

Original

Relationship between smoking status and the prevalence and progression of abdominal aortic calcification in men

Sara Fernández Villabrille^{1,5}, Carlos Gómez Alonso^{1,5}, Carmen Palomo Antequera^{2,5}, Minerva Rodríguez García^{3,5}, Teresa Naves López¹, Mónica Llana Faedo¹, Laura Naves Mendiál¹, Javier Montero Muñoz^{4,5}, Manuel Naves Díaz^{1,5}

¹Bone Metabolism Unit. Clinical Management Unit of Internal Medicine. Hospital Universitario Central de Asturias. Universidad de Oviedo.

Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo, Spain. ²Clinical Management Unit of Internal Medicine. Hospital Universitario Central de Asturias. Universidad de Oviedo. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo, Spain.

³Clinical Management Area of Nephrology. Hospital Universitario Central de Asturias. Universidad de Oviedo. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo, Spain. ⁴Geriatrics Service. Hospital Monte Naranco. Universidad de Oviedo. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA). Oviedo, Spain. ⁵RICORS2040-RENAL (RD24/0004/006)

Abstract

Introduction and objective: abdominal aortic calcification (AAC) often precedes the development of coronary artery calcification, contributes to arterial stiffness, and predicts cardiovascular events and mortality. The aim of this study was to evaluate the association between smoking status and the presence and progression of AAC in a male population.

Materials and methods: a total of 306 men aged > 50 years who underwent dorsolumbar radiographic imaging, repeated 4 years later, were selected to determine the presence and progression of AAC. Data collected included age, body mass index (BMI), diabetes status, and smoking history (age at initiation, cigarettes per day, and duration of smoking).

Results: current smokers and former smokers showed a higher prevalence of AAC (52.7 % and 52.6 %, respectively) compared with never smokers (25 %), with former smokers being older. After adjustment for age and BMI, current smoking was associated with AAC prevalence (odds ratio [OR] = 3.95; 95 % confidence interval [95 % CI], 2.00-7.82). A similar association was observed in former smokers (OR, 2.93; 95 % CI, 1.56-5.51). Ten years of aging was associated with AAC (OR, 1.64; 95 % CI, 1.35-1.93), representing a 4.6- and 3-fold lower risk compared with being a current or former smoker, respectively. After 4 years of follow-up, both current and former smoking were associated with AAC progression (OR, 2.57; 95 % CI, 1.08-6.14; and OR, 2.34; 95 % CI, 1.07-5.13, respectively). Heavy smoking and longer smoking duration further increased this risk.

Conclusions: smoking status was associated with a higher prevalence and progression of AAC. In conclusion, smoking conferred a greater risk of AAC than aging itself.

Keywords: Aortic calcification. Smoker. Former smoker. Aging.

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Correspondence:

Manuel Naves Díaz. Bone Metabolism Unit.
Clinical Management Unit of Internal Medicine.
Hospital Universitario Central de Asturias.
Avenida de Roma, s/n. 33011 Oviedo, Spain
e-mail: mnaves.huca@gmail.com

INTRODUCTION

Cardiovascular diseases (CVDs) have been the leading cause of death since the early 20th century, representing a substantial burden on health care systems (1). Among cardiovascular conditions, atherosclerosis has traditionally been the primary underlying cause. Early identification of individuals at high risk of developing atherosclerosis is essential to prevent disease progression (2). Abdominal aortic calcification (AAC) is considered a key marker of atherosclerosis and an independent predictor of cardiovascular morbidity and mortality (3). Previous studies indicate that severe AAC is associated with an increased risk of cardiovascular events, reflecting impaired cardiovascular health (4).

Epidemiological studies indicate that CVD is a common process associated with aging, a nonmodifiable risk factor (5,6). However, numerous modifiable risk factors can accelerate physiological aging and contribute to the development of CVD. Among these, smoking is one of the most well-recognized contributors to atherosclerosis and other CVDs and represents a major public health problem (7,8). Globally, approximately 11 % of cardiovascular deaths are attributable to tobacco exposure (9). Although several studies have examined the relationship between aging or smoking and atherosclerotic events, evidence regarding the interaction between age and smoking in aortic calcification remains limited (10). A deeper understanding of this interaction may provide new insights into atherosclerosis development and help identify individuals who may benefit most from smoking cessation programs.

This study hypothesized that the relationship between age and aortic calcification is strongly influenced by tobacco exposure in a representative sample of men aged > 50 years. Therefore, the objective was to assess the effect of smoking on the prevalence and progression of AAC in an unselected population of men older than 50 years.

MATERIALS AND METHODS

This study was based on data obtained from a substudy of the multicenter European Vertebral Osteoporosis Study (EVOS), which aimed to assess the prevalence of vertebral fractures (11). The Bone Metabolism Unit of the Clinical Management Unit of Internal Medicine at the Hospital Universitario Central de Asturias (Asturias, Spain) randomly selected a cohort of 306 men aged > 50 years. Participants completed a questionnaire covering various osteoporosis-related risk factors, including diabetes and smoking status, specifying age at smoking initiation, number of cigarettes smoked per day, and smoking duration. Former smokers were de-

finied as individuals who had abstained from smoking for at least one year. Two lateral dorsolumbar radiographs were obtained to assess vertebral fractures and aortic calcifications. Anthropometric measurements (height and weight) were recorded to calculate BMI. All participants were ambulatory enough to climb 2 flights of stairs without an elevator, and 99 % lived independently in their own homes.

After 4 years, participants were invited to repeat the study, including new radiographic examinations, anthropometric measurements, and a second questionnaire on osteoporosis-related risk factors. Individuals receiving osteoporosis treatment were excluded from the analysis at follow-up. A total of 148 men participated in this 2nd phase.

Random selection of the general population was performed by age groups, with 50 individuals per group (50-54, 55-59, 60-64, 65-69, 70-74, and > 75 years), without applying inclusion or exclusion criteria. Although renal function was not considered during recruitment, follow-up revealed that only 9 % had an estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m²; most participants were classified as stage 2 (59.6 %), followed by stage 3a (26.3 %) and stage 3b (5.1 %). These findings are consistent with age-related renal impairment in a cohort with a mean age of 68 years. Lipid-lowering therapy and cardiovascular events were not recorded; diabetes was the only cardiovascular risk factor analyzed.

ASSESSMENT OF PREVALENCE AND PROGRESSION OF VASCULAR CALCIFICATION

AAC was assessed on radiographs by 2 independent investigators blinded to both AAC status and smoking history. AAC was classified into 3 grades:

- Grade 0: absent.
- Grade 1: mild to moderate.
- Grade 2: severe.

Mild-to-moderate AAC was defined as isolated punctate calcifications, a linear calcification involving fewer than 2 vertebral bodies, or a single dense calcified plaque. Severe AAC was defined as a linear calcification extending over at least 2 vertebral bodies and/or the presence of 2 or more dense calcified plaques. Inter- and intraobserver agreement was excellent, reaching 92 % and 90 %, respectively, with κ coefficients of 0.78 and 0.73, indicating high reproducibility (12).

AAC progression was defined as an increase in the extent of baseline aortic calcification or the appearance of new calcifications over the 4-year follow-up period.

All procedures were conducted in accordance with the Declaration of Helsinki and were formally approved by the Research Ethics Committee for Medicinal Products (CEIm) of the Principality de Asturias (Asturias, Spain).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 25.0 for Windows. Quantitative variables were analyzed using the Student *t* test or the Mann-Whitney U test, depending on whether they followed a normal distribution. Categorical variables were analyzed using the chi-square test.

Multivariable logistic regression analyses were conducted to assess the association between smoking status and both the presence and progression of AAC, adjusting for age and BMI.

RESULTS

At baseline, 30.1 % of the study subjects were current smokers, 43.8 % former smokers, and 26.1 % never smokers. No significant differences were observed in BMI values or diabetes prevalence among these three groups; however, differences were found in age. Current smokers were the youngest group (63.9 ± 8.2 years), followed by never smokers (64.3 ± 9.4 years), whereas former smokers were significantly older (67.8 ± 8.8 years; $p < 0.05$ compared with each of the other two groups separately) (Table I). No differences were found in the age at smoking initiation between current and former smokers, which was approximately 17 years in both cases, nor in the number of cigarettes smoked, which averaged around one pack per day in both groups. When current and former smokers were analyzed together, it is noteworthy that 75 % of individuals who consumed more than 40 cigarettes per day had started smoking early, before the

age of 15. In addition, among those who smoked between 21 and 40 cigarettes per day, nearly half initiated smoking between 15 and 19 years of age.

Regarding smoking duration, the number of years of smoking was significantly higher among current smokers, with a mean of 46.0 ± 9.9 years, compared with 36.5 ± 12.8 years in former smokers ($p = 0.007$) (Table I). Current and former smokers showed a higher prevalence of AAC (52.7 % and 52.6 %, respectively) than never smokers (25 %; $p < 0.001$) (Fig. 1). AAC progression was also significantly higher in current and former smokers (61.0 % and 58.7 %, respectively) compared with never smokers (37.8 %; $p = 0.032$) (Fig. 1).

Differences were also observed in AAC prevalence according to the degree of clinical involvement (mild-moderate vs severe) across smoking status groups. The prevalence of mild-moderate AAC was significantly higher in current smokers (28.6 %) and former smokers (25.6 %) than in never smokers (17.5 %; $p = 0.012$ and $p = 0.020$, respectively). These differences were even more pronounced for severe AAC, whose prevalence was considerably higher in current smokers (24.2 %) and former smokers (27.1 %) compared with never smokers (7.5 %; $p = 0.001$ and $p < 0.001$, respectively). After adjusting for variables such as age and BMI, smoking status remained significantly associated with AAC prevalence. Being a current smoker was associated with AAC prevalence (odds ratio [OR] = 3.95; 95 % confidence interval [95 % CI], 2.00-7.82), an association also observed in former smokers (OR, 2.93; 95 % CI, 1.56-5.51). In addition, each 10-year increase in age was associated with a 64 % increase in AAC prevalence (OR, 1.64; 95 % CI, 1.35-1.93), representing an association approximately 4.6 times weaker than that observed in current smokers and 3 times weaker than that observed in former smokers. Inclusion of diabetes in the multivariate model did not modify these results.

Cumulative tobacco consumption, expressed as pack-years, and its association with AAC prevalence and progression are shown in table II. Compared with never smokers, cumulative tobacco consumption cat-

Table I. Demographic and smoking habit variables

Variables	Current smoker (<i>n</i> = 92)	Former smoker (<i>n</i> = 134)	Never smoker (<i>n</i> = 80)
Age (years)	62.9 ± 8.2	67.8 ± 8.8^{ab}	64.3 ± 9.4
BMI (kg/m ²)	26.8 ± 3.6	27.0 ± 3.0	27.3 ± 3.5
Diabetes, <i>n</i> (%)	6 (6.5 %)	16 (11.9 %)	5 (6.2 %)
Habit onset (years)	16.7 ± 5.9	17.4 ± 5.7	-
Habit cessation (years)	-	54.1 ± 12.0	-
Smoking duration (years)	46.0 ± 9.9^a	36.5 ± 12.8	-
Number cigarettes/day	19.0 ± 12.8	22.0 ± 14.3	-

^a*p* < 0.05 vs never smoker; ^b*p* < 0.05 vs current smoker.

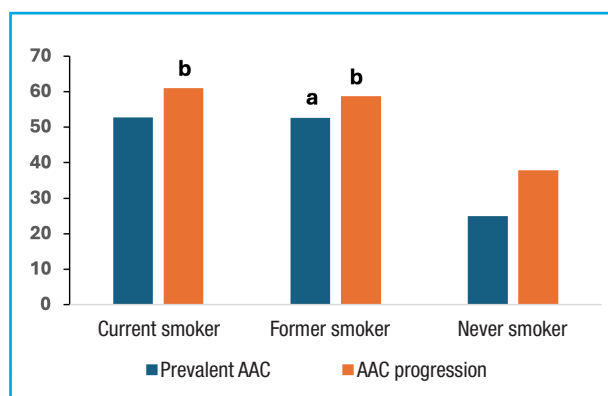


Figure 1. Proportion of men with prevalent AAC and AAC progression according to smoking status. ^a $p < 0.01$, ^b $p < 0.05$ vs never smokers.

lence, with the highest association observed in tertile 3 (> 45.46 pack-years) (OR, 7.73; 95 % CI, 3.65-16.38). Both tertile 2 (26.58-45.46 pack-years) and tertile 1 (< 26.58 pack-years) were also associated with AAC prevalence (OR, 2.44; 95 % CI, 1.19-5.01 and OR, 2.73; 95 % CI, 1.33-5.61, respectively).

To provide an alternative perspective on total tobacco exposure, smoking was dichotomized according to the number of cigarettes smoked per day and duration of smoking. The effect of the number of cigarettes smoked per day on AAC prevalence is particularly noteworthy (Table III). Using never smokers as the reference group, logistic regression analysis adjusted for age and BMI showed that smoking more than 40 cigarettes per day was associated with an almost 12-fold increase in AAC risk (OR, 11.95; 95 % CI, 2.78-51.29). To a lesser but still statistically significant extent, smoking 20-39 cigarettes per day was associated with more than a fourfold increase in AAC risk (OR, 4.43; 95 % CI, 1.97-9.94), a value similar to that observed for smoking 11-20 cigarettes per day (OR, 3.72; 95 % CI, 1.89-7.32). Notably, even smoking 10 cigarettes or fewer per day was significantly associated with an increased AAC risk (OR, 2.62; 95 % CI, 1.23-5.59).

Smoking duration also had a substantial impact on AAC risk (Table III). Using never smokers as the reference group, logistic regression analysis adjusted for age and BMI showed that current smokers, with a mean smoking duration of 46 years, had nearly a fourfold higher risk of AAC (OR, 3.88; 95 % CI, 1.96-7.64). Former smokers with more than 40 years of smoking exposure showed a similar AAC risk (OR, 4.14; 95 % CI, 1.90-9.03), whereas former smokers with 20-39 years of exposure had an almost threefold higher risk (OR, 2.69; 95 % CI, 1.29-5.57). In contrast, being a former smoker with less than 20 years of smoking exposure was not significantly associated with increased AAC risk (OR, 1.59; 95 % CI, 0.43-5.94) (Table III). It is also worth noting that only 8.3 % of former smokers with less than 20 years of smoking exposure had smoked more than 20 cigarettes per day, a proportion more than three times lower than that observed among those who had smoked for more than 20 years.

Given the relatively short follow-up duration of the cohort (4 years), one might expect a low probability of detecting an association between ever smoking and AAC progression. Nevertheless, analysis of the effect of smoking status on AAC progression showed that both current and former smoking were associated with greater AAC progression (OR, 2.57; 95 % CI, 1.08-6.14 and OR, 2.34; 95 % CI, 1.07-5.13, respectively), independent of age and BMI.

Total tobacco exposure in pack-years showed that the two highest tertiles were associated with greater AAC progression [(OR, 3.51; 95 % CI, 1.33-9.28) for tertile 3 and (OR, 2.69; 95 % CI, 1.04-3.99) for tertile 2] (Table II). The number of cigarettes smoked per day was also associated with AAC progression. Smoking more than 20 cigarettes per day was associated with a significant increase in the risk of AAC progression (OR, 3.51; 95 % CI, 1.49-8.00), similar to that observed among those smoking 11-20 cigarettes per day (OR, 3.09; 95 % CI, 1.08-8.81). In contrast, smoking 10 cigarettes or fewer per day was not associated with an increased risk of AAC progression (Table IV).

Table II. Association of cumulative tobacco consumption in pack-years with AAC prevalence in smokers and former smokers

Outcome	Covariate (pack-years)	Number	OR (95 % CI)
AAC prevalence	Tertile 3 (< 25.58)	71	7.73 (3.65-16.38)
	Tertile 2 (26.58-45.46)	70	2.44 (1.19-5.01)
	Tertile 1 (> 45.46)	69	2.73 (1.33-5.61)
	Never smoker	80	Reference
AAC progression	Tertile 3 (< 25.58)	31	3.51 (1.33-9.28)
	Tertile 2 (26.58-45.46)	31	2.69 (1.04-6.95)
	Tertile 1 (> 45.46)	31	1.61 (0.65-3.99)
	Never smoker	45	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in *italics*.

Table III. Association of stratification of the number of cigarettes consumed per day and the number of years with smoking habit with AAC prevalence in smokers and former smokers

Covariate (cigarettes/day as a smoker)	Number	OR (95 % CI)
> 40 cigarettes/day	12	<i>11.95 (2.78-51.29)</i>
21-40 cigarettes/day	46	<i>4.43 (1.97-9.94)</i>
11-20 cigarettes/day	94	<i>3.72 (1.89-7.32)</i>
≤ 10 cigarettes/day	58	<i>2.62 (1.23-5.59)</i>
Never smoker	80	Reference
Covariate (number years as smoker)	Number	OR (95 % CI)
Current smoker (> 46 years smoking)	91	<i>3.88 (1.96-7.64)</i>
Former smoker with ≥ 40 years smoking	56	<i>4.14 (1.90-9.03)</i>
Former smoker with 20-39 years smoking	62	<i>2.69 (1.29-5.57)</i>
Former smoker with < 20 years smoking	13	<i>1.59 (0.43-5.94)</i>
Never smoker	80	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in italics.

Table IV. Association of stratification of the number of cigarettes consumed per day and the number of years of smoking habit with AAC progression in smokers and former smokers

Covariate (cigarettes/day as smoker)	Number	OR (95 % CI)
> 20 cigarettes/day	23	<i>3.09 (1.08-8.81)</i>
11-20 cigarettes/day	47	<i>3.51 (1.49-8.30)</i>
≤ 10 cigarettes/day	27	<i>0.97 (0.36-2.60)</i>
Never smoker	45	Reference
Covariate (number years as smoker)	Number	OR (95 % CI)
Current smoker (> 46 years smoking)	41	<i>2.57 (1.08-6.14)</i>
Former smoker with ≥ 40 years smoking	17	<i>3.95 (1.18-13.19)</i>
Former smoker with 20-39 years smoking	37	<i>1.65 (0.36-7.46)</i>
Former smoker with < 20 years smoking	8	<i>1.94 (0.80-4.69)</i>
Never smoker	45	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in italics.

Smoking duration was also associated with AAC progression. Both current smokers with more than 40 years of smoking exposure and former smokers with the same duration showed a higher risk of AAC progression (OR, 2.57; 95 % CI, 1.08-6.14 and OR, 3.95; 95 % CI, 1.18-13.19, respectively). However, although former smokers with less than 40 years of exposure showed increased AAC progression, this association was not statistically significant (Table IV), possibly due in part to the smaller number of participants in the follow-up study.

sociated with an approximately fourfold and threefold higher risk, respectively, of AAC prevalence compared with never smokers. Moreover, despite the relatively short follow-up of 4 years, both current and former smokers exhibited an approximately twofold higher risk of AAC progression compared with never smokers. In addition, cumulative tobacco exposure (pack-years), number of cigarettes smoked per day, and duration of smoking were key determinants of increased AAC prevalence and progression.

Former studies have reported associations similar to those observed in the present work, although most focused on prevalence, with very few analyzing AAC progression over time. A prevalence study conducted in a Japanese population aged 40-79 years showed that being a current smoker was associated with an AAC OR of 4.29, nearly identical to that observed in

DISCUSSION

The results of this cohort of men older than 50 years showed that being a current or former smoker was as-

our study (OR, 3.95), although AAC was assessed using computed tomography rather than plain radiography. Very similar results were observed among former smokers in that study, with an OR of 2.55 (13), again close to the OR of 2.93 found in our work. Another study in a South Korean population aged 40-81 years also showed an association between current smoking and increased AAC prevalence (OR, 5.05), a value higher than that found in our study using computed tomography; however, the association was slightly lower among former smokers (OR, 2.10) (14).

Regarding AAC progression, our findings are consistent with those reported in the only available 5-year prospective study evaluating the association between smoking and AAC at the time this article was written. That study, conducted in a Japanese population aged 40-79 years using computed tomography, showed that being a smoker was associated with a 2.47-fold increased risk of AAC progression (15), almost identical to that observed in our study (OR, 2.57) with only 4 years of follow-up. Heavy tobacco exposure has also been shown to be a strong risk factor for AAC. The highest cumulative exposure (tertile 3, pack-years) was associated with increased AAC prevalence. These results are consistent with those reported by other authors using computed tomography, although with an OR (3.90) approximately half of that observed in our study. Differences in population age, race, and the inclusion of only current smokers may partly explain these discrepancies (13). It is also noteworthy that in our study, cumulative exposure in the higher tertiles (tertiles 2 and 3) was associated with AAC progression, whereas other authors did not observe this association (15), possibly due to differences in race and the younger age of the cohorts studied (40-79 years).

To further explore the effect of smoking, tobacco exposure was analyzed separately by number of cigarettes smoked per day and total duration of smoking. As shown in table III, AAC risk increased proportionally with the number of cigarettes smoked per day, reaching a 12-fold higher risk among those smoking more than two packs per day (> 40 cigarettes). Notably, even moderate consumption of 10 cigarettes or fewer per day was associated with a 2.5-fold higher AAC risk compared with never smokers. These findings are consistent with those reported by Jung et al. in a Japanese population (14), as well as with other studies (16,17).

Although tobacco smoke contains multiple substances potentially harmful to the cardiovascular system (18), the precise mechanisms linking smoking to CVD are not fully understood. Nicotine, carbon monoxide, and certain oxidizing agents have been implicated in processes related to cardiovascular health (19). Some studies have reported a relationship between smoking and impaired endothelium-dependent arterial dilation, as well as increased carotid intima-media thickness (20,21). Free radicals and nicotine present in tobacco

smoke may also contribute to structural changes in blood vessels, although these effects may vary according to the intensity and duration of exposure.

As noted in the Results section, not only high daily cigarette consumption but also longer smoking duration contributed to increased AAC risk, with the exception of former smokers with less than 20 years of exposure, in whom no association with AAC prevalence was observed. Other authors have similarly reported that smoking duration longer than 20 years was associated with an OR of 5.28 for AAC prevalence (14), consistent with our findings, where smoking for 20-40 years was associated with an OR of 4.43, increasing to 11.95 among those with more than 40 years of exposure. Some studies have also suggested that the association between smoking and AAC risk diminishes with longer smoking cessation (13). Lv et al. showed that quitting smoking for more than 10 years may partially attenuate the damage caused by tobacco exposure (22). These findings confirm that smoking is a powerful risk factor for CVD and that its harmful effects increase with both duration and intensity of exposure (23,24). Therefore, health care professionals should be aware that there is no safe level of smoking. Promoting abstinence, beyond merely reducing consumption, should be a priority in medical care, even when patients' symptoms are not directly related to cardiovascular system disorders. Smoking cessation remains one of the most effective interventions for reducing the long-term risk of cardiovascular events.

In Spain, most smokers begin smoking during adolescence or early adulthood, meaning that individuals with more than 20 years of exposure are often at an age when chronic diseases such as metabolic syndrome begin to emerge, accelerating atherosclerosis (25). Atherosclerosis is a slow, age-related process (26), and smoking acts as a major accelerator of vascular deterioration, promoting calcification in structures such as the abdominal aorta (27-29). Although postmortem studies have shown early atherosclerotic changes even in young individuals, radiologic detection of calcifications typically occurs at more advanced stages (30,31). Thus, our results highlight the need to reinforce preventive medical counseling, particularly among middle-aged and older patients with long-term smoking exposure or those who continue to smoke. It is essential to address not only the general health effects of smoking but also its relationship with vascular calcification and cardiovascular risk.

Although smoking cessation may slow the progression of atherosclerosis, vascular events, and possibly calcification, it is unlikely to reverse established calcification in smokers with heavy cumulative exposure. In moderate former smokers, quitting at an early age may delay or prevent this process, with benefits increasing with longer cessation duration (32).

Age is a well-established risk factor for CVD and specifically for AAC (12). In the present study, each 10-year increase in age was associated with a 60 % higher AAC risk. However, this risk was 4.6 and 3 times lower than that associated with current and former smoking, respectively, underscoring the importance of preventive interventions aimed at smoking cessation regardless of population aging.

Despite the findings obtained, the present study has several limitations. The study design was observational and prospective, which does not allow the observed associations to be interpreted as causal relationships. However, cumulative exposure expressed as cigarettes per day and duration of smoking provides information on both past and current exposure, suggesting a possible causal relationship. Another potential limitation is the lack of statistical handling of losses to follow-up. We cannot rule out as a likely limitation that the primary outcome of this cohort was not AAC but vertebral fracture. Nevertheless, given the strong association between fragility fractures and vascular calcification, this limitation may be partially mitigated. On the other hand, the use of plain radiography is a much less sensitive technique than computed tomography. However, comparisons between the diagnosis of vascular calcification and arterial plaques using these techniques have shown that X-ray assessment remains a reliable marker of vascular calcification and cardiovascular disease, being comparable in usefulness to techniques such as carotid intima-media thickness measurement (33,34), while also offering the advantage of greater availability and accessibility in clinical practice. Finally, although some of the main known confounding factors were carefully controlled for, it is possible that the results of this study were partially influenced by differences in unmeasured confounders, such as the presence of cardiovascular risk factors or the use of lipid-lowering therapies, which may have led to an overestimation of the observed associations. In fact, the highest cumulative tobacco exposure (tertile 3) remained associated with AAC progression, although more modestly, decreasing from (OR, 3.51; 95 % CI, 1.33-9.28) to (OR, 2.95; 95 % CI, 1.05-8.25) when AAC prevalence and estimated glomerular filtration rate—this latter covariate collected only at follow-up—were added to age and BMI as covariates. All these limitations, together with a small sample size such as ours, may have limited the strength of the associations observed.

Nevertheless, despite these limitations, the results have important clinical and public health implications, as lateral dorsolumbar spine radiography could be used to determine AAC in these higher-risk patients. This technique is a simple, inexpensive, and commonly performed test in clinical settings and during routine health examinations; however, AAC is often overlooked. In conclusion, the results of this study allow us to conclude that being a current or former smoker

was significantly associated with a higher risk of AAC prevalence and progression. Even moderate daily consumption of < 10 cigarettes increases the risk of AAC by 2.5-fold compared with never smokers. Smoking as a risk factor showed a stronger association than aging per se. Therefore, given the increasing burden of cardiovascular disease and the continued prominence of smoking, the detection of AAC may represent an important early indicator of severe atherosclerosis and possibly other adverse effects among smokers, and should serve as a strong warning signal to recommend smoking cessation.

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