# Proton pump inhibitors and fracture risk. The HUNT study, Norway.

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**SUMMARY**

Proton pump inhibitors (PPIs) have been linked to increased risk of fracture, the data have, however, been diverging. We did not find any increased risk of fractures among users of PPIs in a Norwegian population of 15,017 women and 13,241 men aged 50-85 years with detailed information about lifestyle and comorbidity.

**INTRODUCTION:**

Proton pump inhibitors (PPIs) are widely prescribed, and have been linked to increased risk of fracture.

**METHODS:**

We used data from the Nord-Trøndelag Health Study (HUNT3), The Fracture registry in Nord-Trøndelag, and the Norwegian Prescription Database, including 15,017 women and 13,241 men aged 50-85 years.

The study population was followed from the date of participating in HUNT3 (2006-2008) until date of first fracture (forearm or hip), death or end of study (31.12.2012).

Cox' proportional hazards model with time-dependent exposure to PPIs was applied, and each individual was considered as unexposed until the first prescriptions was filled. To be included the prescription of PPIs should minimum be equivalent to 90 defined daily doses (DDD) in the period. Individuals were defined as exposed until 6 months after end of drug supply.

**RESULTS**

The proportion of women and men using PPIs was 17.9% and 15.5%, respectively. During a median of 5.2 years follow-up, 266 women and 134 men had a first hip fracture and 662 women and 127 men a first forearm fracture.

The combined rate/1000 patient-years for forearm and hip fractures in women was 49.2 for users of PPIs compared to 64.1 among non-users; for men 18.6 and 19.8, respectively.

The hazard ratios with 95% confidence interval for a first forearm or hip fracture among users of PPIs in the age-adjusted analysis were 0.82 (0.67-1.01) for women and 1.05 (0.72-1.52) for men. Adjusting for age, use of anti-osteoporotic drugs and FRAX, the HR declined to 0.80 (0.65-0.98) in women and 1.00 (0.69-1.45) in men.

**CONCLUSIONS:**

Use of PPIs was not associated with an increased risk of fractures.

**BACKGROUND:**

Proton pump inhibitors (PPIs) are widely used for acid-related diseases, such as gastro-esophageal reflux disease. In Norway, more than 15% in the age group 50-69 years and over 20% in the age group 70-85 years used this medication in 2017 [1].

One of the concerns regarding PPIs is that they have been associated with an increased risk of fractures, first reported in 2006 [2, 3]. In the US, FDA ordered in 2010 all manufacturers of PPIs to include in their product labels a warning of the increased risk for fractures of the hip, wrist, and spine when used at high dose or for more than one year [4].

Data on the effect of PPIs on fracture risk have, however, been diverging. A large meta-analysis from 2019 with 24 observational studies and 2,103,800 participants concluded with a modestly increased risk of hip fractures in those treated with PPIs (RR=1.20, 95% confidence interval 1.14-1.28) [5]. A meta-analysis from 2016, including 18 observational studies conducted from 2006-2014, concluded with an increased risk of vertebral fractures (RR=1.58, 95% CI 1.38–1.82) and any-site fractures (RR=1.33, 95% CI 1.15–1.54) among users of PPIs [6]. There was no difference between short-time (< 1 year) and longer use (> 1 year) [6]. An increased risk has also been seen in those taking low and medium doses of PPI compared to non-users, and both after short- and long-term therapy with PPIs [5]

Fracture risk is determined by several factors, including bone mineral density (BMD), bone quality and bone turnover. Both animal and human studies have shown an association between PPI use and a reduced BMD [7-10], whereas others have failed to demonstrate a reduction in BMD [11, 12]. Attenuated BMD was observed in rats given PPIs for 3 months [7] and in H+/K+-ATPase deficient mice [8], and two prospective studies in humans reported a decline in BMD among PPI users [9, 10]. On the other hand, a longitudinal observational study of PPI use over 10 years did not show accelerated BMD loss [11, 12]

Regarding bone quality, a recent study revealed lower trabecular bone score (TBS) at the spine in current users of PPIs, but not in recent or previous users [13]. A study applying quantitative computed tomography did not show any structural differences between users and non-users of PPIs [14].

Finally, enhancement of fracture risk could also be attributed to increased propensity to fall. Accordingly, Lewis et al. observed a higher number of falls among PPIs users, whereas no effect on hip BMD or bone quality assessed by heal ultrasound was seen [15].

Several mechanisms by which PPIs may impair bone have been postulated. The effect could be due to gastric hypoacidity, causing reduced calcium absorption with subsequent secondary

hyperparathyroidism [2, 8, 16-18]. However, recent studies have not been able to show reduced calcium absorption in humans [12, 14, 19],

Hypoacidity also induces hypergastrinemia that has been proposed to have a negative effect on bone both directly and indirectly via the parathyroid hormone [8, 17, 18, 20].

PPIs also seem to inhibit intestinal magnesium absorption, accordingly there are several reports on hypomagnesemia among PPIs users [18, 21, 22]. In middle-aged Caucasian men, low serum magnesium was associated with an increased fracture risk [23].

Moreover, it has also been suggested that a reduced absorption of vitamin B12 may lead to muscle weakness and subsequent falls [15].

At the cellular level, several studies have shown that PPIs inhibit the osteoclasts both *in vitro* [24, 25] and *in vivo* [26]. *In vitro* studies have shown diverging effects of PPIs on the osteoblast. Prause et al. observed a stimulatory effect [27], whereas another showed an inhibitory effect on osteoblasts in ovariectomized rats on a low calcium diet given PPIs similar to therapeutic dosages [28].

The mechanisms by which PPIs may affect bone adversely are, however, not settled and no clear dose dose-response relationship has been demonstrated. Whether use of PPIs truly increases fracture risk has therefore been questioned [14, 29-31].

It has been argued that the apparent association may be due to confounding; that individuals prescribed PPIs are frail, elderly people who are already at high fracture risk [29, 31, 32].

The aim of our study was to examine the association between use of PPIs and risk of fractures in a large cohort comprising men and women 50-85 years of age with detailed information about lifestyle and comorbidity.

## MATERIALS AND METHODS

### Data sources

We used data from the Norwegian Prescription Database (NorPD), the third survey of the Nord-Trøndelag Health Study (HUNT3) and the Fracture Registry of Nord-Trøndelag. The data were linked via the individual's personal identification numbers

Norwegian Prescription Database (NorPD)

Data on prescriptions of PPIs, anti-osteoporotic drugs (AODs) and oral glucocorticoids (GCs) were collected from the Norwegian Prescription Database (NorPD) established 01.01.2004. NorPD contains information on all prescribed drugs that are dispensed at all pharmacies in Norway to individual patients in ambulatory care. Drugs prescribed to patients who had been

hospitalized or were in other institutions, are not registered in NorPD [33]. Use of PPIs, AOD and GCs was registered from one year before participation in HUNT3.

The HUNT study

HUNT3 was performed from 2006 to 2008 in the county of Nord-Trøndelag, which is located in mid-Norway. The geographic, demographic and occupational structure is considered fairly representative of the country as a whole [34]. All individuals 20 years and older were invited to participate.

In the current study, we included the age group 50-85 years. Of the 43,760 invited, 28,692 (65.6 %) responded, completed a comprehensive questionnaire and underwent a short clinical examination at the screening station. Of these, 231 were excluded due to lack of data on height (N=213) or weight (N=220). Time of death was retrieved form the NorPD. Those with missing information in the NorPD were therefore excluded, (N= 203, 58 women and 145 men), leaving 15017 women and 13241 men (Figure 1).

For all those included, Fracture Risk Assessment Tool (FRAX) for Norway, which estimates fracture risk (www.shef.ac.uk/FRAX) was calculated [35]. Both $FRAX_{hip}$ and FRAX for major osteoporotic fracture ($FRAX_{MOF}$) without BMD were calculated based on information from the HUNT study and the NorPD, details are previously described [36].

The Fracture Registry of Nord-Trøndelag

The registry covers all forearm and hip fractures in individuals older than 16 years treated or followed up in the only two hospitals in Nord-Trøndelag from August 15, 1995 to December 31, 2012. The data were collected from the medical records through the electronic discharge registers, the Patient Administrative System (PAS) for the whole period, as well as the X-ray registry in the period August 15, 1995 to December 31, 2007. In the period 2003 to 2008, no additional fractures were found on X-rays. Therefore, from 2008 the search for fractures was only done from the PAS.

Individuals with potential fractures were identified in PAS based on diagnoses according to the International Classification of Diseases (ICD), as well as surgical procedures according to NOMESKO Classification of Surgical Procedures (NCSP). The ICD 10 codes included were S52.X for forearm fractures and S72.0, S72.1, S72.2 and S72.9 for hip fractures. The fracture diagnoses were retrospectively validated by specially trained health personnel.

A fracture was defined when the ICD code was accompanied by a NCSP procedure code of reduction, surgical intervention, or intervention with a rigid device or diagnosed by X-ray.

Fractures due to metastatic disease were excluded. When in doubt if there was a new fracture or a control of an earlier fracture, or if the procedure code was missing, the medical record was reviewed by a medical doctor.
Details about the classification and validity of this fracture information have been published previously [37-39].

**Exposure: Proton pump inhibitors**

Information on filled prescriptions of PPIs (ATC code A02BC) collected from the NorPD was used to classify individuals as exposed to PPIs. The dose is registered as defined daily dose (DDD), that is the assumed average maintenance dose per day for a drug used for its main indication in adults [40]. DDDs for the included PPIs are: omeprazole 20 mg; lansoprazole 30 mg; esomeprazole 30 mg; pantoprazole 40 mg.
Time-dependent exposure was applied to estimate the association between PPI use and risk of fractures. Each individual was considered as unexposed until the first prescriptions of PPIs was filled and to be included the prescription of PPIs should minimum be equivalent to 90 DDD in the period [40]. Since exposure to drugs would be expected to have an effect on bone also after termination, we defined individuals as exposed to PPIs until 6 months after end of drug supply.
As a measure of the dose PPIs, Medication Possession Ratio (MPR) was calculated, defined as the sum of the DDD for all fills of a given drug in a particular time period, divided by the number of days in the time period.

**Outcome: Fracture**

Data on first forearm or hip fracture were obtained from the Fracture Registry of Nord-Trøndelag. The ICD 10 codes included for hip fractures were S72.0-2 and 9; and for forearm fractures S52.0 - S52.9.

**Covariates**

- FRAX (for Norway) which estimates fracture risk without including BMD (www.shef.ac.uk/FRAX) [35]. The following variables collected at baseline are included in the FRAX calculation:
  Gender, age, body mass index (BMI) in addition to self-reported previous fracture, parent hip fracture, current smoking, use of oral GCs, rheumatoid arthritis (RA),

secondary osteoporosis, and use of alcohol (units per week). Data on GCs use were retrieved from the NorPD, other information was collected from HUNT3.
Both FRAX for major osteoporotic fracture ($FRAX_{MOF}$) and $FRAX_{hip}$ without BMD were assessed, details are previously described [36].

- AODs were defined as: Bisphosphonates (ATC code M05BA), denosumab (M05BX04), raloxifene (G03XC01) and teriparatide (H05AA02). Time-dependent exposure was applied. Each individual was considered as unexposed until the first of at least two prescriptions of an AOD was filled during a 6 months period. Since exposure to drugs would be expected to have an effect on bone also after termination, we defined individuals as exposed 6 months after end of drug supply.
- GCs were classified as ATC codes H02AB.
  As for PPIs, each individual was considered as unexposed until the first prescription of GCs, and to be included the use of GCs should minimum be equivalent to 90 DDD. We defined individuals as exposed until 6 months after end of drug supply.
- Self-reported intake of milk products at baseline.

**Statistics**

Descriptive data are given as mean with standard deviation (SD) for continuous data and numbers and percentages for categorical data. 95% confidence intervals (CIs) for counts were calculated by the continuity-corrected score interval method [41].
All individuals were included in the study from the date of their participation in HUNT.
Cox' proportional hazards model with time-dependent exposure to PPIs (exposure) as well as AODs and GCs (covariates) was used.
The study population was followed from the date of participating in HUNT3 (baseline) until date of first fracture, death or end of study (31.12.2012), whichever came first.
We present four models adjusted for different covariates:
Model 1) Adjusted for age.
Model 2) Adjusted for age, $FRAX_{MOF}$ without BMD ($FRAX_{HIP}$ without BMD is used when assessing hip fractures) and use of AODs;
Model 3) Adjusted for age, milk intake, use of AODs and use of GCs; and
Model 4) Adjusted for age, FRAX, milk intake, use of AODs and use of GCs.
The proportional hazards assumption was tested by visual inspection of log minus log plots.

In our main analyses, we assessed the composite endpoint of first hip or forearm fracture, as well as forearm and hip fracture separately, stratified for gender.
To examine the effect of the dose PPIs, MPR was used as a continuous variable as well as stratified in low and high dose in the time-dependent Cox regression model. Cut-off was set at 1.0 DDD. To identify even higher use a cut-off of 1.2 DDD was also examined.
MPR was calculated as: The total amount DDD prescribed/ (Last fill date - first fill date + DDD of the last prescription)

Sensitivity analyses

It is difficult to correctly classify exposure to drugs, and we also applied models with different assumptions on length of exposure to PPIs, AODs and GCs after the last filled prescription. As the potential biological mechanism is unclear, there is no a priori consensus on how long an effect of PPIs, AODs and GCs on the bone would last. In addition to our primary analysis, assuming the effect of PPIs on bone would last for 6 months after termination of drug supply, we also performed analyses in model 4 assuming both shorter and longer exposure (3 and 9 months, respectively).
In separate sensitivity analyses, we estimated propensity scores for PPIs exposure by logistic regression using the same independent variables as in model 4. We compared the distribution of propensity scores between users and never users of PPIs and performed separate analyses in propensity score strata (quintiles) to assess whether the association seemed to differ between strata. These analyses were performed both in the entire sample and restricted to women only.
All four models were repeated in a sample restricted to individuals who used PPIs for more than a year as well as for individuals who had at least two prescriptions of PPIs.
Interaction analysis were performed by likehood-ratio-test
P-values below 0.05 were regarded as statistically significant. All analyses were done using STATA 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

**Ethics**

Participants in HUNT 3 gave written, informed consent for use of their data in research including linkage to named registries, such as NorPD. The study was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway

(2012/1906/REK). Linkage of databases was approved by the Norwegian Data Protection Authority.

## RESULTS

During a median of 5.2 years follow-up (25-75 percentile 4.8-5.6 years), 266 women and 134 men had a first hip fracture and 662 women and 127 men suffered their first forearm fracture. Six individuals had fractures in both forearm and hip. In analyses including both forearm and hip fracture, only the first fracture was included; when evaluating forearm or hip fractures separately, all forearm and all hip fractures were included.

The proportion who had used a minimum of 90 DDD PPIs was 2685 (17.9%) women and 2047 (15.5%) men. Of those, 2571 (17.1 %) women and 1919 (14.5%) men had filled more than one prescription of PPIs, whereof 1756 (11.7 %) and 1326 (10.0 %), respectively used PPIs for more than a year. During the follow-up time, median time of PPI use was 3.8 years (25-75 percentile 1.3-5.6years). MPRs were 0.74 (SD 0.39) in women and 0.77 (0.39) in men. Regarding fracture risk, users of PPIs were older, had higher BMI, higher FRAX, more previous fractures and used more GCs than non-users. However, they were also more often treated with AODs (Table 1).

An overview of the different types PPIs is depicted in Table 2. The PPIs most frequently used were pantoprazole and esomeprazole which amounted to 65% of the total number of users, and as much as 83% in alternating with the other PPIs (Table 2).

### PPIs and fracture risk

The fracture rate per 1000 person-years in women was 49.2 (41.4-58.2) for users of PPIs compared to 64.1 (59.9-86.6) among non-users. The respective rates for men were 18.6 (13.3-25.7) and 19.8 (17.4-22.6).

In Table 3, we present estimated hazard ratios for fracture with and without exposure to PPIs for different models. None of the models showed an increased risk of fracture with exposure to PPIs, and all estimated HRs were close to or below 1. Among women, the HR among PPI users were numerically lower for forearm fracture compared to hip fractures, although not significant (Table 3).

In a model including PPIs as a continuous variable expressed as MPR, the HR for fracture among women was 0.76 (0.62-0.77) and men 0.83 (0.56-1.23) adjusted for age. The estimated HRs in model 4 were 0.77 (0.62-0.96) and 0.88 (0.59-1.32), respectively.

No difference was observed between individuals with high and low doses of PPIs (Table 4).

The numbers of fracture with a cut-off of 1.2 DDD was only 27 of 517 (23 out of 290 women and 4 out of 223 men) leading to too low precision.

**Sensitivity analyses**

Different classification of exposure to PPIs, i.e. the assumed effect on bone after termination of drug supply, had small effects on the estimated hazard ratio. In model 4 for women assessing the composite fracture endpoint, the HR was 0.78 (0.63-0.96) when exposure time was defined as 3 months after termination of PPIs compared to 0.88 (0.72-1.07) when exposure time was defined as 9 months after PPIs termination. The estimated association between use of PPIs and fracture risk was not affected by different definitions of length of AODs or GCs exposure, supplementary Table S1.

The distribution of propensity scores did not differ between individuals exposed and not exposed to PPIs. The estimated association between exposure to PPIs and fracture risk did not differ between the five propensity score strata (data not shown).

The results were quite similar when only including individuals who had used PPIs more than one year as exposed, with a composite endpoint HR for PPIs (model 4) of 0.71 (0.55-0.90) in women and 0.80 (0.51-1.26) in men, supplementary Table S2 or among individuals with minimum 2 prescriptions, supplementary Table S3.

There were no statistically significant interactions between PPIs and age in women (p=0.29) or men (p=0.87). In a model including both genders (Model 4), there was no statistically significant interaction between PPIs and sex (p=0.10)

## DISCUSSION

In the present study, we examined the association between use of PPIs and risk of forearm and hip fractures in women and men from the HUNT study aged 50 to 85 years. In this large population-based study, we observed no increased risk for fractures among users of PPIs compared to non-users. This finding contrasts with the majority of previous studies [5, 6]. The discrepancy could be due to differences in duration of exposure, type of PPIs, characteristics of the population studied, as well as methodological challenges such as sufficient adjustment for potential confounding factors.

According to Yang et al., the duration of PPI therapy seems to influence the risk of hip fracture, especially when given at a high dosage, and they observed a gradual increase in hip fracture risk from one year up to four years of exposure to PPIs [2]. In the latest meta-

analysis addressing hip fracture risk, long-term use (more than 3 years) of PPIs was also associated with somewhat higher risk than short-term use [5].
In our study the duration of exposure to PPIs ranged from 6 months to 7 years, (with a median of 3.8 years) which may be too short to cause see a negative effect on bone. On the other hand, true duration may be longer since some individuals may have used PPIs during a longer period than one year before study start.

The type of PPIs may also influence the fracture risk, and in one study, rabeprazole use showed the strongest association with fractures [42]. This was also the case in the meta-analysis by Poly et al, showing increase of hip fracture risk by 27% in those treated with rabeprazole and 13% in users of omeprazole and pantoprazole [5]. On the other hand, use of esomeprazole and lansoprazole was not associated with increased hip fracture risk (RR 0.93 and 1.08). In our cohort pantoprazole and esomeprazole were the most commonly prescribed PPIs, while rabeprazole, which seems to be most harmful to the skeleton, is not approved for use in Norway.

Our results could also be influenced by other medications with effects on bone. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are frequently used drugs with gastrointestinal side effects that often trigger initiation of PPIs. Previous studies have reported that use of NSAIDs and ASA is associated with a modest increase in fracture risk [43, 44]. On the other hand, more recent studies show a modest beneficial effect on BMD in postmenopausal women using ASA or NSAIDs regularly [45, 46]. However, no clinically significant protective effect on the subsequent risk of fractures was observed. The increased risk of fractures observed in previous studies may be attributed to common causes of NSAIDs and ASA use and fractures [47]. Unfortunately, we were not able to retrieve data at an individual level in our participants, as in Norway, NSAIDs are available without prescription. We are therefore unable to include this in the analysis. Based on the existing data, it does not appear likely that use of these drugs can explain our findings
It is possible that residual confounding may play a role in explaining the reported association between use of PPIs and fractures [29]. This hypothesis is also supported by the lack of a clear mechanism or a dose-response relationship. Inclusion of FRAX in the model is expected to reduce confounding, since it is a well-documented tool to assess fracture risk [29, 35]. $FRAX_{hip}$ without BMD has previously been validated in this cohort and is found to predict hip fractures reasonably well [36]. We present models adjusted for different covariates, and

there were only minor differences regarding the estimated HRs. None of our analyses seem to suggest an increased risk of fractures, and use of PPIs in some analyses indeed seemed rather to be associated with a reduced fracture risk. While we in no way believe PPIs to be protective, we consider this as an indication that any confounding factor not included in the models would have to be very strong to lead to a different conclusion. A healthy adherer effect might nevertheless partly explain the apparently reduced risk.

The sensitivity analyses comparing associations in different propensity score strata also give some reassurance to the result of the primary analysis. Furthermore, there was no interaction between use of PPIs and sex, and even if the fracture risk for users of PPIs seems higher among men, the precision was low due to fewer fractures than among women.
It is, however, reassuring that exposure to PPIs for a median of 4 years was not associated with increased fracture risk.

The strength of our study is the population-based design, the large registers, and a reasonably high participation rate of 65.6% in this age group in HUNT3. The HUNT study also includes substantial information regarding risk for fractures, which reduces residual confounding. We had access to FRAX without BMD for all participants.
We have used time-dependent drug exposure to evaluate the effect of PPIs, AODs and GCs during the follow-up period. This will avoid immortal time bias, which refers to a period of follow-up during which, by design, death or the study outcome cannot occur [48].
Our study has some limitations. The main challenge is the classification of exposure since no consensus exists on how long an effect of PPIs on the bone would last. However, the different assumptions on length of exposure had only small effects on the estimated HR.
Next, PPIs up to a 14-day course has been available without prescription in Norway from 2010, the price is, however, high compared to prescribed PPIs. In Norway patients are qualified for reimbursement if in need of medical treatment for 3 months or more within a year due to chronic illness. Thus, we assume that a large majority of individuals who use PPIs for a long time will prefer to have a prescription.
Calcium supplements with or without vitamin D were not included in the analysis as they are available without prescription in Norway. As a proxy measure for calcium, self-reported milk intake was included in one of the models. Furthermore, protein intake and physical activity were not registered. With respect to the FRAX calculation, we were not able to retrieve data on hip fractures in parents; instead, self-reported parental osteoporosis was included in the

calculation. FRAX without BMD is used as we did not have BMD measurements in all participants.

Moreover, the number of fractures was limited, and we only had information regarding hip and forearm fractures, which leads to wide confidence intervals. The relative risks are not precisely estimated. However, the upper limits of the respective 95% confidence intervals seem to preclude any large increase in the risk of fractures. Finally, the follow-up time of 4 years may be too short to find any negative effect of PPIs on bone.

In conclusion, exposure to the PPIs (, pantoprazole, esomeprazole, lansoprazole and omeprazole) was not associated with increased risk of hip or forearm fractures in our population-based study. Based on these findings and other recent studies there is no strong case for targeting additional osteoporosis risk assessment to patients solely based on their use of these PPIs.

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**CONFLICTS OF INTERESTS**

BA has institutional research contracts with UCB and Novartis with funds paid to the institutions.

US has received research grants from or served as a Principal Investigator in studies conducted by Amgen, Eli Lilly, Novartis, Merck and Wyeth pharmaceuticals

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**Figure 1. Flow chart of the included subjects**

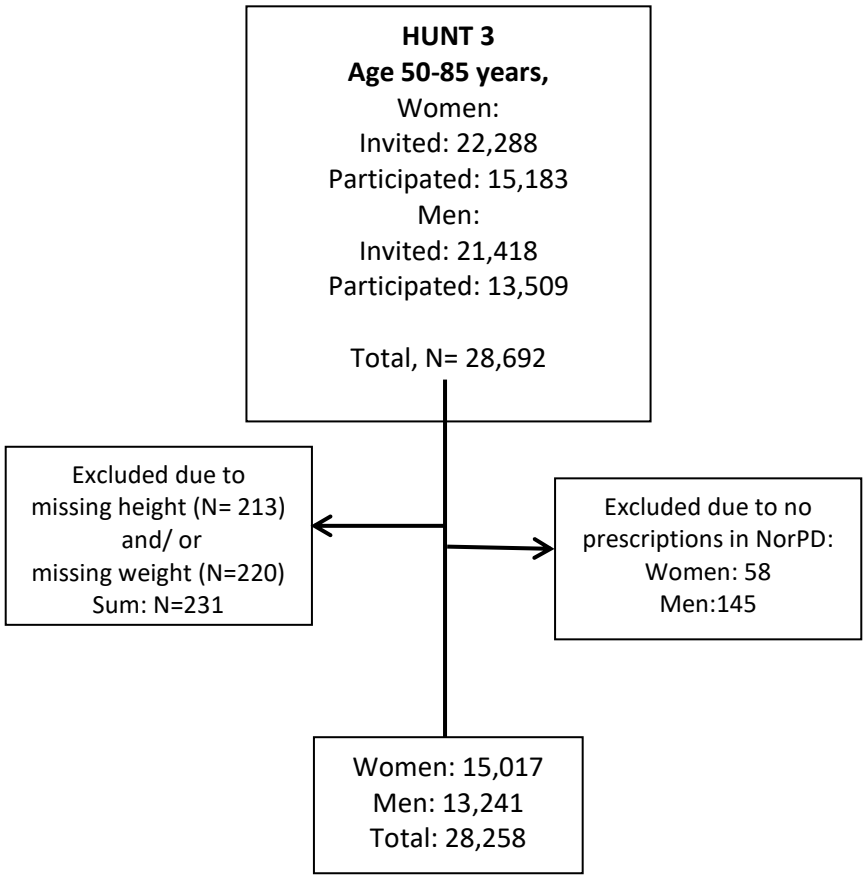

**Table 1: Baseline values stratified for exposure to proton pump inhibitors in the follow-up period**

| | Exposed to proton pump inhibitors N=4490 | | Not exposed to proton pump inhibitors N=23768 | |
|---|---|---|---|---|
| | **Women N=2685** | **Men N=2047** | **Women N=12332** | **Men N=11194** |
| **Age, mean (SD)** | 65.6 (9.2) | 65.6 (8.9) | 63.5 (9.1) | 63.3 (8.8) |
| **BMI, mean (SD)** | 28.7 (4.9) | 28.2 (3.7) | 27.3 (4.6) | 27.6 (3.6) |
| **FRAX, mean (SD)** | 16.1 (12.7) | 7.2 (4.4) | 13.1 (10.6) | 6.3 (3.8) |
| **Previous fractures[a,b], N (%)** | 586 (21.9%) | 262 (12.8%) | 2031 (16.5%) | 1069 (9.5%) |
| **Osteoporosis among parents[a], N (%)** | 390 (14.5%) | 134 (6.5%) | 1548 (12.6%) | 696 (6.2%) |
| **Current smoker[a], N (%)** | 647 (24.1%) | 430 (21.0%) | 2871 (23.3%) | 2395 (21.4%) |
| **More than 2 glass milk/ day[a], N (%)** | 1594 (60.1%) | 755 (37.9%) | 7510 (61.6%) | 4258 (39.0%) |
| **Alcohol consumption, units/ week [a] (SD)** | 2.5 (3.9) | 4.8 (6.4) | 3.0 (4.1) | 5.3 (6.3) |
| **Alcohol consumption ≥3 units/ day [a], N (%)** | 2 (0.1%) | 5 (0.3%) | 2 (0.0%) | 23 (0.2%) |
| **Secondary osteoporosis[a,c], N (%)** | 728 (27.1%) | 141 (6.9%) | 2248 (18.2%) | 568 (5.1%) |
| **Exposed to anti-osteoporotic drugs[d]** | 373 (14.5%) | 61 (3.2%) | 1054 (8.5%) | 142 (1.3%) |
| **Exposed to glucocorticosteroids[d]** | 729 (27.2%) | 480 (23.4%) | 1304 (10.6%) | 1059 (9.5%) |

[a]Self-reported
[b]Previous fractures in hip, wrist, or spine after 40 years
[c]Secondary osteoporosis defined as menopause or surgical removal of ovaries before 45 years, rheumatoid arthritis, diabetes mellitus type 1, or hyperthyroidism
[d]Exposed to the drug during the follow-up period, Data is from the Norwegian prescription register

**TABLE 2: Use of different types proton pump inhibitors in the follow-up period, N=4732**

| | Type proton pump inhibitor | N (%) |
|---|---|---|
| **Use of one proton pump inhibitor N= 2737 (60.9%)** | Pantoprazole | 1396 (29.5) |
| | Esomeprazole | 823 (17.4) |
| | Lansoprazole | 445 (9.4) |
| | Omeprazole | 313 (6.6) |
| **Combination of two proton pump inhibitors N=1485 (33.1%)** | Pantoprazole + Esomeprazole | 847 (17.9) |
| | Pantoprazole + Lansoprazole | 182 (3.8) |
| | Pantoprazole + Omeprazole | 131 (2.8) |
| | Esomeprazole + Lansoprazole | 184 (3.9) |
| | Esomeprazole + Omeprazole | 108 (2.3) |
| | Lansoprazole + Omeprazole | 35 (0.7) |
| **Combination of three proton pump inhibitors N=256 (5.7%)** | Pantoprazole + Esomeprazole + Lansoprazole | 132 (2.8) |
| | Pantoprazole +Esomeprazole + Omeprazole | 94 (2.0) |
| | Pantoprazole + Lansoprazole + Omeprazole | 12 (0.3) |
| | Esomeprazole + Lansoprazole + Omeprazole | 18 (0.4) |
| **Four proton pump inhibitors N=12 (0.3%)** | Pantoprazole + Esomeprazole + Lansoprazole + Omeprazole | 12 (0.3) |

**TABLE 3: Hazard ratios (with 95% confidence interval) for the association between use of proton pump inhibitors and fractures in the four different models**

| | N | Fractures | Rate/ 1000 | Model 1<br>Adjusted for age | Model 2<br>Adjusted for age, FRAX and use of anti-osteoporotic drugs | Model 3<br>Adjusted for age, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids | Model 4<br>Adjusted for age, FRAX, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids |
|---|---|---|---|---|---|---|---|
| **Women**<br>**Hip and forearm fractures** | 15017 | 923 | 61.5 (57.8-65.5) | | | | |
| • **PPIs yes** | 2685 | 132 | 49.2 (41.4-58.2) | 0.82 (0.67-1.01) | 0.80 (0.65-0.98) | 0.84 (0.68-1.03) | 0.83 (0.67-1.02) |
| • **PPIs no** | 12332 | 791 | 64.1 (59.9-68.6) | Reference | Reference | Reference | Reference |
| **Men**<br>**Hip and forearm fractures** | 13241 | 260 | 19.6 (17.4-22.2) | | | | |
| • **PPIs yes** | 2047 | 38 | 18.6 (13.3-25.7) | 1.05 (0.72-1.52) | 1.00 (0.69-1.45) | 1.08 (0.74-1.57) | 1.05 (0.72-1.54) |
| • **PPIs no** | 11194 | 222 | 19.8 (17.4-22.6) | Reference | Reference | Reference | Reference |
| **Women**<br>**Hip fractures** | 15017 | 266 | 17.7 (15.7-20.0) | | | | |
| • **PPIs yes** | 2685 | 52 | 19.4 (14.6-25.5) | 0.97 (0.69-1.37) | 0.95 (0.68-1.34) | 0.93 (0.65-1.33) | 0.92 (0.65-1.33) |
| • **PPIs no** | 12332 | 214 | 17.4 (15.2-19.9) | Reference | Reference | Reference | Reference |
| **Men**<br>**Hip fractures** | 13241 | 134 | 10.8 (8.5-12.0) | | | | |
| • **PPIs yes** | 2047 | 21 | 10.3 (6.5-15.9) | 1.00 (0.60-1.66) | 0.97 (0.58-1.62) | 1.00 (0.59-1.70) | 0.99 (0.58-1.68) |
| • **PPIs no** | 11194 | 113 | 10.1 (8.4-12.2) | Reference | Reference | Reference | Reference |
| **Women**<br>**Forearm fractures** | 15017 | 662 | 44.1 (40.9-47.5) | | | | |
| • **PPIs yes** | 2685 | 81 | 30.2 (24.2-37.5) | 0.78 (0.61-1.01) | 0.78 (0.61-1.00) | 0.82 (0.64-1.06) | 0.82 (0.64-1.06) |
| • **PPIs no** | 12332 | 581 | 47.1 (43.5-51.0) | Reference | Reference | Reference | Reference |
| **Men**<br>**Forearm fractures** | 13241 | 127 | 9.6 (8.0-11.4) | | | | |
| • **PPIs yes** | 2047 | 17 | 8.3 (5.0-13.6) | 1.14 (0.67-1.96) | 1.11 (0.64-1.90) | 1.19 (0.69-2.06) | 1.19 (0.69-2.06) |
| • **PPIs no** | 11194 | 110 | 9.8 (8.1-11.9) | Reference | Reference | Reference | Reference |

**TABLE 4: Hazard ratios (with 95% confidence interval) for the association between use of proton pump inhibitors (PPIs) and fractures stratified for high and low dose. Cut-off PPIs ≥ 1.0 defined daily doses (DDD).**

| | N | Fractures | Rate/ 1000 | Model 1 Adjusted for age | Model 2 Adjusted for age, FRAX and use of anti-osteoporotic drugs |
|---|---|---|---|---|---|
| **Women** | 15017 | 923 | 61.5 (57.8-65.5) | | |
| **Hip and forearm fractures** | | | | | |
| • **PPIs ≥ 1.0 DDD** | 776 | 46 | 59.3 (44.2-78.9) | 0.83 (0.62-1.13) | 0.80 (0.59-1.08) |
| • **PPIs <1.0 DDD** | 1909 | 86 | 45.0 (26.4-55.6) | 0.64 (0.51-0.80) | 0.62 (0.50-0.78) |
| • **PPIs no** | 12332 | 791 | 64.1 (59.9-68.6) | Reference | Reference |
| **Men** | 13241 | 260 | 19.6 (17.4-22.2) | | |
| **Hip and forearm fractures** | | | | | |
| • **PPIs ≥ 1.0 DDD** | 665 | 11 | 16.5 (8.7-30.3) | 0.78 (0.42-1.42) | 0.75 (0.41-1.37) |
| • **PPIs < 1.0DDD** | 1392 | 27 | 19.4 (13.1-28.5) | 0.86 (0.57-1.28) | 0.82 (0.55-1.23) |
| • **PPIs no** | 11194 | 222 | 19.8 (17.4-22.6) | Reference | Reference |

# *Online Supplement*
# *Sensitivity analysis*

**Table S1: Hazard ratios (95% confidence interval) in women for the association between use of proton pump inhibitors and fractures in forearm and hip, with different length of exposure to drugs (model 4)**

| Months after exposure of drugs | Proton pump inhibitors<br>3 months | Proton pump inhibitors<br>6 months<br>(used in the calculations) | Proton pump inhibitors<br>9 months |
|---|---|---|---|
| **Anti-osteoporotic drugs and glucocorticoids<br>3 months** | 0.78 (0.63-0.96) | 0.83 (0.67-1.02) | 0.88 (0.72-1.07) |
| **Anti-osteoporotic drugs and glucocorticoids<br>6 months (used in the calculations)** | 0.78 (0.63-0.96) | 0.82 (0.67-1.01) | 0.88 (0.72-1.08) |
| **Anti-osteoporotic drugs and glucocorticoids<br>9 months** | 0.77 (0.62-0.96) | 0.82 (0.67-1.01) | 0.87 (0.71-1.07) |

**TableS2: Hazard ratios (95% confidence interval) for the association between use of proton pump inhibitors (PPIs) and fractures among individuals using PPIs for more than one year**

| | N | Fractures | Rate/ 1000 | Model 1<br>Adjusted for age | Model 2<br>Adjusted for age, FRAX and use of anti-osteoporotic drugs | Model 3<br>Adjusted for age, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids | Model 4<br>Adjusted for age, FRAX, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids |
|---|---|---|---|---|---|---|---|
| **Women** | 15017 | 923 | 61.5 | | | | |
| **Hip and forearm fractures** | | | | | | | |
| • **PPI yes** | 1756 | 85 | 48.4 | 0.70 (0.55-0.88) | 0.68 (0.54-0.86) | 0.71 (0.56-0.90) | 0.71 (0.55-0.90) |
| • **PPI no** | 13261 | 838 | 63.2 | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 260 | 19.6 | | | | |
| **Hip and forearm fractures** | | | | | | | |
| • **PPI yes** | 1326 | 24 | 18.1 | 0.83 (0.53-1.28) | 0.78 (0.50-1.21) | 0.83 (0.53-1.30) | 0.80 (0.51-1.26) |
| • **PPI No** | 11915 | 236 | 19.8 | Reference | Reference | Reference | Reference |
| **Women** | 15017 | 266 | 17.7 (15.7-20.0) | | | | |
| **Hip fractures** | | | | | | | |
| • **PPI yes** | 1756 | 30 | 17.1 (11.8-24.6) | 0.78 (0.52-1.16) | 0.76 (0.51-1.13) | 0.75 (0.49-1.14) | 0.76 (0,40-1,42) |
| • **PPI no** | 13261 | 236 | 17.8 (15.6-20.2) | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 134 | 10.1 (8.5-12.0) | | | | |
| **Hip fractures** | | | | | | | |
| • **PPI yes** | 1326 | 14 | 10.6 (6.0-18.1) | 0.80 (0.44-1.46) | 0.77 (0,42-1,41) | 0.78 (0,42-1,46) | 0.78 (0,42-1,45) |
| • **PPI no** | 11915 | 120 | 10.1 (8.4-12.1) | Reference | Reference | Reference | Reference |
| **Women** | 15017 | 662 | 44.1 (40.8-47.4) | | | | |
| **Forearm fractures** | | | | | | | |
| • **PPI yes** | 1756 | 55 | 31.3 (23.9-23.2) | 0.67 (0.50-0.90) | 0.67 (0.50-0.90) | 0.70 (0.52-0.94) | 0.70 (0.53-0.95) |
| • **PPI No** | 13261 | 607 | 45.8 (42.3-49.5) | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 127 | 9.6 (8.0-11.4) | | | | |
| **Forearm fractures** | | | | | | | |
| • **PPI yes** | 1326 | 10 | 7.5 (3.8-14.3) | 0.87 (0.46-1.67) | 0.84 (0.44-1.60) | 0.90 (0.47-1.74) | 0.89 (0.47-1.73) |
| • **PPI No** | 11915 | 117 | 9.8 (8.2-11.8) | Reference | Reference | Reference | Reference |

**TABLE S3: Hazard ratios (95% confidence interval) for the association between use of proton pump inhibitors (PPIs) and fractures among individuals with minimum two prescriptions**

| | N | Fractures | Rate/ 1000 | Model 1<br>Adjusted for age | Model 2<br>Adjusted for age, FRAX and use of anti-osteoporotic drugs | Model 3<br>Adjusted for age, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids | Model 4<br>Adjusted for age, FRAX, milk intake, use of anti-osteoporotic drugs and use of glucocorticoids |
|---|---|---|---|---|---|---|---|
| **Women** | 15017 | 923 | 61.5 (57.7-65.5) | | | | |
| **Hip and forearm fractures** | | | | | | | |
| • **PPIs yes** | 2571 | 126 | 49.0 (0.41-0.58) | 0.82 (0.67-1.01) | 0.80 (0.65-0.98) | 0.84 (0.68-1.03) | 0.83 (0.67-1.02) |
| • **PPIs no** | 12446 | 797 | 64.0 (0.60-0.69) | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 260 | 19.6 (17.4-22.2) | | | | |
| **Hip and forearm fractures** | | | | | | | |
| • **PPIs yes** | 1919 | 36 | 18.8 (13.4-26.2) | 1.04 (0.72-1.52) | 1.00 (0.69-1.45) | 1.08 (0.77-1.57) | 1.05 (0.72-1.54) |
| • **PPIs No** | 11322 | 224 | 19.8 (17.3-22.6) | Reference | Reference | Reference | Reference |
| **Women** | 15017 | 266 | 17.7 (15.7-20.0) | | | | |
| **Hip fractures** | | | | | | | |
| • **PPIs yes** | 2571 | 48 | 18.7 (13.9-24.9) | 0.97 (0.69-1.37) | 0.95 (0.68-1.34) | 0.93 (0.65-1.33) | 0.93 (0.65-1.32) |
| • **PPIs no** | 12446 | 218 | 17.5 (15.3-20.0) | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 134 | 10.8 (8.5-12.0) | | | | |
| **Hip fractures** | | | | | | | |
| • **PPIs yes** | 1919 | 20 | 10.4 (6.6-16.4) | 1.00 (0.60-1.66) | 0.97 (0.58-1.62) | 1.00 (0.59-1.70) | 0.99 (0.58-1.68) |
| • **PPIs no** | 11322 | 114 | 10.1 (8.3-12.1) | Reference | Reference | Reference | Reference |
| **Women** | 15017 | 662 | 44.1 (40.9-47.5) | | | | |
| **Forearm fractures** | | | | | | | |
| • **PPIs yes** | 2571 | 79 | 30.7 (24.6-38.3) | 0.78 (0.61-1.01) | 0.71 (0.46-1.09) | 0.82 (0.64-1.06) | 0.76 (0.48-1.15) |
| • **PPIs No** | 12446 | 583 | 46.8 (43.2-50.7) | Reference | Reference | Reference | Reference |
| **Men** | 13241 | 127 | 9.6 (8.0-11.4) | | | | |
| **Forearm fractures** | | | | | | | |
| • **PPIs yes** | 1919 | 16 | 8.3 (4.9-13.8) | 1.14 (0.67-1.96) | 1.11 (0.64-1.90) | 1.19 (0.69-2.06) | 1.19 (0.69-2.06) |
| • **PPIs No** | 11322 | 111 | 9.8 (8.1-11.8) | Reference | Reference | Reference | Reference |

PPIs: proton pump inhibitors