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Adverse Effects of Smoking on Peak Bone Mass May Be Attenuated by Higher BMI in Young Female Smokers

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ABSTRACT

Smoking is associated with postmenopausal bone loss and fracture, but the effect of smoking on bone in younger women is unclear. Peak bone mass is an important determinant for fracture risk, therefore our aim was to evaluate the association between smoking and bone mass in 25 year-old women. Specifically, to elucidate the influence of daily cigarette consumption and total exposure, duration, age at starting smoking and time since smoking cessation on bone density and fracture risk.

Smoking and BMD data was available for 1054 women from the PEAK-25 cohort. Analyses comparing current smokers with women who never smoked were performed using: number of cigarettes per day; pack-years; smoking duration; age smoking started and for former smokers, age at quitting.

BMD did not differ between never, former and current smokers and the relative fracture risk in smokers was not significant (RR=1.2; 95%CI: 0.8-1.9). Among current smokers, BMD decreased with a dose response as cigarette consumption increased (femoral neck; $p=0.037$). BMD was not significantly lower in young women who had smoked for long duration or started smoking early ($p=0.07-0.64$); long duration and early start were associated with higher BMI ($p=0.038$). Lower BMD persisted up to 24 months after smoking cessation ($p=0.027-0.050$) becoming comparable to never-smokers after 24 months.

Hip BMD was negatively associated with smoking and dose-dependent on cigarette consumption. Smoking duration was not associated with BMD although young women with a long smoking history had higher BMI which might attenuate adverse effects from smoking.

Keywords: Bone mineral density, peak bone mass, smoking, young females, fracture

INTRODUCTION

Osteoporosis has been associated with a number of risk factors related to lifestyle, one of which is smoking. Other factors contributing to lower bone mass and increased fracture risk include early menopause, changes in the micro architecture of the bone, co-existing morbidity and lower levels of physical activity [1].

Smoking has been recognized as having a role in postmenopausal bone loss and lowering the fracture threshold in women [1-3] and it has been suggested that one in eight hip fractures is attributable to smoking [4]. Partially, the increased fracture risk is explained by the low body mass index (BMI) commonly observed in elderly women who smoke, but the negative association remains even after adjustment for BMI [3, 5]. Further, aggravating the adverse effects on bone is the induced hypoestrogenic state observed in women who smoke compared to non-smokers [6]. In addition, among elderly smokers there is a tendency towards a higher risk of falling [4].

However, the influence of smoking on bone mass is inconsistent, with some studies indicating an association between smoking and bone mass [3, 7-11] and others not [4, 12-17]. Possible explanations may be the different classifications of smoking status employed or dose- and time-dependent effects from smoking on bone as proposed in independent studies [18, 19] and a meta-analysis [2].

The majority of studies performed to evaluate the association between smoking and bone properties in women have been performed in older women, either around menopause or at more advanced ages [4, 7-9, 16] and fewer studies in younger female populations [12-14, 20]. The adverse effects of smoking and how these apply to a younger population, with a clearly shorter smoking duration and hence lower

exposure is less clear. Hence, in females, it is not fully known to what extent harmful effects are related to the age of starting to smoke during adolescence when the skeleton is still under development, nor is it clear if stopping smoking during this accrual period attenuates the likely negative effects from smoking and the attainment of maximum bone mass.

Therefore, there are many unresolved issues regarding to what extent smoking and early smoking habits in young women are associated with adverse bone effects prior to and up to the age of 25. The aim of this study was to evaluate the association between smoking and bone in young adult women at an age close to peak bone mass which is estimated to occur during the third decade of life; specifically we aimed to elucidate the influence of age at starting, the duration, the time since smoking cessation, the effect of daily consumption and total exposure and finally fracture risk. To answer these questions we have used the PEAK -25 cohort of 1061 women, all age 25 at inclusion.

SUBJECTS AND METHODS

Subjects

Between 1999 until 2004, 25-year old Swedish women living in the city of Malmö, Sweden were invited to take part in a study whose focus was bone health in young adult women. Twenty-five year old women were selected on the assumption that this age is closely representative of peak bone mass. The PEAK -25 cohort consists of total of 1061 women, all exactly 25 years of age and has been fully described previously [21]. The study was approved by the local ethics committee and followed the principles of the declaration of Helsinki. Written informed consent was obtained from all participating subjects.

Questionnaire

A questionnaire was completed at the visit, comprising questions related to life-style factors, risk factors for bone health, physical activity and fracture. The response-reliability of the questionnaire has been reported previously (Sign Test, p-value: 0.125-1.0) [21]. Physical activity was classified using the Recreation Activity Level score (RAL-score) [21]. Fracture history was self-reported. Fractures classified as pediatric, i.e. occurring before the age of 15 were excluded from the analyses.

Smoking Classification

Based on the information from 1054 of the 1061 women who completed the smoking section of the questionnaire the participants smoking status was classified as current smokers, former smokers or never smoked. In addition, information on number of

cigarettes smoked per day, and duration of smoking (years) were available, allowing the calculation of pack-years ($((\text{cig/day}) \times \text{smoking years}/20)$). The variable cigarettes/day estimates the amount of tobacco during the active smoking period reflecting the short term adverse effects of smoking [22] while pack-years reflects to some extent total smoking tobacco exposure. Information on age at which smoking started and for former smokers, the age at which they stopped, was also available.

For the analyses we primarily compared current smokers versus women who had never smoked. The data was used as continuous variables and additionally we used categories as follows: cigarettes/day: <10; 10-20; >20; duration: <5 years; 5-10 years; >10 years; pack-years: <2; 2-6; >6 and age smoking started: <14y; 15-17y; >18y; time since cessation of smoking: <6, 6-12, 12-24 and >24 months.

Bone Mineral Density Measurement

Bone mineral density (BMD, g/cm^2) was measured using dual energy X-ray absorptiometry (DXA, Prodigy, Lunar Corp., GE, Madison, Wisconsin, USA). Regions of interest (ROI) were femoral neck (FN), trochanter (TR), total hip (TH) and lumbar spine L1-L4 (LS).

The absolute precision error (CV%) of the DXA measurements in our cohort are 0.90% (FN), 0.56% (TR), 0.50% (TH) and 0.65% (LS) [21]. System stability of the DXA equipment was checked daily by the use of a manufacturer-supplied phantom. Height (cm) and weight (kg) and BMI (kg/m^2) were measured as routine.

Statistical methods

Data was assessed for normal distribution using the Shapiro-Wilk test. ANOVA was used to determine differences in continuous variables between smoking categories. In addition, Fisher's least significant difference (LSD) was also used. Regression analysis was performed to identify independent predictors of bone density, including BMI, physical activity and calcium intake as covariates in the model. Unstandardized β -values (β) and standardized β -values (β_{std}) are reported. Overall, the PEAK-25 study has adequate power to identify differences in bone density from biological risk factors. Based on *a priori* power calculations, with over 1,000 participants the PEAK-25 study has 90% power identify differences in BMD of 0.028 g/cm² at the femoral neck. In this and similar studies this may lead to low power to detect small differences between certain sub-groups in the analysis. This includes the fracture risk analyses acknowledging that fracture incidence in this age group is low.

P-values of <0.05 were considered nominally significant. The phenotypes are not independent; therefore applying a Bonferroni correction would be over-stringent. We therefore report the uncorrected p-values and acknowledge that multiple tests were performed.

Data was analyzed using SPSS 19.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Of the 1054 women for whom smoking data was available 26.2% (n=276) were current smokers, 17.7% (n=187) former smokers and 56.1% (n=591) had never smoked.

Descriptive data for these categories are reported in Table 1. The mean number of cigarettes smoked per day was slightly higher in the current compared to the former smokers (9.4 vs 8.4). The mean age at which the young women began smoking was 15.3-15.5, and the age when former smokers stopped smoking was 23.0 ± 2.3 . This equates to 10.0 years and 7.6 years smoking duration in the current and former smokers respectively. Reflecting these differences, the number of pack-years was higher in the current smokers. Height, weight and BMI did not differ significantly between the 3 smoking categories. Compared to women who had never smoked, women who had ever smoked (Current + Former) also reported higher alcohol and coffee consumption and were less physically active (data not shown).

No significant differences in BMD were observed between women in the three smoking categories (Current-Former-Never), however, compared to women who had never smoked, BMD was between 0.6% and 1.5% lower in current smokers at all skeletal sites (FN -1.4%, TR -1.4%, TH -1.5%, LS -0.6%) (Table 1). Smoking status was not an independent predictor of BMD, only BMI ($\beta_{\text{std}} = 0.19\text{-}0.30$) and physical activity ($\beta_{\text{std}} = 0.13\text{-}0.22$) ($p < 0.001$ for both).

We analysed the association between current cigarette consumption (cigarettes per day) and bone density. The majority of current smokers smoked <10 cigs/day (60.7%, n=165); 35.7% (n=97) smoked 10-20 per day and <4% (n=10) were heavy smokers,

reporting more than 20 cigs/day. Daily cigarette consumption had a small but significant negative effect on BMD. Regression analysis indicated that the effect size on FN-BMD was ($\beta = -0.003$; $p = 0.003$), which is equivalent to a decrease of 0.003 g/cm^2 (CI -0.005 ; -0.001 ; $p = 0.003$) in FN-BMD for each cigarette consumed on a daily basis. A similar trend towards decreased BMD with increased cigarette consumption was also observed among women who had ever smoked (data not shown). Categorical analysis demonstrated a clear dose response on BMD. Although the difference was nominally significant only at the femoral neck ($p = 0.037$), compared to women who had never smoked, the percentage difference in BMD ranged from -0.1% with less than 10 cigs/day to almost -7% in the heaviest smokers (Figure 1). The number of very heavy smokers was too small to allow a more detailed analysis of them as a group, however BMI was not significantly different between the three categories ($23.8 \text{ v } 23.6 \text{ v } 23.0$; $p = 0.453$).

Duration of smoking was not associated with BMD and among the current smokers the mean duration was 10.0 years. To explore this further we created three categories <5 years duration; 5-10 years and >10 years. Among current smokers no significant differences in BMD were observed between the different categories. However we observed that women who had smoked for <5 years had the lowest BMD values at all sites ($\sim 4\text{-}7\%$ lower) compared to non-smokers. In contrast, among women who had smoked for much longer periods, although BMD was still lower than those who had never smoked the percentage difference was much less ($0.5\text{-}1\%$ at the hip sites and 0.7% at the spine) (Table 2). This may be explained by the fact that BMI was significantly different ($p = 0.038$), increasing with number of years of smoking duration. In those who had smoked for 10 years or more, BMI was 3% higher than those who had never smoked (Table 2). A similar trend was also observed among women who had ever smoked (data not shown). Although duration and age at starting to smoke are highly correlated in a

young population ($r=-0.75$), duration alone does not allow for pin-pointing contribution from earlier or later smoke start; 38% of current smokers began at 14 or younger (range 11-14). Similar to the trends we observed with smoking duration, BMD was as much as 3.5% lower in those who started smoking after the age of 18 and lowest in the youngest starters. Again, this may be explained by BMI increasing incrementally the earlier smoking began.

The variable 'pack years', combining cigarette number and smoking duration, is an estimation of total exposure and was associated with femoral neck BMD (adjusted/unadjusted $\beta = -0.161/-0.157$; $p = 0.009/0.014$). To further explore the effect of pack-years on bone density we used the categories <2 pack-years; 2-6 and >6 pack-years. Among current smokers pack-years was significantly associated with BMD at the femoral neck BMD ($p=0.019-0.039$) (Figure 2), equivalent to a 0.004 g/cm^2 (CI -0.008; -0.001) decrease in BMD for every pack-year consumed. The association remained even after adjustment for confounding factors. BMD at all sites was lowest in women with the highest pack years, although there was no dose response (Figure 2). A similar trend was also observed among women who had ever smoked (data not shown).

A key question is whether, after cessation of smoking, BMD returns to a level comparable to the BMD of an individual who has never smoked. Among the former smokers time since cessation ranged from 0-120 months. Our results showed that among women who had stopped smoking within 6 months prior to BMD measurement had BMD values that were 1.4-2.4% higher at all sites than among those women who had never smoked. Women who had stopped smoking 6-24 months previously had decreased BMD values. BMD was lowest in those measured 12-24 months after smoking

cessation, but thereafter returned to the level of someone who had never smoked (Figure 3).

In the cohort, 26% (n=275/1051) of women reported having had a previous fracture at any time in their life. Of those, 94/275 (34%) occurred after the age of 15. The proportion of women who had sustained a fracture was not significantly different between women who had never smoked and those who had ever smoked (8% v 10%). The relative risk estimate for having a fracture although not significant, was 28% compared to women who had never smoked (RR 1.28 95% CI [0.89-1.88] (Table 3). An interaction between the smoking variables was observed for fracture (p=0.029), but was abolished when other covariates were included in the model.

DISCUSSION

In this study, evaluating the effects of smoking on bone mass in young adult women we have been able to show that smoking contributes to small but biologically relevant reductions in BMD, particularly at the femoral neck and that there is a clear dose response with increasing cigarette consumption. The results, as expected support what is already known, but importantly we have been able to demonstrate in a large population-based study of young adult women that the cessation of smoking appears to quickly resolve negative effects on bone health even when the smoking habit was established during adolescence.

Previous studies of the associations between smoking and BMD, but also fractures, have mainly been addressed in older populations [2, 3] and less in young adults. The older populations generally have a higher tobacco exposure due to longer duration, but it is also important to understand the short-term adverse effects of smoking and from beginning smoking at a young age. In this study, in a cohort of women at an age closely representing peak bone mass, we show that smoking is associated with lower BMD in the hip in current smokers and is dose-dependent on quantity of cigarettes smoked, however we could not verify a threshold dose with longer duration or age when smoking started, as has been shown in older smokers [19]. Further, we did not find an association between higher prevalence of fractures with smoking in our cohort of women, as has been shown in men [23].

The effects of smoking on bone mass are not large, hence using the rather crude dichotomized variable of current smoking status, does not facilitate the identification of significant effects from smoking [4, 24]. This may be a possible reason for the conflicting

information on the influence of smoking on bone and of particular importance in a cohort of young individuals such as ours; hence we have primarily focused on comparing current smokers to those who had never smoked.

Our findings confirm a dose-dependent reduction in BMD with increasing number of cigarettes smoked per day, and while only significant at the hip, an observation in line with previous studies [8, 9, 25]. Based on the estimated effect size from consumption on femoral neck BMD, a consumption of one pack (20 cigarettes) per day corresponds to a difference of 0.06 g/cm² or approximately 0.5 SD difference in BMD. Bearing in mind that an increase in peak bone mass by 1 SD may decrease the risk of a future fracture by 50% [26], our finding suggests an increase in fracture risk at old age from smoking in youth and thus the implications for fracture prevention are clear.

In older women, the association between smoking duration and lower BMD [2] is a consequence of longer exposure times. In our cohort of young women we didn't see a progressive difference in BMD over time; on the contrary, those with the shortest duration of smoking have the lowest BMD by 4-8 percent, in comparison to women who had never smoked. This lack of time effect may be explained by the observation that in the young women of the PEAK-25 cohort, BMI was generally higher in those who had smoked for the longest durations. This may also explain why we did not identify detrimental effects on BMD from starting smoking at an early age and contradicting our expectations of early puberty as a vulnerable period in bone accrual in girls. This observation also contradicts the well documented observation of an inverse relationship between BMI and smoking in elderly and perimenopausal women [27, 28]. This higher BMI, and the resultant increased mechanical load appears to modulate the negative effects on bone, possibly together with an increased, although minor contribution, from

adipocyte-produced estrogen [29]. This may explain to some extent our observation that BMD doesn't get progressively lower with smoking duration, even in combination with other risk behaviors such as higher alcohol and caffeine consumption and less exercise among smokers. This may also indicate a general disregard concerning an overall healthy lifestyle in this age group [30], although we can only speculate whether smokers also had a higher calorie intake and ate less healthily compared to women who never smoked.

Meta-analyses have suggested that smoking-induced bone loss may be partially reversed by cessation of smoking [2, 31]. In older populations, it has been shown that this reversibility takes time; BMD improves within 10 years and approaches the BMD levels of never smokers after >30 years of smoking cessation [24]. Former smokers in the PEAK-25 cohort had on average smoked less than eight years and less than ten cigarettes per day; we wanted to know if there was a time-dependent relationship between cessation and bone mass or an identifiable minimum repair time already in young women. Unexpectedly, it appeared that those women who had stopped smoking within a year of the BMD measurement had BMD values similar to those who had never smoked, whereas those who were between one and two years post-stopping had significantly lower BMD. Beyond two years from smoke cessation, BMD was again similar to never-smokers. We interpret this as a transient negative effect that does not persist, although the underlying reason is unclear. One possible contributing factor to these results may be a weight gain upon cessation which can act protectively [32] and we have no information on specific post-cessation activities or an individual's reasons for choosing to quit.

Despite the fact that in these young women the prevalence of fracture did not differ between those who had or who had never smoked, the risk estimate, although not significant, does not exclude an interaction with smoking. This is of interest because even if the quantifiable effects of smoking on BMD are quite small, we can speculate that accumulated over time this may be translated into a substantial risk. In studies of elderly women the resolution of fracture risk extends over more than ten years to reach the level of non-smokers [33]. Other studies have reported a higher incidence of fracture in young men who smoked, however this may reflect gender related differences in lifestyle and other risk behaviors contributing to fracture [23, 30].

Strengths and Limitations

A limitation of using self-reported data to identify smoking behavior is the risk of recall bias and underestimation of exposure (risk behavior) [34]. Although there are inherent difficulties associated with the characterization of smoking habits, we have circumvented these problems to some extent by using a number of quantitative and spatial variables for smoking. While our study does not allow for detailed socio-economic profiling, we have not identified any systematic difference among participants, smoking category and for example educational level (data not shown). A limitation of the study is the low numbers in some of the smoking subgroups and the low number of fractures in this young population. Since smoking has documented small effects on bone density (while larger on fracture), Law and Ward in their meta-analyses found a BMD differences between smokers and non-smoker of less than one tenth to one third of a standard deviation [2, 4], our post-hoc power analysis indicates that a difference of 0.034 g/cm² in BMD between smokers and non-smokers would be necessary to reach 99% power. Hence, this is a limitation common to other similar studies.

This study has a number of important strengths. In addition to the cohort size, the population based approach to its collection and the focused age category, a strength of this study is the scope of the smoking data collected, which has enabled us to address specific aspects of smoking to bone health, such as adolescent starting age and dose versus duration at an important bone developmental period which have not been possible in many other studies.

Conclusion

In conclusion, among current smokers, negative effects were observed for BMD in the hip, but not at other sites, and it was related to the amount of cigarettes smoked, indicating dose-dependency. Early start and duration of smoking were not associated with BMD or fracture, although young women with a long history of smoking had a higher BMI which might attenuate harmful effects from smoking. The findings of this study indicate that attainment of peak bone mass is adversely associated with smoking in young women and while complete smoking cessation is the ideal, reducing the number of cigarettes may also be beneficial for the skeleton.

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TABLES

Table 1 Descriptive data based according to smoking status

	Current Smoker (n=276)	Former Smoker (n=187)	Never Smoked (n=591)
Weight (kg)	65.1 ± 11.4	65.0 ± 10.4	64.4 ± 11.7
Height (cm)	167.4 ± 5.9	168.4 ± 6.0	167.4 ± 6.2
BMI (kg/cm ²)	23.2 ± 3.7	22.9 ± 3.6	23.0 ± 4.0
Age at Menarche (years)	12.7 ± 1.3	12.7 ± 1.3	12.8 ± 1.4
Cigarettes/day (n)	9.4 ± 6.9	8.4 ± 7.0	-
Smoking duration (years)	10.0 ± 2.3	7.6 ± 3.1	-
Calculated Pack-years	5.0 ± 4.1	3.5 ± 3.2	-
Age smoking started (years)	15.5 ± 2.3	15.3 ± 2.2	-
Age smoking stopped (years)	-	23.0 ± 2.3	-
FN-BMD (g/cm ²)	1.042 ± 0.114	1.060 ± 0.127	1.057 ± 0.125
TR-BMD (g/cm ²)	0.823 ± 0.101	0.831 ± 0.114	0.835 ± 0.109
TH-BMD (g/cm ²)	1.050 ± 0.109	1.065 ± 0.124	1.066 ± 0.125
LS-BMD (g/cm ²)	1.212 ± 0.126	1.222 ± 0.121	1.218 ± 0.131

Values are reported as mean and standard deviation

Table 2 Effect on BMD of smoking duration and age at which smoking started

	FN-BMD	TR-BMD	TH-BMD	LS-BMD	BMI
Never smoked	1.057 ± 0.125	0.835 ± 0.109	1.066 ± 0.125	1.218 ± 0.131	23.0 ± 4.0
<i>Smoking duration</i>					
<5 years (n=7)	1.010 ± 0.118 -4.4%	0.785 ± 0.088 -6.0%	1.003 ± 0.080 -5.9%	1.126 ± 0.116 -7.5%	20.8 ± 2.4 -9.3%
5-10 years (n=108)	1.035 ± 0.116 -2.1%	0.812 ± 0.101 -2.7%	1.039 ± 0.108 -2.5%	1.215 ± 0.112 -0.3%	22.8 ± 3.3 -0.7%
>10 years (n=153)	1.046 ± 0.114 -1.0%	0.831 ± 0.102 -0.5%	1.059 ± 0.111 -0.7%	1.209 ± 0.136 -0.7%	23.7 ± 3.9* 3.0%

Reported data is from current smokers. Values are reported as mean (standard deviation) Percentage differences are calculated compared to BMD in the never smoked category. All associations were non-significant except * p=0.038

Table 3 Prevalence of fractures that occurred at age 15 and over in relation to smoking status

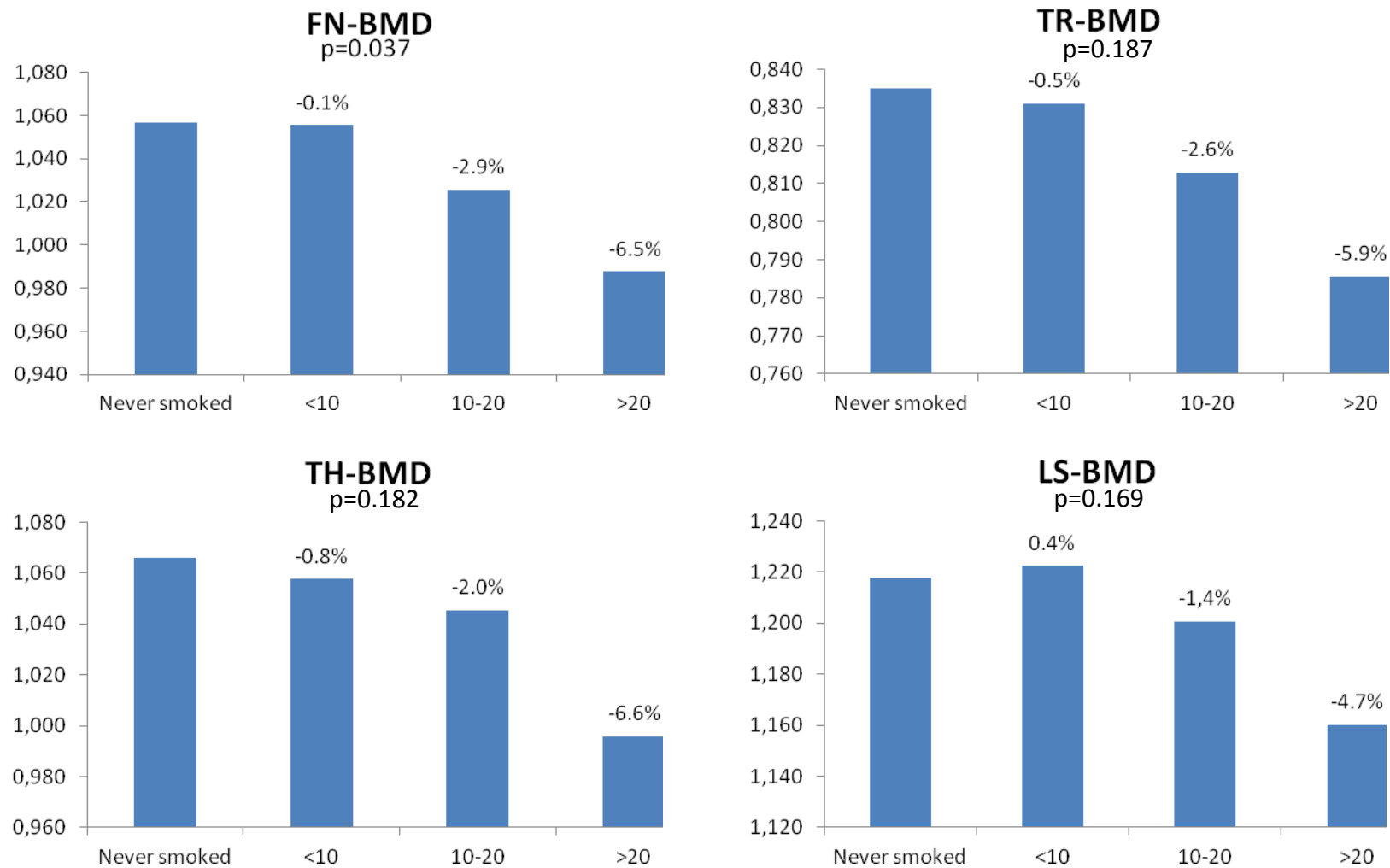
Smoking Category	Fracture* (n=94)	No fracture (n=960)	<i>Chi2</i> <i>p-value</i>	<i>Risk ratio</i>
Current smokers (n=276)	27 (10%)	249 (90%)	Never vs Current p=0.37	1.23 [0.784-1.931]
Ever smoked (n=463)	47 (10%)	416 (90%)	Never vs Former p=0.24	1.35 [0.818-2.212]
Never smoked (n=591)	47 (8%)	544 (92%)	Never vs Ever p=0.21	1.28 [0.868-1.876]

*Number of women who sustained a fracture after age 15 (pediatric fractures are not included in this analysis)

Prevalence of fractures in each smoking category reported as number (%). Risk ratios are reported with 95% confidence intervals.

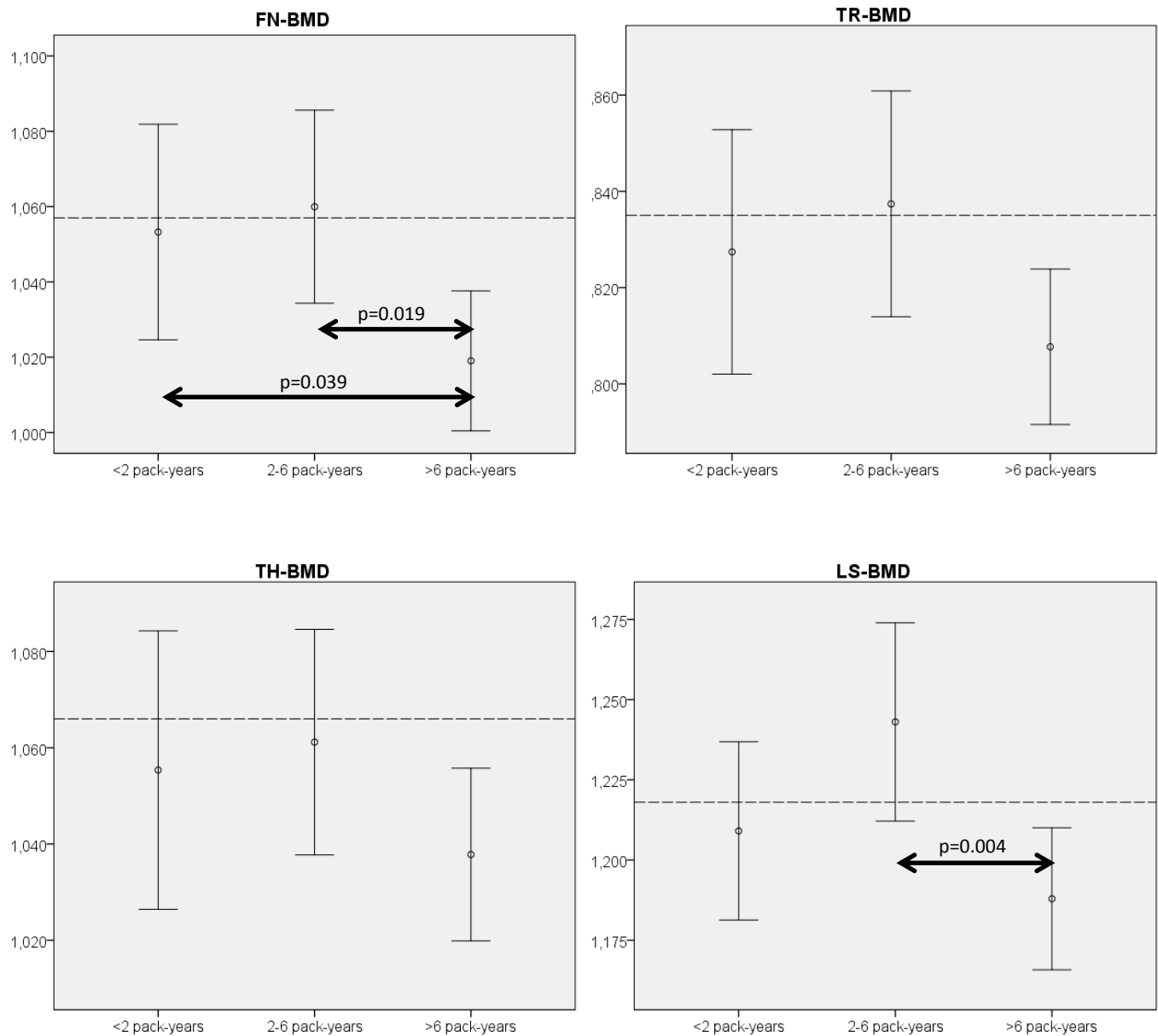
FIGURES

Figure 1 Effect of cigarette consumption (cigarettes/day) on bone density in current smokers



Y-axis is BMD (g/cm²). X-axis shows categories of cigarettes consumed per day. Percentage values are the category mean compared to the never smokers. P-values from ANOVA
Never smoked (n=591), <10 cig/day, (n=165) 10-20 cig/day (n=97), >20 cig/day (n=10)

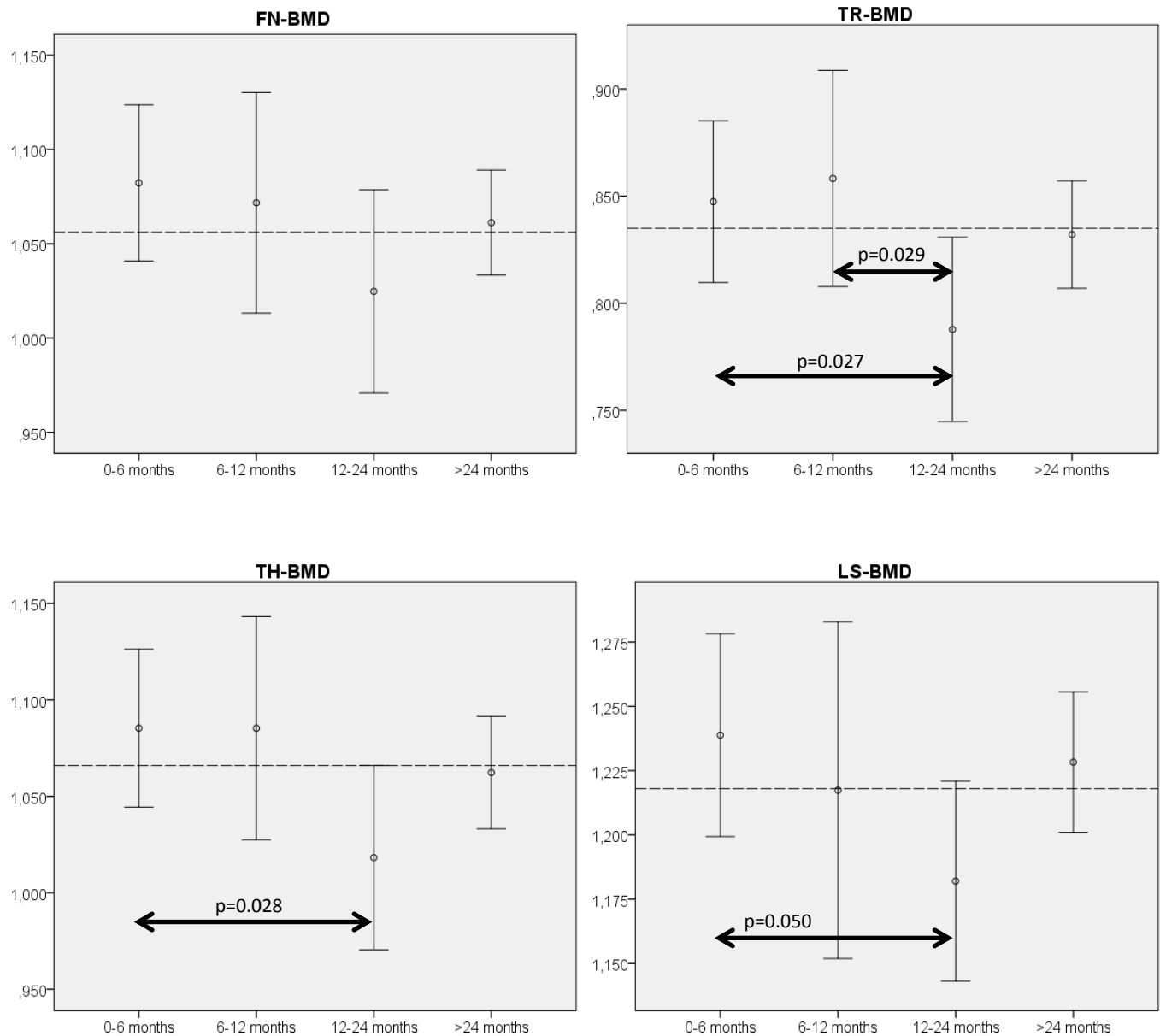
Figure 2 Effect of cigarette exposure (pack-years) among current smokers on bone density



Reported values are mean and 95%CI for each category of pack-years. P-values are reported, where significant. The dashed line represents mean BMD of an individual who has never smoked.

<2 pack-years (n=87), 2-6 pack-years (n=74) and >6 pack-years (n=105)

Figure 3 BMD and time since smoking cessation (months) in former smokers



Reported values are mean and 95%CI for each category of time since smoking cessation. P-values are reported, where significant. The dashed line represents mean BMD of an individual who has never smoked.

0-6 months (n=42), 6-12 months (n=21), 12-24 months (n=31), >24 months (n=74)

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