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## RESEARCH

# Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study

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## Abstract

**Objective** To examine the association between chronic use of proton pump inhibitors (PPIs) and risk of hip fracture.

**Design** Prospective cohort study.

**Setting** Nurses' Health Study, which originally recruited from the 11 most populous states in the US.

**Participants** 79 899 postmenopausal women enrolled in the Nurses' Health Study who provided data on the use of PPIs and other risk factors biennially since 2000 and were followed up to 1 June 2008.

**Main outcome measure** Incident hip fracture

**Results** During 565 786 person years of follow-up, we documented 893 incident hip fractures. The absolute risk of hip fracture among regular users of PPIs was 2.02 events per 1000 person years, compared with 1.51 events per 1000 person years among non-users. Compared with non-users, the risk of hip fracture among women who regularly used PPIs for at least two years was 35% higher (age adjusted hazard ratio 1.35 (95% confidence interval 1.13 to 1.62)), with longer use associated with increasing risk ( $P_{\text{trend}} < 0.01$ ). Adjustment for risk factors, including body mass index, physical activity, and intake of calcium did not materially alter this association (hazard ratio 1.36 (1.13 to 1.63)). These associations were also not changed after accounting for reasons for PPI use. The relation between PPI use and fracture differed by smoking history ( $P_{\text{interaction}} = 0.03$ ). Among current and former smokers, PPI use was associated with greater than 50% increase in risk of fracture, with a multivariate hazard ratio for fracture of 1.51 (1.20 to 1.91). In contrast, among women who never smoked there was no association (multivariate hazard ratio 1.06 (0.77 to 1.46)). In a meta-analysis of these results with 10 prior studies, the pooled odds ratio of hip fracture associated with PPI use was 1.30 (1.25 to 1.36).

**Conclusion** Chronic use of PPIs is associated with increased risk of hip fracture, particularly among women with a history of smoking.

## Introduction

Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide.<sup>1</sup> In the US, PPI use increased dramatically since 2003 after the Food and Drug Administration approved the drugs for "over the counter" use. Primarily used for the treatment of heartburn symptoms, gastroesophageal reflux, or peptic ulcer, PPIs antagonise hydrogen-potassium adenosine triphosphatase pumps located on gastric parietal cells,<sup>2</sup> thereby reducing acid production to a greater extent than histamine receptor-2 ( $H_2$ ) blockers.<sup>3</sup> Although short term use of PPIs is generally well tolerated, concern has grown over potential association between long term use and bone fractures, especially of the hip, which are known to be associated with substantial morbidity and mortality.<sup>4-6</sup> PPIs may inhibit calcium absorption,<sup>7</sup> directly interfere with osteoclast function,<sup>8</sup> or induce hypergastrinaemia, resulting in reductions in bone mineral density related to hyperparathyroidism.<sup>9</sup>

Several studies have investigated the association between PPI use and risk of hip fracture.<sup>3 10-17</sup> Many of these studies have had important limitations, including retrospective design,<sup>10 12-14 16 17</sup> inability to control for important dietary and lifestyle confounders,<sup>3 10 12-14 16</sup> small sample size,<sup>17</sup> and limited ascertainment of PPI exposure.<sup>11</sup> None the less, in May 2010 the Food and Drug Administration issued a warning regarding a potential association, but acknowledged that more data were needed.<sup>18</sup>

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Appendix: Details of studies used in meta-analysis and of supplementary analysis

We therefore sought to examine the association between long term PPI use and risk of hip fracture among postmenopausal women enrolled in a large prospective cohort, the Nurses' Health Study, where detailed information about dietary and lifestyle factors are collected biennially.<sup>19-23</sup> This cohort offered us an opportunity to examine PPI use in the context of other dietary and lifestyle risk factors that may either confound or modify its association with fracture. We also conducted a systematic review of our findings with prior studies to provide a more comprehensive estimate of the association.

## Methods

### Study population

The Nurses' Health Study is a prospective cohort that began in 1976 when 121 700 US female registered nurses aged 30–55 years completed a mailed health questionnaire. We sent questionnaires to study participants every two years to update information and identify new cases of fracture; follow-up has consistently exceeded 90%. A validated assessment of physical activity is administered every two years,<sup>24</sup> and a validated semi-quantitative food frequency questionnaire is administered every four years.<sup>25 26</sup> The institutional review board at the Brigham and Women's Hospital approved this study.

### Outcome ascertainment

In 1982 participants were first asked to report all previous hip fractures (date, bone site, and circumstances). Subsequently, in each biennial questionnaire, women were specifically asked, "Over the past two years have you had a hip fracture?" Participants who responded "yes" received a follow-up questionnaire asking them to "describe the circumstances that caused the hip fracture, bone site, and the month/year of fracture." We included cases of hip fracture that were associated with reports of low or moderate trauma (such as slipping on ice or falling from the height of a chair). We excluded fractures associated with high trauma (such as from skiing or falling down a flight of stairs—about 15% of the reports). In an analysis of 30 study participants, all self reported fractures were validated by medical record review.<sup>27</sup>

### Assessment of proton pump inhibitor and H<sub>2</sub> blocker use

In 1994 participants were asked whether they had regularly used "cimetidine (Tagamet) or ranitidine (Zantac)" over the previous two years. In the 1996, 1998, and 2000 questionnaires, participants were asked whether, over the previous two years, they had regularly used "cimetidine (Tagamet) or other H<sub>2</sub> blockers (e.g. Zantac, Pepcid, etc)." In 2002, 2004, and 2006 participants were asked whether, over the previous two years, they had regularly used any "H<sub>2</sub> blockers (e.g. Zantac, cimetidine, Pepcid, Axid, etc.)." In 2000 and 2002 participants were asked whether, over the previous two years, they had regularly used "Prilosec or Prevacid." In 2004 and 2006, participants were asked whether, over the previous two years, they had regularly used "Prilosec, Prevacid (lansoprazole), Protonix, Nexium, or Aciphex." Women were not asked about dose or to specify the brand or type of PPI.

### Other covariates

On each biennial questionnaire, women were asked about their menopause status; body weight; time spent in recreational and leisure time activities; smoking status; alcohol use; daily cigarette consumption; use of hormone replacement therapy,

thiazide diuretics, corticosteroids, bisphosphonates, and calcium supplements; and incident diagnosis of osteoporosis. Participants' self reported body weight and physical activity have been previously validated.<sup>28</sup> Using a validated semi-quantitative food frequency questionnaire,<sup>25 26</sup> we calculated total intake of calcium and vitamin D from the reported consumption of foods and use of multivitamins and specific vitamin and mineral supplements. As in previous analyses, we used cumulatively averaged nutrient intake, body weight, and physical activity to reduce within person variation and to reflect long term exposure.<sup>29</sup> We included these variables according to categories which we have previously shown to be most strongly associated with risk of hip fracture.<sup>21 29 30</sup>

### Reasons for PPI use

We considered the possibility that the previously observed association between PPI use and risk of hip fracture could be related to the reason for use of the drug. In 2000, a supplemental questionnaire that inquired about the frequency, severity, and duration of heartburn and acid regurgitation was sent to 11 080 participants in the Nurses' Health Study with asthma and chronic obstructive pulmonary disease and 11 080 randomly selected controls (response rate 86%, n=19 060).<sup>30</sup> Detailed description and validation of this questionnaire were previously reported.<sup>29</sup> Among the respondents, 16 478 provided complete information regarding PPI use and the reasons for it and therefore were eligible for our analysis.

### Statistical analysis

At baseline, we included postmenopausal women who returned the 2000 biennial questionnaire in which they were first specifically queried about their use of PPIs. We excluded participants who had previously reported hip fracture or cancer. After these exclusions, 79 899 women were eligible for analysis. Person time for each participant was calculated from the date of return of the baseline questionnaire to the date of first hip fracture, date of last questionnaire report, death from any cause, or last day of outcome ascertainment (1 June 2008), whichever came first. Women were defined as PPI users if they responded that they had regularly used PPI in the previous two years. We also assessed consistent use by restricting our analysis to follow-up after 2002 and examining women who reported regular PPI use on the two previous questionnaires (that is, 2000 and 2002 at baseline) compared with women who did not report use on these questionnaires.<sup>31</sup>

We used Cox proportional hazards modelling using time varying variables with the most updated information for PPI use and other covariates before each two year interval to calculate adjusted hazard ratios and 95% confidence intervals. We also examined the association between PPI use and hip fracture according to strata of other risk factors. We used SAS version 9.1.3 (Cary NC, USA) for these analyses. All P values were two sided, and values <0.05 were considered statistically significant.

### Systematic review of results with prior studies

We also conducted a meta-analysis of our data with the results of published studies assessing the relation between chronic PPI use and risk of hip fracture. We included the seven studies that were cited by the Food and Drug Administration in the May 2010 report.<sup>18</sup> In addition, we conducted a Medline search (last accessed 20 December 2010) with the search terms "proton pump inhibitor" AND "fracture" and identified four additional studies for inclusion.<sup>12 32-34</sup> We excluded the study by Roux et al<sup>34</sup> since the primary outcome was vertebral fracture and there

were only 11 cases of hip fracture reported. In addition, three studies<sup>3 16 32</sup> used the UK General Practice Research Database, although there may have been differences in the populations included. Thus, we included all three studies in our meta-analysis but also conducted sensitivity analyses in which we computed the pooled odds ratio with inclusion of only one of the three studies each in turn.

We used the adjusted odds ratio for hip fracture as our metamer of interest. However, in two studies, data were reported only as adjusted hazard ratios. For the study by Gray et al,<sup>11</sup> we estimated the odds ratio by calculating the numbers of cases in the control and exposed groups using the reported incident rate and person time. For the study by Yu et al,<sup>17</sup> because the number of cases of fracture was not reported or provided by the authors after our request, we used the reported hazard ratio. We pooled estimates by random effects meta-analysis according to the method of Desimonian and Laird.<sup>35</sup> We used the Q statistic to estimate heterogeneity among the studies. We used Comprehensive Meta-Analysis software (Biostat, Englewood NJ, USA) for these analyses (see appendix on bmj.com).

## Results

Among 79 899 postmenopausal women, we documented 893 incident hip fractures over 565 786 person years of follow-up. In 2000, 6.7% of women regularly used a PPI, rising to 18.9% by 2008. Compared with participants who did not regularly use a PPI, regular users had a higher body mass index, were less physically active, consumed less alcohol, were more likely to have a history of osteoporosis, and were more likely to use hormone replacement therapy, thiazide diuretics, corticosteroids, or bisphosphonates (table 1↓).

The absolute risk of hip fracture among regular users of PPIs was 2.02 events per 1000 person years, compared with 1.51 events per 1000 person years among non-users. Compared with non-users, regular users of PPIs had a 35% increase in risk of hip fracture (age adjusted hazard ratio 1.35 (95% confidence interval 1.13 to 1.62)) (table 2↓). The relation remained largely unchanged even after adjusting for body mass index (hazard ratio 1.45 (1.21 to 1.73)) or intake of dietary and supplemental calcium (hazard ratio 1.35 (1.12 to 1.62)). After additionally accounting for other risk factors for fracture—including smoking status, physical activity, and history of osteoporosis—these risk estimates were not materially altered (hazard ratio 1.37 (1.14 to 1.64)). We also did not observe any change in risk after adjusting for concomitant use of drugs known to affect the risk of fracture, including hormone replacement, bisphosphonates, corticosteroids, and thiazide diuretics (fully adjusted multivariate hazard ratio 1.36 (1.13 to 1.63)).

We first asked participants in the Nurses' Health Study about PPI use in the 2000 questionnaire. We considered the possibility that women who reported use in 2000 had probably used PPIs for varying durations. Thus, we conducted an analysis in which we excluded women who reported use in 2000 and restricted the analysis to follow-up after 2002. Women who first reported PPI use in 2002 had a fully adjusted hazard ratio of hip fracture of 1.42 (1.14 to 1.76) compared with women who had not used PPIs. To test if the association between PPI use and fracture might be due to its effect on gastric acid suppression, we examined regular use of less potent acid suppressors, H<sub>2</sub> blockers, in relation to risk of fracture after excluding participants who used PPIs. Compared with PPI use, regular use of H<sub>2</sub> blockers was associated with a more modest risk of

fracture (fully adjusted hazard ratio 1.23 (1.02 to 1.50) v non-use).

The risk of hip fracture associated with PPI use increased with the duration of use ( $P_{\text{trend}} < 0.01$ ) (table 3↓). Compared with non-users, the fully adjusted hazard ratios of fracture were 1.36 (1.12 to 1.65) for women with two years' use of PPIs, 1.42 (1.05 to 1.93) for four years' use, and 1.55 (1.03 to 2.32) for six to eight years' use. To assess consistent use, we focused our analyses on women who reported PPI use in two consecutive biennial follow-up questionnaires and compared the incidence of fracture among women who did not use PPIs in two consecutive intervals. Among consistent users, the fully adjusted hazard ratio of fracture was 1.42 (1.06 to 1.88).

We also considered time since stopping PPI use in relation to risk of fracture (table 4↓). Although risk persisted for women who stopped PPI use within two years, women who had stopped use more than two years previously had a fully adjusted hazard ratio of fracture of 1.10 (0.63 to 1.92), similar to that of women who had never used a PPI.

We evaluated potential differences in the influence of PPI use according to strata of known risk factors (table 5↓). The risk of hip fracture seemed to differ according to history of cigarette smoking ( $P_{\text{interaction}} = 0.03$ ). Among women who either previously or currently smoked, the fully adjusted hazard ratio of fracture was 1.51 (1.20 to 1.91). In contrast, there was no significant association between PPI use and risk of fracture among women who never smoked (fully adjusted hazard ratio 1.06 (0.77 to 1.46)). The effect of PPIs was not modified by strata defined by age, body mass index, use of hormone replacement therapy, use of corticosteroids, history of osteoporosis, or intake of calcium (all  $P_{\text{interaction}} > 0.10$ ).

We considered the possibility that the observed association of PPIs with hip fracture could be related to the reason for taking the drug. In 2000 we collected detailed information about symptoms of acid reflux and heartburn from 16 478 participants through a supplementary questionnaire. Among these participants, the fully adjusted hazard ratio of fracture associated with regular use of PPIs was 1.45 (1.01 to 2.10) and was not materially altered after accounting for the reason for PPI use. Specifically, the fully adjusted hazard ratio of fracture was 1.53 (1.04 to 2.25) after adjusting for heartburn; 1.37 (0.94 to 2.02) after adjusting for acid reflux; and 1.39 (0.96 to 2.02) after adjusting for peptic ulcer disease. These effect estimates did not vary according to the participants' case or control status ( $P_{\text{interaction}} = 0.57$ ). Moreover, in separate analyses, there were no independent associations between reported heartburn, acid reflux, or peptic ulcer disease and risk of hip fracture (data not shown). We also conducted several sensitivity analyses to confirm that our associations were robust (see appendix on bmj.com).

## Systematic review

Finally, we performed a systematic review of our results with the 10 published epidemiological studies on risk of hip fracture with chronic use of PPIs (see table in appendix).<sup>3 10-14 16 17 33 34</sup> There was moderate heterogeneity across studies ( $Q_{\text{statistic}} = 22.0$ ;  $I^2 = 50.0$ ,  $P = 0.02$ ). Among the 1 562 862 individuals included within the 11 studies, the pooled odds ratio of hip fracture associated with PPI use was 1.28 (1.19 to 1.37) using a random effects meta-analysis (figure↓). We observed similar results using a fixed effects meta-analysis (odds ratio 1.30 (1.25 to 1.36)). We also computed the pooled odds ratio with inclusion of only one of the three studies from the UK General Practice Research Database each in turn.<sup>3 16 32</sup> Using a random effects

meta-analysis, we found the pooled odds ratio of hip fracture associated with PPI use was 1.30 (1.20 to 1.40) including the study of Yang et al,<sup>3</sup> 1.27 (1.18 to 1.36) including de Vries et al,<sup>32</sup> and 1.25 (1.15 to 1.37) including Kaye et al.<sup>16</sup>

## Discussion

Findings from this large prospective cohort of postmenopausal women and a systematic review of epidemiological studies show a significant association between regular use of PPIs and risk of hip fracture. Furthermore, our results show that risk increases with longer duration of PPI use and seems to be confined to women with a history of smoking. These associations remained largely unchanged even after carefully adjusting for factors associated with both use of PPI and risk of hip fracture, as well as the reasons for PPI use. The increased risk of hip fracture was no longer evident after PPI use had been stopped for two or more years.

## Comparison with other studies

Our results are supported by several prior findings, including recent meta-analyses.<sup>36,37</sup> In two large case-control studies based on the UK General Practice Research Database and the Kaiser Permanente, Northern California, integrated healthcare delivery system,<sup>3,10</sup> PPI use for at least one year was associated with an increase in risk of hip fracture of similar magnitude to our risk estimates. Because these case-control studies had limited information on several key risk factors for fracture, our cohort analysis, with careful adjustment for such factors, significantly extends these findings.

Our results do, however, contrast with data from other studies. In an independent analysis of the UK General Practice Research Database, PPI use was not associated with hip fracture.<sup>16</sup> However, this study was limited to individuals without risk factors for hip fracture. More recently, in the Women's Health Initiative, PPI use was associated with risk of total fracture, spine fracture, and wrist fracture, but not hip fracture or changes in bone mineral density.<sup>11</sup> However, data on PPI use was collected only in 1997 and 2000, when the prevalence of use was extremely low (2.1% in 1997, 5.8% in 2000). By not accounting for the dramatic increase in use of these drugs after 2000, the researchers may have misclassified PPI exposure and led to their finding no association for hip fracture. In support of this explanation, we also observed no significant association with risk of hip fracture when we considered PPI use only according to our baseline assessment in 2000 (multivariate adjusted hazard ratio 1.20 (0.94 to 1.54)). Moreover, it is possible that the association between PPI and fracture may be mediated independently of changes in bone mineral density.

Consistent with prior studies,<sup>3,10</sup> we did observe a significant, though more modest, association with hip fracture among women who used H<sub>2</sub> blockers, which are less potent acid suppressors than PPI. These data suggest mechanistically that PPIs may increase fracture risk through their effect on gastric acid secretion, which could impair absorption of calcium. However, in our analysis, as well as others,<sup>11</sup> risk of fracture did not seem to be modified by intake of calcium. This is further supported by two recent studies that showed no association between PPI use and gut calcium absorption.<sup>38,39</sup> Moreover, several studies have not observed a significant association between PPI use and short term changes in bone mineral density.<sup>11,17,40</sup>

Nevertheless, our finding that the risk of fracture was confined to women with a history of smoking, an established risk factor for fracture,<sup>19</sup> may provide additional mechanistic insight.

Smoking has been shown to inhibit calcium absorption.<sup>41</sup> Thus, smoking and PPIs may have a synergistic effect on fracture risk mediated by impaired calcium absorption. In addition, experimental studies have postulated that both PPIs and smoking influence osteoclast function,<sup>8,42</sup> perhaps suggesting a shared negative effect on bone remodelling. Future experimental studies or additional analyses of other cohorts should also examine joint exposure to PPI use and smoking.

## Strengths and limitations of the study

An important strength of our study compared with prior analyses was the detailed, prospectively collected, and validated information on several potential confounding risk factors, including body mass index, use of postmenopausal hormones, smoking, calcium intake, and physical activity. In our cohort, each of these factors has previously been associated with risk of fracture.<sup>19,23</sup> Thus, we were able to carefully adjust for these potential confounders to determine more clearly the specific effect of PPI use on the risk of fracture. We were also able to minimise confounding by disease indication or protopathic bias by accounting for the clinical reason for PPI use.

Most prior studies, including the two large case-control studies that showed strong associations,<sup>3,10</sup> had a substantial amount of incomplete information on body mass index and smoking and were unable to assess adequately diet, physical activity, and the indication for PPI use. Thus, our results provide additional assurance that these previously reported associations are not due to incomplete adjustment of confounding factors. In our analysis, we also collected information on PPI use every two years and used time-varying PPI exposure in our Cox models. Thus, our study was uniquely able to account for the effect of changes in PPI use and the substantial increase in PPI use over the past decade on risk of fracture, minimising misclassification of exposure. Lastly, despite significant heterogeneity between studies, our systemic review and meta-analysis, which included 1 562 862 patients, showed consistent results.

Our study has several limitations. Firstly, we did not have information about PPI use in participants before 2000. However, the prevalence of use in 2000 was low (6.7%) and steadily increased through 2008, reflecting secular trends. Thus, PPI use before 2000 was probably extremely low. None the less, we did observe a significant relation between duration of PPI use and risk of hip fracture; any misclassification of PPI use before 2000 would be expected to attenuate our risk estimates. Moreover, when we limited our analysis to new users of PPI beginning in 2002, we observed similar results.

Secondly, we did not have specific information on the type or brand of PPI and the doses used. However, heterogeneity in risk associated with PPI type or dose would tend to bias our results toward the null. In addition, compared with prescription data, reports of regular use of PPI in the general questionnaire by medical professionals are likely to be a better reflection of the actual intake of the drug.

Thirdly, information about hip fracture is self reported and not confirmed by medical records. However, our validation study showed that self reported hip fracture is extremely reliable in this cohort of medical professionals. Fourthly, we did not have information about bone mineral density, but prior studies have not demonstrated an association between PPI use and changes in bone mineral density.<sup>11,17,40</sup> Fifthly, our study is observational, and we cannot exclude the possibility of residual confounding. However, adjustment for the most important risk factors previously identified for hip fracture did not appreciably alter our results. Moreover, our data are remarkably consistent with

the risk estimates obtained from a systematic review of prior studies. Finally, because our sample size was large, it is possible that even small differences in the prevalence of risk factors could be statistically significant but may not be clinically significant. However, our associations are reasonable in magnitude, in line with other published estimates,<sup>12 17 34</sup> and biologically plausible.

## Conclusion and policy implication

In summary, regular use of PPI was associated with increased risk of hip fracture among postmenopausal women, with the strongest risk observed in individuals with the longest duration of use or with a history of smoking. Our results, considered in the context of a systematic review of prior studies, provide compelling evidence of a significant association between PPI use and fracture. Furthermore, in view of the steadily growing prevalence of regular PPI use, our estimates of an absolute increase in risk of five hip fractures per 10 000 person years associated with PPI use suggest the potential for a high burden of fractures attributable to PPIs across the population. These findings further support the recent decision of the Food and Drug Administration to revise labelling of PPIs to incorporate concerns about a possible increase in risk of fractures with these drugs.<sup>18</sup> Our data suggest the importance of carefully evaluating the need for long term, continuous use of PPIs, particularly among individuals with a history of smoking.

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Contributors: HK was responsible for study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. ESH was responsible for acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. BCJ was responsible for acquisition of data and critical revision of the manuscript for important intellectual content. CAC was responsible for acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. DF was responsible for acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. ATC was responsible for study concept and design, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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Ethical approval: The institutional review board at the Brigham and Women's Hospital approved this study.

Data sharing: Requests for access to data, statistical code, questionnaires, and technical processes may be made by contacting the corresponding author at [achan@partners.org](mailto:achan@partners.org)

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**What is already known on this topic**

Studies exploring the association between use of proton pump inhibitors and hip fracture have produced conflicting results  
 Many studies have limited information on key lifestyle and dietary factors that could influence or modify this association

**What this study adds**

Among postmenopausal women, regular use of proton pump inhibitors was associated with a 35% increased risk of hip fracture  
 The risk seemed to be confined to women with a history of smoking

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## Tables

**Table 1 | Baseline characteristics of 79 899 postmenopausal women enrolled in the Nurses' Health Study according to use of proton pump inhibitors (PPIs) in 2000. Values are numbers (percentages) unless stated otherwise, and all variables are age adjusted (standardised to the age distribution of the study population)**

	Non-user of PPIs (n=74 558)	Regular PPI user (n=5341)
Mean (SD) age (years)	66.6 (6.9)	67.0 (7.0)
Mean (SD) body mass index (kg/m <sup>2</sup> )	26.6 (5.2)	28.2 (5.6)
Smoking status*:		
Never	32 983 (44.3)	2194 (41.2)
Former use ≥10 years	28 100 (37.7)	2204 (41.3)
Former use <10 years	6411 (8.6)	544 (10.2)
Current use <15 cigarettes/day	3399 (4.5)	202 (3.7)
Current use ≥15 cigarettes/day	3492 (4.7)	185 (3.4)
Missing data†	173 (0.2)	12 (0.2)
Mean (SD) physical activity (METs-hour/week)‡	17.7 (15.6)	14.5 (13.2)
Mean (SD) Alcohol intake (g/day)§	5.6 (8.5)	4.7 (7.7)
Mean (SD) Calcium intake (mg/day)§	982 (341)	1001 (347)
Use of hormone replacement therapy:		
Current	32 234 (43.2)	2570 (48.1)
Former or never	37 920 (50.9)	2481 (46.5)
Missing data†	4404 (5.9)	290 (5.4)
History of osteoporosis	22.0	31.0
Use of bisphosphonate	6.0	7.0
Use of corticosteroid	5.0	11.0
Use of thiazide	15.0	24.0
Mean (SD) vitamin D intake (IU/day)§	443 (265)	461 (274)

SD=standard deviation. METs=metabolic equivalents.

\*Categories were selected based on prior studies.

†The missing data category could not be included in our multivariate models because the numbers of participants in the missing categories were too low. Thus, in our models we carried forward values from prior questionnaires.

‡381 participants did not complete the physical activity assessment. For these participants, we assigned the median value of physical activity derived from the entire cohort.

§1443 did not complete the semi-quantitative food frequency questionnaire. For these participants, we assigned the median value of calcium, alcohol, and vitamin D derived from the entire cohort.



**Table 2| Risk of hip fracture according to use of proton pump inhibitors (PPIs) among 79 899 postmenopausal women enrolled in the Nurses' Health Study**

	Non-users of PPIs	Regular PPI user
No of cases/No of person years	744/492 154	149/73 632
Hazard ratio (95% CI):		
Adjusted for age	1.00	1.35 (1.13 to 1.62)
Adjusted for age + body mass index*	1.00	1.45 (1.21 to 1.73)
Adjusted for age + calcium intake†	1.00	1.35 (1.12 to 1.62)
Multivariable adjusted‡	1.00	1.37 (1.14 to 1.64)
Fully adjusted§	1.00	1.36 (1.13 to 1.63)

\*Body mass index categorised as <20, 20–24.9, 25–29.9, ≥30 kg/m<sup>2</sup>.

†Energy adjusted calcium intake calculated from diet and dietary supplements, categorised as <600, 600–899, 900–1200, >1200 mg/day.

‡Adjusted for age (months), body mass index, alcohol intake (<5, 5–15, >15 g/day), total energy adjusted calcium intake, level of physical activity (<1.7, 1.7–4.5, 4.6–10.6, 10.7–22.1, >22.1 metabolic equivalents-hours/week), smoking status (never, past ≥10 years, past <10 years, current <15 cigarettes/day, current >15 cigarettes/day), vitamin D intake (<400, 400–600, >600 IU/day), and history of osteoporosis (yes, no).

§Adjusted for age (years), body mass index, alcohol intake, total energy adjusted calcium intake, history of osteoporosis, level of physical activity, smoking status, vitamin D intake, bisphosphonate use (yes, no), thiazide use (yes, no), corticosteroid use (yes, no), and use of postmenopausal hormone replacement therapy (never, past, current).

**Table 3| Risk of hip fracture according to duration of use of proton pump inhibitors (PPIs) among 79 899 postmenopausal women enrolled in the Nurses' Health Study**

	No of years of regular PPI use*				P <sub>trend</sub> †
	0	2	4	6–8	
No of cases/No of person years	691/470 109	127/62 081	48/21 582	27/12 015	
Hazard ratio (95% CI):					
Age adjusted	1.00	1.36 (1.12 to 1.65)	1.42 (1.05 to 1.92)	1.48 (0.99 to 2.20)	<0.01
Multivariable adjusted‡	1.00	1.36 (1.12 to 1.65)	1.42 (1.05 to 1.93)	1.54 (1.03 to 2.31)	<0.01

\*Women who reported PPI use on a biennial questionnaire were assigned a duration of use of 2 years, and this variable increased in biennial increments (thus women who reported PPI use on two biennial questionnaires were assigned a duration of use of 4 years, those who reported use on three questionnaires were assigned a duration of 6 years, etc).

†P<sub>trend</sub> was estimated by entering the duration of regular PPI use in the model as a continuous variable.

‡Adjusted for age (months), body mass index, alcohol intake, total energy adjusted calcium intake, history of osteoporosis, level of physical activity, smoking status, vitamin D intake, bisphosphonate use, thiazide use, corticosteroid use, and use of postmenopausal hormone replacement therapy (see table 2 for details).

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**Table 4 | Risk of hip fracture according to time since stopping use of proton pump inhibitors (PPIs) among 79 899 postmenopausal women enrolled in the Nurses' Health Study**

	Never used PPI	Stopped PPI use		Current PPI use
		≥2 years ago	<2 years ago	
No of cases/No of person years	691/470 109	13/5028	40/17 017	149/73 632
Hazard ratio (95% CI):				
Age adjusted	1.00	1.09 (0.62 to 1.91)	1.54 (1.11 to 2.14)	1.38 (1.15 to 1.66)
Multivariable adjusted*	1.00	1.10 (0.63 to 1.92)	1.53 (1.10 to 2.12)	1.39 (1.15 to 1.68)

\*Adjusted for age (months), body mass index, alcohol intake, total energy adjusted calcium intake, history of osteoporosis, level of physical activity, smoking status, vitamin D intake, bisphosphonate use, thiazide use, corticosteroid use, and use of postmenopausal hormone replacement therapy (see table 2 for details).

**Table 5| Risk of hip fracture according to use of proton pump inhibitors (PPI) in selected strata of 79 899 postmenopausal women enrolled in the Nurses' Health Study**

Stratum	Non-user of PPIs	Regular PPI user	P <sub>interaction</sub> *
<b>Age</b>			
≤65 years:			1.00
No of cases/No of person years	66/160 861	12/21 360	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.51 (0.80 to 2.86)	
Multivariable adjusted†	1.00	1.34 (0.70 to 2.60)	
>65 years:			
No of cases/No of person years	678/331 294	137/52 273	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.34 (1.10 to 1.61)	
Multivariable adjusted†	1.00	1.36 (1.12 to 1.64)	
<b>Body mass index</b>			
<25:			0.54
No of cases/No of person years	455/218 797	85/25 372	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.54 (1.21 to 1.95)	
Multivariable adjusted†	1.00	1.45 (1.14 to 1.85)	
≥25:			
No of cases/No of person years	289/273 357	64/48 260	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.30 (0.99 to 1.72)	
Multivariable adjusted†	1.00	1.23 (0.93 to 1.64)	
<b>Postmenopausal hormone use</b>			
Never or previously used:			0.72
No of cases/No of person years	625/350 735	125/54 534	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.36 (1.11 to 1.66)	
Multivariable adjusted†	1.00	1.36 (1.11 to 1.66)	
Currently used:			
No of cases/No of person years	119/141 419	24/19 099	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.44 (0.91 to 2.28)	
Multivariable adjusted†	1.00	1.36 (0.84 to 2.19)	
<b>Smoking status</b>			
Never:			0.03
No of cases/No of person years	322/220 553	49/31 829	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.07 (0.78 to 1.45)	
Multivariable adjusted†	1.00	1.06 (0.77 to 1.46)	
Current or past:			
No of cases/No of person years	422/271 600	100/41 803	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.54 (1.23 to 1.93)	
Multivariable adjusted†	1.00	1.51 (1.20 to 1.91)	
<b>Corticosteroid use</b>			
User:			0.10
No of cases/No of person years	71/29 054	40/9816	
Hazard ratio (95% CI):			

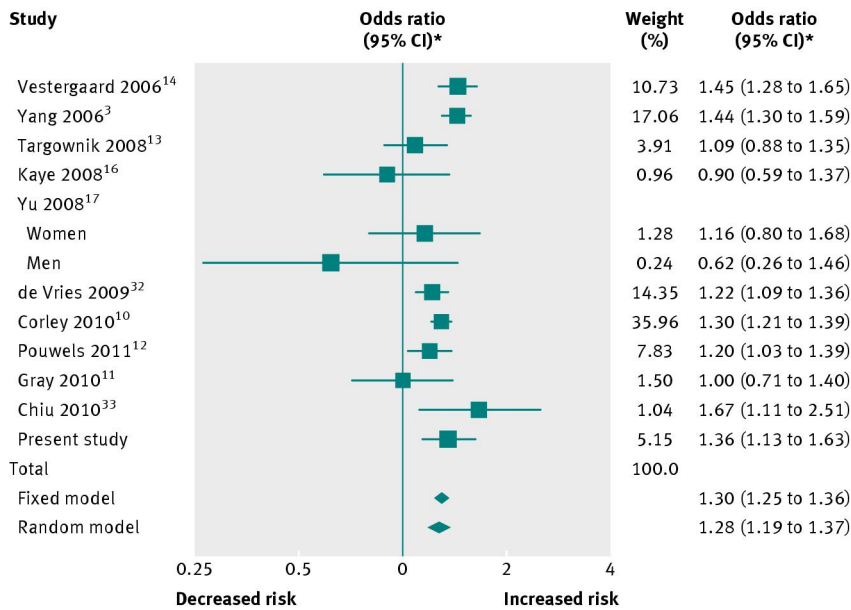
Table 5 (continued)

Stratum	Non-user of PPIs	Regular PPI user	P <sub>interaction</sub> *
Age adjusted	1.00	1.87 (1.22 to 2.86)	
Multivariable adjusted†	1.00	2.09 (1.32 to 3.30)	
<b>Non-user:</b>			
No of cases/No of person years	673/463 101	109/63 817	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.19 (0.97 to 1.47)	
Multivariable adjusted†	1.00	1.26 (1.02 to 1.55)	
<b>History of osteoporosis</b>			
Yes:			0.76
No of cases/No of person years	392/353 613	62/45 687	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.25 (0.98 to 1.60)	
Multivariable adjusted†	1.00	1.28 (1.00 to 1.64)	
<b>None:</b>			
No of cases/No of person years	352/138 542	87/27 945	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.31 (1.00 to 1.73)	
Multivariable adjusted†	1.00	1.41 (1.07 to 1.87)	
<b>Calcium intake</b>			
≥900 mg/day:			0.38
No of cases/No of person years	371/274 346	79/42 070	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.41 (1.10 to 1.82)	
Multivariable adjusted†	1.00	1.42 (1.10 to 1.83)	
<900 mg/day:			
No of cases/No of person years	373/217 810	70/31 563	
Hazard ratio (95% CI):			
Age adjusted	1.00	1.26 (0.97 to 1.64)	
Multivariable adjusted†	1.00	1.25 (0.95 to 1.64)	

\*We evaluated effect modification using cross classified categories of hip fracture risk factors and PPI use. We tested significance of interactions using the log-likelihood ratio test comparing the model with cross classified categories with a model that included the risk factors as independent variables.

†Adjusted for same variables as Table 3 minus the stratum covariate.

### Figure



\*Hazard ratios used for Yu 2008<sup>17</sup>

Results of meta-analysis of our results with 10 published studies of risk of hip fracture with chronic use of a proton pump inhibitor (PPI). For the study by Yu et al,<sup>13</sup> risk estimates were only provided for men and women separately