Thiazide Use and Fracture Risk: An updated Bayesian Meta-Analysis

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The association between thiazide use and fracture risk is still controversial. We conducted an updated meta-analysis on the association between thiazide use and fracture risk. We systematically searched PubMed, Embase, and Cochrane library databases for all types of human studies, including observational and experimental studies that were published up until July 2019. We also manually searched the reference lists of relevant studies. The pooled relative risks (RRs) with 95% credible interval (CrI) were calculated using a Bayesian hierarchical random effect model. A total of 19 case-control (N = 496,568 subjects) and 21 cohort studies (N = 4,418,602 subjects) were included in this meta-analysis. The pooled RR for fractures associated with thiazide use was 0.87 (95% CrI: 0.70–0.99) in case-control and 0.95 (95% CrI: 0.85–1.08) in cohort studies. The probabilities that thiazide use reduces any fracture risk by more than 0% were 93% in case-control studies and 72% in cohort studies. Significant heterogeneity was found for both case-control (p < 0.001, I² = 75%) and cohort studies (p < 0.001, I² = 97.2%). Thiazide use was associated with reduced fracture risk in case-control studies, but not in cohort studies. The associations demonstrated in case-control studies might be driven by inherent biases, such as selection bias and recall bias. Thus, thiazide use may not be a protective factor for fractures.

Hypertension and osteoporotic fracture are two major public health problems because they result in a substantial financial burden among the elderly as well as considerable increases in morbidity and mortality1,2. Thiazide diuretics are one of the most common types of antihypertension medications3,4. There is evidence suggesting that thiazide diuretics reduce urinary calcium excretion5 and stimulate osteoblast differentiation and bone mineral formation6. Although a previous meta-analysis suggested that thiazide use was associated with reduced fracture risk7–9, results of individual studies are still inconsistent, ranging from positive to negative effects10–19. In addition, two previous meta-analyses were published over a decade ago17–19, and the most recent meta-analysis that was published in 2018 was limited to only prospective cohort studies8. Therefore, an updated meta-analysis that is inclusive of all types of study designs is warranted. We conducted a Bayesian meta-analysis on the association between thiazide use and fracture risk as it uses a probabilistic approach to make clinically relevant decisions in the face of uncertainty. For example, using the Bayesian method, we can determine the probability that thiazide use reduces fracture risk by more than 0%, 10% or 20%; this probability is unable to be provided by classical analysis20. Therefore, we utilized an advanced methodology in meta-analysis research to address the much controversial relationship between thiazide use and fracture risk that encapsulates all peer-reviewed publications in the field thus far.

Methods

Data searching. This study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)21. We systematically searched PubMed, Embase, and Cochrane library databases for all types of human studies, including observational and experimental studies that were published up until July 2019. The keywords and medical subject headings (MeSH) used for the search were: “thiazide” OR “Sodium Chloride Symporter Inhibitors” AND “Bone fracture” OR “Fracture” OR “Osteoporosis”. We also manually searched the reference lists of relevant studies. Studies were included in the meta-analysis if they met the following criteria: (a) were original human studies; (b) used thiazide as an exposure; (c) had risk estimates for fracture outcome. When more than one study used the same data, we included the most recent and best quality study in our meta-analysis.
Data extraction and quality assessment. Two investigators (TGC, SY) independently identified and extracted all potential articles for inclusion. Any disagreement between the above two investigators was resolved by discussing it with the third author (YL). The following information was retrieved from each study: first author’s name, year of publication, the percentage of female participants, sample size, fracture outcome, mean age, country, and fracture risk estimates. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of each individual study. Briefly, the NOS score was assessed using the following items: selection, comparability, exposure, and outcome; a NOS score of 7 or higher is considered as high quality.

Statistical analysis. We synthesized the data using both classical and Bayesian hierarchical random-effects models. In classical meta-analysis, we used the DerSimonian-Laird method to calculate the pooled risk ratio. In the Bayesian model, the risk ratios (RRs) for all the studies were converted into a logarithmic scale (denoted as \( \phi_i \)). Each \( \phi_i \) was assumed to have a normal distribution with a true, but unknown effect size (\( \theta_i \)) and known within-study variance (\( \delta_i^2 \)). The collection of \( \theta_i \) across the studies was assumed to have a normal distribution, with unknown mean (\( \mu \)) and variance (\( \tau^2 \)). The prior information of \( \tau^2 \) was assumed to be an inverse gamma distribution (0.001, 0.001). The prior function for \( \mu \) was assumed equivocal prior; i.e., thiazide use does not affect fracture risk (\( \mu = 0 \), variance = 10,000). We also examined the probability that thiazide use reduces fracture risk by more than 0%, 10%, and 20% (i.e., \( \text{RR} < 1.0, 0.9, 0.8 \)). Heterogeneity of the included studies was assessed with Cochran’s Q-statistic test, and inconsistency was quantified by I² statistic. Funnel plots were generated to identify potential publication bias using Egger’s test. All analyses were performed by the programs WinBUGS (Version 1.4.3, MRC Biostatistics Unit, Cambridge, UK) and R (Version: 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).

Results
Characteristics of studies. We identified a total of 959 articles from different electronic databases and other sources. Of these, 633 duplicate articles and 181 irrelevance articles were excluded after reading the title or abstract. Finally, 19 case-control studies and 21 cohort studies were met for inclusion in this meta-analysis (Fig. 1). A majority (72.5%) of the included studies were considered as high quality based on NOS standards (Table 1). In the case-control studies, approximately 79% of the participants (Total sample size = 496,568) were female; the average participant
Approximately 63% of the subjects (Total sample size = 4,418,602) were female in cohort studies. The average participant age in the cohort studies was 73 years old. In the classical meta-analysis of case-control studies, we found a negative association between thiazide use and fracture risk (Risk ratio (RR): 0.87, 95% confidence interval (CI): 0.76–0.98). We observed moderate heterogeneity between studies (p < 0.001, I² = 75%; Fig. 2). In the Bayesian analysis, the pooled RR for fractures associated with thiazide use was 0.87 (95% credible interval (CrI) 0.70–0.99). The probabilities that thiazide use reduces fracture risk by more than 0%, 10%, and 20% were 93%, 66%, and 23%, respectively (Table 2).

Table 1. Descriptive characteristics for included studies. *Mean ages are reported separately for case-control studies (case/control). Abbreviations: NA: Not available; NOS: Newcastle Ottawa Scale.

| Author(s) | Percentage of females | Sample size | Fracture outcome | Mean agea | Country | NOS score |
|-----------|-----------------------|-------------|------------------|-----------|---------|-----------|
| Case-control study |
| Rashiq16  | 49 306 Hip fracture    | 79/78 UK    | 7               |
| Ray14    | 74 6137 Hip fracture   | NA Canadian | 7               |
| Stevens19 | 79 307 Hip fracture    | 79/77 UK    | 5               |
| Heinrich20 | 76 924 Hip fracture   | NA USA     | 7               |
| Felson21  | 100 848 Hip fracture   | 77/78 UK    | 9               |
| Jensen22  | 83 400 Hip fracture    | 80/80 Denmark | 7          |
| Cumming26 | NA 416 Hip fracture    | 65/65 Australia | 9         |
| Herings44 | 74.9 772 Hip fracture | 78/78 Netherland | 8     |
| Barengolts45 | NA 436 Hip fracture | 70/70 USA | 6           |
| Weiland46  | 100 725 Hip fracture   | 73/73 Germany | 8         |
| Wang47    | 84 6110 Hip fracture   | 84/84 USA    | 7               |
| Luetters48 | 77 3286 Foot fracture  | 59/65 USA    | 7               |
| Schlienger49 | NA 151420 Any fracture | NA UK    | 8               |
| Kelsey50  | 78 2594 Pelvis        | NA USA      | 5               |
| Rejmark51  | 65 258810 Any/hp/vertebral | 66/66 Denmark | 9     |
| Kelsey52  | 77 2578 Tibia, fibula | 45/45 USA    | 7               |
| Peters53   | 60 3845 Any fracture   | 84/84 USA    | 4               |
| Berry54    | NA 56,416 Hip fracture | NA UK    | 8               |
| Vecchis54  | 100 238 Vertebral      | 69 Italy     | 4               |
| Cohort study |
| Cauley55  | 100 9704 Any/hp/humerus | 72 USA    | 9               |
| Cumming56  | 100 9516 Hip fracture   | NA Australia | 8       |
| Nguyen57   | 0 820 Any/hp/vertebral | NA Australia | 6     |
| Gust60    | 74 1608 Hip fracture    | 82 Sweden    | 7               |
| Feskanich61 | 100 83728 Any/hp fracture | NA USA | 7          |
| Schools62  | NA 7891 Hip fracture    | NA Netherland | 7     |
| Solomon58  | 80 376061 Any/hp/humerus | 80 USA    | 8               |
| Buty3     | 81 1463 Hip fracture    | 81 Canadian  | 8               |
| LaCroix64  | 61 9518 Hip fracture    | 74 UK        | 8               |
| Chow65     | 66 439 Any fracture     | 71 China     | 7               |
| Carbone66  | 0 6969 Vertebral fracture | 59 USA    | 4               |
| Bekezant67 | 55 60893 Any fracture   | 66 Sweden    | 7               |
| Ruthe68    | 56 906422 Hip fracture  | 73 Norway    | 8               |
| Kruse69    | NA 1123670 Any/hp/vertebral | 69 Denmark | 7          |
| Paik70     | 100 55780 Vertebral fracture | 67 UK    | 3               |
| Chen71     | 56 1144 Any fracture    | 77 Taiwan    | 8               |
| Puttnam72  | 43 22180 Hip/Pelvic     | 70 USA       | 7               |
| Torstensson73 | 54 1586554 Any fracture | 75 Denmark  | 5               |
| Lin12     | 42 7470 Hip fracture    | NA Taiwan    | 5               |
| Kim74      | 59 137304 Any fracture  | 73 South Korea | 7     |
| Lin75      | 42 9468 Vertebral fracture | NA Taiwan | 6        |

Table 1. Descriptive characteristics for included studies. *Mean ages are reported separately for case-control studies (case/control). Abbreviations: NA: Not available; NOS: Newcastle Ottawa Scale.

Thiazide use and fracture risk in case-control studies. In the classical meta-analysis of case-control studies, we found a negative association between thiazide use and fracture risk (Risk ratio (RR): 0.87, 95% confidence interval (CI): 0.76–0.98). We observed moderate heterogeneity between studies (p < 0.001, I² = 75%; Fig. 2). In the Bayesian analysis, the pooled RR for fractures associated with thiazide use was 0.87 (95% credible interval (CrI) 0.70–0.99). The probabilities that thiazide use reduces fracture risk by more than 0%, 10%, and 20% were 93%, 66%, and 23%, respectively (Table 2).

Thiazide use and fracture risk in cohort studies. In the classical meta-analysis of cohort studies, there was no significant association between thiazide use and fracture risk (RR: 0.93, 95% CI: 0.83–1.05). The heterogeneity between studies was significant (p < 0.001, I² = 97.2%; Fig. 3). In the Bayesian analysis, the pooled RR for
The controversy regarding the relationship between thiazide use and fracture risk involves conflicting mechanisms. On one hand, thiazide could exert beneficial effects on the bone via decreasing urinary calcium excretion by 25–40%.31,32 In addition, thiazides are associated with an increased level of metabolic alkalosis, which is an important factor in the prevention of fractures.33,34 However, these effects may be offset by the increased risk of hip fractures associated with thiazide use, which was observed in the current meta-analysis.

### Discussion

This meta-analysis provides evidence to support that thiazide exposure is associated with a 13% reduction of fracture risk in case-control studies. However, while an inverse association was noted in cohort studies, it failed to reach statistical significance. Our findings were partly comparable with the effect shown in the previous two meta-analyses reported by Wiens et al.8 and Xiao et al.9; both studies suggested that thiazide was associated with the reduction of fracture risk by 14%. However, to the best of our knowledge, our meta-analysis is the first to distinguish a difference in the relationship between thiazide use and fracture risk by study design. We found that there is a null relationship between thiazide use and fracture risk in cohort studies. A recently published meta-analysis also suggested that the effect of thiazide use on fracture risk was weaker in cohort studies.9 Although the results from the Bayesian meta-analysis were consistent with that generated from the classical meta-analysis approach, the Bayesian meta-analysis provides additional regarding the probabilities that thiazide use reduces fracture risk by certain percentages. Such information is useful for making clinically relevant decisions about the use of thiazides, and cannot be obtained using the traditional meta-analysis methodology.

The controversial relationship between thiazide diuretics and fractures involves conflicting mechanisms. On the one hand, thiazide could exert beneficial effects on the bone via decreasing urinary calcium excretion by 25–40%.31,32 In addition, thiazides are associated with an increased level of metabolic alkalosis, which is an important factor in the prevention of fractures.33,34 However, these effects may be offset by the increased risk of hip fractures associated with thiazide use, which was observed in the current meta-analysis.
inhibitor of bone resorption. On the other hand, thiazides diuretics could induce hyponatremia, which has a negative impact on the metabolism and integrity of the bone. In addition, thiazide induced-hyponatremia could have harmful neurological side effects, such as gait disturbances and imbalance, which leads to an increased risk of falls and fractures.

This meta-analysis has several limitations. First, due to the absence of relevant experimental studies in humans, our meta-analysis included only observational studies. A meta-analysis based on observational studies cannot make causal inferences about thiazide use and fracture risk. Second, we observed considerable heterogeneity between individual studies, which might bias our results. Lastly, due to insufficient data from individual studies, we did not evaluate the effect of dose and duration of thiazide use on bone fractures.

In conclusion, this meta-analysis included 19 case-control and 21 cohort studies to examine the relationship between thiazide use and fracture risk. Our results suggest that thiazide use was associated with reduced fracture risk in case-control studies, but not in cohort studies. The associations demonstrated in case-control studies might be driven by inherent biases such as selection bias and recall bias. Thus, thiazide use may not be a protective factor for fractures. Randomized clinical trials are still warranted to confirm our findings.
References

1. Cappuccio, F. P., Meilahn, E., Zmuda, J. M. & Cauley, J. A. High blood pressure and bone-mineral loss in elderly white women: a prospective study. Study of Osteoporotic Fractures Research Group. Lancet 354, 971–975 (1999).

2. Johnell, O. & Kanis, J. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 17, 1726–1733 (2006).

3. Ilic, K., Obradovic, N. & Vujasinovic-Stupar, N. The relationship among hypertension, antihypertensive medications, and osteoporosis: a narrative review. Calcif Tissue Int 92, 217–227 (2013).

4. Wright, J. & Musini, V. First-line drugs for hypertension. Cochrane Database Syst Rev, CD001841 (2009).

5. Butt, D. A. et al. The risk of hip fracture after initiating antihypertensive drugs in the elderly. Arch Intern Med 172, 1739–1744 (2012).

6. Dvorak, M. M. et al. Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by interacting with a sodium chloride co-transporter in bone. J Am Soc Nephrol 18, 2509–2516 (2007).

7. Jones, G., Nguyen, T., Sambrook, P. N. & Eisman, J. A. Thiazide diuretics and fractures: can meta-analysis help? J Bone Miner Res 10, 106–111 (1995).

8. Wiens, M., Elminan, M., Gill, S. & Takkouche, B. Effects of antihypertensive drug treatments on fracture outcome: a meta-analysis of observational studies. J Intern Med 260, 350–362 (2006).

9. Xiao, X., Xu, Y. & Wu, Q. Thiazide diuretic usage and risk of fracture: a meta-analysis of cohort studies. Osteoporos Int 29, 1515–1524 (2018).

10. Kim, S. Y. et al. Number of daily antihypertensive drugs and the risk of osteoporotic fractures in older hypertensive adults: National health insurance service-senior cohort. J Cardiovasc Dis Res 8, 85–85 (2017).

11. Kruse, C., Eiken, P. & Vestergaard, P. Continuous and long-term treatment is more important than dosage for the protective effect of thiazide use on bone metabolism and fracture risk. J Intern Med 279 (2016).

12. Lin, S. M., Yang, S. H., Cheng, H. Y., Liang, C. C. & Huang, H. K. Thiazide diuretics and the risk of hip fracture after stroke: a population-based propensity-matched cohort study using Taiwan’s National Health Insurance Research Database. BMJ Open 7, e016992 (2017).

13. Lin, S. M., Yang, S. H., Wang, C. Y. & Huang, H. K. Association between diuretic use and the risk of vertebral fracture after stroke: a population-based retrospective cohort study. BMC Musculoskelet Disord 20, 96 (2019).

14. Paik, J. M., Rosen, H. N., Gordon, C. M. & Curhan, G. C. Diuretic Use and Risk of Vertebral Fracture in Women. Am J Med 129, 1299–1306 (2016).

15. Putnam, R. et al. Antihypertensive, Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Association of 3 Different Antihypertensive Medications With Hip and Pelvic Fracture Risk in Older Adults: Secondary Analysis of a Randomized Clinical Trial. JAMA Intern Med 177, 67–76 (2017).

16. Rashiq, S. & Logan, R. F. A. Role of drugs in fractures of the femoral neck. Br Med J 292, 861–863 (1986).

17. Rejnmark, L., Vestergaard, P. & Mosekilde, L. Reduced fracture risk in users of thiazide diuretics. Calcif Tissue Int 76, 167–175 (2005).

18. Ruths, S. et al. Risk of hip fracture among older people using antihypertensive drugs: a nationwide cohort study. BMC Geriatr 15, 153 (2015).

19. Solomon, D. H., Mogun, H., Garneau, K. & Fischer, M. A. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res 26, 1561–1567 (2011).

20. Burton, P. R., Gurrin, L. C. & Campbell, M. J. Clinical significance not statistical significance: a simple Bayesian alternative to p-values. J Epidemiol Community Health 52, 318–323 (1998).

21. Liberati, A. et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 62, e1–34 (2009).

22. Zeng, X. et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 8, 2–10 (2015).

23. Poorolajal, J. & Darvishi, N. Smoking, and Suicide: A Meta-Analysis. Community Med 7, 27–34 (1989).

24. Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. BMJ 331, 557–560 (2003).

25. Abrams, K. & Sanso, B. Bayesian Data Analysis (Chapman & Hall/CRC, New York, 1996).

26. DerSimonian, R. & Laird, N. Meta-analysis in clinical trials. Control Clin Trials 7, 177–188 (1986).

27. Higgins, J. P. Thompson, S. G., Deeks, J. J. & Altman, D. G. Measuring inconsistency in meta-analyses. BMJ 327, 557–560 (2003).

28. Egger, M. D., Smith, G., Schneider, M. & Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ 315, 629–634 (1997).

29. Duarte, C. G., Winnacker, J. L., Becker, K. L. & Pace, A. Thiazide-induced hypercalcemia. The New England Journal of Medicine 284, 828–830 (1971).

30. Lamberg, B. A. & Kuhlback, B. Effect of chlorothiazide and hydrochlorothiazide on the excretion of calcium in urine. Scandinavian Journal of Clinical and Laboratory Investigation 11, 351–357 (1959).

31. Arnett, T. R. & Spowage, M. Modulation of the resorptive activity of rat osteoclasts by small changes in extracellular pH near the physiological range. Bone 18, 277–279 (1996).

32. Peh, C. A. et al. The effect of chlorothiazide on bone-related biochemical variables in normal post-menopausal women. J Am Geriatr Soc 41, 513–516 (1993).

33. Upala, S. & Sanguankeow, A. Association Between Hypometraemia, Osteoporosis, and Fracture: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab 101, 1880–1886 (2016).

34. Hovis, J. G. et al. Intracellular calcium regulates insulin-like growth factor-I messenger ribonucleic acid levels. Endocrinology 132, 1931–1938 (1993).

35. Rennegbog, B., Musch, W., Vandermeergel, X., Manto, M. U. & Decaux, G. Mild chronic hyperparathyroidism is associated with falls, unsteadiness, and attention deficits. Am J Med 119, 71 e71–78 (2006).

36. Ray, W. A., Griffin, M. R., Downey, W. & Melton, L. J. Long-term use of thiazide diuretics and the risk of hip fracture. Lancet 1, 687–690 (1989).

37. Stevens, A. & Mulrow, C. Drug’s affecting postural stability and other risk factors in the hip fracture epidemic case-control study. Community Med 7, 27–34 (1989).

38. Heidrich, F. E., Stermachis, A. & Gross, K. M. Diuretic drug use and the risk for hip fracture. Ann Intern Med 115, 1–6 (1991).
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