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Clinical Research Study

Association between electronic cigarette use and fragility fractures among US adults

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ABSTRACT

Background: The popularity of electronic cigarette (e-cigarette) use continues to rise in the United States. While conventional cigarette smoking is an established risk factor for osteoporosis and osteoporotic fracture, the effects of e-cigarette use on bone health are unknown. We aimed to examine the association between e-cigarette use and fragility fractures.

Research Design and Methods: We pooled 2017–2018 data from the National Health and Nutrition Examination Survey (NHANES). We included men and women with complete information on key variables. E-cigarette use was categorized as either never or ever users. Ever users were further classified as former and current users. Fragility fracture was defined as a composite of self-reported fracture of the hip, spine or wrist which resulted from minimal trauma such as a fall from standing height or less.

Results: Of 5569 participants, there were 4519 (81.2%) never e-cigarette users, 1050 (18.8%) ever e-cigarette users, and 444 (8.0%) with self-reported fragility fracture. In adjusted models, ever e-cigarette users had a 46% higher prevalence of self-reported fragility fractures compared to never users (aPR: 1.46, 95% CI: 1.12, 1.89). We also observed a higher prevalence of fragility fractures among former and current e-cigarette users compared to never users (aPR: 1.89, 95% CI: 1.44, 2.48 and aPR: 1.77, 95% CI: 1.04, 3.02 respectively).

Conclusion: E-cigarette use was associated with a higher prevalence of self-reported fragility fracture. These findings suggest that e-cigarette use may be harmful to bone health. These data highlight the critical need for longitudinal studies exploring the potential effect(s) of e-cigarette use on bone health.

Introduction

Since their introduction over a decade ago, electronic cigarettes (e-cigarettes) have been marketed as a healthier alternative and an aid to conventional cigarette smoking cessation.[1–3] E-cigarettes contain a combination of propylene glycol, vegetable glycerin and variable levels of nicotine and additives, generating flavored vapor.[4] As a result of their attractive design and vapor delivery system, the use of e-cigarettes has gained increasing popularity. In a 2016 survey, about 11 million Americans were estimated to be active e-cigarette users.[5] Observational studies have reported an association between e-cigarette use and various disease processes affecting different organ systems.[6–10] Due to a lack of long term data, the full spectrum of potential health consequences from e-cigarette use remains unknown.

Osteoporosis, a disorder of the skeletal system characterized by low bone mineral density predisposes subjects to increased risk of fractures and causes significant physical, psychological, and financial burden.[11] Conventional cigarette smoking is an established risk factor for osteoporosis and osteoporotic fracture.[12,13] However, the effects of e-cigarette use on bone health are unknown. Because e-cigarettes contain significant amounts of nicotine,[14,15] it is plausible that they may have similar deleterious effects on bone health as traditional cigarette smoking. To this effect, evidence from laboratory studies shows that e-cigarette liquids have cytotoxic properties and induce osteotoxicity.[16–19] Hence, understanding the relationship between e-cigarette use and bone health may have important clinical implications.

Using data from the National Health and Nutrition Examination Survey (NHANES), we evaluated the association between e-cigarette use and fragility fractures among US adults. We hypothesized that e-cigarette use would be associated with increased fragility fractures.

Research design and methods

Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey of non-institutionalized adults and

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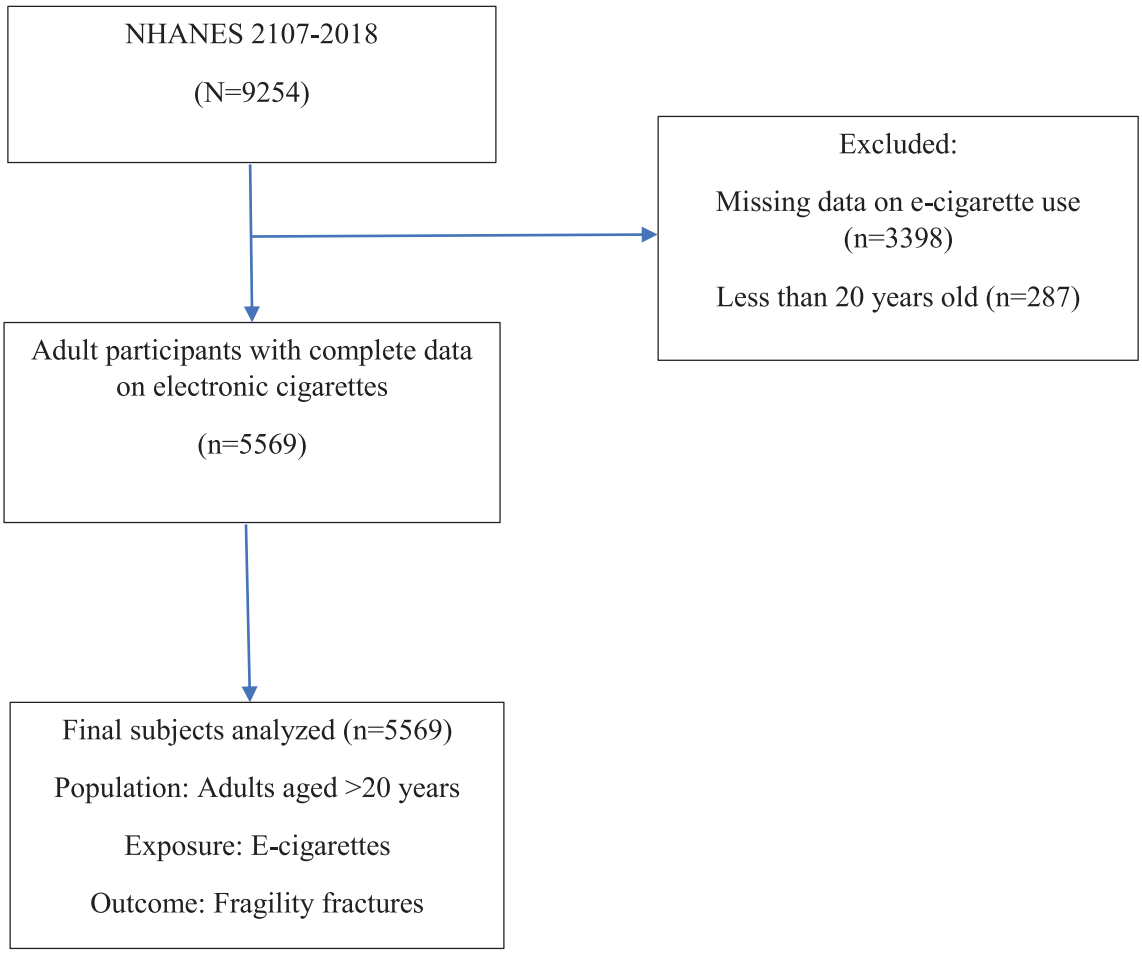

Fig. 1. Flowchart of study participant selection.

children in the United States. It is conducted by the Centers for Disease Control and Prevention (CDC) and designed to study the health and nutrition status of adults and children in the United States.[20] For this cross-sectional analysis we pooled NHANES data from 2017 to 2018 and included individuals with complete data on e-cigarette use. Of the 9254 eligible individuals, there were 3398 with missing data for e-cigarette use. We excluded individuals who were less than 20 years of age (n = 287). After applying these exclusions, 5569 adult men and women were included in our final analyses (Fig. 1).

Ascertainment of electronic cigarette use

Study participants were categorized as ever or never e-cigarette users based on their response to the question, "*Have you ever used an e-cigarette or other vaping product, even one time*?" Participants who answered in the affirmative were further asked the question, "*During the past 30 days, on how many days did you use e-cigarettes*?" Participants who reported zero e-cigarette use during the past 30 days were classified as former e-cigarette users, and those who reported using ≥1 e-cigarette were classified as current e-cigarette users.

Ascertainment of fragility fractures

Participants were asked, "Has a doctor ever told you that you had broken or fractured your hip, spine or wrist?" Those who answered yes, were asked the follow up question, "Did the fracture occur as a result of minimal trauma (such as falling from standing height or less), a hard fall (such as falling off a ladder, step stool, downstairs), or a car accident or other severe trauma?" Fragility fracture, the dependent variable of interest, was defined as a composite of self-reported fracture of the hip, spine or wrist which resulted from minimal trauma such as a fall from standing height or less.[21]

Assessment of covariates

Baseline characteristics including age, sex, race, level of education, body mass index (BMI), smoking status, family history of osteoporosis, history of steroid medication use, and level of physical activity were obtained using standardized questionnaires. Participants who responded in the affirmative to the question "*Have you smoked at least 100 cigarettes in your entire life?*" were categorized as ever combustible cigarette smokers. Ever combustible cigarette smokers were further categorized as former or current smokers based on the response to the question "*Do you now smoke cigarettes?*" Physical activity was defined as participating in moderate-intensity sports or activities that cause an increase in breathing or heart rate for 10 min continuously. Bone mineral density (BMD) was measured by Dual-Energy X-ray Absorptiometry (DEXA).

Statistical analyses

Baseline characteristics were presented by e-cigarette status (ever vs. never users) as mean (SD) for continuous variables and percentage for categorical variables. Participant characteristics were compared using the Student t-test, One-way Analysis of Variance (ANOVA), and $\chi 2$ test as appropriate. Poisson regression models with robust variance were used to assess the association between e-cigarette use and fragility fractures.

Table 1
Baseline characteristics of study participants by electronic cigarette (e-cig) use status.

Characteristics	Entire sample (n = 5569)	Never e-cig users (n = 4519)	Ever e-cig users (n = 1050)	p value
Age, years	51.5 (17.8)	54.3 (17.2)	39.6 (15.2)	<0.001
Men,%	48.5	46.8	56.1	<0.001
Race,%				<0.001
Non-Hispanic white	34.8	32.7	43.6	
Non-Hispanic black	23.3	23.5	22.6	
Other	41.9	43.8	33.8	
Education,%				<0.001
Less than high school	20.1	21.1	16.1	
High school graduate	23.8	22.7	28.6	
Attended college or higher	55.9	56.1	55.4	
Body mass index, kg/m^2	29.9 (7.4)	29.8 (7.1)	30.2 (8.4)	0.124
Current smoker,%	18.1	10.3	51.7	<0.001
Physical activity*,%	39.4	39.1	40.4	0.453
Hypertension,%	38.1	39.9	29.7	<0.001
Diabetes,%	15.7	17.1	10.1	<0.001
Steroid use,%	7.8	7.2	13.1	0.002
Family history of osteoporosis,%	12.4	11.6	19.3	<0.001
Bone mineral density, g/cm^2)				
Femur neck	0.76 (0.14)	0.75 (0.14)	0.76 (0.15)	0.353
Total spine	0.99 (0.01)	0.99 (0.17)	1.01 (0.18)	0.023
Fragility fracture,%	7.9	8.3	6.6	0.063

Data are mean (SD) or proportion (%) as appropriate. SD indicates standard deviation.
* Physical activity was defined as moderate-intensity sports, fitness, or recreational activity capable of increasing breathing or heart rate for 10 min continuously in a typical week.P value compares characteristics between Never, and ever e cigarette users.

We adjusted for confounding variables using a sequential approach. The first model adjusted for age, sex, race, and level of education (Model 1). The second model adjusted for covariates in Model 1 in addition to BMI, physical activity, combustible cigarette smoking status, family history of osteoporosis, and steroid medication use (Model 2). BMD appears to be in the causal pathway between conventional cigarette smoking and osteoporotic fractures.[13,22] We assumed BMD is also along the causal pathway between e-cigarette use and fragility fractures, hence does not constitute a confounder. Thus we did not include BMD in our regression models.

A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 15 (StataCorp, College Station, TX).

Results

Characteristics of study population

A total of 5569 individuals were included with a mean age of 51.5 (SD: 17.8) years and 51.5% were female. Ever e-cigarette users more likely to be younger, female, current combustible cigarette smokers, have a history of daily steroid medication use and have a family history of osteoporosis (Table 1).

Compared to never e-cigarette users, current users (ever cigarette users who reported using ≥ 1 e-cigarette in the past 30 days) were more likely to be younger, male, have less than high school level of education, obese, concurrently use combustible cigarette, and have a family history of osteoporosis (**Supplementary Table**).

Electronic-cigarette use and fragility fractures

In multivariate adjusted analyses, e-cigarette use was associated with an increase in the prevalence of self-reported fragility fractures. We observed a 1.87-fold higher prevalence of self-reported fragility fractures among ever e-cigarette users compared to never users (adjusted prevalence ratio [aPR]: 1.87, 95% CI: 1.44, 2.41) adjusting for age, sex, race, and level of education (Table 2). Additional adjustment for other covariates attenuated the magnitude of the association but did not change the significance (aPR: 1.46, 95% CI: 1.12, 1.89) (Table 2).

Table 2
Association between electronic cigarette (e-cig) use and fragility fracture.

E-cigarette category	PR (95% CI)*	p value	PR (95% CI)†	p value
Never users	1 (Reference)	…	1 (Reference)	…
Ever users	1.87 (1.44, 2.41)	<0.001	1.46 (1.12, 1.89)	0.005
Former users	1.89 (1.44, 2.48)	<0.001	1.46 (1.10, 1.94)	0.008
Current users	1.77 (1.04, 3.02)	0.035	1.43 (0.84, 2.45)	0.191

* Adjusted for age, gender, race, level of education (Model 1).
† Adjusted for age, gender, race, level of education, BMI, smoking, physical activity, steroid use, and family history of osteoporosis (Model 2)PR: prevalence ratio; CI: confidence interval.

When we subdivided ever e-cigarette users into former and current users, we also observed a higher prevalence of self-reported fragility fractures among former and current e-cigarette users compared to never users (aPR: 1.89, 95% CI: 1.44, 2.48 and aPR: 1.77, 95% CI: 1.04, 3.02 respectively) in multivariate-adjusted analysis (Table 2). With adjustment for additional covariates (Table 2), the association remained significant for former e-cigarette users (aPR: 1.46, 95% CI: 1.10, 1.94) but was not significant for current e-cigarette users (aPR: 1.43, 95% CI: 0.84, 2.45).

Among sole traditional cigarette smokers, there was a 63% higher prevalence of self-reported fragility fractures (aPR: 1.63, 95% CI: 1.18, 2.25) compared to individuals who were never combustible cigarette smokers and never e-cigarette users. Dual combustible cigarette smokers and e-cigarette users had a 2.41-fold higher prevalence of self-reported fragility fractures compared to never combustible cigarette smokers and never e-cigarette users (aPR: 2.41, 95% CI: 1.28, 4.55) (Table 3).

Discussion

We evaluated the association of e-cigarette use with self-reported fragility fractures in a large population of adult men and women in the United States. We observed a higher prevalence of self-reported fragility fractures among ever e-cigarette users compared to never users. We also

Table 3
Association between electronic cigarette (e-cig) use and conventional smoking with fragility fracture.

Smoking status	PR (95% CI)*	*p* value	PR (95% CI)†	*p* value
Never smoker, never e-cig user (*n* = 2974)	1 (Reference)	…	1 (Reference)	…
Never e-cig user & current smoker (*n* = 463)	1.82 (1.34, 2.47)	<0.001	1.63 (1.18, 2.25)	0.003
Dual smoker & e-cig user (*n* = 143)	2.70 (1.47, 4.97)	0.001	2.41 (1.28, 4.55)	0.006
P for trend		<0.001		<0.001

* Adjusted for age, gender, race, level of education (Model 1).
† Adjusted for age, gender, race, level of education, BMI, smoking, physical activity, steroid use, and family history of osteoporosis (Model 2)PR: prevalence ratio; CI: confidence interval.

found a similarly higher prevalence of fragility fractures among former and current e-cigarette users compared to never users. In addition, we observed a graded increase in the prevalence of fragility fractures among sole traditional cigarette smokers and dual users of traditional and e-cigarettes. These findings suggest that e-cigarette use may be detrimental to bone health.

To our knowledge, this is the first study to evaluate the relationship between e-cigarette use and fragility fractures. Our study fills an important knowledge gap given the rising popularity of e-cigarette use and the significant economic burden, and the known morbidity and mortality associated with osteoporotic fractures.[21,23] In fully adjusted multivariate analyses (Table 2), we observed a non-significant association between current e-cigarette use and fragility fractures (aPR:1.43, 95% CI: 0.83, 2.45) whereas former e-cigarette use was significantly associated with fragility fractures (aPR:1.46, 95% CI: 1.10, 1.94) despite both groups (current and former e-cigarette users) having similar point estimates (aPR 1.43 vs aPR 1.46 respectively). It is possible this is due to the pathophysiology of bone remodeling, where osteoblastic activity is reflexively increased in the early phase of increased nicotine-mediated osteoclast activity.[24–26] Nevertheless, this mechanism remains unclear.

Studies have established traditional cigarette smoking as a risk factor for osteoporosis and osteoporotic fractures[12,22,27,28] but the effects of e-cigarettes use on bone health are unknown and there is a paucity of population studies on the subject. Accruing evidence from laboratory studies demonstrates that some flavored e-cigarette liquids have cytotoxic properties.[16,17,19] Otero et al. recently showed that exposure to e-cigarette liquid induced osteotoxicity and increased expression of type I collagen even independently of nicotine.[18] This highlights the potential hazard e-cigarettes may pose to bone health.

The mechanisms by which e-cigarettes may affect bone health are unknown. E-cigarette aerosols have been associated with suppression of cellular antioxidant activity, oxidative stress, and DNA damage.[29,30] Because e-cigarettes are rife with significant amounts of nicotine,[14,15] it is plausible e-cigarettes share similar bone-destructing mechanisms. The pathogenesis of the deleterious effect of cigarette smoking on the musculoskeletal system is complex. However, two main mechanisms by which cigarette smoking leads to bone destruction have been proposed; First, nicotine in combustible cigarette has direct cytotoxic effects on bone forming osteoblast activity. Second, cigarette smoking leads to dysregulation in parathyroid hormone, cortisol, vitamin D and sex hormone production and metabolism.[22,31,32] This reduces bone mineral density (BMD) and predisposes smokers to fractures. Mechanistic studies are warranted to elucidate the potential mechanisms of e-cigarettes on bone health.

The potential public health implications of our findings are telling. In the USA, the prevalence of e-cigarette use is highest among persons aged 18 to 25 years and the majority of e-cigarette users without a history of conventional cigarette smoking are also in this age group.[5,33] Hence, it is possible that young e-cigarette users may have impaired bone development and consequently increasing their susceptibility to osteoporotic fractures later in life. Also, our findings may provide data to inform researchers, healthcare policy makers, and tobacco regulators about the potential association of e-cigarette use with reduced bone health. Finally, healthcare providers especially in primary care practice should consider routine collection of information pertaining to e-cigarette use and offer routine counseling to users about the potential detrimental effects of e-cigarette use.

Our study has limitations that need to be acknowledged and considered in the interpretation of our results. First, the cross-sectional nature of our study design limits our ability to make causal inferences between e-cigarettes and fragility fractures. Second, while we were able to control for many potential confounders, the effect estimates we observed may be subject to residual confounding. Third, granular characteristics of e-cigarette use such as brand of e-cigarette used, duration of vaping were not systematically available to allow for such sub-group analyses. Fourth, the exposure variable and outcome of interest were self-reported, which may be subject to recall bias and nonrandom misclassification. Also, there is the possibility that for some individuals e-cigarette use may have started after fracture occurrence and diagnosis. Furthermore, this study did not analyze the relationship between current e cig users who were former conventional cigarettes users and the rates of fragility fractures. Doing so might have opened up a wider reach of clinical implications.

Conclusion

In summary, in a large, nationally representative survey of US adults we found an increased prevalence of self-reported fragility fractures among e-cigarette users and also a graded increase in prevalence among current conventional cigarette smokers who do not use e-cigarettes and dual users of conventional and e-cigarettes. These findings suggest that e-cigarette use may be detrimental to bone health. Longitudinal studies are needed to investigate the risk of osteoporotic fractures associated with e-cigarette use.

Conflict of Interest

None

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Authors' contributions

All authors contributed to this study. DDA, BBA KEE, FAM and JMC were involved in the conception and design of the study. DDA, BBA KEE, FAM and JMC acquired the data. DDA analyzed the data. DDA, BBA KEE, FAM and JMC interpreted the data. DDA, BBA KEE, FAM and JMC wrote the article, revised it critically for important intellectual content and approved the final manuscript for publication.

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Data availability

Data used for analysis of this study is available upon reasonable request from the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ajmo.2021.100002.

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