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).

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.

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
(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 c, 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
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 ± 3.3 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

### RESULTS

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

### SOCIOECONOMIC STATUS, LIFESTYLE HABITS, AND SUBCLINICAL ATHEROSCLEROSIS RISK

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Lifestyle Habits, Biochemical Parameters, and Atherosclerosis Extent According to Education Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n = 2,512)</strong></td>
<td><strong>Women (n = 1,513)</strong></td>
</tr>
<tr>
<td><strong>University</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>University</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>University</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Nonsmoker</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Social smoker</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Former smoker</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Active smoker</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Cigarettes/day (smokers or former)</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Years since stopping smoking</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Dietary pattern</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Alcohol, g/day</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Moderate-vigorous physical activity, min/day</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Hours of sleep/day</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Total cholesterol, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>LDL-C, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>HDL-C, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>TG, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>VLDL-C, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Cholesterol, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Fasting glucose, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>C-reactive protein, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Platelets, 10^9/μl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Fibrinogen, mg/dl</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Generalized atherosclerosis disease</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>No</strong></td>
<td><strong>University</strong></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td><strong>University</strong></td>
</tr>
</tbody>
</table>

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).

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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), and dietary pattern.

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
towards atherosclerosis, and the mediation effect of
different countries have yielded mixed results,
practically, with a higher probability of
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 multiteritory 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

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

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Effect on Mediator (Path a: X – M)</th>
<th>Multiple Mediator Model: Mediator Effect on Generalized Atherosclerosis (Path b: M – Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Smoking status</td>
<td>-0.2877</td>
<td>-0.3744 to -0.201</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>-2.66</td>
<td>-3.46 to -1.86</td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>-0.344</td>
<td>-0.1958 to -0.0922</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Indirect Effect (a*b: X – M – Y)</th>
<th>% Mediated (a*b/c)</th>
<th>Total Effect (Path c: X – Y adj M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>Multiple m.model</td>
</tr>
<tr>
<td>Smoking status</td>
<td>-0.0595</td>
<td>-0.0841 to -0.0391</td>
<td>34.9%</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>-0.0547</td>
<td>-0.0824 to -0.0339</td>
<td>32.1%</td>
</tr>
<tr>
<td>Dietary pattern</td>
<td>-0.006</td>
<td>-0.0173 to 0.003</td>
<td>3.5%</td>
</tr>
<tr>
<td>Total</td>
<td>-0.1202</td>
<td>-0.156 to -0.0861</td>
<td>70.5%</td>
</tr>
</tbody>
</table>

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


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

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