Thiazide diuretics and the risk of hip fracture (Review)

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[Intervention Review]

Thiazide diuretics and the risk of hip fracture

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ABSTRACT

Background

Thiazide diuretics are one of the most commonly prescribed antihypertensive agents worldwide. Thiazides reduce urinary calcium excretion. Chronic ingestion of thiazides is associated with higher bone mineral density. It has been suggested that thiazides may prevent hip fracture. However, there are concerns that diuretics, by increasing the risk of fall in elderly, could potentially negate its beneficial effects on hip fracture.

Objectives

To assess any association between the use of thiazide diuretics and the risk of hip fracture in adults.

Search methods

We searched eligible studies up to December 2008 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts, the Database of Abstracts of Review of Effects (DARE) and reference lists of previous reviews and included studies.

Selection criteria

All randomized controlled trials and observational studies, which assessed the association between thiazide diuretic use and hip fracture.

Data collection and analysis

Two review authors independently applied the selection criteria, extracted data and assessed risk of bias of each study selected. The results were summarized descriptively and quantitatively. Cohort studies and case control studies were analysed separately.

Main results

No randomized control trials were found. Twenty-one observational studies with nearly four hundred thousand participants were included. Six of them were cohort studies and 15 were case-control studies. Two cohort studies appear to involve the same cohort so there were only 5 unique ones. The risk of bias was assessed with the Newcastle-Ottawa Scale (NOS). Five cohort studies had low risk of bias and one had moderate risk of bias. Seven case control studies had low risk of bias and 8 had moderate risk of bias. Meta-analysis of cohort studies showed that thiazide use was associated with a reduction in risk of hip fracture by 24%, pooled RR 0.76 (95% CI 0.64-0.89; p = 0.0009). We chose not to provide a pooled summary statistics for case-control studies because of high heterogeneity (Tau^2 = 0.03, I^2 = 62%, p = 0.0008).

Authors' conclusions

Thiazides appear to reduce the risk of hip fracture based on observational studies. Randomized controlled trials are needed to confirm these findings.

PLAIN LANGUAGE SUMMARY

Thiazide diuretics and hip fracture

Twenty-one studies of observational nature with nearly four hundred thousand participants were included in this systematic review. Studies looked for an association between thiazide diuretic use and hip fracture. The majority of included studies have low to moderate risk of bias. Thiazide diuretic use was associated with a reduction in risk of hip fracture. Randomized controlled trials are needed to confirm these findings.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Thiazide users compared with nonusers for the risk of hip fracture

Patient or population: adults 40 years or older
Intervention: use of thiazide diuretics
Comparison: nonusers

Outcomes	Relative effect (95% CI)	Quality of the evidence (GRADE)	Comments
Hip Fracture	**RR 0.76** (0.64 to 0.89)	⊕⊕◯◯ **low**	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Thiazide diuretics have been a cornerstone of antihypertensive therapy for longer than half a century. They have been proven in large scale randomized controlled trials (MRC 1985, SHEP 1991, Hansson 1999, ALLHAT 2000, ALLHAT 2002) and systematic reviews (Psaty 2003, Wright 2009) to reduce cardiovascular morbidity and mortality, particularly related to stroke, in individuals with persistently elevated blood pressure. One of the benefits of thiazides outside of the cardiovascular system is their hypocalciuric effect. In 1959, Lamberg and Kuhlbäck found that chlorothiazide and hydrochlorothiazide reduced the excretion of calcium in urine (Lamberg 1959). This effect was used to prevent recurrence of calcium containing urinary stones (Nassim 1965). In 1973, Middler et al demonstrated in an experimental study that thiazide diuretics reduced urinary calcium excretion by about 40% in individuals with intact parathyroid glands (Middler 1973).

Epidemiological studies have associated chronic ingestion of thiazides with higher bone mineral density in both women and men (Wasnich 1983, Bauer 1993, Morton 1994, Glynn 1995). A cohort study (LaCroix 2000) demonstrated that thiazide use preserved bone mineral density at the hip and spine in normotensive healthy men and women. In a randomized controlled trial of healthy women in their early menopause, bendroflumethiazide 5 mg/day for 6 months was associated with no reduction in bone mineral content of the forearms measured by single photon absorptiometry while a decrease of 2% per year took place in the placebo group (Transbol 1982). The active treatment continued for a total of 2 years, followed by placebo in both bendroflumethiazide group and placebo group for one more year. At the end of 3 years, no difference in bone mineral content was found. A randomised, double-masked, placebo-controlled trial of chlorthalidone and bone loss in hypertensive postmenopausal women showed that after a mean duration of 2.6 years, chlorthalidone use, at doses of 12.5-25 mg/day, was associated with bone gain at the calcaneus and distal radius, and reduction of bone loss at proximal radius, resulting in an average increment for three appendicular sites of 0.9% per year (Wasnich 1995). This study was conducted as a prospective ancillary study among women participating in SHEP (Systolic Hypertension in Elderly Program), a double-masked placebo controlled study employing a thiazide-like diuretic chlorthalidone, at the SHEP Center in Hawaii.

Whether the physiological effects of lowering urinary calcium excretion and slowing the reduction of bone mineral density lead to reduction in hip fractures, the most clinically important fracture related to osteoporosis in older adults, is uncertain. While endocrinologists are interested in potential beneficial effects of thiazides on calcium metabolism and bone health, geriatricians are legitimately concerned about diuretics' potential effect on increasing

the risk of falls in older adults. A small case-control study on drug use and accidental falls in an intermediate care facility reported that the use of diuretics was significantly greater in the population who had fallen (Sobel 1983). A larger study, the St. Louis OASIS (Older Adult Service and Information System) found a statistically significant increase in odds of multiple falls in elderly users of diuretics, adjusted for age, gender, depression, cognitive impairment, use of antipsychotics, use of 5 other medications, and a few other variables (Cumming 1991). The data on thiazide and non-thiazide diuretics were not separately reported in the paper.

The beneficial effect of thiazides on bone density could potentially be offset by the increased in incidence of falls resulting in hip fracture, especially in the elderly caused by orthostatic hypotension (Myers 1978) or dizziness. Available studies within the last few decades have shown conflicting results regarding the effects of thiazides on the incidence of hip fracture (Heidrich 1991; Schoofs 2003). Nearly half a century ago, results of metabolic studies led to recommending thiazides to prevent bone loss (Rose 1966). Whether the beneficial effects on surrogate outcomes such as urinary calcium excretion and bone mineral density translate to a favourable hard outcome that matters to a patient, i.e., reduction of hip fracture, remains unclear. This warrants a systematic review of the available evidence regarding the effects of thiazides on risk of hip fracture.

OBJECTIVES

The objective of this systematic review is to assess any association between the use of thiazide diuretics and the risk of hip fractures as compared to nonusers in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We recognized that randomized controlled trials specifically designed to compare thiazides and placebo or drugs for their effect on hip or other fractures may not exist since thiazide diuretics are primarily used as antihypertensive agents not as medications to prevent hip fracture. Moreover, the magnitude of the effect found in previous studies showed that a randomized controlled study of adequate power is unlikely to be pursued (Jones 1995). Such trials were searched for to be included if any were found. Because of the high likelihood of lack of such randomized controlled trials, we also searched for observational studies to be included in this review. Cohort studies comparing the incidence of hip fractures between one group taking thiazides and another not taking thiazides were included. Case-control studies in which use and non-use of thiazides are compared between the group of patients with hip fractures and the group of age- and sex-matched controls without hip fracture were also included in this review.

Types of participants

The participants of this review were adult males and females, aged 40 and above, who took thiazide diuretics and comparators for hypertension or any other reasons.

Types of interventions

The intervention of interest was the use of any thiazide diuretic, including hydrochlorothiazide, chlorthalidone, bendroflumethiazide, chlorothiazide, cyclothiazide, methyclothiazide, hydroflumethiazide, trichlormethiazide, benzthiazide, polythiazide, buthiazide, cyclopenthiazide, metolazone, quinethazone, fenquizone, clorexolone, clopamide, indapamide, diapamide, isodapamide, mefruside and xipamide.

Types of outcome measures

The primary outcome measure was the incidence of hip fracture.

Search methods for identification of studies

Electronic searches of the following databases were conducted: Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts, and the Database of Abstracts of Reviews of Effects (DARE). The search was be limited to human. No restrictions were made based upon language of the report. A modified, expanded version of the standard search strategy of the Hypertension Group for randomized controlled trials and observational studies, with additional terms related to hip fracture and thiazide diuretic agents were used to identify the relevant articles. The following search terms were used: DIURETICS, THIAZIDE (MeSH), HYDROCHLOROTHIAZIDE (MeSH), CHLORTHALIDONE (MeSH), BENDROFLUMETHIAZIDE (MeSH), CHLOROTHIAZIDE (MeSH), cyclothiazide.tw, METHYCLOTHIAZIDE (MeSH), HYDROFLUMETHI-
AZIDE (MeSH), TRICHLORMETHIAZIDE (MeSH), benzthiazide.tw, POLYTHIAZIDE (MeSH), cyclopenthiazide.tw, buthiazide.tw, metolazone.tw, quinethazone.tw, fenquizone.tw, clorexolone.tw, clopamide.tw, indapamide.tw, diapamide.tw, isodapamide.tw, mefruside.tw, xipamide.tw, HIP FRACTURES (MeSH), (hip adj25 fracture$).tw, FEMORAL NECK FRACTURES (MeSH), ((femur$ or femoral$) adj25 neck adj25 fracture$).tw, (hip$ or femur$ or femoral$ or trochant$ or

pertrochant$ or intertrochant$ or subtrochant$ or intracapsular$ or extracapsular$).tw, and FRACTURES (MeSH). Search terms were modified to match EMTREE keywords when using EMBASE. Ongoing clinical trials and unpublished studies were searched via the worldwide web on the following sites: http://www.controlled-trials.com, http://www.clinicaltrials.gov, http://www.centerwatch.com.

Data collection and analysis

Identification of studies: Using the search strategy described above, two reviewers independently selected studies for inclusion in the review. The initial searches of all the databases were performed to identify citations with potential relevance. The articles whose titles and/or abstracts were clearly irrelevant were excluded in initial screening. The full texts of remaining articles were then retrieved. The reference lists of retrieved articles, reviews and texts were searched for additional citations.

Assessment of methodological quality of included studies: Each included study was classified as a randomized controlled trial or observational study, and the risk of bias assessed for each study. For cohort studies, selection of exposed and nonexposed cohort, comparability of cohorts, assessment of outcome, and adequacy of follow-up were addressed. For case-control studies, selection of cases and controls, comparability of cases and controls, and ascertainment of exposure were emphasized. The Newcastle-Ottawa Scale (NOS) was used for assessing the risk of bias in observational studies (Wells).

Data extraction and synthesis: Two reviewers independently performed data extraction and the results were cross-checked by double-data entry. Disagreements were resolved by discussion and consensus. The information collected from each study included study design, time and setting of study, study population, and methods of ascertainment of thiazide diuretic use and hip fracture. Data entry and analyses were performed using the Cochrane Review Manager software (RevMan 5; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Randomized and observational (non-randomized) studies were planned to be analysed separately as a direct comparison between the estimates of observational studies and randomized trials can be misleading. Non-randomized comparisons can both exaggerate and underemphasize compared to randomized comparisons but the magnitude and direction of the effect are inconsistent. Among observational studies, cohort and case-controlled studies were analysed separately since case control studies could give different estimates to cohort studies and the direction of the discrepancy tend to be inconsistent (Reeves 1999). Generic inverse variance method was used. Standard error around log [risk ratio] and log [odds ratio] were calculated by dividing the difference between log [upper confidence interval] and log [risk ratio] or log [odds ratio] by 1.96. Heterogeneity between trials was tested using a standard Chi-squared test and the newer concept of I^2 (Higgins 2003) as measures of inconsistency. Formal meta-analytic techniques were applied. The results were reported as risk ratio or odds ratio with corresponding 95% confidence intervals. Random effects model of DerSimonian and Laird was used when there was evidence of heterogeneity between studies (DerSimonian 1986). Fixed-effect model (Mantel Haenszel methods) was used when there was no evidence of heterogeneity (Mantel 1959). A funnel plot of precision in the estimation of underlying treatment effect was used to check the publication bias.

RESULTS

Description of studies

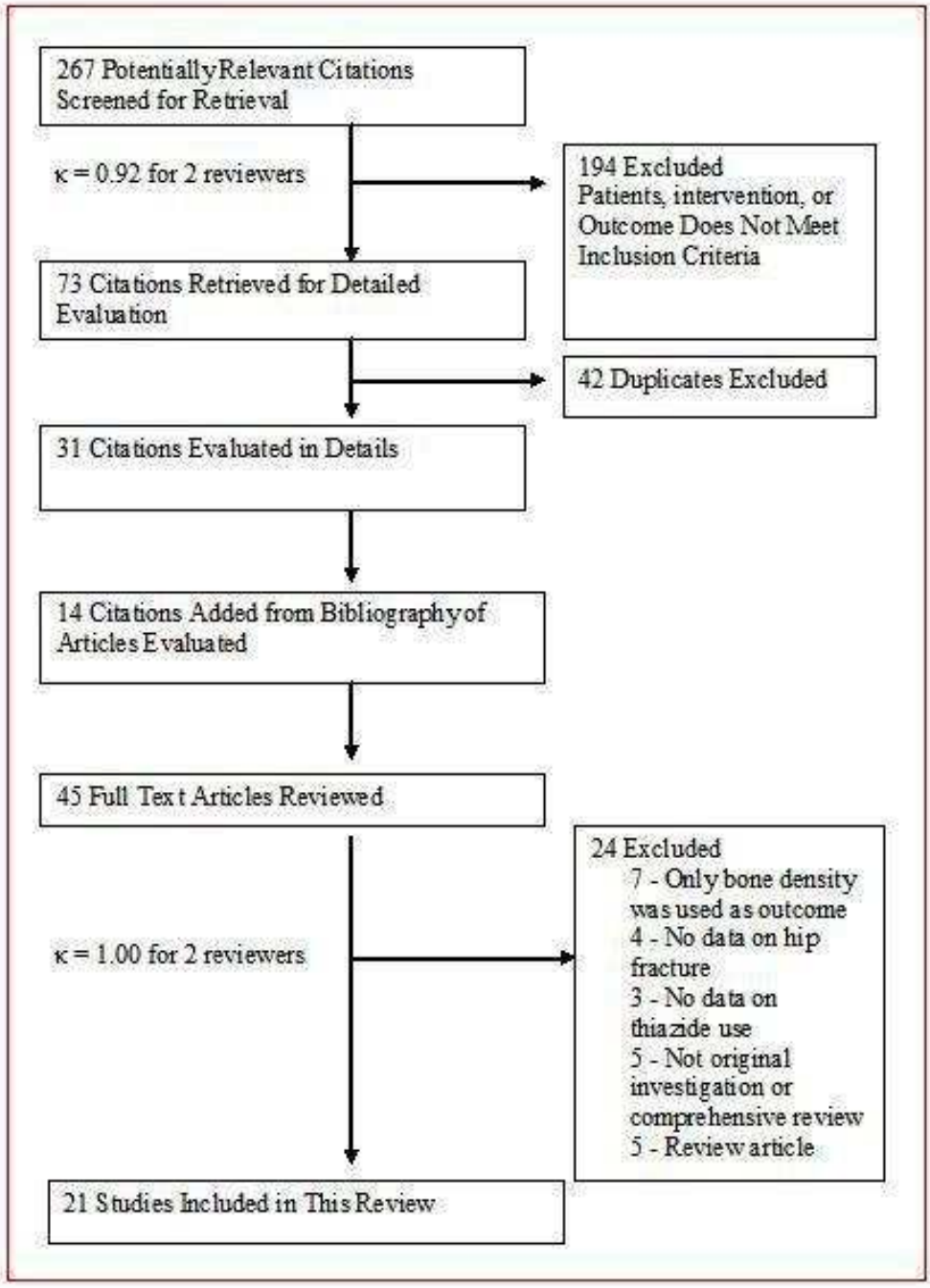
See: Characteristics of included studies; Characteristics of excluded studies.

See: Characteristics of included studies; Characteristics of excluded studies.

A total of 267 potential relevant citations were screened for retrieval. Among those, 194 were excluded because patients, intervention or outcome did not meet the inclusion criteria. 73 citations were then retrieved for detailed evaluation. 42 duplicates were excluded. The remaining 31 citations were evaluated for details. 14 citations were added from bibliography of articles evaluated. A total of 45 full text articles were reviewed. 24 of them were excluded. The reasons for exclusion were using bone density and not hip fracture as the outcome measure, lack of data for hip fracture instead of all fractures, lack of data on thiazide use instead of all diuretics, and not being original investigations.

We identified no randomized controlled trials and 21 observational studies (Figure 1), of which 6 were cohort studies (Cauley 1993, Cummings 1995, Feskanich 1997, Guo 1998, LaCroix 1990, Schoofs 2003) and 15 were case-control studies (Barengolts 2001, Cumming 1993, Felson 1991, Grisso 1994, Heidrich 1991, Herings 1996, Jensen1991, Paganini-Hill 1981, Rashiq 1986, Ray 1989, Rejnmark 2005, Stevens 1989, Taggart 1988, Wang 2001, Weiland 1997).

Figure 1. Figure 1. Flow Chart of Study Selection Process



The cohort studies of Cauley 1993 and Cummings 1995 appear to originate from the same cohort and were conducted by the same group of investigators. The minor variations in the numbers of participants and duration of follow-up appear to be as a result of different time of analyses. Adjusted relative risks of hip fracture in current thiazide user reported in these two studies were very similar: 0.82 (95% CI, 0.56-1.12) in Cauley 1993, 0.8 (95% CI, 0.6-1.2) in Cummings 1995. Hence, the 6 cohort studies we reviewed were essentially 5 cohort studies. Descriptives were extracted from all 6 cohort studies but data from only 5 unique cohort studies were used in quantitative analyses (calculating median risk of bias scores and conducting meta-analysis).

Included studies

The 21 studies included a total of 399,362 participants (121,965 in cohort studies and 277,397 in case-control studies) from seven countries. Ten studies were carried out in the United States (Barengolts 2001, Cauley 1993, Cummings 1995, Feskanich 1997, Guo 1998, Heidrich 1991, Jensen1991, LaCroix 1990, Paganini-Hill 1981, Wang 2001), 3 in the United Kingdom (Rashiq 1986, Stevens 1989, Taggart 1988), 2 in Denmark (Jensen1991, Rejnmark 2005), 2 in Netherlands (Herings 1996, Schoofs 2003), 1 in Australia (Cumming 1993), 1 in Canada (Ray 1989), 1 in Germany (Weiland 1997), and 1 in Sweden (Guo 1998). The studies were published between 1981 and 2005.

Sponsorship

Of the 21 studies, 13 declared sponsorship of studies. In the United States and Canada, the United States Public Health Service Grants, National Institute of Health, the United States Department of Agriculture, the National Institute of Aging, the Robert Wood Johnson Foundation, Foundation for Group Health Cooperative, the Center for Disease Control, National Institute for Drug Abuse, and the United States Food and Drug Administration sponsored grants to support the studies. In Sweden, Swedish Medical Research Council, Swedish Council for Social Research, Swedish Municipal Pension Institute, National Corporation of Swedish Pharmacies' Fund for Research and Studies in Health Economics and Social Pharmacies, the Torsten and Ragnar Söderbergs Foundation, and the Foundation for Medical Research sponsored grants support the study (Guo 1998). One study from Germany (Weiland 1997) was funded by Sandoz AG, Nürnberg. One study from Netherlands (Schoofs 2003) declared no external funding. Co-investigators from one American (Heidrich 1991) and one Canadian study (Ray 1989) included Burroughs Wellcome Scholars in Pharmacoepidemiology.

Eight studies did not declare sponsorship in their publications. Three were from U.K. (Rashiq 1986, Stevens 1989, Taggart 1988), two from Denmark (Jensen1991, Rejnmark 2005), one from Netherlands (Herings 1996), one from Australia (Cumming 1993), and one from the United States (Barengolts 2001), which was published only as an abstract. While the study from the United States did not declare sponsorship, it can be safely assumed that the United States Department of Veterans Affairs was the funding source since it involved population from the Veterans Affairs Health System.

Risk of bias in included studies

The risk of bias assessment of included observational studies was carried out using the NOS for cohort (Appendix 1) and case-control studies (Appendix 2). When considering comparability in NOS, we assessed whether thiazide users and nonusers were matched in the design and/or whether confounders were adjusted in the analysis. One star point was awarded if age was controlled by the study and another point was awarded if one additional factor was controlled.

Cohort studies

The median score (the number of stars awarded) was 8 (out of 9) for the 5 unique cohort studies with a range of 4 to 9 points (Table 1). Among 6 reports of cohort studies, 5 had low risk of bias and reached 8 or more star points (Cauley 1993, Cummings 1995, Guo 1998, LaCroix 1990, Schoofs 2003). One had moderate risk of bias and reached 4 star points (Feskanich 1997). This study reached fewer star points because being part of the Nurses Health Study, the exposed cohort was drawn from the selected group of individuals (nurses) who are not truly representative of the average women in the community. The ascertainment of exposure and outcome relied upon self-report of the participants. The investigators contended, and we concurred, that accurate reporting of fracture and medication use was expected in the cohort of registered nurses. This was reportedly validated in a sample of 30 cases for which all self reports were confirmed by medical records.

Case-control studies

The median score (the number of stars awarded) was 6 (out of 9) for the 15 case-control studies with an overall range of 5 to 8 points (Table 2). Seven case-control studies had low risk of bias and reached 7 or more star points. The remaining eight had moderate risk of bias and reached 5 to 6 points.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings (cohort studies); **Summary of findings 2** Summary of findings (case-control studies)

The findings are summarized in Table 3 and Figure 2 for cohort studies and in Table 4 and Figure 3 for case-control studies.

Figure 2. Forest plot of comparison: Current thiazide users vs nonusers (Cohort), outcome: Hip Fracture.

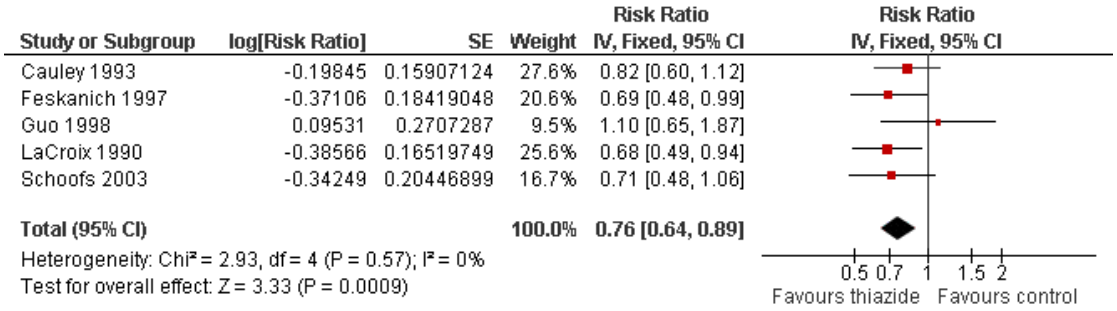
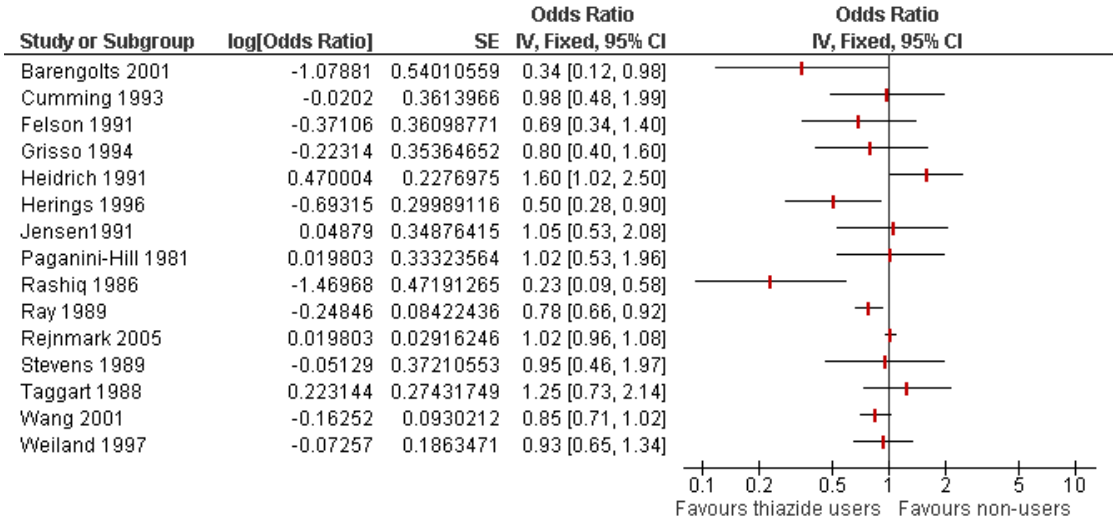


Figure 3. Forest plot of comparison: Current thiazide users vs nonusers, outcome: Hip Fracture.



Among the cohort studies, one found that use of thiazide diuretic agents was associated with a reduction of approximately one third in the risk of hip fracture (LaCroix 1990); three found that thiazide use was not significantly associated with the risk of hip fracture (Cauley 1993, Cummings 1995, Guo 1998); two found both ways depending on which group was used in final analyses (Feskanich 1997, Schoofs 2003). In the cohort of Feskanich 1997, no statistically significant association of thiazide use and hip fracture was found (adjusted RR 0.97; 95% CI, 0.82-1.64) when the entire cohort of 83,728 participants was analysed. It should be noted that this cohort, as described above, was part of the Nurses Health Study. The age of enrolment in the cohort began at 35. The prevalence of osteoporotic hip fracture is very rare in premenopausal women. When analysis was confined only to postmenopausal women from this cohort, thiazide use was associated with reduced risk of hip fracture (adjusted RR 0.69; 95% CI, 0.48-0.99). We chose to use the data on postmenopausal women for our pooled analyses (see below) to be consistent with the study population of other cohort studies. In the cohort of Schoofs 2003, no beneficial association of thiazide use and the risk of hip fracture was found (adjusted RR 0.71; 95% CI, 0.47-1.06) when the data from the entire cohort, where thiazide use was defined as any current use, was analysed. However, a statistically significant association of thiazide use and reduction of the risk of hip fracture was detected (adjusted RR 0.46; 95% CI, 0.21-0.96) when the analy-

ses was confined to the participants who had been on thiazide use for at least a year. We chose to use the data of the entire cohort defining thiazide use as any current use to be consistent with the data from the rest of the cohort studies. The investigators of all cohort studies attempted to control and adjust for potential confounding variables. Various covariates and potential confounding factors adjusted in each cohort study are shown in Table 5.

As discussed under description of studies, two cohort studies involved the same cohort. When conducting our meta-analysis, we included the data from Cauley 1993 only because it is primarily focused on association between thiazide use and hip fracture while the focus of Cummings 1995 was multiple risk factors for hip fracture, thiazide use being one of them.

Among the case-control studies, seven demonstrated statistically significant association between thiazide use and reduction of the risk of hip fracture (Barengolts 2001, Felson 1991, Herings 1996, Paganini-Hill 1981, Rashiq 1986, Ray 1989, Wang 2001). Eight studies showed no such association (Cumming 1993, Grisso 1994, Heidrich 1991, Jensen1991, Rejnmark 2005, Stevens 1989, Taggart 1988, Weiland 1997). As in cohort studies, investigators of case-control studies also attempted to control and adjust for potential confounding variables. Various covariates and potential confounding factors adjusted in each case-control study are shown in Table 6.

Meta-analysis of 5 cohort studies (Figure 2) showed that thiazide use was associated with a reduction of risk of hip fracture by 24% (pooled RR 0.76; 95% CI 0.64-0.89; p = 0.0009). Fixed effect model was used in this analysis because no significant heterogeneity among studies was found (p = 0.57, I^2 = 0). Including Cummings 1995 in meta-analysis instead of Cauley 1993 (two studies from identical cohort; see above under Description of studies) found almost identical results (pooled RR 0.75; 95% CI 0.63-0.89; p = 0.0010; p for heterogeneity = 0.61, I^2 = 0).

Forest plot of meta-analysis of 15 case-control studies is shown in Figure 3. We chose not to show pooled summary statistics in the forest plot because it could be misleading in the presence of high degree of heterogeneity (Tau^2 = 0.03, I^2 = 62%, p = 0.0008). Clinical diversity such as variations in study location, study setting, age, gender, dosage of thiazide and duration of thiazide use may have contributed to heterogeneity. Adjustment for potential confounding covariates were done in case-control studies but each of them was not adjusted for precisely the same covariates and not conducted under similar conditions. While the investigators of case-control studies made attempts for adjustment of confounding factors to the best they could under given circumstances of each study, several potential risk factors were not assessed in all studies. For example, exposure to sunlight, vitamin D intake and thyroid hormone therapy were not assessed in Grisso 1994. Calcium consumption could not be assessed in most studies. Obese individuals are expected to have higher rates of hypertension (hence thiazide use), yet increased weight is also predictive of lower rates of fractures. However, BMI was not adjusted in all case-control studies. Further, residual confounding by factors that could not be ascertained by chart abstraction, such as strength, balance, endurance, mobility and many other factors, may have occurred in some studies. Each of these factors could have contributed to clinical heterogeneity among case-control studies. It is noteworthy that while the largest case-control study (Rejnmark 2005) showed no statically significant association between current use of thiazides and the risk of hip fracture overall (adjusted OR=1.02; 95% CI, 0.96 - 1.08), stratification by defined daily dosages showed dose-response relationship with statistically significant reduction of the risk of hip fracture in the subgroups of higher defined daily dosages. In an attempt to identify the source of heterogeneity, we performed subgroup analyses by geographic regions (North American Sudies and European Studies). Heterogeneity continued to exist in each subgroup (Tau^2 = 0.03, p=0.06, I^2 = 51% for North American subgroup; Tau^2 = 0.07, p = 0.01, I^2 = 63% for European subgroup) indicating that the source of heterogeneity was more than variation in study location. The small number of studies in the cohort group and differences in the characteristics among the case-control studies precluded the use of meta-regression, a technique that can be used to investigate heterogeneity.

We assessed the publication bias within the included studies using funnel plots. The funnel plot for cohort studies (Figure 4) was not asymmetrical but a small study effect may be difficult to spot among only five studies. The funnel plot for case-control studies (Figure 5) was somewhat asymmetrical. This could be due to a relative lack of studies with odds ratio of greater than 1 or differences in methodological quality of smaller studies.

Figure 4. Funnel plot of comparison: Current thiazide users vs nonusers (cohort studies), outcome: Hip Fracture.

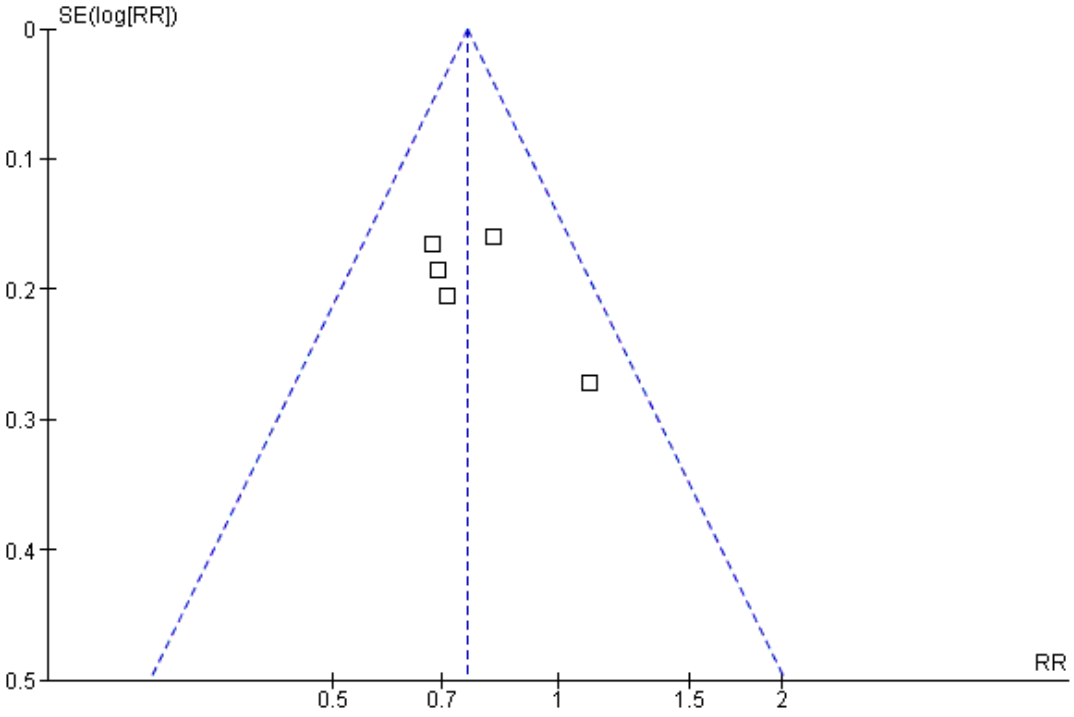
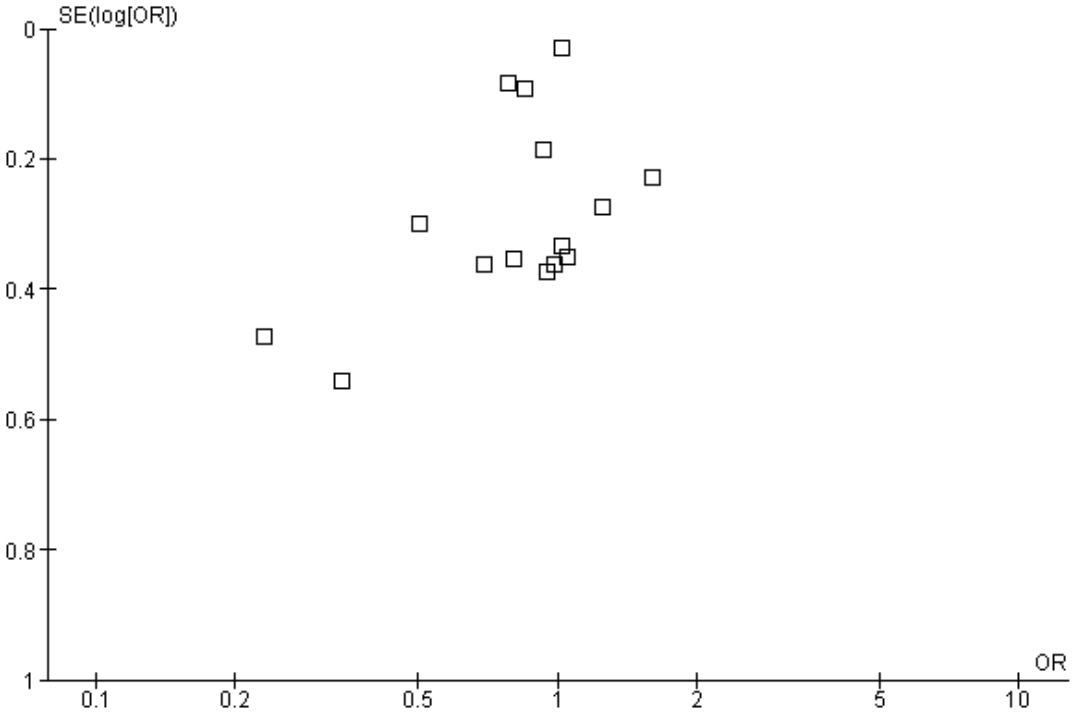


Figure 5. Funnel plot of comparison: Current thiazide users vs nonusers (case-control studies), outcome: Hip Fracture.



Given differences in baseline risk of hip fractures, we intended to stratify subgroups and analyses performed based on gender. The percentages of females in each included study are shown in Table 3 and Table 4. Approximate percentages of females were 86% in cohort studies and 67% in case-control studies. We were unable to perform such subgroup analysis because only few studies reported separate data for each gender. We also intended to perform subgroup analysis based on length of thiazide use but we were unable to do so since few studies reported stratified data for different duration of thiazide use.

GRADE assessment of total body of evidence

The evidence from cohort studies showed that thiazide diuretic use was associated with reduction of the risk of hip fracture (RR = 0.76; 95% CI: 0.64, 0.89). Quality of evidence, measured using the criteria of GRADE Working Group grades of evidence, is low because the result was relied solely on observational studies with low to moderate risk of bias (Summary of findings for the main comparison).

The evidence from case-control studies showed that it is indeterminate to conclude whether thiazide diuretic use was associated with reduction of the risk of hip fracture or not. Heterogeneity is high; hence we decided not to report summary statistics of results from case control studies. Quality of evidence, measured using the criteria of GRADE Working Group grades of evidence, is very low (Summary of findings 2).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Thiazide users compared with nonusers for the risk of hip fracture

Patient or population: adults 40 years or older
Intervention: use of thiazide diuretics
Comparison: nonusers

Outcomes	Relative effect (95% CI)	Quality of the evidence (GRADE)	Comments
Hip Fracture	summary statistic not calculated	⊕◯◯◯ **very low**	Summary statistic not calculated due to high heterogeneity

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

DISCUSSION

Hip fracture is associated with significant morbidity and mortality in older adults. In the year 2000 there were an estimated 9.0 million osteoporotic fractures worldwide, of which 1.6 million were at the hip (Johnell 2006). The greatest number of hip fractures was in Europe, followed by the Western Pacific region, the Americas, and southeast Asia. The epidemiologic projections estimate that, this worldwide annual number will rise to 6.26 million by the year 2050 (Kannus 1996). While the aging of the world's population contributes to this rise in great part, the age-specific incidence rates of hip fractures have also increased during the recent decades in many parts of the world. The aim of this review was to examine the possible association between thiazide use and the risk of hip fracture. This review includes data from 21 observational studies. We found that current thiazide use was associated with statistically significant reduction of the risk of hip fracture, and could potentially reduce the incidence of hip fracture by approximately 24%. Our findings are consistent with the results of an earlier meta-analysis of 13 observational studies (Jones 1995) where current thiazide users were found to have approximately 18% reduction in risk of hip fracture, and a more recent meta-analysis of 19 observational studies (Wiens 2006) where thiazide use was associated with approximately 17% reduction in risk of hip fracture. Wiens 2006 analysed cohort studies and case-control studies together but in this review we analysed them separately.

While several medications such as calcium supplements, estrogen, raloxifene, bisphosphonates and zoledronic acid are available in contemporary treatment of osteoporosis, not all medications were shown to reduce the risk of hip fracture. Their adverse effects may also be limiting factors when used for prevention of hip fracture. Many individuals with high risk for hip fracture cannot take any of these medicines due to adverse reactions or contraindications. The potential effectiveness of thiazides in preventing hip fracture could be an alternative option to be considered under such circumstances.

The biological plausibility of the association of thiazides with a lower incidence of hip fracture has been described for several decades. Thiazide use has been related to higher bone mineral density in several observational studies and a few randomized controlled trials as described under the Background section. In addition to their effect on lowering urinary calcium excretion (Lamberg 1959, Middler 1973), additional mechanisms were also proposed. Thiazides increase intestinal calcium absorption (Caldwell 1971, Jorgensen 1974, Zerwekh 1980) and skeletal retention of calcium (Caldwell 1971). Thiazide treatment in some patients is capable of changing a negative calcium balance into a positive direction (Harrison 1968). Thiazides may potentiate the renal action of parathyroid hormone, resulting in retention of calcium and partial suppression of parathyroid hormone secretion (Middler 1973). It

has also been suggested that thiazides may stimulate parathyroid glands (Paloyan 1969, Pickleman 1969). One of the properties of thiazides is inhibition of carbonic anhydrase enzyme. The carbonic anhydrase inhibitors are known to inhibit osteoclastic bone resorption in vivo and in vitro in other species (Pierce 1991), so it is biologically plausible that thiazides could reduce bone resorption in humans.

Many antihypertensives can cause postural hypotension, which has long been considered an important cause of falls. Receiving hydrochlorothiazide was associated with the highest prevalence of postural hypotension in elderly veterans (Poon 2005) but the rates of falls among these subjects were not collected in this study. Cauley 1993 found that thiazide diuretics had no effect on the risk of falls in older women. Many studies have found no association between falls and antihypertensives (Cumming 1998). Falls were recorded as a potential adverse effect in the Systolic Hypertension in the Elderly Program (SHEP), where chlorthalidone was used as the primary antihypertensive agent. The rates of falls were the same in the treated and placebo groups (Curb 1993). A systematic review and meta-analysis of drug and falls (Leipzig 1999) showed no statistically significant association between thiazide use and falls. Another meta-analysis (Woolcott 2009) showed no statistically significant association of diuretics and falls although no separate data was available for only thiazides. All these findings were based on observational data and no data from randomized controlled trials were available. A population based case-control study (Gribbin 2010), which was published after these two meta-analyses, found that current prescribing of thiazides was associated with an increased risk of falling and that this was strongest in the first 3 weeks. An updated systematic review and meta-analysis is warranted to explore whether withholding thiazide diuretics in older adults because of the concerns related to risk of falls is justified.

Our review has several limitations. Included primary studies in our review consist of only observational studies and no randomized trials. Associations detected in observational studies could be due to the possibility that the association was caused by a third factor linked to both exposure/intervention and outcome. Statistically significant associations found in observational studies could be subject to *post hoc ergo propter hoc* and *cum hoc ergo propter hoc* fallacies so caution should be exercised against overinterpretation of the summary statistics. While heterogeneity was very low among the cohort studies, it was fairly high among the case-control studies. Potential sources of clinical heterogeneity among case-control studies and the role of confounding covariates left unadjusted are discussed under Results above. There are potentially unpublished case-control studies with effect sizes of odds ratios greater than 1 indicated by funnel plot. Validity can be affected by losses to follow-up in cohort studies but we suspect that it is unlikely to introduce bias to our results because only small proportion were lost to follow-up in most included studies. Assessment of thiazide use only at baseline in some cohort studies could have precluded its introduction at a later date affecting accuracy of ascertainment of exposure. Recall bias could be another potential limitation of case-control studies but most of the included studies used medical records or pharmacy database to ascertain thiazide use so it may not be much of a threat to the validity of our results. Detection bias could occur when cases and controls are not identified independently of the exposure in case control studies. Case-control studies could be susceptible to the healthy volunteer effect since previous fracture is a strong predictor of fracture and those who do not go to see the doctors for fractures are the same people as those who do not see their doctors for hypertension. Finally, we were unable to determine the minimum duration of thiazide use necessary to achieve the preventive effect for hip fractures in our pooled analyses of included studies because only few included studies had information on duration of thiazide use. We were also unable to determine the dose response relationship of such association because most included studies did not address this issue.

The limitations of contemporary therapy for osteoporosis make thiazides attractive as an alternative option. Many older adults who are at high risk for hip fracture also have hypertension as a coexisting medical condition. Use of thiazides has a convincing effect on stroke prevention in hypertensive individuals so using the same medication for reduction of risk of hip fracture would be an appropriate choice. However, potential adverse effects of thiazides such as hypokalaemia, hyponatraemia, precipitation of gout, volume depletion and orthostatic hypotension should be weighed in clinical decision making.

AUTHORS' CONCLUSIONS

Implications for practice

Thiazides appear to reduce the risk of hip fracture based on observational studies. Randomized controlled trials are needed to confirm these findings. Until randomised control trials assessing the effect of thiazides on incidence of hip fracture are conducted and the results from such trial are available, physicians and clinical practice guideline writers should consider this potential advantageous effect of thiazides over other antihypertensives in treating hypertension particularly in individuals with high probability of hip fracture.

Implications for research

Future research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate, based on our GRADE assessment of the total body of evidence. Rigorously assessing the benefits of thiazides in preventing osteoporotic hip fractures in clinical trials is crucial to selecting appropriate antihypertensive agents in the population with high probability of hip fracture. There is a need to conduct large scale randomized control trials to assess the efficacy of thiazides

in prevention of hip fracture, and their relative safety in individuals without a history of hypertension. Such trials should also determine the minimum dose and duration of thiazide use necessary to achieve effective reduction of the risk of hip fracture. Hip fractures can have serious morbidity and mortality consequences. After sustaining a hip fracture, a person may be unable to perform activities of daily living and/or unable to live independently. Development of serious complications such as pneumonia or venous thromboembolism could lead to death. Adverse effects of available medications for treatment of osteoporosis and their cost can prohibit individuals with high probability of hip fracture from receiving appropriate therapy, and thiazides could be an alternative option for such individuals. Because of the serious nature of hip fracture, worldwide expansion of the population prone to risk fracture and limitations of current treatment of osteoporosis, such trials assessing the efficacy of thiazides should be given a priority. The pharmaceutical industry would have very little commercial incentive to fund such trials, given that the patents of thiazide diuretics have long run out. We call upon public and private nonprofit organizations around the globe to give priority in funding such trials to evaluate this inexpensive and potentially effective therapeutic option for prevention of hip fracture in older adults.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barengolts 2001

Methods	Case-control study
Participants	218 patients admitted to Chicago VA Hospital for hip fracture and 218 race- and age-matched controls
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Unclear how thiazide use was ascertained. Hip fracture was ascertained by VA hospital records

Cauley 1993

Methods	Cohort study
Participants	9704 ambulatory non-black women aged 65 and above from 4 clinical centers in the United States (Baltimore, MD, Minneapolis, MN, Portland, OR, and Monogahela Valley, PA)
Interventions	N/A
Outcomes	Incident fracture, adjusted for age
Notes	Thiazide use was ascertained by a questionnaire, interview and examination. Incident fractures were ascertained every 4 months

Cumming 1993

Methods	Case-control study
Participants	209 cases from hospitals, 207 controls from private homes and nursing homes
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from the participants or their proxys by a questionnaire. Hip fracture cases were ascertained from hip fracture team in the hospital and from emergency department log books in Westmead Hospital, review of ED log book in 4 hospitals, contact with admissions office in 4 hospitals, contact with medical record department in 2 hospitals, and from a rehabilitation specialist in one hospital

Cummings 1995

Methods	Cohort study
Participants	9516 white women age 65 and above who are able to walk from 4 geographic regions in the United States (Portland, OR, Minneapolis, MN, Baltimore, MD and Monongahela Valley, PA)
Interventions	N/A
Outcomes	Incident fracture adjusted for age.
Notes	Thiazide use was ascertained by structured interviews. Hip fracture was ascertained by postcard or telephone contact every 4 months, confirmed by reviewing radiographs

Felson 1991

Methods	Case-control study
Participants	176 postmenopausal female members of Framingham Cohort and 672 age-matched controls
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by patients' reports during biennial examinations. Hip frature was ascertained by patients' reports during biennial examinations & telephone calls, hospital records, death reviews, fracture list of Framingham Study

Feskanich 1997

Methods	Prospective cohort study
Participants	83, 728 women nurses, age 35-61, from the United States who participated in the Nurses Health Study
Interventions	N/A
Outcomes	Incident hip fracture adjusted for age and follow-up period
Notes	Thiazide use was ascertained by initial and biennial follow-up mailed questionnaire asking current use and duration. Hip fracture was ascertained by initial and biennial follow-up mailed questionnaire to the participants

Grisso 1994

Methods	Case-control study
Participants	144 black women admitted to New York City and Philadelphia hospitals and 388 controls 218 controls lived in the community, and matched for age, ZIP code and telephone exchange. 181 controls were hospitalised women matched for age and hospital

Grisso 1994 (*Continued*)

Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Hip fracture was ascertained by x-rays and obtained from admission records. Thiazide use was ascertained by interviewing participants

Guo 1998

Methods	Prospective cohort study.
Participants	1608 residents, age 75 and above who has not had a hip fracture, from Kungsholmen District of Stockholm, Sweden
Interventions	N/A
Outcomes	Incident hip fracture adjusted for age, gender, education, institutional residence status, activities of daily living, visual problem, history of stroke, history of tumour and cognitive impairment
Notes	Thiazide use was ascertained during interviews. Use is defined as any use within 2 weeks before the date of interview. Hip fracture cases were defined through computerized in-patient register system that covers all hospitals in Stockholm area

Heidrich 1991

Methods	Case-control study
Participants	462 patients aged 50 & above, hospitalised for hip fractures in Western Washington State, USA. Equal number of Age and sex-matched population-based controls
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from medical records and computerized pharmacy records. Hip fracture was ascertained from hospital discharge records showing primary ICD-9 code of 820 or equivalent

Herings 1996

Methods	Case-control study
Participants	386 patients hospitalised for femur fractures aged 45 and above who were residents of a defined population from The Netherlands. An age-, sex-, pharmacy-, and general practitioner-matched control was randomly selected from drug-dispensing records for each case
Interventions	N/A

Herings 1996 (*Continued*)

Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from computerized pharmacy records. Femur fracture was ascertained from hospital records showing admission with ICD-9 code of 820 (fracture of neck of femur) or 821 (fracture of other and unspecified parts of femur)

Jensen1991

Methods	Case-control study
Participants	200 consecutive patients (age>59) admitted with femoral neck fracture in a hospital in Denmark and 200 controls selected from social security register, matched by age, sex, nursing home residency and number of hospital admissions
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by interviewing the participants by one of the 3 physicians within 4 days of hospital admission. Hip fracture was ascertained by hospital admission diagnosis

LaCroix 1990

Methods	Cohort study
Participants	9518 participants from 3 geographic regions of the United States (East Boston, MA, New Haven, CT, Iowa and Washington Couties, IA)
Interventions	N/A
Outcomes	Incident hip fracture adjusted for age, gender, impaired mobility, body mass index and smoking status
Notes	Thizide use was ascertained by interviews during household surveys. Hip fracture was ascertained by annual follow-up interviews

Paganini-Hill 1981

Methods	Case-control study
Participants	83 females with hip fracture fro greater Los Angeles area, California, U.S.A., and166 controls matched by age, race and date of entry to the community
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture

Paganini-Hill 1981 (*Continued*)

Notes	Thiazide use was ascertained by personal interviews and abstracts of medical records. Hip fracture was ascertained from hospital discharge records

Rashiq 1986

Methods	Case-control study
Participants	102 patients (age 60 and above) with hip fracture from University Hospital, Nottingham, UK and 204 age- and sex-matched controls
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by review of medical records during a year before the date of fracture. Hip fracture was ascertained by operating theatre records from the hospital

Ray 1989

Methods	Case control study
Participants	905 patients (age 65 and above) with hip fracture and 5131 age- and sex-matched controls selected from residents of Saskatchewan, Canada
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from computerized pharmacy records. Hip fracture was ascertained from ICD-9 codes with primary or secondary diagnoses of hip fractures from hospital discharged records

Rejnmark 2005

Methods	Case-control study
Participants	64,999 patients aged 40 and above with fractures selected from hospital discharge records of national health system in Denmark and 194,111 age and gender-matched controls selected from national civil registration system. Number of patients with hip fracture was10319 (out of 64,999 cases)
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by national electronic pharmacy database. Hip fracture was ascertained by hospital discharge records from nationwide electronic medical records

Schoofs 2003

Methods	Prospective cohort study
Participants	7891 residents of Ommord (Rotterdam, Netherlands) aged 55 and above who did not have hip fracture before 6/1/91
Interventions	N/A
Outcomes	Incident hip fracture adjusted for age, gender, lower limb disability, oestrogen use, and smoking status
Notes	Thiazide use was ascertained from the computer database of pharmacies where the participants filled their prescriptions. Hip fractures were reported by the doctors of the participants through computerized system (80%). Research physicians annually checked medical records of the participants not covered by computer system (20%)

Stevens 1989

Methods	Case-control study
Participants	173 patients with new non-pathological hip fractures from hospital admissions and 134 age and sex-matched controls from non-emergency surgery admissions in Southeast Thames Region
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from interviews with patients and review of their medical records, validated independently by questionnaires to general practitioners. Hip fracture was ascertained from casualty and orthopedic ward record review of hospitals in Southeast Thames Region

Taggart 1988

Methods	Case-control study
Participants	280 women admitted to a city hospital with hip fracture and 145 controls from general academic family practice list in North Ireland
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by taking careful medication histories from patients and family doctors. Hip fracture was ascertained by admission diagnoses

Wang 2001

Methods	Case-control study
Participants	1222 individuals, age 65 and above, hospitalised for surgical repair of hip fracture and 4888 age- and gender-matched controls from New Jersy Medicaid Program in the United States
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained by pharmacy claim data. Hip fracture was ascertained by the claim for surgical repair of hip fracture

Weiland 1997

Methods	Case-control study
Participants	311 females age 70-79 yrs with hip fracture and 414 controls from West Germany
Interventions	N/A
Outcomes	Association of thiazide use and hip fracture
Notes	Thiazide use was ascertained from patients' records. Hip fracture was ascertained by the reports from the patients' doctors

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adland-Davenport 1985	Fracture data is available only for hip, wrist, vertebra and wrist combined
Allen 2004	Referenced to another article on Annals of Internal Medicine (Sept 16, 2003). Not an original study
Anonymous 2003	Pt education article. Not original research.
Anonymous 2004	Not an original investigation. Made reference to Schoofs 2003
Benetos 2007	Review article
Bolland 2007	Bone density was the only outcome addressed. No data on rate of fracture
Bouwmeester 2004	Not an original investigation. Made reference to Schoofs 2003
Cumming 1998	Review article

(*Continued*)

Grisso 1991	Thiazide use was not addressed.
Hale 1984	No specific data for thiazide users. Lumped as diuretics, which included non-thiazides
Jergas 1994	Only used bone density as the primary outcome measure. No fracture outcomes were analyzed
Jones 1995	Review article
LaCroix 2000	Bone density was the only outcome addressed. No data on rate of fracture
Lim 2005	Bone mineral density only. No fracture.
Nguyen 1996	Only OR for total fractures can be extracted from the article. OR for hip fractures in reference to thiazide use cannot be extracted
Ray 1991	It is an editorial; not an original study.
Reid 2000	Bone density was used as outcome. Fracture was not used as an outcome measure
Sernbo 1987	No data on thiazide use was available. It was analysed only as diuretic use
Sigurdsson 2001	Bone density was used as outcome. Fracture was not used as an outcome measure
Thapa 1993	Review article
Wasnich 1983	Only fracture of lumbar spine was addressed.
Wasnich 1986	Hip fracture outcome was not addressed. Fractures were classified as spine fracture and non-spine fractures
Wasnich 1990	Rate of bone loss in calcaneus and radius were used as outcome measures. Hip fracture outcome was not addressed
Wiens 2006	Review article

DATA AND ANALYSES

Comparison 1. Current thiazide users vs nonusers (cohort studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hip Fracture	5		Risk Ratio (Fixed, 95% CI)	0.76 [0.64, 0.89]

Comparison 2. Current thiazide users vs nonusers (case-control studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hip Fracture	15		Odds Ratio (Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Current thiazide users vs nonusers (cohort studies), Outcome 1 Hip Fracture.

Review: Thiazide diuretics and the risk of hip fracture

Comparison: 1 Current thiazide users vs nonusers (cohort studies)

Outcome: 1 Hip Fracture

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Cauley 1993	-0.19845 (0.15907124)		27.6 %	0.82 [0.60, 1.12]
Feskanich 1997	-0.37106 (0.18419048)		20.6 %	0.69 [0.48, 0.99]
Guo 1998	0.09531 (0.2707287)		9.5 %	1.10 [0.65, 1.87]
LaCroix 1990	-0.38566 (0.16519749)		25.6 %	0.68 [0.49, 0.94]
Schoofs 2003	-0.34249 (0.20446899)		16.7 %	0.71 [0.48, 1.06]
Total (95% CI)			**100.0 %**	**0.76 [0.64, 0.89]**

Heterogeneity: Chi² = 2.93, df = 4 (P = 0.57); I² =0.0%

Test for overall effect: Z = 3.33 (P = 0.00088)

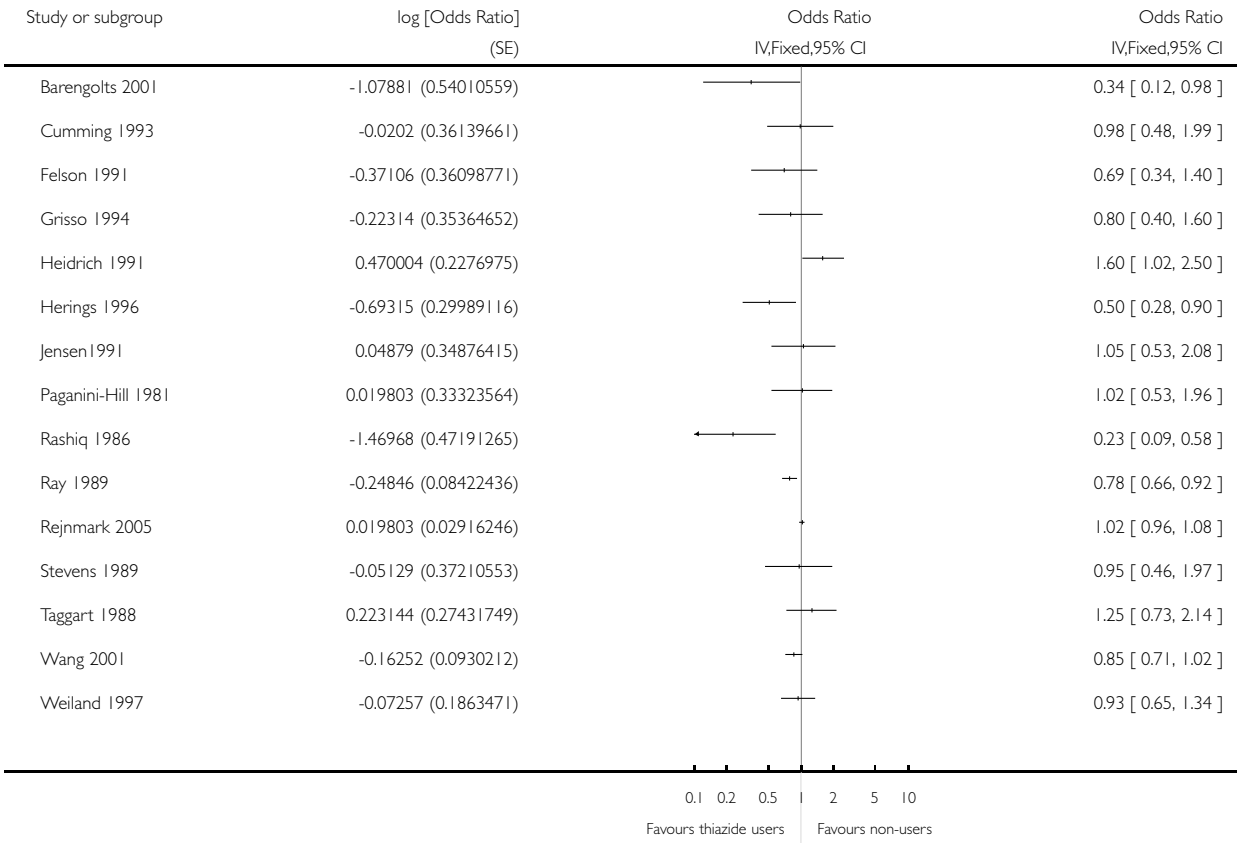
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Current thiazide users vs nonusers (case-control studies), Outcome 1 Hip Fracture.

Review: Thiazide diuretics and the risk of hip fracture

Comparison: 2 Current thiazide users vs nonusers (case-control studies)

Outcome: 1 Hip Fracture



ADDITIONAL TABLES

Table 1. Risk of Bias Assessment for Cohort Studies

Study	Selection	Comparability	Outcome
Cauley 1993	***	**	***
Cummings 1995	****	**	***
Faskanich 1997	*	**	*

Table 1. Risk of Bias Assessment for Cohort Studies (*Continued*)

Guo 1997	****	**	***
LaCroix 1990	****	**	**
Schoofs 2003	****	**	***

Table 2. Risk of Bias Assessment for Case-control Studies

Study	Selection	Comparability	Exposure
Barengolts 2001	*	**	**
Cumming 1993	***	**	***
Felson 1991	***	**	***
Grisso 1994	* *	**	*
Heidrich 1991	**	**	**
Herings 1996	***	**	**
Jensen 1991	**	**	*
Paganini-Hills 1981	***	**	**
Rashiq 1986	**	**	**
Ray 1989	**	**	**
Renjmark 2005	**	**	**
Stevens 1989	*	**	****
Taggart 1988	**	*	**
Wang 2001	****	**	**
Weiland 1997	***	**	**

Table 3. Cohort Studies

Study	Female (%)	Ethnicity	Age	N	Location	Mean follow-up yrs (person-yrs)
Cauley 1993	100	Non-black	>65	9,704	U.S. (MD, MN, OR, PA)	3.3 (32,217)
Cummings 1995	100	White	>65	9,516	U.S. (MD, MN, OR, PA)	4.1 (39,015)
Faskanich 1997	100	98% White	>35	83,728	U.S.	9.2 (771,605)
Guo 1997	74	unknown	>75	1,608	Sweden	4.4 (7,124)
LaCroix 1990	60	unknown	>65	9,518	U.S. (MA, CT, IA)	3.6 (34,426)
Schoofs 2003	61	unknown	>55	7,891	Netherlands	7.4 (58,009)

Table 4. Case-control Studies

Study	Female (%)	Ethnicity	Age	N (Cases; Control)	Location
Barengolts 2001	0	40% black	>55	218; 218	U.S (Chicago, IL)
Cumming 1993	75	unknown	>65	299; 207	Sydney, Australia
Felson 1991	100	unknown	postmenopausal	176; 672	U.S. (Framingham, MA)
Grisso 1994	100	100% black	>45	144; 399	U.S. (NYC & Philadelphia)
Heidrich 1991	76	97% white	>50	462; 462	U.S. (MA, CT, IA)
Herings 1996	75	unknown	>45	386; 386	Netherlands
Jensen 1991	82	unknown	>59	200; 200	Denmark
Paganini-Hill 1981	100	unknown	Postmenopausal <80	83; 166	U.S. (Los Angeles, CA)
Rashiq 1986	88	unknown	>60	102; 204	UK
Ray 1989	74	95% white	>65	905; 5,131	Canada
Renjmark 2005	66	unknown	>40	64,699; 194,111	Denmark
Stevens 1989	79	Mostly white	?	173; 134	UK
Taggart 1988	100	unknown	>74	280; 145	North Ireland
Wang 2001	84	86% white	>65	1,222; 4,888	U.S. (NJ)

Table 4. Case-control Studies (*Continued*)

Weiland 1997	100	unknown	70-79	311; 414	West Germany

Table 5. Covariates adjusted in cohort studies

Study	Adjustment
Cauley 1993	age, weight, functional status, total calcium intake, years of estrogen replacement, self-reported health status
Cummings 1995	age
Feskanich 1997	age, follow-up period, BMI, menopausal status, postmenopausal estrogen use, cigarette smoking, dietary intake of calcium, vitamin D, protein, alcohol, caffeine and sodium, calcium supplements, previous diagnosis of heart disease, previous diagnosis of osteoporosis
Guo 1998	age, gender, education, residence, limitation of activities of daily living, visual problem, history of stroke, history of tumor, cognitive impairment
Lacroix 1990	age, gender, impaired mobility, BMI, current smoking, former smoking
Schoofs 2003	age, gender, lower limb disability, BMI, oestrogen use, current smoking

Table 6. Covariates adjusted in case-control studies

Study	Covariates adjusted
Barengolts 2001	age, body weight, BMI, statin use
Cumming 1993	age, sex, type of residence, alcohol consumption, BMI, cognitive status, dairy consumption, health status, physical activity, proxy status, smoking history, use of other medications
Felson 1991	BMI, oestrogen use, number of cigarettes smoked, alcohol consumption, age at menopause
Grisso 1994	age group, zip code, telephone exchange, age as continuous variable, BMI, BMI-squared
Heidrich 1991	alcoholism, organic brain syndrome, leg paralysis, history of stroke, days of hospitalizations in preceding year, nursing home residence, BMI, use of phenobarbital, corticosteroids and furosemide
Herings 1996	days hospitalised before index date, history of hospitalizations for nonhip fractures, presence of severe rheumatological disease, anaemia, organic brain syndrome, cerebrovascular disease, peripheral arterial disease, incontinence, osteoporosis, current use of benzodiazepines, antidepressants, H-1 antagonists, neuroleptics, furosemide and corticosteroids
Jensen 1991	?

Table 6. Covariates adjusted in case-control studies (*Continued*)

Paganini-Hills 1981	?
Rashiq 1986	?
Ray 1989	demographics, hospital admissions, use of other medications
Renjmark 2005	prior fracture, Charlon index, hx of using corticosteroid, antiepileptics, other diuretics, other antihypertensives, anxiolytics/sedatives, neuroleptics, and antidepressants, number of days hospitalised in prior year, number of contacts with the doctors in prior year, employment status, income, living alone
Stevens 1989	age, gender
Taggart 1988	age
Wang 2001	age, gender, race, use of zolpidem, benzodiazepines, antipsychotics, antidepressants, other psychoactive medication, comorbidity index, hospital days in prior 6 months, nursing home days in prior 6 months
Weiland 1997	age, BMI, smoking habits, alcohol consumption, uncontrolled hypertension, impaired mobility, cardiac insufficiency, cerebral insufficiency

BMI = body mass index

APPENDICES

Appendix 1. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (COHORT STUDIES)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average ..... (describe) in the community *

b) somewhat representative of the average ..... in the community *

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort *

b) drawn from a different source

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview *

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes *
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for ..... (select the most important factor) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost - > .... % (select an adequate %) follow up, or description provided of those lost) *
c) follow up rate < ....% (select an adequate %) and no description of those lost
d) no statement

Appendix 2. NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (CASE-CONTROL STUDIES)

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.
Selection
1) Is the case definition adequate?
a) yes, with independent validation *
b) yes, e.g. record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated
3) Selection of Controls
a) community controls *
b) hospital controls
c) no description
4) Definition of Controls
a) no history of disease (endpoint) *
b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for ..... (Select the most important factor.) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Exposure
1) Ascertainment of exposure
a) secure record (e.g. surgical records) *
b) structured interview where blind to case/control status *

c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes *
b) no
3) Non-Response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Appendix 3. Coding manual for Newcastle-Ottawa Quality Assessment Scale

CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal oestrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of oestrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users users of oestrogen).

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category
Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age = * , Other controlled factors = *

OUTCOME

1) Assessment of Outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.) *

b) Record linkage (e.g. identified through ICD codes on database records) *

c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)

d) No description.

2) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1) Is the Case Definition Adequate?

a) Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) *

b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record

c) No description

2) Representativeness of the Cases

a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample) *

b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (i.e. same community as cases and would be cases if had outcome) *

b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population

c) No description

4) Definition of Controls

a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. *
b) No mention of history of outcome

COMPARABILITY

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)
Age = * , Other controlled factors = *

EXPOSURE

1) Ascertainment of Exposure

Allocation of stars as per rating sheet

2) Non-Response Rate

Allocation of stars as per rating sheet

HISTORY

Protocol first published: Issue 1, 2005

Review first published: Issue 10, 2011

Date	Event	Description
12 November 2008	Amended	Contact details updated
12 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

K. Aung contributed to all parts of the review.

T. Htay contributed to background, identification of studies, assessment of risk of bias (methodological quality) of included studies, data extraction, discussion, and conclusions.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Bone Density [*drug effects]; Case-Control Studies; Cohort Studies; Hip Fractures [*prevention & control]; Postmenopause; Risk; Sodium Chloride Symporter Inhibitors [*therapeutic use]

MeSH check words

Adult; Female; Humans; Male