

Association Between Hyponatremia, Osteoporosis, and Fracture: A Systematic Review and Meta-analysis

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Context: Hyponatremia is the most common electrolyte disorder. Recent research shows that it may associate with osteoporosis and fracture. However, whether it directly associates or is a surrogate marker of other causes is still unclear.

Objectives: To explore the hypothesis of an association of osteoporosis or fracture with hyponatremia.

Data Sources: MEDLINE and EMBASE databases from inception to October 2015.

Study Selection: The inclusion criteria were published studies evaluating bone mineral density, risk or prevalence of osteoporosis or fracture in patients with hyponatremia.

Data Extraction: Both authors independently reviewed titles and abstracts of all citations that were identified.

Data Synthesis: A meta-analysis using a random-effects model comparing between hyponatremia and normal serum sodium groups was performed. We calculated pooled mean difference in bone mineral density, pooled hazard ratio (HR) or odds ratio (OR) of fracture and osteoporosis. Factors that may predict these associations were evaluated in subgroup analysis and meta-regression.

From 29 full-text articles, 15 observational studies involving 212 889 participants met our inclusion criteria. Twelve studies were included in the meta-analysis. There was a significant association with fracture and osteoporosis in patients with hyponatremia with OR of fracture = 1.99 (95% confidence interval, 1.50–2.63; $p < .001$) for studies that reported OR, and increase risk of fracture with HR = 1.62 (95% confidence interval, 1.28–2.05; $P < .001$) for studies that reported HR.

Conclusions: Hyponatremia significantly associates with osteoporosis and fracture. More prospective studies evaluating osteoporosis and fracture risk reduction after hyponatremia correction should be performed. (*J Clin Endocrinol Metab* 101: 1880–1886, 2016)

Hyponatremia is defined as plasma sodium level less than 135 mEq/L (1). Severe hyponatremia may cause brain injury presenting as confusion, change in mental status, and may lead to death (2, 3). Its rapid correction may lead to central pontine myelinosis, a condition in which neurons swell due to intracellular shifting of water (4). Hyponatremia is also found to associate with other

conditions such as respiratory failure, hypocalcemia, and hyperparathyroidism (5).

Since the recent work by Verbalis et al (6) in animals, which suggested that hyponatremia might induce osteoporosis, there were several publications regarding association between serum sodium level, hyponatremia, and decreased bone mineral density (BMD), osteoporosis, falls,

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; HR, hazard ratio; ICD, international classification of diseases; OR, odds ratio.

and fracture risk (7, 8). However, because hyponatremia is considered a novel risk factor of bone disorder, it is still uncertain whether this association is due to a direct effect of low level of sodium on bone or whether it is a surrogate marker of another etiology such as fracture from falls or medication-induced osteoporosis (9).

We performed a systematic review and meta-analysis of available observational studies that assess association between hyponatremia and BMD, osteoporosis, and fracture in the general population and patients who came to the hospital. Our objective was to test the hypothesis of an association between osteoporosis or fracture and hyponatremia and to see whether there are any factors that predict these associations.

Materials and Methods

This systematic review and meta-analysis was conducted and reported according to the Meta-analysis Of Observational Studies in Epidemiology statement (10) and was registered in PROSPERO (registration number, CRD42015024011).

Search strategy

Both authors (A.S., S.U.) independently searched published studies indexed in the MEDLINE and EMBASE from date of inception to October 2015. References of all selected studies were also examined. The following main search terms were used: hyponatremia, hyponatraemia, osteoporosis, BMD, bone mass, and fracture. The full search terms used are detailed in the [Supplemental Materials and Methods](#).

Inclusion and exclusion criteria

This review included all published observational studies including cross-sectional, prospective cohort, retrospective cohort and case-control studies that assessed the association of hyponatremia and osteoporosis, BMD, or fractures. Reviews, case reports, and abstracts were excluded because their quality of studies could not be assessed.

We included studies that recruited participants from the general population or used data from medical records from healthcare facilities. Participants had to be at least 18 years old and have had serum sodium measured at least once before outcome assessment. We compared outcome between patients who had hyponatremia, which is defined as a plasma sodium level of less than 135 mEq/L (135 mmol/L), and participants with normonatremia (135–145 mEq/L). The main outcome of this study was incidence or prevalence of fractures at any of these anatomical sites: upper limb (distal forearm, proximal humerus), axial skeleton (spine, sacrum and pelvis), and lower limb (femur-neck, -trochanter, and -shaft, distal tibia, and lateral or medial malleolus). The secondary outcomes were BMD measured by dual-energy x-ray absorptiometry (DXA), and incidence or prevalence of osteoporosis, which was defined as having BMD with a T-score less than -2.5 SD at the lumbar spine, femur neck, or total hip (11).

Data extraction

Both authors independently reviewed titles and abstracts of all citations that were identified. After all abstracts were reviewed, data comparisons between the 2 investigators were conducted to ensure completeness and reliability. The inclusion criteria were independently applied to all identified studies. Differing decisions were resolved by consensus.

Full-text versions of potentially relevant papers identified in the initial screening were retrieved. If multiple articles from the same source of population were found, only the article with the longest follow-up period was included in the meta-analysis. Data concerning study design, source of information, participant characteristics, medication, time of sodium measurement, definition of outcome measures, and factors adjusted in multivariate model were independently extracted. We contacted the authors of the primary reports to request any unpublished data. If the authors did not reply, we used the available data for our analyses.

Assessment of bias risk

A subjective assessment of methodological quality for observational studies was evaluated by the 2 authors using the Newcastle-Ottawa scale (12), which is a quality assessment tool for nonrandomized studies. It uses a “star system” based on 3 major perspectives: the selection of the study groups (0–4 stars, or 0–5 stars for cross-sectional studies), the comparability of the groups by controlling for important and additional relevant factors (0–2 stars), and the ascertainment of outcome of interest or exposure (0–3 stars). A total score of 3 or less was considered poor, 4–6 was considered moderate, and 7–10 was deemed high quality. We excluded studies from our meta-analysis if they had poor quality. Discrepant opinions between authors were resolved by consensus.

Statistical analysis

We performed meta-analysis of the included studies using Comprehensive Meta-Analysis 3.3 software from Biostat, Inc. We calculated pooled odds ratio (OR) of outcome for cross-sectional and case-control studies. We calculated pooled hazard ratio (HR) of outcome for cohort studies. We calculated pooled mean difference of BMD at each anatomical site. All outcomes were reported as effect estimates and their 95% confidence intervals (CIs). These were compared between hyponatremia and normonatremia groups using a random-effects model. If a study reported multiple anatomical sites for osteoporosis or fracture, we used the outcome from each site and calculated the pooled effect size with other studies. We excluded studies from meta-analysis and only presented the result with narrative description (qualitative analysis) when there were not sufficient data available for calculating pooled effect size. The heterogeneity of effect estimates across these studies was quantified using the Q statistic and I^2 ($P < .10$ was considered statistically significant). The Q statistic compared the observed between-study dispersion and expected dispersion of the effect size, and was expressed in p-value for statistical significance. An I^2 is the ratio of true heterogeneity to total observed variation. An I^2 of 0%–40% was considered to exclude heterogeneity, of 30%–60% was considered to represent moderate heterogeneity, of 50%–90% was considered to represent substantial heterogeneity, and of 75%–100% was considered to represent considerable heterogeneity (13). A sensitivity analysis was performed to assess influence of the individual studies on the overall results by omitting 1 study

at a time and using fixed-effect analysis when I^2 was less than 40%. Subgroup analysis and meta-regression were performed to find factors that may explain heterogeneity or difference in outcome between each study. Publication bias was assessed using funnel plot, Egger's regression test, and its implications with the trim and fill method (14).

Results

Description of included studies

The initial search yielded 608 articles (Supplemental Figure 1); 579 articles were excluded because they were not original observational studies (199 articles), had no data on serum sodium status in participants (129 articles), included participants younger than 18 years old (36 articles), or did not measure fracture, BMD, or osteoporosis as outcome (215 articles). A total of 29 articles underwent full-length review. Data were extracted from 15 studies involving a total of 212209

participants for qualitative analysis (6, 7, 15–27). All of them were observational studies. Seven were cross-sectional, 4 studies were cohort, and 4 were case-control studies. The included studies varied in study location, sample size, source of data, time of serum sodium measurement, definitions of osteoporosis and fracture, and factors adjusted in multivariate model. The characteristics of the 15 extracted studies included in this review were outlined in Table 1.

Included studies were performed in the United States, Switzerland, Italy, China, the Netherlands, Belgium, Ireland, and Denmark. None of them used the same database. Most studies included participants aged 50 years or older, except for Lawson et al (24) and Usala et al (27) that had mean age of 25.6 and 47, respectively. All participants in Chow et al (18) had thiazide-induced hyponatremia, but most other studies did not have diuretics data. Most studies had serum sodium measured once before encounter or

Table 1. Characteristics of Included Studies

Study, Year, Country	Design	Source of Population	Participants (n)	Serum Sodium	Time of Sodium Measurement	Outcome Definition		Factors Adjusted in Multivariate Model
						Osteoporosis	Fracture	
Afshinnia, 2015, United States	Cross-sectional	Outpatient units	24 784	140.2 (2.3)	Time-averaged measurements	T-score < -2.5 SD		Age, sex, race, BMI, medications, comorbidities
Arampatzis, 2013, Switzerland	Cross-sectional	ED	10 823	134 (4) ^a	Single measurement on admission		Low-impact fractures of the upper limb, axial skeleton, and lower limb	Age, sex, amiloride, furosemide
Cervellin, 2014, Italy	Case-control	Hospital	1243	138 (136–140) ^a	Single measurement on admission		Femoral neck fracture	Age, sex
Chow, 2011, China	Retrospective cohort	General population with thiazide-induced hyponatremia	439	116 (98–128) ^a	Record of hyponatremia		Radiology reports	Age, sex, BMI, DM, smoking
Hoorn, 2011, Netherlands	Prospective cohort	Population aged 55 y and older	5208	133.4 (2.0) ^a	Single measurement at baseline visit		ICD-10	Age, sex, BMI, DM, medication, falls
Jamal, 2015, United States	Prospective cohort	Men aged 65 y and older	5122	132.3 (1.8) ^a	Single measurement at baseline visit		Medical records and x-ray reports	Age, BMI, alcohol, falls
Kengne, 2008, Belgium	Case-control	Hospital database	1026	131 (3) ^a	Measurement at pretreatment of fall		ED physician diagnosis	Age, medication, comorbidities, alcohol
Kinsella, 2010, Ireland	Cross-sectional	Hospital database	1408	132.2 (1.8) ^a	Within 1 y before DXA	T-score < -2.5 SD	Radiology reports	Age, osteoporosis treatments
Kruse, 2015, Denmark	Cross-sectional	Hospital database	1575	131.5 (2.5) ^a	Within 14 d before or after the DXA scanning date	T-score < -2.5 SD		Age, gender, and BMI
Holm, 2015, Denmark	Retrospective cohort	Hospital database	5610	132.7 (2.6) ^a	Single measurement at baseline	T-score < -2.5 SD	Lumbar spine, femoral neck, total hip	Age, loop diuretics, and thiazide diuretics
Lawson, 2012, United States	Cross-sectional	Hospital database	404	140.6 (0.3)	Monitored for consistency over the study timeframe			
Sandhu, 2009, United States	Cross-sectional	Ambulatory patients	728	131 (2) ^b	Single measurement on initial encounter		Radiology reports	
Tolouian, 2012, United States	Case-control	Hospital databases	293	137.4 (3.8) ^a	Single measurement on initial encounter		Orthopedic surgeon confirm hip fracture	Age
Usala, 2015, United States	Case-control	MedStar Health database	153 546	N/A	At least 1 measurement	ICD-9	ICD-9	BMI, medication, comorbidity
Verbalis, 2010, United States	Cross-sectional	NHANES III participants		133.0 (0.2) ^a		T-score < -2.5 SD		Age, sex, BMI, diuretics

Values are presented as mean (SD) or median (interquartile range). DM, diabetes mellitus; ED, emergency department; NHANES, National Health and Nutrition Examination Survey; OS, osteoporosis group.

^a Data from hyponatremia group.

^b Data from fracture group.

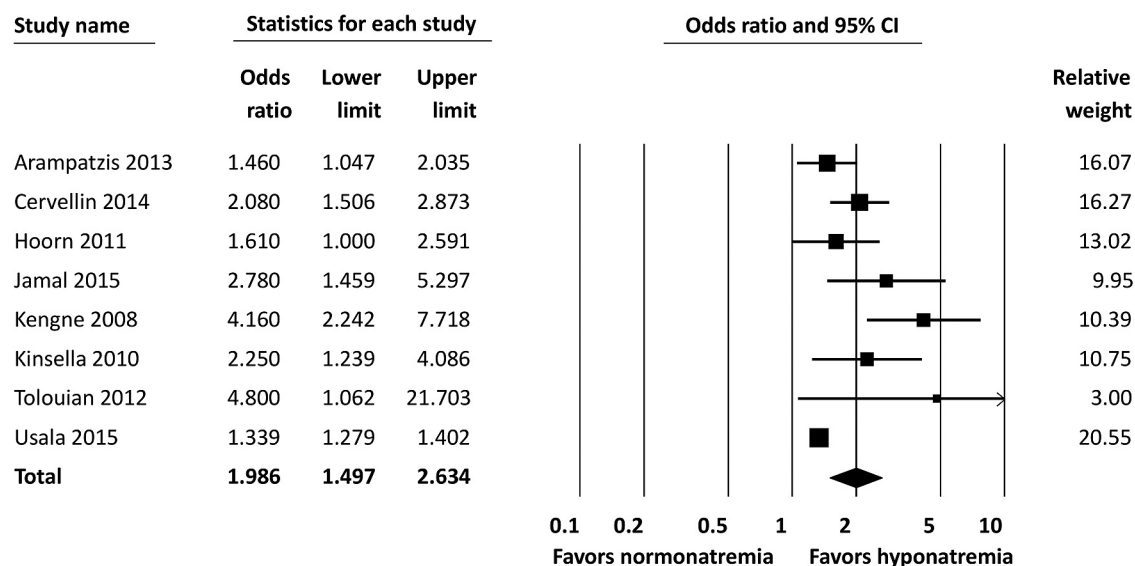


Figure 1. Forest plot of comparison in odds of fracture between hyponatremia and normonatremia in studies reporting OR. Heterogeneity (I^2) = 77%, $P < .001$. Square data markers represent OR; horizontal lines represent 95% CIs; marker size reflecting the statistical weight of the study using random-effects model meta-analysis. A diamond data marker represents the overall OR and 95% CI for the outcome of interest.

outcome assessment. Few studies measured sodium months to years before outcome assessment. Most studies adjusted for confounders including age, sex, and medication in the multivariate analysis.

Quality assessment of included studies

The quality of included studies was evaluated by Newcastle-Ottawa scale (Supplemental Table 1). Total score ranged from 1 to 9. All cohort studies had high quality (total score = 9). Three cross-sectional studies (6, 24, 25) had low quality (total score < 4) and were excluded from the meta-analysis.

Meta-analysis results

Twelve studies were included in the meta-analyses comparing fracture, osteoporosis, and BMD between hyponatremia and normal serum sodium. Eight studies were

included in the meta-analysis of fractures that reported OR (16, 17, 19, 20, 21, 22, 26, 27). There were statistically significant higher odds of fracture in hyponatremic patients with a pooled OR of 1.99 (95% CI: 1.50–2.63, $P < .001$; $I^2 = 77%$, $P_{\text{heterogeneity}} < .001$) (Figure 1). Four cohort studies were included in the meta-analysis of fractures that reported HR (7, 18–20). In this meta-analysis, there was significant increased risk of fracture in hyponatremia patients with pooled HR of 1.62 (95% CI: 1.28–2.05, $P < .001$; $I^2 = 39%$, $P_{\text{heterogeneity}} = .15$) (Figure 2). Four studies were included in the meta-analysis of osteoporosis (15, 22, 23, 27). There was a statistically significant increase in odds of osteoporosis in hyponatremia patients with pooled OR of 1.23 (95% CI: 1.06–1.43, $P = .04$; $I^2 = 60%$, $P_{\text{heterogeneity}} = .06$) (Figure 3). Meta-analysis of BMD at the femur, lumbar spine, and hip (15, 19, 23) were

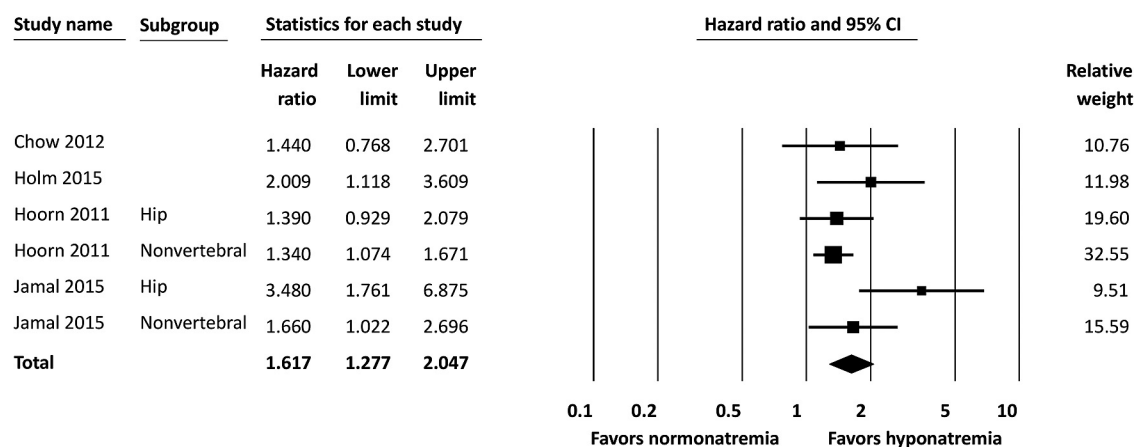


Figure 2. Forest plot of comparison in risk of fracture between hyponatremia and normonatremia in studies reporting HR. Heterogeneity (I^2) = 39%, $P = .14$. Square data markers represent HR; horizontal lines represent 95% CIs; marker size reflecting the statistical weight of the study using random-effects model meta-analysis. A diamond data marker represents the overall HR and 95% CI for the outcome of interest.

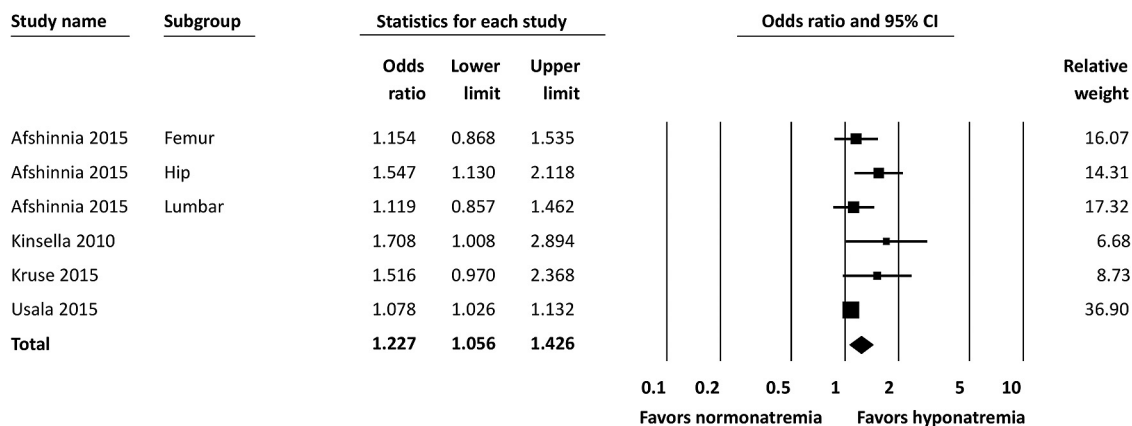


Figure 3. Forest plot of comparison in odds of osteoporosis between hyponatremia and normonatremia. Heterogeneity (I^2) = 60%, P = .06. Square data markers represent OR; horizontal lines represent 95% CIs; marker size reflecting the statistical weight of the study using random-effects model meta-analysis. A diamond data marker represents the overall OR and 95% CI for the outcome of interest.

performed for each anatomical site. There was significantly lower BMD only at the hip in patients with hyponatremia with mean difference of -0.05 g/cm² (95% CI: -0.06 to -0.04 , P < .001; I^2 = 0%, $P_{\text{heterogeneity}}$ = .56) (Supplemental Figure 2).

Sensitivity analysis

To assess the stability of the results in the meta-analysis of osteoporosis and fracture as outcome, sensitivity analyses were conducted by excluding 1 study at a time and using fixed-effects analysis in analysis with heterogeneity less than 40%. The results were not significantly altered, indicating that our results were robust.

Subgroup analysis and meta-regression

We performed subgroup analysis by factors adjusted in multivariate model (basic (age, sex) or additional factors), quality of study (high or moderate), and anatomical sites (femoral neck, hip, or lumbar spine) in the meta-analysis using a random-effects model. For analysis of fracture, there were no significant differences in all subgroup analyses. For osteoporosis and BMD, there were too few studies to perform subgroup analysis.

A univariate meta-regression for meta-analysis of fracture found that age (P = .95) and serum sodium (P = .51) were not predictors of association between hyponatremia and fracture. Other factors (study duration, diuretics use, antiepileptic, and fall prevalence) were not used in meta-regression because of too few included studies.

Publication bias

To investigate potential publication bias, we examined the contour-enhanced funnel plot of the included studies in meta-analysis of fracture reporting OR (Supplemental Figure 3). Vertical axis represents study size (standard error), whereas horizontal axis represents effect size (log OR). From this plot, publication bias exists because there

is asymmetrical distribution of studies on toward the right side. The Egger's regression test was significant (P = .004). Using the trim and fill methods for missing studies to the left of the mean in random-effects model, there was not much difference of the imputed OR and its 95% CI.

Discussion

This is the first systematic review and meta-analysis that evaluates the association between hyponatremia, fractures, and osteoporosis. From 12 included observational studies, we found that hyponatremia increases risk of fracture, and is associated with increased prevalence of both fracture and osteoporosis. However, we found a lower BMD in hyponatremic patients only at the hip.

Our analysis supports the hypothesis that hyponatremia has a direct negative impact on metabolism and integrity of bone, leading to osteoporosis and fracture. Risk of osteoporosis and fracture from hyponatremia has been found in animal models (6) and humans, in case reports (28), and small (21) and large observational studies (27). Studies in rat (29) found that hyponatremia can stimulate osteoclast formation and increase resorptive activity contributing to the osteoporosis associated with hyponatremia. In rat models, abnormal histomorphology of bone by having reduction in both trabecular and cortical bone has also been found. Another mechanism found in animals is an elevated level of circulating arginine-vasopressin hormone released from posterior pituitary when there is hyponatremia. Chronic increases in this hormone can also stimulate osteoclastic activity leading to bone resorption. A significant association between hyponatremia, lower BMD at the hip and osteoporosis found in our meta-analysis supported these underlying mechanisms.

Among studies that assessed association between hyponatremia and fracture, most studies found that this as-

sociation is independent of history of fall. This association is irrespective of anatomical sites (femoral neck, hip, or lumbar spine fractures). Previously, mechanism of fracture in hyponatremia was thought to be from gait, attention impairments and balance instability, leading to fall and fracture. Studies included in our meta-analysis assessed both vertebral and nonvertebral fractures. Because vertebral fractures are typically not caused by trauma, this argues against a primary role for falling on the association between hyponatremia and vertebral fractures.

Hyponatremia is strongly related to the use of diuretics. Loop diuretics are significantly associated with osteoporosis and fracture in a number of studies. It decreases both bone sodium and calcium either indirectly via renal excretion or directly via bone resorption from hyponatremia. Thiazide diuretics, however, are found not to be associated with osteoporosis or fracture in many studies (7, 16, 18, 20). In fact, thiazide diuretics were found to associate with a higher T-score and reduced fracture risk under long-term therapy (30). The mechanism is through modulating calcium uptake by intestinal cells and enhancing bone calcium uptake by the inhibition of the thiazide-sensitive sodium chloride cotransporter. Although we did not perform analysis in the subgroup of patients who used thiazide diuretics, most of the included studies reported that an increased risk of fracture was independent of thiazide diuretics.

Our finding is important because it suggests that fracture and osteoporosis in hyponatremia might be preventable by correcting hyponatremia (31). In addition, medication-induced hyponatremia should be prevented, especially in populations at risk including the elderly and those with low bone density (32). At present, there is no study evaluating effects of sodium correction on risk of fracture or osteoporosis.

The strengths of our analysis include a comprising of a large population from various countries. We also used effect size from a multivariate model that adjusted for potential confounding factors such as age, sex, body mass index (BMI), diuretic, antiepileptic, and comorbidities. However, there are several limitations in our study. First, most of the included studies measured serum sodium at a single time point at entry into the study. There are currently an insufficient number of studies that have verified chronicity of hyponatremia. Only the study by Usala et al (27) assessed sustained hyponatremia and found that OR for both osteoporosis and fractures increased dramatically when only subjects with chronic persistent hyponatremia were analyzed. Therefore, an association between hyponatremia and osteoporosis in our study might be underestimated. Second, this is a systematic review of observational studies that included many cross-sectional and

case-control studies, which might not be able to conclude the causal relationship by temporality between hyponatremia and osteoporosis or fracture. Third, there is a difference in fracture assessment from the included studies which varied from physician diagnosis, radiologic confirmation, and international classification of diseases (ICD) code. Fourth, there is no measurement of BMD in most of the studies and this limits our ability to perform subgroup analysis or meta-regression in the analysis of those outcomes.

Conclusion

This systematic review and meta-analysis of observational studies adds to the existing evidence that hyponatremia is significantly associated with osteoporosis and fracture. This suggests that physicians should be aware of this risk from hyponatremia. Further randomized-controlled trials evaluating risk reduction of osteoporosis or fractures after treatment of hyponatremia are warranted.

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