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Cigarette smoking and hip volumetric bone mineral density and cortical volume loss in older adults: the AGES-Reykjavik Study

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Abstract

This study aimed to explore the relationships of several indicators of cigarette smoking habits (smoking status, pack-years, age at smoking initiation and smoking cessation) with quantitative computed tomographic (QCT) -derived proximal femur bone measures (trabecular vBMD, integral vBMD and the ratio of cortical to total tissue volume (cvol/ivol)) and with subsequent change in these measures over the next five years. A total of 2673 older adults (55.9% women), aged 66–92 years at baseline from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, who had two QCT scans of the hip were studied. In multivariable linear regression models, compared to never-smokers, current smokers had lower cvol/ivol at baseline and former-smokers had poorer measures on all outcomes (lower trabecular vBMD, integral vBMD and cvol/ivol), even when adjusted for several potential confounders. Further, among former smokers, those with higher pack-years had worse bone outcomes and those with longer duration since smoking cessation had better bone health at baseline. Analyses of change in bone measures revealed that compared to never-smokers, current smokers had significantly greater loss of trabecular vBMD, integral vBMD, and cvol/ivol. The regression models included adjustment for sex, age, education, and

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Author's roles: EAM was responsible for the study concept and design, analysis, and interpretation of data, and drafted the manuscript. ME participated in the analysis and interpretation of data, and in the critical revision of the manuscript. TA, TL, and KS were responsible for the acquisition of participants and data, and approved the final version. VG, GS, SS, LL, GE, and TBH were responsible for the study concept and design, acquisition of participants and data, critical revision of the manuscript or important intellectual content and approval of the final version. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflicts of interest: none

baseline body mass index, creatinine, % weight change from age 50, 25OHD, physical activity level, high-sensitive C-Reactive protein levels, alcohol and coffee consumption, history of diabetes mellitus, arthritis, and respiratory diseases. In conclusion, both current and former smoking showed adverse associations with bone health assessed with QCT. Results suggest that current smoking in particular may aggravate the rate of bone loss at older age and highlight implications for targeting this risk factor in populations that present higher smoking prevalence and vulnerability to bone fragility.

Keywords

Aging; bone QCT; general population studies; proximal femur; smoker

Introduction

Smoking remains one of the most common risk behaviors worldwide. In addition to its well-established impact on cardiac and respiratory disease, smoking was recognized over 40 years ago as a deleterious factor for bone metabolism.⁽¹⁾ Since then, several studies have reported a relationship between smoking and adverse bone mass outcomes in diverse populations and in animal models.⁽²⁾ However, results are mixed and some studies have found no association between smoking and bone mass.⁽³⁾ Most prior studies relied on areal bone mineral density (aBMD) measured using dual X-ray absorptiometry (DXA). Although DXA is an excellent clinical tool, it provides a two-dimensional bone measure that does not differentiate between the cortical and trabecular compartments of the endosteal surface. The very few studies that have explored these compartments separately have reported differential relationships between history of smoking and trabecular and cortical vBMD.^(4–6) Thus, it is reasonable to expect that the association between cigarette smoking and bone parameters may not be consistent or at least may have different magnitudes. Testing this hypothesis has implications for fracture risk prediction, because although both cortical and trabecular compartments are key determinants of bone strength, during a fall the cortical shell is subjected to higher strains and carries a larger portion of the load⁽⁷⁾.

Importantly, very few previous prospective studies have examined the association between smoking and bone loss in older adults and their results are mixed;^(8–10) and, to date, no longitudinal studies have addressed the relationship of smoking behavior and change in compartmental measures of vBMD. The relationship between smoking and bone loss is particularly relevant for older adults because they are at increased risk for osteoporosis and fracture and consequently they often suffer from limited mobility, increased morbidity, and mortality.⁽¹¹⁾

Several potential mechanisms have been proposed to explain the relationship between smoking and poorer bone health; these include mechanisms that represent more direct effects of smoking on bone cells, and other mechanisms influenced by factors such as body weight, physical activity, calcitropic processes, and sex-hormones.^(12,13) The latter proposed mechanisms emphasize the need to properly take into account these potential confounders to better estimate the association of smoking with bone health. However, prior studies reporting

an association between cigarette smoking and lower aBMD did not adjust for important confounders.⁽¹⁴⁾ In addition, prior studies focused only on smoking status and lacked more detailed data on smoking exposure such as pack-years, age at smoking initiation, and years since smoking cessation. In the current study, we aimed to examine the cross-sectional and longitudinal associations between cigarette smoking and quantitative computed tomography (QCT)-derived proximal femur bone data.

Based on previous findings relating cigarette smoking with aBMD, we hypothesize that (1) smoking exposure and bone mass/bone loss would be inversely associated, (2) more adverse smoking-related measures (e.g., more pack-years and earlier age of smoking initiation) will be associated with poorer bone measures (lower vBMD and tissue volume) and (3) the worsening of these measures at older age.

Methods

Study Population

The present study is based on the Age, Gene/Environment Susceptibility (AGES) – Reykjavik Study, a single-center prospective population study of Icelandic older men and women. Specifically, data come from the baseline examination (AGES) and one follow-up examination (AGES II), occurring on average 5.2 years later (maximum follow-up of 8.2 years). Design and recruitment have been described in detail.⁽¹⁵⁾ At baseline, there were 5764 participants enrolled (mean age of 77 years; range 66–96); of those 2720 had complete data for the proximal femur outcomes (trabecular vBMD, integral vBMD and tissue volumes, n=4831) at the two-time points, allowing the computation of the rate of change in these bone parameters (Supplemental Figure 1). We further excluded 47 individuals who were missing data on relevant covariates, leaving 2,673 participants who constituted our analytical sample. Written informed consent was obtained from all participants, and the study was approved by the Icelandic National Bioethics Committee (VSN: 00-063) and the Institutional Review Board of the Intramural Research Program of the National Institute on Aging.

Scanning procedures

The left hip was scanned and analyzed using a four-row detector CT system (Sensation; Siemens Medical Systems, Erlangen, Germany) as described in detail,⁽¹⁶⁾ following a standardized protocol and encompassed the proximal femur from a level 1 cm superior to the acetabulum to a level 3–5 mm inferior to the lesser trochanter at settings of 120 kVp, 140 mAs, 1-mm slice thickness, pitch=1, in-plane voxel size of 0.98 mm × 0.98 mm². The baseline scan and the follow-up scan (repeated after an average follow-up of 5.2 years; range 2.7–8.2 years) for each participant were analyzed together to ensure that the hip was properly positioned in both analyses. The analysis was done by a single observer.

Femoral outcome measures from QCT

Proximal femur QCT three-dimensional images were processed to extract measures of compartmental vBMD (mg/cm³), thus trabecular and cortical bone were measured separately and tissue volume, as previously described in detail⁽¹⁷⁾. These included trabecular

vBMD (mg/cm^3), integral vBMD (mg/cm^3) a measure reflecting an integration of both cortical and trabecular bone, and percent cortical volume (computed as cortical volume divided by integral volume times 100), all defined for the total hip region.

Smoking

Information on cigarette smoking was self-reported at baseline (AGES) through a standardized questionnaire. Participants reported whether they currently smoked; if they answered yes, they were asked the number of cigarettes they smoke on average per day and the age of smoking initiation. If participants reported that they were not current smokers, they were asked if they smoked in the past, the number of cigarettes they smoked on average per day when they smoked, the age of smoking initiation, and the age at which they stopped smoking.

Based on these data, we defined smoking status (never, former, current-smoker). For each of the former smoking and current smoking groups, we computed for each subject the number of pack-years by multiplying the number of cigarettes smoked per day by the number of years of smoking, which was computed as [current age – age at smoking initiation] for current smokers, and as [age at smoking cessation – age at smoking initiation] for former smokers. Each pack-year represents exposure to 7300 cigarettes [1 year * 365 days * 1 pack/day * 20 cigarettes/pack]. We also examined age at smoking initiation and years since smoking cessation (computed for former-smokers as [current age – age at smoking cessation]).

Covariate measures

In our analysis, we adjusted for the following potential confounding variables, measured at the baseline examination, that were found to be associated with either smoking status or bone variables in our sample: Age, sex, education (high defined as >12 years of education, indicating participants completed college or more, or low ≤ 12), body mass index (BMI, kg/m^2), total 25-hydroxyvitamin D (25OHD, nmol/L) and creatinine ($\mu\text{mol}/\text{L}$) both measured in the IHA laboratory, using blood samples drawn after overnight fasting, as previously described,⁽¹⁸⁾ percent weight change from age 50 (defined as: $\text{baseline weight} - \text{midlife weight} / \text{midlife weight} \times 100$), and physical activity level (defined as moderate-high or occasionally physically active at most).⁽¹⁸⁾

In additional analyses, we also adjusted for factors that have been associated with either smoking or bone health in prior literature: high-sensitivity C-Reactive Protein (hsCRP, mg/L) measured in the IHA laboratory, using blood samples drawn after overnight fasting) as previously described,⁽¹⁸⁾ coffee intake (high defined as ≥ 3 cups/day, or low < 3 cups/day) and alcohol intake (defined as current drinker – if answered yes to the question “Do you drink alcoholic beverages now?” or non-drinker, if answered no) measured by questionnaire, baseline history of diabetes (defined as self-reported history of diabetes, use of glucose-modifying medications, or fasting blood glucose of ≥ 7.0 mmol/L), arthritis (self-reported at baseline), and respiratory diseases (defined as self-reported history of lung diseases or asthma at baseline).

Statistical analysis

Mean $\pm$ SD or percentages for categorical variables were used to summarize subject characteristics. Differences in baseline characteristics were compared by ANOVA followed by Hochberg's GT2 post hoc test (allows for unequal sample sizes) for continuous variables and by the chi-squared test for categorical data. To estimate annual percent change ($\Delta\%$) in each bone parameter we divided the inter-visit difference relative to absolute baseline, divided by the number of years between the visits, as follows: [(follow-up value – baseline value)/ baseline value * time between CT scans] * 100.

Linear regression models were used to examine the cross-sectional and longitudinal associations between smoking variables and bone outcomes. We evaluated the relationship of pack-years and age at smoking initiation with the outcomes of interest in current smokers and former smokers, separately; for the latter group, we also examined the association of smoking cessation duration and bone outcomes. We found no strong indication of differences between men and women in the relationships of the various smoking exposures and outcomes of interest. Therefore, all analyses were pooled by sex. Two multivariate models were performed: Model 1 adjusted for sex, age, education, and BMI; and Model 2 additionally adjusted for creatinine, % weight change from age 50, 25OHD, and physical activity level. Results are expressed as regression regular coefficient, 95% confidence interval (CI), and p-value for all models.

In an additional analysis (in Supplemental Table 1) we further adjusted for hsCRP (dichotomized into high (> 3.0 mg/L) and low hsCRP (≤ 3.0 mg/L) according to baseline hsCRP levels), baseline history of diabetes, arthritis, and respiratory diseases, coffee and alcohol consumption. This analysis was based on 2621 participants due to missing data in these additional covariates. Significance testing was two-sided and based on a 5% probability level. Analyses were conducted using SPSS version 22 (IBM, USA), and SAS software version 9.3 (SAS Institute, Cary NC 2011).

Results

Study sample characteristics

The study population consisted of 2673 older adults aged 66–92 years (mean age $\pm$ SD; 74.7 ± 4.7 years) and 55.9% were women. Former smokers constituted 44% of the sample and 8.3% were current smokers. Overall, current smokers had a higher proportion of women (73%), were younger, and had lower educational attainment, BMI, and 25OHD levels, and higher coffee consumption and prevalence of high hsCRP levels (a marker of inflammation) than never or former smokers (Table 1). Physical activity was similar among the three groups ($p = 0.11$). Mean pack-years was 34.4 for current smokers and 19.9 for former-smokers; these participants started smoking in their early twenties (at mean age 22.7 ± 7.6 years for current smokers and 20.4 ± 6.4 years for former smokers). On average, former-smokers had stopped smoking 28 ± 14.5 years at the baseline bone assessment and 10% reported stopping within the last 9 years. Current smokers had a significantly lower baseline integral vBMD than former smokers and lower percent cortical volume compared to participants who never smoked. No significant difference was observed in baseline

trabecular vBMD between groups ($p=0.15$). Current smokers had a significantly higher rate of bone loss in all outcomes compared to former smokers.

Smoking status, baseline bone measures, and bone loss

In multivariable linear regression (Table 2), after adjusting for sex, age, education, and BMI (Model 1), both former smoking and current smoking were negatively associated with lower integral vBMD and percent cortical volume, and regression coefficients were higher for current smoking. After adjusting for additional potential confounders (Model 2), conclusions were similar for the association of former smoking and lower integral vBMD and percent cortical volume; compared to never-smokers, former smokers had 3.88 mg/cm³ lower vBMD (95% CI: -6.97, -0.79) and 0.65 lower percent cortical volume (95% CI: -1.0, -0.3). Results were also similar in Model 2 for the association of current smoking and percent cortical volume, with smokers having a 0.9% lower percent cortical volume, but the association between current smoking and integral vBMD was attenuated and no longer significant (coefficient= -4.22 mg/cm³; 95% CI: -9.74, 1.30). Only former smoking was negatively associated with trabecular vBMD in both Model 1 (coefficient= -3.25 mg/cm³; 95% CI: -5.80, -0.71) and Model 2 (coefficient= -3.10 mg/cm³; 95% CI: -5.65, -0.55).

Analyses of change in bone measures revealed that compared to never-smokers, current smokers had a greater loss of trabecular vBMD, integral vBMD, and percent cortical volume (with estimated 0.24% additional loss in trabecular vBMD, 0.20% in integral vBMD, and 0.16% additional loss in change in percent cortical volume). These associations remained significant in the fully-adjusted models (Model 2).

In additional analysis, we further adjusted for factors that have been associated with either smoking or bone health in the literature (Model 2+ hsCRP, alcohol and coffee consumption, history of diabetes mellitus, arthritis, and respiratory diseases) and conclusions were not substantially altered (See Supplemental Table 1).

Smoking characteristics and bone outcomes

Among former smokers, increasing pack-years were associated with poorer baseline bone measures. In parallel, the longer the duration of smoking cessation in this group, the better the bone health baseline measurements (Table 3). Adjusting for the additional covariates (hsCRP, alcohol and coffee consumption, history of diabetes mellitus, arthritis, and respiratory diseases) did not alter these conclusions and only resulted in a weaker association between years since cessation and trabecular vBMD ($p=0.10$). Age at smoking initiation was not associated with the bone outcomes. We found no indications of dose-response associations for current smoking and for any of the change in bone outcomes (Supplemental Table 2).

Discussion

In this large prospective cohort, we found several associations between cigarette smoking and bone outcomes and changes in these outcomes at older age. Specifically, a history of smoking was associated with lower vBMD (integral and trabecular compartment) and proportion of cortical bone at baseline; further these associations followed a dose-response

pattern with higher pack-years and shorter periods of smoking cessation being associated with poorer baseline bone measures. Current smokers at baseline had a lower proportion of cortical bone and a faster decline in all bone measures over the subsequent five years compared to never-smokers. Taken together, these findings suggest that smoking is associated with bone health characteristics, and that smokers at older age may be at an additional risk for accelerated bone loss.

The association between smoking and low BMD has been described in several reviews^(3,14,19) which concluded that results are not consistent, and that higher effects are expected in the elderly compared to young cohorts. Concordantly, in our older sample, we found associations between smoking and lower vBMD, although some inconsistencies were also observed. Namely, it is not clear why former smoking was associated with all QCT bone measures at baseline, whereas current smoking was only associated with lower percent cortical volume. This finding could suggest that smoking may have longer term relationships with bone health; this is consistent with previous studies using QCT to measure central⁽⁵⁾ and peripheral⁽⁴⁾ bone sites, that reported a significant association between vBMD and former smoking (but not current smoking) in multivariable models. However, it is worth noting that current smoking was also associated with a significantly lower integral vBMD in model 1 and the magnitude of associations observed with current smoking were larger than former smoking. Therefore, it is possible that associations did not reach statistical significance for current smoking because of lower number of subjects in that group. Another possible explanation might be related to unmeasured confounding, such as potential hormonal differences between groups or reduced calcium absorption. Also, other environmental and behavioral differences (such as physical activity and nutrition) between former and current smokers, particularly during younger age, could lead to suboptimal peak bone mass, which may contribute to increased bone fragility.⁽²⁰⁾ As we did not measure these variables, we cannot exclude such effects.

Overall, the existing literature on the cross-sectional association between current smoking and bone QCT measures is mixed in both younger and older cohorts.^(5,6,21–25) However, our analyses of change in bone measures suggest a potentially important role for smoking in influencing these outcomes. Indeed, in this first investigation of smoking and compartmental measures of bone loss assessed with QCT, current smoking was consistently associated with faster decline in all bone measures compared to never smoking, and this association was observed after accounting for several confounders, including body weight and medical conditions. Prior studies on the relationship between smoking behavior and proximal femur bone loss in older cohorts are few and were based on DXA scans to measure BMD and on shorter follow-up (≤ 4 years). After adjustment for potential confounders, a study with 4 years of follow-up including older women and men from the population-based Framingham Osteoporosis Study found a negative association among smokers for trochanter aBMD only in men.⁽⁹⁾ However, most studies do not support a significant relationship between smoking and bone loss rates.^(8,10)

While associated with all baseline bone measures, former smoking was not associated with trabecular and cortical bone loss, in line with earlier DXA or single photon absorptiometry studies.^(8,9,26) This could suggest that a longer period to measure bone loss may be needed

for a difference in bone health to be detected for former-smokers. For instance, average years since cessation for former-smokers was 28 years before baseline and hence the association observed at baseline for that group might have been accumulating over decades and not observable over the 5-year follow-up over which the change in bone was measured. Finally, the observations that former-smokers were not different than never-smokers with regards to the longitudinal change in bone measures, and that longer periods of smoking cessation were associated with better baseline bone measures suggest potentially important benefits of smoking cessation for bone health. Results could also be reflecting the other healthy lifestyle adjustments that former-smokers might have done after cessation of smoking. For example, a normalization of the 25OHD level was reported in former smokers^(21,27,28) in agreement with our data. While the current evidence on the benefits of smoking cessation and bone density is scarce and mixed,^(26,29–31) our results suggest that clinical and public health efforts to target smoking behavior may be valuable for improving and preserving bone health at older ages.

Further, among former-smokers, a greater number of pack-years was associated with worse baseline QCT bone measures, suggesting a role for duration of smoking and further highlighting the value of modifying this risky behavior. However, we did not consistently detect dose-dependent associations between pack-years in smokers, which could be explained by the smaller number of subjects and potentially limited variability within this group. Other studies that investigated the dose-response association of smoking with bone outcomes are limited and have produced mixed findings. The discrepancies in findings among these studies may be explained by methodological differences. Our findings highlight the value of looking at former and current smokers separately, to better understand whether these groups are fundamentally different with regards to their smoking habits and bone outcomes. Regarding age at smoking initiation, some studies have reported a detrimental effect of smoking on baseline bone parameters^(6,32) and on bone gains⁽³³⁾ at young age, although there are no cohort studies in older adults supporting this relation. It was hypothesized that a young age at smoking onset, when peak bone mass is especially sensitive to sex hormones, maturational timing, and lifestyle, would be associated with worse bone outcomes. However, our results suggest that age of onset is not a key factor to understand the link between smoking behavior and bone health later in life.

Several potential mechanisms have been proposed for the deleterious skeletal effects of smoking, including a direct toxic effect on osteogenesis,⁽³⁴⁾ collagen metabolism⁽³⁵⁾ in combination with increased bone resorption and osteoclast activity and osteoclastogenesis.⁽³⁶⁾ In addition, it is suggested that smoking also contributes indirectly by alterations in calciotropic hormone metabolism^(37,38) and dysregulation of sex hormones.⁽³⁹⁾ Thus, our findings support the rationale for the deleterious skeletal effects of current smoking, which were most consistently observed (both cross-sectionally and longitudinally) in the cortical bone compartment.

The strengths of the AGES- Reykjavik Study include the large sample size, inclusion of men and women participants, detailed baseline data that enabled us to control for several potentially relevant factors, and examination of several indicators of cigarette smoking. Participants had two QCT scans of the hip over a median follow-up of 5.2 years enabling us

to explore both the cross-sectional and longitudinal (bone loss) relationship with smoking. Whereas QCT has been previously applied to examine the cross-sectional relationship of smoking with bone health, it has not been used in prospective studies irrespective of age group. This study targeted the proximal femur that is one of the most clinically relevant sites, as it is associated with significant morbidity, excess mortality and health and social service expenditure.⁽⁴⁰⁾

There are also limitations of this study. Although we controlled for several potential confounders of the smoking/bone relationship, other factors that may also influence bone health (quality of diet or resistance exercise training) were not measured. Recall bias in ascertainment of smoking habits (status, number of cigarettes reported and the duration of smoking - age of smoking initiation and cessation) is possible due to the extensive time that elapsed between participants' initial smoking behaviors and study baseline examination, and these variables were based only on self-reported data. Because all participants were older than 65 years and Caucasian, our results may not be generalizable to other populations and ethnic groups. An important technical limitation of the QCT technique is the effect of partial volume artifacts in the cortical regions caused by the limited spatial resolution. We selected the percent cortical volume (and not cortical vBMD) as it might be a better measure of bone health. It was previously observed that percent cortical volume is a significant predictor of hip fracture risk.⁽⁴¹⁾

In conclusion, our data suggest that a history of smoking is associated with worse bone health characteristics at older age and that subjects who keep smoking in their older age experience faster bone loss. We found associations with all bone outcomes investigated, trabecular and integral vBMD and cortical bone, with results being most consistent with cortical bone, a key compartment to the structural stability of whole bone. The findings also show benefits of quitting smoking for bone characteristics and that former smokers were not different than never-smokers with regards to the rate of bone loss at older age. These data highlight that lifestyle alterations, including smoking cessation, should be a major component of bone therapeutic programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

History of smoking was associated with lower baseline hip vBMD

Associations followed a dose-response pattern

Current smoking was consistently associated with faster decline in all bone measures

Former smoking was not associated with trabecular and cortical bone loss

Table 1
Participants' demographic and clinical characteristics according to smoking status (n=2673)

	Never-smokers (n=1275)		Former-smokers (n=1176)		Current smokers (n=222)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age, yrs	75.1	4.7	74.5 ^a	4.7	73.0 ^{a, b}	4.6	<0.001
BMI, kg/m ²	27.1	4.2	27.6 ^a	4.0	26.2 ^{a, b}	4.0	<0.001
Weight change from age 50, %	4.6	11.1	7.4 ^a	12.7	5.8	13.2	<0.001
Creatinine, µmol/L	88.1	21.5	89.7	21.3	80.3 ^{a, b}	19.2	<0.001
25OHD, nmol/L	55.5	23.1	54.8	23.5	48.6 ^{a, b}	21.9	<0.001
Smoking characteristics:							
Pack-years	-	-	19.9 ^c	17.8	34.4	23.5	<0.001
Age at smoking initiation	-	-	20.4 ^d	6.4	22.7	7.6	<0.001
Years of smoking cessation	-	-	28.3 ^e	14.5	-	-	-
Baseline QCT measures:							
Trabecular vBMD, mg/cm ³	142.8	34.4	144.4	33.5	139.8	35.9	0.152
Integral vBMD, mg/cm ³	223.5	41.8	224.9	40.8	217.3 ^b	44.6	0.042
Percent cortical volume, %	34.9	4.6	34.6	4.5	34.1 ^a	5.3	0.032
Annual Δ%:							
Trabecular vBMD	-1.5	1.3	-1.4 ^a	1.4	-1.7 ^b	1.4	<0.001
Integral vBMD	-0.9	1.0	-0.8	1.1	-1.0 ^b	1.0	0.003
Percent cortical volume	-0.8	0.9	-0.7	0.9	-0.9 ^b	0.9	0.034
	N	%	N	%	N	%	
Female	799	62.7	533	45.3	162	73.0	<0.001
High education	392	30.7	314	26.7	40	18.0	<0.001
Moderate-high PA level	257	20.2	257	21.9	35	15.8	0.108
High hsCRP levels	349	27.4	339	28.8	90	40.5	<0.001
Alcohol drinker	780	61.3	905	77.2	173	78.6	<0.001

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	Never-smokers (n=1275)		Former-smokers (n=1176)		Current smokers (n=222)		p-value
	Mean	SD	Mean	SD	Mean	SD	
High coffee consumption	639	50.2	686	58.5	163	73.4	<0.001
Baseline history by self-report:							
Arthritis	466	37.0	426	36.8	84	38.5	0.890
Diabetes	130	10.2	132	11.2	21	9.5	0.604
Respiratory diseases	191	15.0	253	21.5	48	21.6	<0.001

BMI = body mass index, hsCRP= high-sensitivity C-Reactive Protein, PA = physical activity, vBMD= volumetric bone mineral density, 25OHD= total 25-hydroxyvitamin D;

^a significantly different from never-smokers;

^b significantly different from former-smokers.

^c 10 observations missing data;

^d 2 observations missing data;

^e 4 observations missing data.

Table 2

Associations between smoking status and QCT-derived bone outcomes (n=2673)

		Model 1		Model 2	
		Coefficient	95% CI	P value	P value
Cross-sectional association					
<i>Trabecular vBMD, mg/cm³</i>					
Never smokers	Ref.				
Former smokers		-3.25	-5.80, -0.71	0.012	-3.10
					-5.65, -0.55
Current smokers		-2.21	-6.77, 2.34	0.340	-0.90
					-5.45, 3.66
<i>Integral vBMD, mg/cm³</i>					
Never smokers	Ref.				
Former smokers		-3.98	-7.07, -0.90	0.011	-3.88
					-6.97, -0.79
Current smokers		-5.78	-11.29, -0.26	0.040	-4.22
					-9.74, 1.30
<i>Percent cortical volume</i>					
Never smokers	Ref.				
Former smokers		-0.61	-0.96, -0.26	0.001	-0.65
					-1.00, -0.30
Current smokers		-1.03	-1.66, -0.41	0.001	-0.92
					-1.55, -0.30
Longitudinal association					
<i>Δ% Trabecular vBMD</i>					
Never smokers	Ref.				
Former smokers		0.05	-0.06, 0.16	0.364	-0.01
					-0.11, 0.11
Current smokers		-0.23	-0.42, -0.04	0.016	-0.24
					-0.43, -0.05
<i>Δ% Integral vBMD</i>					
Never smokers	Ref.				
Former smokers		0.01	-0.07, 0.09	0.833	-0.04
					-0.12, 0.04
Current smokers		-0.19	-0.33, -0.04	0.013	-0.20
					-0.35, -0.06
<i>Δ% Percent cortical volume</i>					
Never smokers	Ref.				
Former smokers		-0.01	-0.08, 0.06	0.733	-0.04
					-0.11, 0.03
					0.215

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	Model 1			Model 2		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Current smokers	-0.14	-0.27, -0.02	0.022	-0.16	-0.28, -0.04	0.012

Note. The coefficient from the linear regression models correspond to the difference in the bone variables (the difference in mg/cm^3 for trabecular and integral vBMD, the difference in percent volume for the percent cortical volume, and the difference in annualized percent change over the 5-year follow-up for the longitudinal change in these variables) between former-smokers (coefficient for former-smokers) compared to never-smokers, and current-smokers (coefficient for current-smokers) compared to never-smokers. Model 1 is adjusted for sex, age, education, and BMI; Model 2 is adjusted for all the factors in model 1 plus creatinine, % weight change from age 50, 25OHD, and physical activity level

Table 3

Smoking characteristics and baseline bone outcomes in former and current smokers

	Model 1			Model 2		
	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Former smokers						
<i>Trabecular vBMD, mg/cm³</i>						
Cumulative pack-years ^a	-0.12	-0.22, -0.02	0.023	-0.10	-0.21, -0.002	0.046
Age at smoking initiation ^b	-0.15	-0.44, 0.15	0.332	-0.18	-0.47, 0.11	0.231
Years since smoking cessation ^c	0.16	0.03, 0.28	0.017	0.15	0.02, 0.28	0.025
<i>Integral vBMD, mg/cm³</i>						
Cumulative pack-years ^a	-0.17	-0.29, -0.04	0.009	-0.15	-0.28, -0.03	0.018
Age at smoking initiation ^b	-0.03	-0.39, 0.32	0.857	-0.07	-0.42, 0.28	0.689
Years since smoking cessation ^c	0.21	0.05, 0.36	0.008	0.20	0.05, 0.36	0.011
<i>Percent cortical volume</i>						
Cumulative pack-years ^a	-0.02	-0.04, -0.01	0.002	-0.02	-0.04, -0.01	0.002
Age at smoking initiation ^b	0.008	-0.03, 0.05	0.693	0.004	-0.04, 0.04	0.831
Years since smoking cessation ^c	0.02	0.01, 0.04	0.007	0.03	0.01, 0.04	0.004
Current smokers						
<i>Trabecular vBMD, mg/cm³</i>						
Cumulative pack-years ^d	0.06	-0.13, 0.25	0.539	0.06	-0.13, 0.26	0.519
Age at smoking initiation ^b	0.13	-0.46, 0.71	0.672	0.06	-0.53, 0.65	0.841
<i>Integral vBMD, mg/cm³</i>						
Cumulative pack-years ^d	0.08	-0.15, 0.31	0.505	0.09	-0.15, 0.32	0.476
Age at smoking initiation ^b	-0.14	-0.85, 0.57	0.698	-0.17	-0.88, 0.55	0.647
<i>Percent cortical volume</i>						
Cumulative pack-years ^d	0.001	-0.03, 0.03	0.942	0.003	-0.03, 0.03	0.826
Age at smoking initiation ^b	-0.05	-0.14, 0.04	0.253	-0.04	-0.13, 0.04	0.315

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p 10 observations missing data;
 q 2 observations missing data;
 c 4 observations missing data;
 d 1 observation missing data Model 1 is adjusted for sex, age, education, and BMI; Model 2 is adjusted for all the factors in model 1 plus creatinine, % weight change from age 50, 25OHD, and physical activity level