-20.9%
Fruit	0.2%	-8.5%
Olive Oil	0.4%	-53.9%



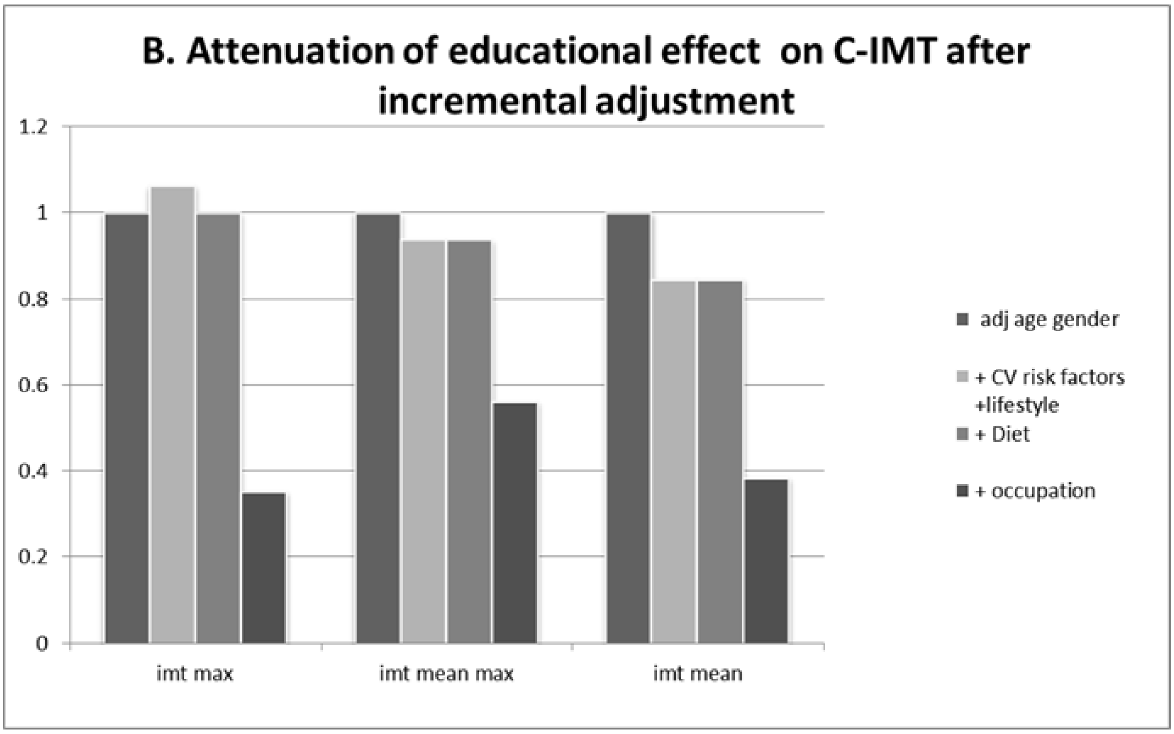
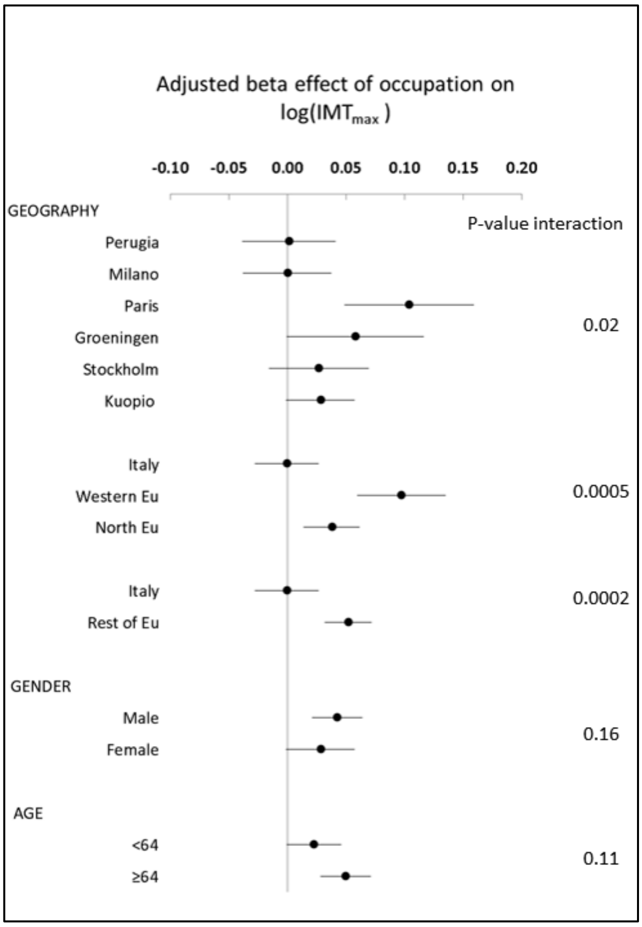


Figure1. Attenuation effect due to the risk factors. A: % residual effect (linear trend) of occupation on C-IMT after incremental adjustment, with respect to the reference model adjusted for age and gender (100%). B: same as A, but considering the effect of education. CV: cardiovascular

a



b

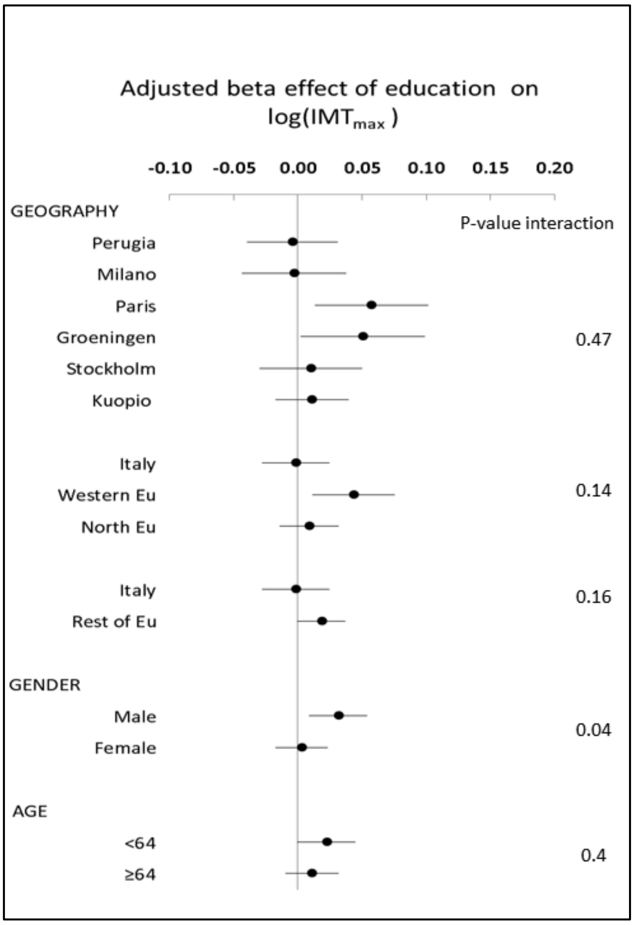
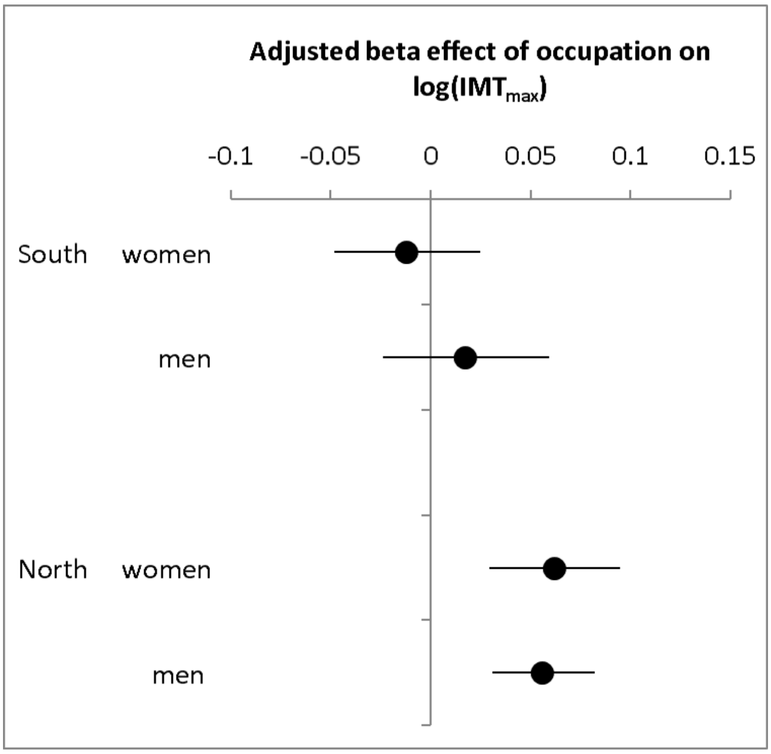


Figure 2. Subgroup analysis of the relation of SES and log IMT_{max} stratified by geography, gender and age classes.

a:effects of Occupation. **b**: effects of education.



Supplemental figure 1. Effects of Occupation vs. log IMT_{max} in men and women, stratified by geographical region.

Bibliography

1. Schwalm JD, McKee M, Huffman MD, Yusuf S. Resource Effective Strategies to Prevent and Treat Cardiovascular Disease. Circulation. 2016;133(8):742-55. doi:10.1161/CIRCULATIONAHA.115.008721.

2. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88(4 Pt 1):1973-98.

3. Gallo V, Mackenbach JP, Ezzati M, Menvielle G, Kunst AE, Rohrmann S et al. Social inequalities and mortality in Europe--results from a large multi-national cohort. PloS one. 2012;7(7):e39013. doi:10.1371/journal.pone.0039013.

4. Diez-Roux AV, Nieto FJ, Tyroler HA, Crum LD, Szklo M. Social inequalities and atherosclerosis. The atherosclerosis risk in communities study. Am J Epidemiol. 1995;141(10):960-72.

5. Lynch J, Kaplan GA, Salonen R, Cohen RD, Salonen JT. Socioeconomic status and carotid atherosclerosis. Circulation. 1995;92(7):1786-92.

6. Camelo LV, Giatti L, Chor D, Griep RH, Bensenor IM, Santos IS et al. Associations of life course socioeconomic position and job stress with carotid intima-media thickness. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Soc Sci Med. 2015;141:91-9. doi:10.1016/j.socscimed.2015.07.032.

7. Carson AP, Rose KM, Catellier DJ, Kaufman JS, Wyatt SB, Diez-Roux AV et al. Cumulative socioeconomic status across the life course and subclinical atherosclerosis. Annals of epidemiology. 2007;17(4):296-303. doi:10.1016/j.annepidem.2006.07.009.

8. Fujishiro K, Diez Roux AV, Landsbergis P, Baron S, Barr RG, Kaufman JD et al. Associations of occupation, job control and job demands with intima-media thickness: the Multi-Ethnic Study of Atherosclerosis (MESA). Occup Environ Med. 2010;68(5):319-26. doi:oem.2010.055582 [pii] 10.1136/oem.2010.055582.

9. Grimaud O, Lapostolle A, Berr C, Helmer C, Dufouil C, Kihal W et al. Gender differences in the association between socioeconomic status and subclinical atherosclerosis. PloS one. 2013;8(11):e80195. doi:10.1371/journal.pone.0080195.
10. Lamotte C, Iliescu C, Beghin L, Salleron J, Gonzalez-Gross M, Marcos A et al. Association of socioeconomic status, truncal fat and sICAM-1 with carotid intima-media thickness in adolescents: the HELENA study. Atherosclerosis. 2013;228(2):460-5. doi:10.1016/j.atherosclerosis.2013.03.007.
11. Lemelin ET, Diez Roux AV, Franklin TG, Carnethon M, Lutsey PL, Ni H et al. Life-course socioeconomic positions and subclinical atherosclerosis in the multi-ethnic study of atherosclerosis. Soc Sci Med. 2009;68(3):444-51. doi:S0277-9536(08)00575-3 [pii]
10.1016/j.socscimed.2008.10.038.
12. Lutsey PL, Diez Roux AV, Jacobs DR, Jr., Burke GL, Harman J, Shea S et al. Associations of acculturation and socioeconomic status with subclinical cardiovascular disease in the multi-ethnic study of atherosclerosis. Am J Public Health. 2008;98(11):1963-70. doi:AJPH.2007.123844 [pii]
10.2105/AJPH.2007.123844.
13. Nash SD, Cruickshanks KJ, Klein R, Klein BE, Nieto FJ, Ryff CD et al. Socioeconomic status and subclinical atherosclerosis in older adults. Prev Med.52(3-4):208-12. doi:S0091-7435(10)00515-3 [pii]
10.1016/j.ypmed.2010.12.009.
14. Ranjit N, Diez-Roux AV, Chambless L, Jacobs DR, Jr., Nieto FJ, Szklo M. Socioeconomic differences in progression of carotid intima-media thickness in the Atherosclerosis Risk in Communities study. Arterioscler Thromb Vasc Biol. 2006;26(2):411-6. doi:10.1161/01.ATV.0000198245.16342.3d.
15. Rosvall M, Ostergren PO, Hedblad B, Isacsson SO, Janzon L, Berglund G. Occupational status, educational level, and the prevalence of carotid atherosclerosis in a general population sample of middle-aged Swedish men and women: results from the Malmo Diet and Cancer Study. Am J Epidemiol. 2000;152(4):334-46.
16. Rosvall M, Ostergren PO, Hedblad B, Isacsson SO, Janzon L, Berglund G. Life-course perspective on socioeconomic differences in carotid atherosclerosis. Arterioscler Thromb Vasc Biol. 2002;22(10):1704-11.
17. Thurston RC, El Khoudary SR, Derby CA, Barinas-Mitchell E, Lewis TT, McClure CK et al. Low socioeconomic status over 12 years and subclinical cardiovascular disease: the study of women's health across the nation. Stroke; a journal of cerebral circulation. 2014;45(4):954-60. doi:10.1161/STROKEAHA.113.004162.
18. Amato M, Montorsi P, Ravani A, Oldani E, Galli S, Ravagnani PM et al. Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. Eur Heart J. 2007;28(17):2094-101. doi:ehm244 [pii]
10.1093/eurheartj/ehm244.
19. Baldassarre D, Nyyssonen K, Rauramaa R, de Faire U, Hamsten A, Smit AJ et al. Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population: the IMPROVE study. Eur Heart J.31(5):614-22. doi:ehp496 [pii]
10.1093/eurheartj/ehp496.
20. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999;340(1):14-22. doi:10.1056/NEJM199901073400103.
21. Baldassarre D, Hamsten A, Veglia F, de Faire U, Humphries SE, Smit AJ et al. Measurements of carotid intima-media thickness and of interadventitia common carotid diameter improve prediction of cardiovascular events: results of the IMPROVE (Carotid Intima Media Thickness [IMT] and IMT-Progression as Predictors of Vascular Events in a High Risk European Population) study. Journal of the American College of Cardiology. 2012;60(16):1489-99. doi:10.1016/j.jacc.2012.06.034.

22. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468-81. doi:358/23/2468 [pii]
10.1056/NEJMsa0707519.
23. Karvanen J, Veronesi G, Kuulasmaa K. Defining thirds of schooling years in population studies. Eur J Epidemiol. 2007;22(8):487-92. doi:10.1007/s10654-007-9144-z.
24. Kershaw KN, Droomers M, Robinson WR, Carnethon MR, Daviglus ML, Monique Verschuren WM. Quantifying the contributions of behavioral and biological risk factors to socioeconomic disparities in coronary heart disease incidence: the MORGEN study. Eur J Epidemiol. 2013;28(10):807-14. doi:10.1007/s10654-013-9847-2.
25. Veronesi G, Ferrario MM, Kuulasmaa K, Bobak M, Chambless LE, Salomaa V et al. Educational class inequalities in the incidence of coronary heart disease in Europe. Heart. 2016. doi:10.1136/heartjnl-2015-308909.
26. Andersen I, Gamborg M, Osler M, Prescott E, Diderichsen F. Income as mediator of the effect of occupation on the risk of myocardial infarction: does the income measurement matter? J Epidemiol Community Health. 2005;59(12):1080-5. doi:59/12/1080 [pii]
10.1136/jech.2005.036848.
27. Geyer S, Hemstrom O, Peter R, Vagero D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J Epidemiol Community Health. 2006;60(9):804-10. doi:10.1136/jech.2005.041319.
28. Brezinka V, Kittel F. Psychosocial factors of coronary heart disease in women: a review. Soc Sci Med. 1996;42(10):1351-65.
29. Mackenbach JP, Cavelaars AE, Kunst AE, Groenhof F. Socioeconomic inequalities in cardiovascular disease mortality; an international study. Eur Heart J. 2000;21(14):1141-51. doi:10.1053/euhj.1999.1990
S0195668X99919905 [pii].
30. Prattala R, Hakala S, Roskam AJ, Roos E, Helmert U, Klumbiene J et al. Association between educational level and vegetable use in nine European countries. Public Health Nutr. 2009;12(11):2174-82. doi:10.1017/S136898000900559X.
31. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67. doi:10.1161/CIRCULATIONAHA.106.628875.

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