Smoking-Induced Risk of Osteoporosis Is Partly Mediated by Cadmium From Tobacco Smoke: The MrOS Sweden Study

Huiqi Li,1 Maria Wallin,1 Lars Barregard,1 Gerd Sallsten,1 Thomas Lundh,2 Claes Ohlsson,3 Dan Mellström,3 and Eva M. Andersson1

1Department of Occupational and Environmental Medicine, School of Public Health and Community Medicine, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden
2Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden
3Center for Bone and Arthritis Research (CBAR), Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT
Cigarette smoking is a risk factor for osteoporosis and bone fracture. Moreover, smoking causes exposure to cadmium, which is a known risk factor for osteoporosis. It is hypothesized that part of smoking-induced osteoporosis may be mediated via cadmium from tobacco smoke. We investigated this hypothesis using mediation analysis in a Swedish cohort of elderly men. This study was performed in 886 elderly men from the Swedish cohort of the Osteoporotic Fractures in Men (MrOS) study. Urinary samples, bone mineral density (BMD), smoking data, and other background information were obtained at baseline in 2002–2004. Urinary cadmium was analyzed in baseline samples and adjusted for creatinine. The cohort was followed until August 2018 for fracture incidence, based on the X-ray register. Mediation analysis was conducted to evaluate the indirect effect (via cadmium) of smoking on both BMD and fractures. Time to first fracture was analyzed using the accelerated failure time (AFT) model and Aalen’s additive hazard model. The mean level of urinary cadmium was 0.25 μg/g creatinine. There were significant inverse associations between smoking and total body, total hip, and trochanter BMD. The indirect effects via cadmium were estimated to be 43% of the total effects of smoking for whole-body BMD, and even more for total hip and trochanter BMD. Smoking was also associated with higher risk of all fractures and major osteoporosis fractures. The indirect effects via cadmium were largest in nonvertebral osteoporosis fractures and hip fractures, constituting at least one-half of the total effects, in both the AFT and Aalen’s model. The findings in this study provide evidence that cadmium exposure from tobacco smoke plays an important role in smoking-induced osteoporosis © 2020 The Authors. Journal of Bone and Mineral Research published by American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; CADMIUM; OSTEOPOROSIS; PROSPECTIVE COHORT; SMOKING

Introduction

Osteoporosis is characterized by low bone mineral density (BMD), resulting in increased risk of fracture. It has become a major public health concern worldwide and will become even more significant in an aging population. Some of the risk factors for osteoporosis are non-modifiable, including age, sex, genetic background, and underlying illness, while others are modifiable, for instance smoking, diet, exercise, medication, body mass index (BMI), and heavy alcohol drinking.[1]

Smoking is well known to cause various health problems, including osteoporosis and bone fracture.[2,3] Tobacco smoke contains over 4000 compounds, and little has been done to clarify which component plays a critical role in the underlying mechanism. One of these may be cadmium. Smoking is a major source of cadmium exposure in smokers, whereas in nonsmokers, the exposure derives mainly from diet or occupational exposure.[4,5] Cadmium has long been considered to be a risk factor for osteoporosis and fracture, especially at high-level exposure. The best-known is the case of Itai-Itai disease in Japan in the 1950s,
where people consumed rice highly contaminated by cadmium and suffered severe symptoms of osteomalacia, osteoporosis, and fractures. Recent studies have indicated that even low-level exposure to cadmium could increase the risk of osteoporosis and fractures.\(^6\)\(^-\)\(^9\) We have previously investigated the association between urinary cadmium and BMD and fracture incidence in elderly men in Sweden, and the results showed that even low cadmium exposure, as found in the general population, increases the risk of low BMD and fractures.\(^10\)

The aim of the present study was to evaluate whether, and to what degree, the smoking-associated risk of osteoporosis and fracture is mediated by cadmium. This was done by mediation analysis\(^11\)\(^,\)\(^12\) investigating the association between smoking, urinary cadmium, and BMD at baseline, and fracture incidence during 14 to 16 years of follow-up, in a cohort of elderly men in Sweden.

**Subjects and Methods**

The study participants have been described in detail elsewhere.\(^10\) In brief, the initial study cohort consisted of 1010 elderly men (age 70–81 years at baseline) in Gothenburg, Sweden. They were part of the Swedish cohort of the Osteoporotic Fractures in Men (MrOS) study, a multicenter study focused on bone metabolism and fractures. Baseline information including a questionnaire, blood and urine samples, BMD measurement, and physical examination was collected during 2002–2004. History of previous fractures was asked for and had been reported.\(^13\) Those with previous fractures are included in the present study, considering that previous fractures were not necessarily osteoporosis-related fractures. The cohort was then followed, with registration of vital status and incidence of new fractures, up to 2018. In the present study, 121 individuals with incomplete information on smoking or urinary cadmium were excluded. Furthermore, three individuals with extreme values of urinary cadmium (>5.0 g/g creatinine) were excluded from the main analyses. The final study population therefore consisted of 886 men.

The study was approved by the ethics committee at the University of Gothenburg (Gbg M 014-01) and was conducted in accordance with the Declaration of Helsinki. All participants provided written consent.

Areal BMD (g/cm\(^2\)) of the total body, total hip including femoral neck, and lumbar spine (vertebrae L\(_1\) to L\(_4\)) were measured at baseline, by dual-energy X-ray absorptiometry (DXA) using the Hologic QDR 4500/A-Delphi equipment (Hologic, Waltham, MA, USA) for all participants. The coefficient of variation for the areal BMD measurement ranged from 0.3% to 5%. Standardized BMD was calculated because parts of the MrOS Sweden in other cities used different equipment to measure areal BMD (data not used in this study).\(^13\)

Morning urine was collected at baseline and frozen at –20°C for later analysis. The urine samples were analyzed for cadmium and creatinine in 2012 at the Department of Occupational and Environmental Medicine, Lund University Hospital. Urinary cadmium was measured by inductively coupled plasma mass spectrometry (Thermo X7, Thermo Elemental, Winsford, UK). The limit of detection was 0.05 μg/L, and the coefficient of variation was 4.4%. Urinary cadmium concentration was adjusted for urinary creatinine, measured by the Jaffé method using a COBAS 6000 analyzer (Roche Diagnostics, Rotkreuz, Switzerland) with a limit of detection of 0.1 mmol/L. Details regarding quality control of the cadmium analyses have been presented.\(^17\)

The participants were followed until August 31, 2018. The X-ray archives from both inpatients and outpatients in Gothenburg and in the Västra Götaland Region were searched regularly for all new fractures. It would be very rare that fractures in this study population would occur in other parts of Sweden, because these men were 70 to 81 years at baseline and they were relatively stationary. Even if fractures occurred outside of Gothenburg and the Västra Götaland Region, the participants would still have a follow-up X-ray in their hometown, and in this way the fractures would be detected. Central Swedish registers were used to identify deaths and dates of death during the follow-up period. None of the participant permanently moved out from Sweden during the follow-up. Date and type of fracture were registered for all new fractures and all fractures were confirmed by a physician’s review of X-ray reports. Participants were followed up to the time of first fracture, end of the study, or death, whichever came first. The following International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes were used to define fractures:

- All fractures: S02, S12, S22, S32, S42, S52, S62, S72, S82, and S92;
- Major osteoporosis fractures: S22.0, S22.1, S32.0, S32.1, S32.4, S32.5, S42.2, S52.5, S52.6, S72.0, S72.1, and S72.2;
- Non-vertebral osteoporosis fractures: S32.1, S32.4, S32.5, S42.2, S52.5, S52.6, S72.0, S72.1, and S72.2;
- Hip fractures: S72.0, S72.1, and S72.2.

Smoking status was obtained through self-reported questionnaire. The number of pack-years (pack of cigarettes smoked per day, multiplied by the smoking duration, in years) was used as the marker for cumulative smoking exposure. Never smokers were set to have 0 pack-years. The effects are presented as per 10 pack-years. Urinary cadmium was the mediator. BMD and time to the first fracture or censoring were the outcomes. The covariates adjusted for were selected based on the scientific literature, our previous study, and the availability of the data: age at baseline, BMI, and daily walking distance. Mediation analysis regarding BMD was performed using the product method, where the indirect effect is estimated as the product of the estimates from the regression model for the outcome and the regression model for the mediator.\(^10\) For the BMD outcome, linear regression models were used. Mediation analysis regarding fractures was performed using two different models, the accelerated failure time (AFT) model and Aalen’s additive hazard model.\(^15\)\(^,\)\(^16\) Results from the AFT model are interpreted as the fold change in survival time, whereas results from Aalen’s model are interpreted as number of additional events per person-time. The mediator, urinary cadmium, was used in its original form in a linear regression model. The proportion mediated (PM) was calculated as the ratio between the indirect effect and the total effect.

To explore the potential bias that might be induced by unmeasured mediator-outcome confounding, a sensitivity analysis was performed using the results for hip fractures as an example. We tested the combinations of several hypothetical effects of an unmeasured confounder on the mediator and the outcome.\(^17\) We considered a hypothetical unmeasured mediator-outcome confounder that would increase cadmium and shorten survival time. If such a confounder was ignored, the indirect effect would be overestimated. The aim of the sensitivity analysis
was to evaluate how strong an influence a confounder has to have to nullify the indirect effect found in our study.

Mediation analyses using AFT models were performed in SAS 9.4 (SAS Institute, Inc., Cary, NC, USA), whereas all other analyses were performed using R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria)(18) with packages OIsurv,(19) timereg,(20) and mvtnorm.(21)

Results

Baseline characteristics, BMD, and fractures

Baseline characteristics are presented in Table 1. There were 353 never-smokers, 463 former smokers, and 70 current smokers in this study. The median cumulative smoking in the study population, including never-smokers, was 5.0 pack-years. The mean urinary cadmium level was 0.31 μg/g creatinine (median 0.25 μg/g creatinine). The variables pack-years and urinary cadmium were correlated with each other \( r = 0.46, p < .0001 \) (data not shown). A total of 303 fractures occurred during follow-up (Table 2). The number of pack-years, urinary cadmium, as well as the number of incident fractures by smoking status are presented in Table S1.

Mediation analysis regarding BMD

The results of the mediation analysis regarding the effect of smoking on BMD are presented in Table 3. Both the total effect and the indirect effect showed an inverse association between smoking and all the BMD outcomes. For total body, total hip, and trochanter BMD, the total and indirect effect were significant. The direct effect of smoking was not significant for any of the BMD outcomes. The indirect effects of smoking on BMD, mediated via cadmium, all showed negative values. The PMs for BMDs of different areas were 43% or higher. For example, each 10 pack-years was expected to lead to a decrease in hip BMD of 0.0058 g/cm\(^2\), and 0.0034 g/cm\(^2\) of this decrease was due to cadmium from tobacco smoke, which corresponds to a PM of 59%.

Mediation analysis regarding fractures

The results of the mediation analysis regarding the effect of cumulative smoking on fracture incidence are presented in Table 4. An effect of smoking on fractures was found, both for all fractures and for the subgroup with major osteoporosis fractures. The total effects regarding these fracture groups were significant in both the AFT model and Aalen’s model. However, none of the direct or indirect effects were statistically significant for these fracture groups. As for the subgroups nonvertebral osteoporosis fractures and hip fractures, the total effects were not significant, but the indirect effects were significant in analyses using the AFT model. The PM in general was lower than effects for BMD. The PM for nonvertebral osteoporosis fracture and hip fracture was ≥49%, whereas PMs for all fractures and major osteoporosis fractures were <25%. For example, each 10 pack-years could lead to a decrease of 5% in survival time until first fracture (the AFT model), and 2% out of this was mediated by cadmium from tobacco smoke (PM = 49%). Each 10 pack-years could lead to 1.06 extra hip fractures per 1000 person-years, and 0.67 of this was due to cadmium from tobacco smoke (PM = 64%).

Sensitivity analysis

Based on the results from the sensitivity analysis for unmeasured mediator-outcome confounding, it is rather unlikely that the indirect effects found in this study could be due merely to confounding (Table S2). For example, to nullify the indirect effect on hip fractures by the AFT model, an unmeasured mediator-outcome confounder U would need to increase urinary cadmium by 0.30 μg/g creatinine, and simultaneously the confounder U should be able to shorten survival time to first hip fracture by 5%. Note that an unmeasured variable V which does not induce direct change in the fracture risk, but only in urinary cadmium, would not be a confounder (even if the pathway \( V \rightarrow \text{cadmium} \rightarrow \text{fracture} \) would induce a change in the fracture risk). In comparison, every 10 pack-years of cigarette smoking could lead to increase of urinary cadmium by 0.063 μg/g creatinine (data not shown), and 10 pack-years of smoking could shorten survival time to first hip fracture by 3% (direct effect in
Mediation Analysis Regarding the Effect of Cumulative Smoking on BMD, With Urinary Cadmium as Mediator

| BMD            | Direct effect | Indirect effect | Total effect | PM (%) |
|----------------|---------------|-----------------|--------------|--------|
| Body BMD       | −0.0030 (−0.0076, 0.0016) | −0.0022 (−0.0044, −0.00012) | −0.0052 (−0.0093, −0.0011) | 43     |
| Hip BMD        | −0.0024 (−0.0079, 0.0031) | −0.0034 (−0.0060, −0.00085) | −0.0058 (−0.011, −0.00092) | 59     |
| Femoral neck BMD | 0.00054 (−0.0049, 0.0060) | −0.0026 (−0.0052, −0.000089) | −0.0021 (−0.0070, 0.0028) | ~100    |
| Trochanter BMD | −0.0017 (−0.0075, 0.0040) | −0.0040 (−0.0068, −0.0014) | −0.0058 (−0.011, −0.00069) | 70     |
| Lumbar spine BMD | 0.0016 (−0.0065, 0.0097) | −0.0024 (−0.0062, 0.0014) | −0.00080 (−0.0080, 0.0064) | ~100    |

Effects are presented as change in BMD (g/cm²) per 10 pack-years. Data is on 886 participants, adjusted for age, BMI, and daily walking distance.

PM = proportion mediated.

1 When the direct effect and the indirect effect have different signs (+/−), the PM cannot be quantified.

Mediation Analysis Regarding the Effect of Cumulative Smoking on Fracture Incidence, With Urinary Cadmium as the Mediator

| Fractures                                      | Direct effect | Indirect effect | Total effect | PM (%) |
|-----------------------------------------------|---------------|-----------------|--------------|--------|
| AFT model (expected survival time)             |               |                 |              |        |
| All fractures                                  | 0.95 (0.90, 1.00) | 0.99 (0.97, 1.02) | 0.94 (0.90, 0.99) | 11     |
| Major osteoporosis fractures                   | 0.96 (0.91, 1.01) | 0.99 (0.97, 1.01) | 0.95 (0.90, 0.99) | 20     |
| Nonvertebral osteoporosis fractures            | 1.00 (0.93, 1.07) | 0.97 (0.95, 0.99) | 0.97 (0.91, 1.03) | 97     |
| Hip fractures                                  | 0.97 (0.91, 1.04) | 0.98 (0.95, 1.00) | 0.95 (0.90, 1.01) | 49     |
| Aalen’s model (additional events per 1000 person-years) | 2.67 (−0.37 to 5.71) | 0.40 (−0.88 to 1.68) | 3.06 (0.43 to 5.67) | 13     |
| All fractures                                  | 1.81 (−0.75 to 4.37) | 0.58 (−0.60 to 1.76) | 2.39 (0.21 to 4.55) | 24     |
| Major osteoporosis fractures                   | −0.16 (−1.92 to 1.60) | 1.00 (−0.060 to 2.09) | 0.84 (−0.56 to 2.24) | ~100    |
| Hip fractures                                  | 0.38 (−1.05 to 1.81) | 0.67 (−0.19 to 1.54) | 1.06 (−0.070 to 2.18) | 64     |

Effects are presented per 10 pack-years. Data is on 886 participants, adjusted for age, BMI, and daily walking distance.

AFT = accelerated failure time; PM = proportion mediated.

1 When the direct effect and the indirect effect have different signs (+/−), the PM cannot be quantified.

Discussion

This study provides evidence for the mediating role of cadmium on smoking-induced osteoporosis in a cross-sectional setting, and on fracture incidence in a prospective cohort analysis.

In general, the results of this study indicate that the smoking-induced decrease in BMD is largely due to the mediating effect of cadmium. For fractures, though the indirect effects were mostly not statistically significant, cadmium from tobacco smoke still seems to be important.

The mediating effects of cadmium on smoking-induced BMD were significant for all sites except the lumbar spine. The proportions mediated by cadmium were >40%, which means that cadmium from tobacco smoke could account for >40% of the BMD decrease induced by smoking.

To analyze time to first fracture, we used two different models, and the results for these should be interpreted differently. The results of the mediation analysis using the AFT model could be interpreted as the expected decrease (%) in time until the first fracture, for each additional 10 pack-years. The numbers were not dramatic, as 10 pack-years would not cause a very strong effect on the time to the first fracture. The results from Aalen’s model could be interpreted as the additional event rate for 10 pack-years (number of additional cases per 1000 person-years). These two models provide results in the same direction, but approach the analysis from different angles. The two models showed similar PM for each type of fracture, indicating that the estimation of the mediating effect of cadmium on smoking-induced fracture is not dependent on the model used.

The results of this study could also be considered in relation to possible interventions, and different interventions would lead to corresponding improvements. If the intervention is to “ban cadmium in tobacco,” the expected effect would correspond to the indirect effect. If the intervention is “never smoke,” the expected effect would correspond to the total effect, which of course would be the preferred and easiest option.

To be able to interpret the results of mediation analysis, the pathway must be biologically plausible. This study was based on the predefined smoking-cadmium-osteoporosis pathway, which we consider to be valid based on current knowledge. However, cigarette smoke is a complicated mixture of substances, and there could be other components in the smoke also causing bone mass loss. This part of the total effect was captured as the direct effect, where the effect of smoking on osteoporosis was not mediated through cadmium. Another concern might be that the never smokers could also be exposed to cadmium through other sources; eg, their diet. However, in this study, smoking was considered the exposure, and the mediating effect of cadmium was not obtained by comparing the “cadmium-exposed” with the “cadmium-free.” This was in fact a comparison between the “smoking-exposed” and the “smoking-free.” It is not important if study participants had cadmium exposure from other sources (eg, via occupation or diet), on the condition that those other sources would not change smoking habits (which corresponds to the “no exposure-mediator confounding” assumption), or would not induce reduced BMD (which...
corresponds to “no mediator-outcome confounding”). These assumptions hold with high probability in this cohort based on our knowledge of cadmium and osteoporosis.

The non-confounding assumption in mediation analysis consists of four parts: one should control for (i) exposure-outcome confounders; (ii) mediator-outcome confounders; and (iii) exposure-mediator confounders; further, (iv) it must be assumed that none of the mediator-outcome confounders is the effect of the exposure. The most relevant potential confounders were considered in this study, but we cannot rule out that unmeasured confounding remains. Thus a sensitivity analysis was performed to assess “how strong would an unmeasured confounder need to be in order to nullify the indirect effects found in our study.” The analysis indicates that if the indirect effects found in this study were merely due to confounding, an unmeasured confounder would have to have very large effects on both urinary cadmium and osteoporosis risk. This is unlikely in this study population.

Previous epidemiological studies and animal experiments provide evidence and plausible mechanistic explanations for cadmium-induced osteoporosis. The biological mechanism of cadmium toxicity on bone has been investigated, and several models have been suggested. An association between osteoporosis and kidney dysfunction induced by cadmium exposure was reported in a Chinese population. Moreover, the adverse effect of cadmium on bone was also found in populations where no sign of impaired kidney function was observed, indicating that cadmium acts directly on bone. Animal experiments have shown that cadmium can disturb bone metabolism both directly, via bone formation and resorption, and indirectly, via disorders in calcium and vitamin D metabolism.

There are several strengths to this study. This is one of the few studies focusing on osteoporosis and fractures in elderly men. The data of fractures is reliable because it was based on an X-ray register. In addition, we used urinary cadmium in this study, which reflects the body burden of cadmium and is considered the best biomarker for long-term cadmium exposure feasible in large population-based studies.

In conclusion, we have found that cadmium exposure is likely to be an important causative factor in smoking-induced osteoporosis. This opens up new insights into disease processes and could be important both for individuals at risk and policy makers. A major strategy for reducing osteoporosis is of course to reduce smoking. In addition, measures should be taken to reduce environmental pollution of cadmium, because cadmium in the environment will be taken up by crops and tobacco leaves.

Disclosures

The authors declare that they do not have any conflict of interest.

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