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Does Socioeconomic Status Influence the Risk of Subclinical Atherosclerosis?

A Mediation Model

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ABSTRACT

BACKGROUND Socioeconomic status (SES)—education, income level, and occupation—is associated with cardiovascular risk.

OBJECTIVES This study aimed to investigate the association between SES and subclinical atherosclerosis and the potential mechanisms involved.

METHODS SES, lifestyle habits (smoking, dietary patterns, physical activity, and hours of sleep), traditional risk factors, and subclinical atherosclerosis extent were prospectively assessed in 4,025 individuals aged 40 to 54 years without known cardiovascular disease enrolled in the PESA (Progression of Early Subclinical Atherosclerosis) study. After factors associated with atherosclerosis were identified, a multiple mediation model was created to quantify the effect of SES on subclinical atherosclerosis as explained by lifestyle behaviors.

RESULTS Although education level was significantly associated with the presence of atherosclerosis, no differences were found according to income level in this population. Participants with lower education presented with a higher risk of generalized atherosclerosis than those with higher education (odds ratio: 1.46; 95% confidence interval: 1.15 to 1.85; $p = 0.002$). Lifestyle behaviors associated with both education level and atherosclerosis extent were: smoking status, number of cigarettes/day, and dietary pattern, which explained 70.5% of the effect of SES on atherosclerosis. Of these, tobacco habit (smoking status 35% and number of cigarettes/day 32%) accounted for most of the explained differences between groups, whereas dietary pattern did not remain a significant mediator in the multiple mediation model.

CONCLUSIONS Despite the relative economic homogeneity of the cohort, lower education level is associated with increased subclinical atherosclerosis, mainly mediated by the higher and more frequent tobacco consumption. Smoking cessation programs are still needed, particularly in populations with lower education level.
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Socioeconomic status (SES) has been commonly defined as the combination of education, income level, and occupation. The relationship between SES and cardiovascular disease (CVD) has been explored mostly for acute cardiovascular (CV) events, with contradictory results depending on cultural factors and country development (1). In studies carried out in the United States and some European countries, higher SES has been correlated with lower risk of CV events (1–4). Nevertheless, in other regions, such as Latin America, a higher socioeconomic status has been associated with a higher risk of obesity and laboratory abnormalities related to CV events (5).

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Studies exploring this association have concluded that most of the associated risk can be explained by dietary patterns (6–8). However, other lifestyle habits, such as tobacco consumption, can act as important mediators in this association as well, taking into account that there are wide differences between men and women and according to SES levels (9). Global trends in smoking are increasing among women, especially in vulnerable groups (understood in terms of income, education, or social exclusion). In several European countries, including Spain, higher smoking uptake rates have been seen in disadvantaged girls (with lower family affluence) age 13 to 15 years, related to higher levels of early experience of smoking as well as weekly smoking, which has not been observed among boys (10). Tobacco diffusion theories described age and education patterns as determinants of change, producing a shift in smoking from young women with high education to older women with lower education level in epidemic stages when cigarette use started to decline (11). A greater decrease in smoking prevalence has been observed in the more highly educated, as they respond more favorably to health promotion campaigns about the hazards of smoking (12).

Other factors, such as limited access to health care facilities, may also play a relevant role as a possible cause of higher CV risk in individuals in the lowest economical level, which may vary depending on the country or health care system. Therefore, studying preclinical disease makes sense to avoid the important confounding by lower access to health care.

A number of studies have explored the association between SES and subclinical atherosclerosis, most often using intima-media thickness or the presence of carotid plaque as diagnostic criteria (13–15), which is not a good surrogate for later clinical CV risk (16,17). No studies have focused on whether there is an association between SES and multiterritorial subclinical atherosclerosis and, if it exists, the mediation effect of lifestyle patterns on this association.

The aims of this study are: 1) to assess whether education and income levels are associated with the prevalence of multiterritory subclinical atherosclerosis in low- to intermediate-risk individuals without previous CV events; and 2) if such association is present, to identify the main factors involved in it, focusing on potentially modifiable lifestyle behaviors.

ABBREVIATIONS AND ACRONYMS

aOR = adjusted odds ratio
CI = confidence interval
CV = cardiovascular
CVD = cardiovascular disease
SES = socioeconomic status

METHODS

POPULATION. PESA (Progression of Early Subclinical Atherosclerosis)-CNIC-Santander is a prospective cohort study of asymptomatic employees of Santander Bank Headquarters in Madrid designed to assess the prevalence and determinants of subclinical atherosclerosis. The study includes 4,149 participants aged 40 to 54 years, recruited between June 2010 and February 2014 and free of established CVD. All employees were invited to participate during their regular annual medical checkup by the company's medical services. Those with prior CVD or any condition reducing life expectancy were excluded. Participants were examined at baseline and 3 years and will be followed at 6 years (18).

DEMOGRAPHIC, SOCIOECONOMIC, LIFESTYLE, AND CVD RISK FACTORS ASSESSMENT. Socioeconomic information (income level and education) was compiled by a self-reported questionnaire. Income level, defined as annual salary, was divided into 4 categories: <€30,000, €30,000 to €50,000, €50,000 to €75,000, and >€75,000. Education level was defined as no university versus university studies. As PESA is a cohort of working persons only, occupation was not considered for the analysis.

Tobacco-related information was assessed by a questionnaire as well, including: smoking status

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(nonsmoker, former smoker, active smoker, or social smoker), number of cigarettes/day in active smokers and former smokers (when smoking), number of years smoking, and years since stopped smoking in former smokers.

Food and alcohol intake was assessed by trained dietitians using a computerized dietary history software (DH-E) (19). Based on 21 food groups, cluster analysis-derived dietary patterns were labeled as Mediterranean (highest consumption of fruits and vegetables, whole grains, and olive oil), Western (highest consumption of refined cereal products, legumes, dairy, and sweets and desserts) and Social-Business (highest consumption of red meat and shellfish, pre-made foods, appetizers, snacks, and alcoholic and sugar-sweetened beverages) as described in a previous study (20).

Physical activity and hours of sleep/day were assessed through triaxial accelerometers (Acti Trainer, ActiGraph, Pensacola, Florida) that were placed on each participant's waist for a week. Moderate and vigorous physical activity intensity was defined according to Troiano cut-off points (21).

Venous blood was collected after 8 h of fasting, and samples were tested for dyslipidemia markers, such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, and triglycerides; for glucose; and for markers of inflammation and thrombogenesis, such as C-reactive protein, platelets, and fibrinogen levels. Arterial blood pressure (both systolic and diastolic) was also obtained at the baseline medical visit.

SUBCLINICAL ATHEROSCLEROSIS ASSESSMENT. Imaging studies used to assess the presence and extent of atherosclerotic plaque were 2-dimensional (2D) ultrasound for carotid, aorta, and iliofemoral arteries and CT scanning for coronary artery calcium score (CACS). Vascular ultrasound was performed with Philips iU22 ultrasound station (Philips Healthcare, Bothell, Washington). A 2D high-resolution transducer was used to assess the presence of plaques. Plaque was defined as a focal protrusion into the arterial lumen of thickness >0.5 mm or >50% of the surrounding intima-media thickness (22). All ultrasound recordings were analyzed at the PESA Central Imaging Core Laboratory of the Centro Nacional de Investigaciones Cardiovasculares. CACS was obtained by noncontrast electrocardiography gated prospective acquisition with 16-slice computed tomography scanner (Philips Brilliance CT, Philips Healthcare, Andover, Massachusetts).

Subclinical atherosclerosis was defined as the presence of any atherosclerotic plaque in the carotid, aortic, or iliofemoral territories or having CACS ≥1. The extent of subclinical atherosclerosis was defined according to the number of sites affected: disease-free if no vascular sites were affected, focal if 1 site was affected, moderate if 2 or 3 sites were affected, and generalized when 4 to 6 sites were affected (18). We used generalized atherosclerosis as the outcome for this study.

STATISTICAL ANALYSIS. Categorical variables are described as proportions, while continuous variables are presented as mean ± SD. Logistic regression models adjusted for sex and age were performed to assess the relationship between SES (income level and education) and generalized atherosclerosis.

Lifestyle patterns and biochemical markers were tested to explore associations with education level. Analysis of covariance adjusted for age and sex was performed for continuous variables (those showing a skewed distribution were log-10 transformed before the analysis). Categorical variables were explored using chi-square test. Given the association found between education level and subclinical atherosclerosis, lifestyle variables proving association with education level and subclinical atherosclerosis were individually included in a multivariate model by logistic regression adjusted for age and sex to check association with generalized atherosclerosis.

Last, variables associated with both education level and generalized atherosclerosis were included in a mediation model that sought to identify and explain the mechanism underlying the observed relationship between the independent variable (education level) and the dependent variable (subclinical atherosclerosis) via the inclusion of third hypothetical variables (significant lifestyle patterns), known as mediators. It also allowed us to quantify the proportion mediated with respect to the total effect of education on atherosclerosis. Different paths were created in this model: Path a, representing the effect of education on lifestyle behaviors; Path b, representing the effect of lifestyle behaviors on atherosclerosis; Path a*b (known as indirect effect), which represents the mediated effect of education on atherosclerosis by the mediators included; Path c, representing total effect of education on atherosclerosis; and Path ć, which represents the remaining effect of education on atherosclerosis not mediated by the variables included in the model. All p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (SPSS, IBM Corporation, Armonk, New York). Mediation models were performed using the

TABLE 1 Lifestyle Habits, Biochemical Parameters, and Atherosclerosis Extent According to Education Level

	Men (n = 2,512)			Women (n = 1,513)			
	University −	University +	p Value*	University −	University +	p Value*	Adjusted p Value†
Age, yrs	47.0 ± 4.3	45.0 ± 3.7	**<0.001**	45.6 ± 4.0	44.8 ± 3.5	**<0.001**	***<0.001***
Smoking status			**<0.001**			**<0.001**	***<0.001***
Nonsmoker	31.2	43.4		27.4	40.6		
Social smoker	5.3	9.1		3.9	7.2		
Former smoker	40.3	29.8		36.0	31.3		
Active smoker	23.2	17.7		32.7	20.9		
Cigarettes/day (smokers or former) (n = 2,504)	17.3 ± 13.1	13.5 ± 12.3	**0.004**	13.9 ± 10.2	11.3 ± 10	**0.042**	***0.001***
Years smoking							
Former smoker (n = 1,338)	19.6 ± 9.2	17.0 ± 8.8	**0.022**	18.5 ± 8.6	16 ± 7.8	0.081	***0.011***
Active smoker (n = 858)	31.3 ± 5.9	28.3 ± 6.7	0.162	29.9 ± 4.9	27.8 ± 5.3	0.057	***0.009***
Years since stopping smoking (n = 1,338)	13.6 ± 9.4	13.3 ± 8.9	0.112	12.4 ± 8.3	12.1 ± 7.3	0.221	***0.006***
Dietary pattern			**<0.001**			**0.013**	***<0.001***
Mediterranean	22.0	30.0		54.1	62.6		
Western	48.1	47.6		33.7	28.7		
Social-business	29.9	22.4		12.2	8.7		
Alcohol, g/day	13.9 ± 14.7	12.8 ± 12.5	**0.031**	5.4 ± 8	5.5 ± 6.5	**0.001**	***<0.001***
Moderate-vigorous physical activity, min/day	43 ± 25	42 ± 23	0.728	31 ± 72	33 ± 18	**0.027**	*0.380*
Hours of sleep/day	6.3 ± 0.9	6.4 ± 0.9	**0.001**	6.6 ± 0.9	6.8 ± 0.9	**<0.001**	***<0.001***
Total cholesterol, mg/dl	205 ± 34	203 ± 34	0.386	195 ± 356	193 ± 31	0.284	*0.407*
LDL-C, mg/dl	138 ± 30	136 ± 31	0.355	129 ± 33	124 ± 28	**0.037**	*0.135*
HDL-C, mg/dl	44 ± 10	45 ± 10	0.255	52 ± 11	54 ± 10	**0.008**	***0.004***
TG, mg/dl	113 ± 79	108 ± 63	0.288	71 ± 28	71 ± 31	0.196	*0.112*
Fasting glucose, mg/dl	95 ± 15	93 ± 15	0.169	86 ± 7	84 ± 8	**0.024**	***0.04***
C-reactive protein, mg/dl	0.2 ± 0.7	0.2 ± 0.2	**0.007**	0.2 ± 0.4	0.1 ± 0.2	**0.002**	***<0.001***
Platelets, $10^3/\mu l$	222 ± 44	218 ± 46	**0.028**	245 ± 5	237 ± 51	**0.01**	***<0.001***
Fibrinogen, mg/dl	268 ± 51	258 ± 43	**0.021**	286 ± 51	272 ± 49	**<0.001**	***<0.001***
Systolic blood pressure, mm Hg	123 ± 12	120 ± 11	**<0.001**	111 ± 12	18 ± 11	**<0.001**	***<0.001***
Diastolic blood pressure, mm Hg	76 ± 9	74 ± 9	**<0.001**	70 ± 9	68 ± 9	**0.001**	***0.004***
Generalized atherosclerosis disease			**<0.001**			**0.001**	***<0.001***
No	73.3	85.3		89.8	95.0		
Yes	26.7	14.7		10.2	5.0		

Values are mean ± SD or %. *p value from univariate analysis. †p value adjusted for age and sex. **Bold** indicates statistically significant p values. *Italic* indicates adjusted p values. ***Italic bold*** indicates statistically significant adjusted p values.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; University − = no university studies; University + = university studies.

Mediation package PROCESS version 2.16 by Andrew F. Hayes for SPSS (23).

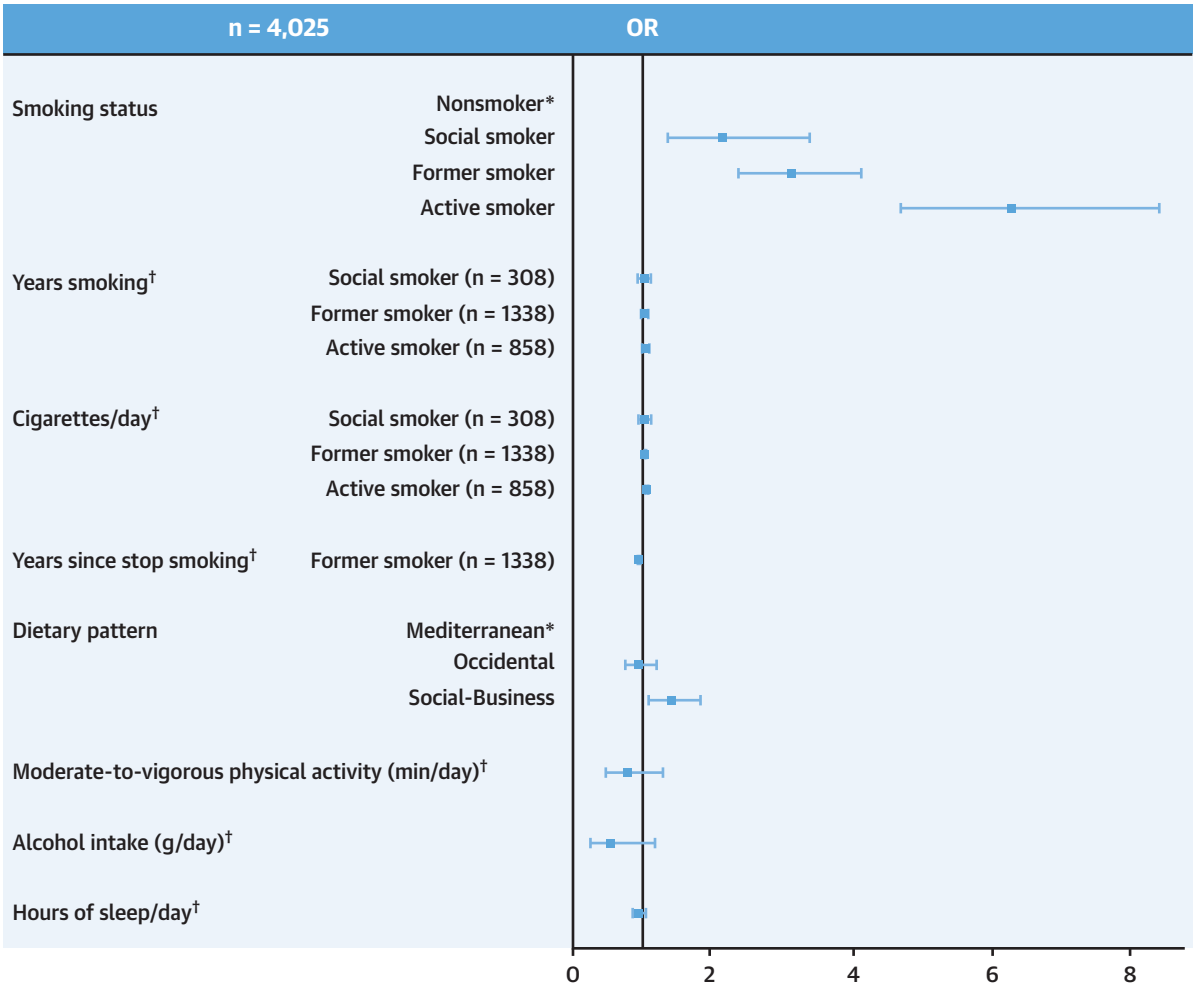
The study was approved by the ethics committee of the Instituto de Salud Carlos III, and all participants provided written informed consent.

RESULTS

The study population comprised 4,025 PESA participants, 1,513 women (37.4%) and 2,512 men (62.6%), with a mean age of 46 ± 4.3 years, 45.5 ± 3.9 years among women and 46.8 ± 4.5 years among men ($p < 0.001$). The majority of the population had undergone university studies (n = 3,089; 74.5%), more often among women (n = 1,182; 77.1%) than among men (n = 1,907; 72.9%; p = 0.003). The range of income levels was: 202 (4.9%) lower than €30,000/year, 1,266 (30.5%) between €30,000 and €50,000/year, 1,217 (29.3%) between €50,000 and €75,000/year, and 1,464 (35.3%) higher than €75,000/year. A total of 2,523 individuals (62.7%) presented subclinical atherosclerosis, 545 of them generalized (13.5%), with significant differences by sex (94 women [6.2%] vs. 451 men [18%] with generalized atherosclerosis; $p < 0.001$).

A logistic regression model adjusting for age, sex and education showed no association between income level and generalized atherosclerosis (using category <€30,000 as the reference, adjusted odds ratio [aOR]: 0.87; 95% confidence interval [CI]: 0.52 to 1.47 for category €30,000 to €50,000; aOR: 0.92; 95% CI: 0.70 to 1.20 for €50,000 to €75,000; and aOR: 0.84; 95% CI: 0.65 to 1.07 for >€75,000). To the contrary, education level did present statistical association with generalized atherosclerosis after adjusting for age, sex, and income level: participants

FIGURE 1 **ORs Adjusted for Age and Sex**



*Category of reference in categorical variables. †Odds ratios (ORs) represent the incremental risk of developing generalized atherosclerosis when a unit of the quantitative variable is increased (1 g alcohol/day, 1 h sleep/day, 1 year smoking, 1 cigarette/day, 1 min/day of moderate to vigorous physical activity).

with no university studies presented higher risk of generalized atherosclerosis than those with university studies (aOR: 1.46; 95% CI: 1.16 to 1.85; p = 0.002).

Table 1 describes the distribution of lifestyle patterns and risk factors according to education level by sex in the PESA population. After adjusting for age and sex, differences were observed in the following lifestyle and biochemical variables: smoking status, cigarettes/day, years smoking (in active or former smokers), years since stop smoking (former smokers), dietary pattern, alcohol intake, high-density lipoprotein cholesterol, fasting glucose, C-reactive protein, platelets, fibrinogen, and systolic and diastolic blood pressure.

Among lifestyle factors proving association with education level, smoking status, cigarettes/day, years since stopping smoking (former smokers), and dietary pattern were also associated with the presence of generalized atherosclerosis (**Figure 1**, Online Table 1). From these results, a multiple mediator model adjusted for age and sex was created for smoking status, cigarettes/day, and dietary pattern (**Table 2, Central Illustration**). Smoking status and cigarettes/day remained significant (both p values <0.001), whereas dietary pattern became nonsignificant (p = 0.202).

The components analyzed in the mediation model are shown in **Table 2**. Path c is the total effect of education level on the number of territories affected by atherosclerosis. Path a represents the association between education and lifestyle behaviors included in the model (p < 0.001). Path b shows the relationship between lifestyle behaviors and the number of

TABLE 2 Mediation Model: Education Level on Number of Territories Affected By Atherosclerosis (n = 3,897)

	Education Level Effect on Mediator (Path a: X→M)				Multiple Mediator Model: Mediator Effect on Generalized Atherosclerosis (Path b: M→Y)			
		95% CI				95% CI		
Mediator	β	Lower	Upper	p Value	β	Lower	Upper	p Value
Smoking status	−0.2877	−0.3744	−0.201	<0.001	0.202	0.1566	0.2474	<0.001
Cigarettes/day	−2.66	−3.46	−1.86	<0.001	0.0209	0.016	0.0257	<0.001
Dietary pattern	−0.144	−0.1958	−0.0922	<0.001	0.0412	−0.0221	0.1045	0.202

	Indirect Effect (a*b: X→M→Y)			% Mediated (a*b/c)	Total Effect (Path c: X→Y adj M)			
		95% CI				95% CI		
Mediator	β	Lower	Upper	Multiple m.model	β	Lower	Upper	p Value
Smoking status	−0.0595	−0.0841	−0.0391	34.9%	−0.1706	−0.2793	−0.062	0.002
Cigarettes/day	−0.0547	−0.0824	−0.0339	32.1%	Direct Effect (Path c': X→Y adj M			
Dietary pattern	−0.006	−0.0173	0.003	3.5%		95% CI		
					β	Lower	Upper	p Value
Total	−0.1202	−0.156	−0.0861	70.5%	−0.0504	−0.1557	0.0548	0.3474

CI = confidence interval; M = mediators (smoking status, cigarettes/day, and dietary pattern); X = independent variable (education level); Y = dependent variable (generalized atherosclerosis).

territories affected by atherosclerosis (smoking status and cigarettes/day: p values <0.001 and 0.20 for dietary pattern). Mediated effects (a*b) represented in the indirect effect columns show the estimated mediator effects and the proportion mediated. Indirect effects were observed for smoking status and cigarettes/day but not for dietary pattern. The total proportion of the overall effect mediated by all of the included lifestyle factors was 70.5%. Path c′, known as the direct association, is the remaining relationship between education level and atherosclerosis after including the presumed mediators in the model.

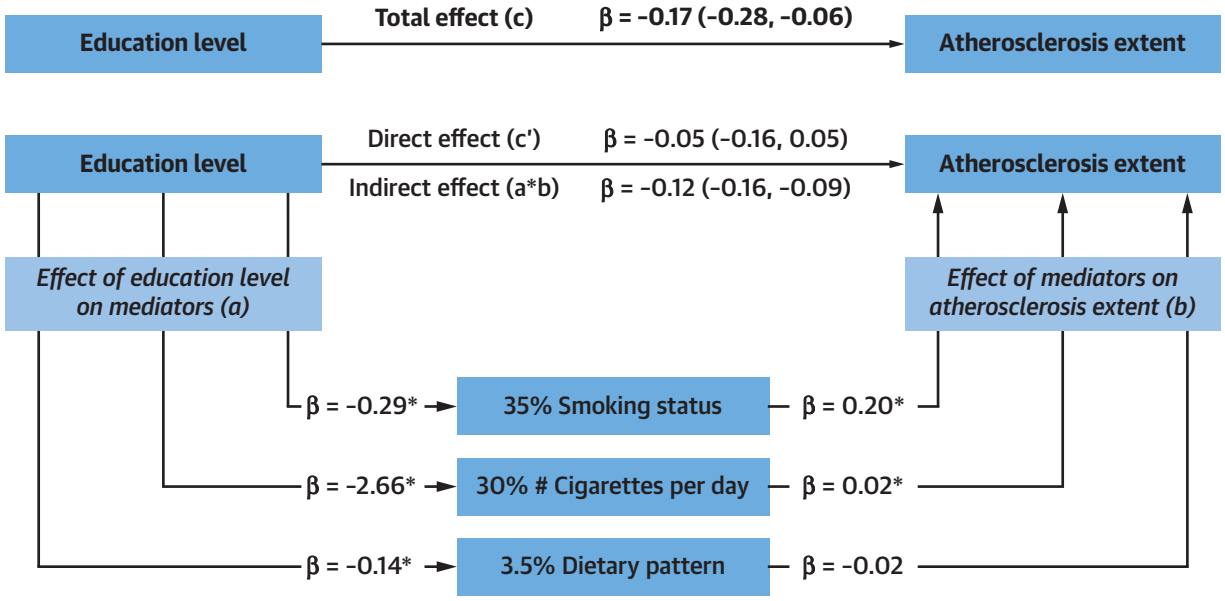
DISCUSSION

SES in general, and education level in particular, are associated with a greater prevalence of diffuse atherosclerosis in young individuals at a low-to-moderate CV risk. This effect seems to be mostly mediated by the greater prevalence of smoking and the higher number of cigarettes smoked, whereas we could not find a significant effect of more unhealthy dietary patterns or other habits or risk factors.

A number of studies have explored the association between atherosclerosis and SES, but most of them used the intima-media thickness ratio or the presence of carotid plaque as the indicator for atherosclerosis (13-15), with conflicting results because studies from different countries have yielded mixed results, reflecting that sociocultural factors might be involved in this relationship (1,5). To the best of our knowledge, no study so far has assessed its effect on multiterritory atherosclerosis, and the mediation effect of different lifestyle behaviors in this association has not been explored. This study provides an innovative approach in terms of methodology, because mediation models are not frequently used in cardiology to determine the relationship among variables from different levels of intervention. In addition, as we aimed to evaluate the role of behavioral risk factors of early adoption, such as SES and lifestyle habits, using a subclinical phase of the CVD as outcome can provide a wider understanding of the disease pointing out the targets for primary and secondary prevention. In this paper we used imaging studies to assess the presence and extent of atherosclerotic plaque with 2D ultrasound for carotid, aorta, and iliofemoral arteries and CT scanning for CACS, which has shown to improve CVD risk prediction (16,17,24-26), creating opportunities for primary prevention through changes in lifestyle behaviors. IMT was not considered since there is uncertainty about its role (27), and carotid plaque has proven to predict more accurately coronary artery disease events (16,28).

Our study did not find an association between economic status and generalized atherosclerosis. However, it must be mentioned that the study population has a quite high income level for the national average, with only 2.8% of men and 8.6% of woman receiving an annual salary under €30,000. In Spain, according to the National Institute of Statistics, the average annual salary ranged from €22,400 to €22,600 during the last 5 years (29), which means that a very small proportion of our population of study have an income level under the Spanish average. Some studies performed in Europe pointed out that a lower income level is associated with worse lifestyle patterns and, likely, with a higher probability of

CENTRAL ILLUSTRATION **Education Level Effect on Atherosclerosis Extent: Mediation Model**



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The mediation model aims to assess the relationship among education, atherosclerosis extent and behavioral patterns. We identified and quantified the mediators between education and atherosclerosis creating different paths: c path: the total effect of education level on atherosclerosis extent; a path: the effect of education level on each mediator; b path: the effect of each mediator on atherosclerosis extent; a*b path (indirect effect): the mediated effect of education on atherosclerosis by smoking status, number of cigarettes/day and dietary pattern; and c′ path (direct effect): the remaining effect of education level on atherosclerosis extent not explained by the mediators included in the model. A total of 70% of the association between education and atherosclerosis was explained by the lifestyle patterns included in our model. Smoking status and the number of cigarettes/day were the main mediators, and those of interest for intervention strategies to decrease the effect of socioeconomic status in atherosclerosis extent.

developing CVD disease (1,4). However, our data suggests that an economic threshold may be present, above which no differences in atherosclerosis extent might be observed. This may vary depending on sociocultural factors and country cost of living. Yet, in studies performed in lower-income countries, a higher SES has been associated with worse lifestyle behaviors and CV risk factors, such as obesity (5,30). This reflects that economic status-related lifestyle patterns may be different according to the local economic situation and/or are modulated by other factors, such as cultural factors, among which education may play a role.

One-quarter of our population cohort did not have university studies. A more stressful occupation, less available time for cooking, and therefore, more consumption of ready-to eat food or fast-food habits have been described in groups with higher educational level (6), but other studies suggest that this may not be the case (31,32). A lower education level in our study was associated with a higher risk of generalized atherosclerosis independent of income level. It is relevant that education still plays a role in the risk of atherosclerosis even in groups with a medium-high and high economic status. So, even when subjects have a good access to health care resources (Spain has a tax-based social security system covering the majority of the population) and present a favorable economic situation, such as in our cohort, education still acts as a decisive factor in CVD risk. To understand the potential mechanisms involved in the effect of education on atherosclerosis, we explored lifestyle habits that could be related to both atherosclerosis extent and education. We observed disparities in all lifestyle variables studied, namely tobacco consumption habits (smoking status, cigarettes smoked, years smoking, and years without smoking, where applicable), dietary patterns (including alcohol intake), physical activity, and hours of sleep, which were patent in both men and women, suggesting that education may play a similar role regardless of sex. Nonetheless, only smoking status, number of cigarettes/day, years since stopping smoking (in former smokers), and dietary pattern showed an effect on

generalized atherosclerosis after adjustment for age and sex, suggesting that these can act as behavioral mechanisms mediating the association between education level and atherosclerosis. In fact, the mediation model shows that the lifestyle habits explored explain roughly 70% of the effect, mostly smoking status (35%) and number of cigarettes/day (32%), with a very small contribution from dietary pattern (3.5%). Although the effect of smoking is obvious, the lack of a relevant role of diet may be explained by the fact that most participants work at the same workplace and, therefore have a similar food offered during working hours, which may dilute differences in dietary pattern and minimize its role on the effect of education level on atherosclerotic disease.

The relationship between education level and smoking is well known. According to the Centers for Disease Control and Prevention, among people having only General Educational Development Test certificate in the United States, smoking prevalence is 40%, the highest of any SES group, whereas in those with a graduate degree, smoking prevalence is 4.5% (33). In our study, the prevalence of active smoking was roughly 50% higher among individuals with nonuniversity studies: 23.2% in men and 32.7% in women with nonuniversity studies compared with 17.7% in men and 20.9% in women with university studies. Thus, differences depending on the country are observed, and similarly the effect of education on atherosclerosis. In low- and middle-income countries, daily tobacco use has been also associated with lower education, constituting a major health problem in both high and low-middle income countries (34). Although it has been suggested that this association may be weaker in women compared with men and in older compared with younger people (35), the effect of education on tobacco consumption among women has been confirmed (36,37), and this is a particular cause of concern because the prevalence of female smoking in developed and developing countries is likely to rise to 20% by 2025 (38), as they are one of the biggest targets of tobacco industry, as pointed out by the World Health Organization (39).

Despite historical advances, our results highlight the current need of improving the implementation of tobacco cessation strategies covering subjects with higher- and lower-level studies, as well as men and women, with a specific focus on implementing strategies targeting the groups with an increased risk, particularly at early stages of education, such as in schools, where learning healthy lifestyle habits should become a priority. If healthy habits are adopted during childhood, the disparities associated with not getting university education on health in general, and on atherosclerosis in particular, might be reduced. Despite the many health promotion strategies and prevention interventions based on diet and physical activity, smoking cessation programs are still needed, and should not only be left to public administrations through regulation, which is a very important measure but still insufficient, particularly in the population with a lower education level (40).

Our mediation model leaves 29.5% of the association unexplained, so further research on potential mechanisms between education level and diffuse atherosclerosis, including other behavioral factors, is warranted. This is needed to target specific lifestyle behaviors prior to intervention programs in the community, increasing the likelihood of being effective and reducing the risk of potential harm. This is important because few studies have assessed the effect of community programs for CVD prevention in different socioeconomic conditions (41,42), and uncertainty regarding the potential to increase health inequalities remains (43).

STUDY LIMITATIONS. A number of limitations should be taken into account when considering these results. The PESA cohort is composed of a relatively homogenous group of bank workers, with a relatively high SES status within the society, which reduces the range of observed education and economical levels and eliminates the known effect of occupation in the relationship between SES and CVD (14,44,45). The lack of effect of diet as a mechanism may be explained in part by the fact that they worked at the same workplace with similar food offerings. This may have reduced differences in dietary patterns, potentially diluting effect of education level on atherosclerotic disease.

CONCLUSIONS

Lower education level may increase CV risk by accelerating the development of atherosclerosis in its earlier stage. As tobacco consumption seems to be the main mediator in this association, smoking prevention campaigns should be considered a key preventative strategy, particularly in populations with a lower education level.

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PERSPECTIVES

COMPETENCY IN SYSTEMS-BASED PRACTICE: Education is a major determinant of CVD, but income level may be less influential than cigarette smoking in explaining this association.

TRANSLATIONAL OUTLOOK: The role of tobacco smoking in the association between education level and atherosclerosis warrants efforts to promote tobacco cessation at early ages and in lower socioeconomic groups.

REFERENCES

1. Méjean C, Droomers M, van der Schouw YT, et al. The contribution of diet and lifestyle to socioeconomic inequalities in cardiovascular morbidity and mortality. Int J Cardiol 2013;168:5190–5.

2. Franks P, Winters PC, Tancredi DJ, Fiscella KA. Do changes in traditional coronary heart disease risk factors over time explain the association between socio-economic status and coronary heart disease? BMC Cardiovasc Disord 2011;11:28.

3. Centers for Disease Control and Prevention. Racial/ethnic and socioeconomic disparities in multiple risk factors for heart disease and stroke. United States, 2003. Morb. Mortal. Wkly. Report 2005;54:113–7.

4. Psaltopoulou T, Hatzis G, Papageorgiou N, Androulakis E, Briasoulis A, Tousoulis D. Socioeconomic status and risk factors for cardiovascular disease: impact of dietary mediators. Hellenic J Cardiol 2017;58:32–42.

5. Quispe R, Benziger CP, Bazo-Alvarez JC, et al. The relationship between socioeconomic status and CV risk factors. Glob Heart 2016;11:121–30.e2.

6. Kirkpatrick S, Tarasuk V. The relationship between low income and household food expenditure patterns in Canada. Public Health Nutr 2003;6:589–97.

7. Hiza HAB, Casavale KO, Guenther PM, Davis CA. Diet quality of Americans differs by age, sex, race/ethnicity, income, and education level. J Acad Nutr Diet 2013;113:297–306.

8. Sijtsma FPC, Meyer KA, Steffen LM, et al. Longitudinal trends in diet and effects of sex, race, and education on dietary quality score change: the Coronary Artery Risk Development in Young Adults study. Am J Clin Nutr 2012;95:580–6.

9. Amos A, Greaves L, Nichter M, Bloch M. Women and tobacco: a call for including gender in tobacco control research, policy and practice. Tob Control 2012;21:236–43.

10. Anon. Currie C, Gabhainn S N, Godeau E, et al. Inequalities in Young People's Health: HBSC International Report from the 2005/2006 Survey. Copenhagen: WHO Europe, 2008.

11. Lopez AD, Collishaw NE, Piha T. A descriptive model of the cigarette epidemic in developed countries. Tob Control 1994;3:242–7.

12. Pampel FC. Age and education patterns of smoking among women in high-income nations. Soc Sci Med 2003;57:1505–14.

13. Thurston RC, Khoudary SRE, Derby CA, et al. Low socioeconomic status over 12 years and subclinical cardiovascular disease: the study of women's health across the nation. Stroke 2014;45:954–60.

14. Nash SD, Cruickshanks KJ, Klein R, et al. Socioeconomic status and subclinical atherosclerosis in older adults. Prev Med 2011;52:208–12.

15. Rundek T, Brown DL. Socioeconomic status and subclinical atherosclerosis: are we closing disparity gaps? Stroke 2014;45:948–9.

16. Gepner AD, Young R, Delaney JA, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging 2015;8:e002262.

17. Gepner AD, Young R, Delaney JA, et al. Comparison of carotid plaque score and coronary artery calcium score for predicting cardiovascular disease events: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2017;6:e005179.

18. Fernández-Friera L, Peñalvo JL, Fernández-Ortiz A, et al. Prevalence, vascular distribution and multi-territorial extent of subclinical atherosclerosis in a middle-aged cohort: the PESA (Progression of Early Subclinical Atherosclerosis) study. Circulation 2015;131:2104–13.

19. Guallar-Castillón P, Sagardui-Villamor J, Balboa-Castillo T, et al. Validity and reproducibility of a Spanish dietary history. PLoS One 2014;9:e86074.

20. Peñalvo JL, Fernández-Friera L, López-Melgar B, et al. Association between a social-business eating pattern and early asymptomatic atherosclerosis. J Am Coll Cardiol 2016;68:805–14.

21. Troiano RP, Berrigan D, Dodd KW, Mâsse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40:181–8.

22. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21:93–111. quiz 189–90.

23. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. Second Edition. New York: Guilford Press, 2017.

24. Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397–406.

25. Peters SAE, den Ruijter HM, Bots ML, Moons KGM. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. Heart 2012;98:177–84.

26. McClelland RL, Jorgensen NW, Budoff M, et al. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) study and the DHS (Dallas Heart Study). J Am Coll Cardiol 2015;66:1643–53.

27. Lorenz MW, Gao L, Ziegelbauer K, et al. Predictive value for cardiovascular events of common carotid intima media thickness and its rate of change in individuals at high cardiovascular risk—results from the PROG-IMT collaboration. PloS One 2018;13:e0191172.

28. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis 2012;220:128–33.

29. Instituto Nacional de Estadística. Decil de salarios del empleo principal. Encuesta de Población Activa (EPA). Año 2016. Notas de Prensa. 2017. Available at: http://www.ine.es/prensa/epa_2016_d.pdf. Accessed June 6, 2019.

30. Cohen AK, Rai M, Rehkopf DH, Abrams B. Educational attainment and obesity: a systematic review. Obes Rev 2013;14:989–1005.

31. Kilander L, Berglund L, Boberg M, Vessby B, Lithell H. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year

follow-up of Swedish 50-year-old men. Int J Epidemiol 2001;30:1119–26.

32. Eguchi E, Iso H, Honjo K, Yatsuya H, Tamakoshi A. No modifying effect of education level on the association between lifestyle behaviors and cardiovascular mortality: the Japan Collaborative Cohort Study. Sci Rep 2017;7:39820.

33. Jamal A, Phillips E, Gentzke AS, et al. Current cigarette smoking among adults—United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:53–9.

34. Do YK, Bautista MA. Tobacco use and household expenditures on food, education, and healthcare in low- and middle-income countries: a multilevel analysis. BMC Public Health 2015;15:1098.

35. Pampel FC, Denney JT, Krueger PM. Cross-national sources of health inequality: education and tobacco use in the World Health Survey. Demography 2011;48:653–74.

36. Sinalkar DR, Kunwar R, Bagal R. Tobacco consumption and its association with education among women residing in a rural area of Maharashtra: a cross-sectional study. Med J Armed Forces India 2012;68:335–8.

37. Graham H, Der G. Patterns and predictors of tobacco consumption among women. Health Educ Res 1999;14:611–8.

38. Mackay J, Amos A. Women and tobacco. Respirology 2003;8:123–30.

39. World Health Organization 2010. 10 facts on gender and tobacco. Available at: http://www.who.int/gender/documents/10facts_gender_tobacco_en.pdf. Accessed June 6, 2019.

40. Kasza KA, Hyland AJ, Brown A, et al. The effectiveness of tobacco marketing regulations on reducing smokers' exposure to advertising and promotion: findings from the International Tobacco Control (ITC) Four Country Survey. Int J Environ Res Public Health 2011;8:321–40.

41. Weinehall L, Hellsten G, Boman K, Hallmans G, Asplund K, Wall S. Can a sustainable community intervention reduce the health gap? 10-year evaluation of a Swedish community intervention program for the prevention of cardiovascular disease. Scand J Public Health Suppl 2001;56:59–68.

42. Weinehall L, Lewis C, Nafziger AN, et al. Different outcomes for different interventions with different focus! A cross-country comparison of community interventions in rural Swedish and US populations. Scand J Public Health Suppl 2001;56:46–58.

43. Pennant M, Davenport C, Bayliss S, Greenheld W, Marshall T, Hyde C. Community programs for the prevention of cardiovascular disease: a systematic review. Am J Epidemiol 2010;172:501–16.

44. Lynch J, Kaplan GA, Salonen R, Cohen RD, Salonen JT. Socioeconomic status and carotid atherosclerosis. Circulation 1995;92:1786–92.

45. Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. Am J Public Health 1992;82:816–20.

KEY WORDS atherosclerosis, education, mediation model, smoking, socioeconomic status

APPENDIX For a supplemental table, please see the online version of this paper.