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Proton pump inhibitor use and risk of hip fractures among community-dwelling persons with Alzheimer's disease—a nested case-control study

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Summary

Background: Hip fractures are a major health concern among older persons with Alzheimer's disease, who usually use many concomitant drugs for several diseases. Evidence of the association between proton pump inhibitor use and risk of hip fracture is contradictory.

Aim: To investigate whether the long-term use of proton pump inhibitor is associated with risk of hip fractures among community-dwelling persons with Alzheimer's disease.

Methods: In this nested case-control study, the nationwide MEDALZ data were utilised. Community-dwelling persons with Alzheimer's disease who encountered incident hip fracture (N = 4818; mean age 84.1) were included as cases. Four controls were matched for each case at the date of hip fracture (N = 19 235; mean age 84.0). The association between hip fracture and duration of current PPI use (ongoing use during 0-30 days before the index date), and cumulative duration of use during 10 years before was investigated with conditional logistic regression.

Results: Long-term or cumulative proton pump inhibitor use was not associated with an increased risk of hip fracture. Current proton pump inhibitor use was associated with an increased risk of hip fracture (adjusted OR 1.12, 95% CI 1.03-1.22). The risk was increased in short-term current use (<1 year) (adjusted OR 1.23, 95% CI 1.10-1.37).

Conclusions: The increased risk of hip fracture was evident only in short-term proton pump inhibitor use, but no association was found for long-term or cumulative use. Thus, our findings do not support previous assumptions that long-term proton pump inhibitor use would be associated with an increased risk of hip fractures.

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1 | INTRODUCTION

Proton-pump inhibitors (PPIs) are commonly and increasingly used among older population,[1-3] although they have been associated with several serious adverse events, such as fractures and pneumonia.[4-6] Indications for PPI use among older persons are dyspepsia, gastro-esophageal reflux disease and peptic ulcer, but due to gastro-protective properties they are also co-prescribed with nonsteroidal anti-inflammatory drugs and corticosteroids.[7,8]

Hip fractures are a major health concern among older persons with Alzheimer's disease, and Alzheimer's disease itself seems to be a risk factor for falling, and consequently, hip fractures.[9,10] In addition, older persons with Alzheimer's disease usually use many concomitant drugs for several diseases, which both are fall risk increasing factors.[11]

Association between PPI use and risk of fractures remains unclear. Several previous studies have found association between PPI use and an increased risk of hip fracture[12-16] but there are also studies which did not find an association.[17-19] According to a novel meta-analysis, the risk seems to be modestly increased (RR = 1.26; 95% CI 1.16-1.36), albeit the studies are heterogeneous.[6] It has been supposed that PPI use lead to bone loss and fractures by reducing calcium absorption.[18] However, some studies have reported that PPI use has no effects on bone structure.[20-22] Other mechanisms suggested are myopathy[23] or vitamin B12 deficiency[24] leading to injurious falls and fractures.[25] To our knowledge, no previous study has investigated whether current use, duration of current use, past use or cumulative PPI use are associated with risk of hip fracture among persons with Alzheimer's disease. Thus, the objective of this study was to investigate whether there is an association between long-term PPI use and risk of hip fractures among community-dwelling persons with clinically verified diagnosis of Alzheimer's disease.

2 | MATERIALS AND METHODS

2.1 | Data source

In this study, the nationwide register-based MEDALZ (Medication use and Alzheimer's disease) data were utilised. It consists of all community-dwelling persons who received clinically verified diagnosis of Alzheimer's disease between 2005 and 2011 (N = 70 718), and has been previously described in detail.[26] Diagnoses of Alzheimer's disease were recorded in the Special Reimbursement Register and were based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association[27] and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria.[28] The verified Alzheimer's disease diagnosis requires computed tomography or magnetic resonance imaging scan and confirmation of the diagnosis by a neurologist or geriatrician. MEDALZ-data contains information from several nationwide registers including the Prescription Register (years 1995-2012), the Special Reimbursement Register (1972-2012), the Hospital Discharge Register (1972-2012) and socioeconomic data from the Statistics Finland (1972-2012). All registers are linked by Personal Identification Numbers which have been assigned to all residents. However, data were de-identified before submission to researchers.

2.2 | Study population

This study was restricted to persons with incident hip fracture. Persons with a hip fracture before the diagnosis of Alzheimer's disease (n = 3714) were excluded (Figure 1), because it is difficult to separate the treatment of previous hip fracture from the new event in the Hospital Discharge Register. After exclusion, our study sample included 4818 cases with an incident hip fracture. For each hip fracture-case, up to four controls without hip fracture (N = 19 235) were matched at the date of hip fracture with incidence density sampling. Controls were matched by time since diagnoses of Alzheimer's disease (± 90 days), age (± 2 years) and sex, at the date of hip fracture. The index date was considered as the date of hip fracture for cases and corresponding matching date for controls.

Hip fractures were identified from Hospital Discharge register based on ICD-10 codes S72.0 (fracture of neck of femur), S72.1 (pertrochanteric fracture) and S72.2 (subtrochanteric fracture). For previous hip fractures, corresponding ICD-8 and ICD-9 codes were utilised.

2.3 | Drug exposure

Drug use was defined from Prescription Register, which contains all reimbursed drug purchases from community pharmacies in Finland. During hospital stay, drugs are provided by the caring unit and are not recorded in the Prescription Register. In addition, Over the Counter drugs are not recorded and small packages (up to 14 tablets) of omeprazole, esomeprazole, pantoprazole and lansoprazole have been available as Over the Counter drugs since the year 2010 in Finland.[29] PRE2DUP (Prescriptions to drug use periods) method was utilised to construct drug use periods according to individual purchasing style and was based on the calculation of sliding averages of daily dose.[30] The method takes into account purchase regularity, stockpiling of drugs and possible hospitalisations, and has been validated against information from self-reported drug use in interview, and by expert opinion.[31,32] All reimbursed drugs (based on Anatomical Therapeutic Chemical classification, ATC codes) were modelled.[33] The result of the PRE2DUP modelling are drug use periods which describe when continuous drug use started and ended, for each participant and for each ATC code.[30]

PPI use was defined as use of ATC code A02BC, including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole (ATC codes A02BC01, A02BC02, A02BC03, A02BC04 and A02BC05, respectively). In subanalysis of drug substance, we defined use of PPI at the index date, and excluded 30 PPI users (five of cases and 25 of controls), who used 2 or more different PPI drug substance concomitantly. Use of antidepressants was defined as use

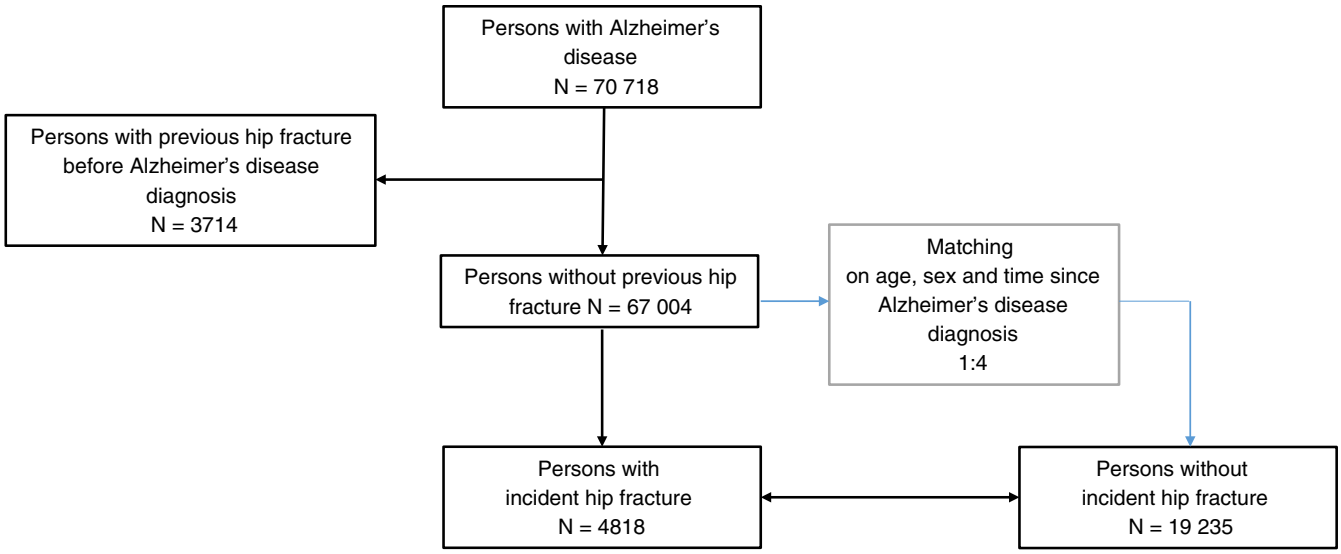

FIGURE 1 Formation of the study sample

of ATC class N06A, antipsychotics as N05A (excluding prochlorperazine N05AB04 and lithium N05AN01), opioids as N02A, benzodiazepines and related drug as N05BA, N05CD or N05CF, acetylcholine esterase inhibitors as N06DA and memantine as N06DX01. Use of these drugs was defined 30 days before the index date. Drug exposure to H2-receptor antagonists was defined as use of A02BA, bisphosphonates as M05BA or M05BB, oral corticosteroids as H02AB and antithrombotic agents as B01A, which were defined since 1995 until the index date. Thus, also short-term treatments, such as oral corticosteroids for asthma exacerbation, were counted.

We defined PPI users as "current users" if the PPI use period was ongoing 0-30 days before the index date, "past users" if the PPI use period was ongoing 31-90 days before (but not 0-30 days before) the index date and "ever users" if PPIs were used during 10 years before the index date. For duration of use, we retrieved "any PPI use" by combining overlapping PPI use periods. Duration of current use was determined for drug use periods which were ongoing at the 0-30 days before the index date, ie duration of use in days of the last PPI use period. Long-term use was defined as ≥1 year of current use. Cumulative use was calculated during 10 years observation period by summing up durations of all drug use periods during the follow-up among "ever users." Duration of use was categorised into classes according to duration in years.

2.4 | Covariates

Study participants' age and sex were obtained from the Social Insurance Institution. Cardiovascular disease was defined as chronic heart failure, arterial hypertension, coronary artery disease or chronic arrhythmia. Other comorbidities were diabetes, asthma/chronic obstructive pulmonary disease, rheumatoid arthritis and disseminated connective tissue diseases, epilepsy, glaucoma, breast cancer, prostatic cancer, gynaecologic cancer, leukaemia, and other malignant tumour. Comorbidities were based on Special Reimbursement Register and defined since 1972 until the index date.

History of diseases was based on Hospital Discharge Register since 1972 until the index date. Previous fracture was defined as ICD-10 codes: S*2 or T02 (any fracture) and limited to 10 years before index date. Substance abuse was defined as diagnoses of alcohol-induced chronic pancreatitis (ICD-10-code K860), mental and behavioural disorders due to psychoactive substance use (ICD10-codes F10-19) or substance abuse as reason for hospital admission before the date of Alzheimer's disease diagnoses. Stroke was defined as ICD-10 codes I60-I64. History of schizophrenia, bipolar disorder and depression were defined as ICD-10 codes (schizophrenia, schizotypal or delusional disorders F20-29; manic episode, F30; bipolar disorder, F31; depression, F32-34, F38-39) at least 5 years before the diagnosis of Alzheimer's disease.[34] Corresponding diagnoses were defined according to ICD-codes 8 and 9. Hospital days were based on Hospital Discharge Register and investigated 10 years before the index date and divided to <90 days and ≥90 days at hospital during the follow-up.

Occupational socioeconomic position was defined based on data from Statistics Finland and divided into four classes, where the lowest position included unemployed persons and students; medium class included employees and lowest clerical workers; the highest class included highest clerical workers and entrepreneurs and fourth class was unknown. We considered the highest position recorded for a person at the age of 45-55.

2.5 | Statistical analysis

Conditional logistic regression model (by taking into account the matched design) was used to investigate whether current, past, or

cumulative drug use was associated with risk of hip fracture. In all analyses, non-use of PPIs was used as a reference. Analyses were adjusted for age, sex, socioeconomic position, ≥90 hospital days during the follow-up, cardiovascular diseases, diabetes, asthma/chronic obstructive pulmonary disease, glaucoma, rheumatoid arthritis, epilepsy; previous fracture, stroke, cancer, depression or bipolar syndrome, schizophrenia, substance abuse; use of acetylcholine esterase inhibitors, memantine, oral corticosteroids, bisphosphonates, antipsychotics, antidepressants, benzodiazepines and related drugs, opioids, antithrombotics and H2-blockers. Covariates for adjustment, drugs and comorbidities associated with PPI use and hip fracture, were chosen based on literature.[1,11,35-37] The results are reported as odds ratios (OR) with 95% CI and *P* values. As an additional analysis, differences between current PPI users and non-users were investigated. All analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Inc., Cary, NC).

According to Finnish legislation, an approval from ethics committee was not needed, because the study persons stayed unidentified and were not contacted.

3 | RESULTS

Mean age of cases was 84.1 (SD 6.0) and controls 84.0 (SD 5.8) years, and most of the study population (75%) were women (Table 1). Previous fracture was more common among cases (35%) compared to controls (20%). Cases were more commonly using antipsychotics, antidepressants, opioids and benzodiazepines and related drugs compared with controls. Acetylcholine esterase inhibitors were more commonly used by controls than cases. Mean time since Alzheimer's disease diagnoses to index date was 849 (SD 611) days in cases and 847 (SD 612) days in controls.

Almost half of the cases (2321; 48%) and controls (9066; 47%) had used PPI during 10 years before the index date (Table 2). Cumulative use was not associated with an increased risk for hip fracture compared to non-users in the adjusted model. Current PPI users comprised 20% (973) of the cases and 17% (3274) of the controls. Current PPI use was associated with an increased risk of hip fracture (adjusted OR 1.12, 95% CI 1.03-1.22) whereas past use of PPI was not. For duration of current use, the risk was increased only in short-term use (<1 year) (adjusted OR 1.23, 95% CI 1.10-1.37). Current use over 1 year was not associated with risk of hip fracture after adjusting for confounders.

Pantoprazole was the most commonly used PPI at the index date (Table 3). There were no significant differences between PPI drug substances and associated risk of hip fracture after adjusting for confounders.

Among current users of PPI (N = 4247), 79% were women compared to 75% of those who did not currently use PPI (N = 19 806). Cardiovascular diseases were more common among current PPI users (59%) than non-users (51%). Current PPI users used oral corticosteroids (34%), bisphosphonate (27%), antidepressants (39%), benzodiazepines and related drugs (36%), opioids (13%) and H2-blockers (34%) more frequently than non-users of PPI (among non-users prevalences were 20%, 16%, 22%, 23%, 5% and 18%, respectively).

TABLE 1 Differences between hip fracture cases and controls

	Cases N = 4818	Controls N = 19 235	*P* value
Women	3632 (75%)	14 520 (75%)	0.881
Age			0.803
<65	30 (<1%)	112 (<1%)	
65-74	312 (6%)	1190 (6%)	
75-84	2209 (46%)	8936 (46%)	
≥85	2267 (47%)	8997 (47%)	
Socioeconomic position			0.033
High	1617 (34%)	6676 (35%)	
Medium	2799 (58%)	11 175 (58%)	
Low	341 (7%)	1156 (6%)	
Unknown	31 (1%)	228 (1%)	
≥90 hospital days	1683 (35%)	5527 (29%)	<0.0001
Comorbidities			
Previous			
Fracture	1662 (35%)	3851 (20%)	<0.0001
Stroke	590 (12%)	2078 (11%)	0.004
Cancer	261 (5%)	877 (5%)	0.012
Depression or bipolar disorder	141 (3%)	659 (3%)	0.084
Schizophrenia	60 (1%)	236 (1%)	0.918
Substance abuse	122 (3%)	412 (2%)	0.100
Cardiovascular disease	2441 (51%)	10 164 (53%)	0.007
Diabetes	627 (13%)	2570 (13%)	0.525
Asthma/COPD	424 (9%)	1626 (8%)	0.441
Glaucoma	514 (11%)	2108 (11%)	0.562
Rheumatoid arthritis	242 (5%)	874 (5%)	0.158
Epilepsy	126 (3%)	380 (2%)	0.006
Drugs			
AChEIs	2646 (55%)	11 505 (60%)	<0.0001
Memantine	1390 (29%)	5600 (29%)	0.719
Oral corticosteroids	1081 (22%)	4349 (23%)	0.797
Bisphosphonate	870 (18%)	3438 (18%)	0.766
Antipsychotics	1165 (24%)	3434 (18%)	<0.0001
Antidepressants	1407 (29%)	4538 (24%)	<0.0001
BZDRs	1260 (26%)	4236 (22%)	<0.0001
Opioids	422 (9%)	1092 (6%)	<0.0001
Antithrombotics	989 (21%)	4161 (22%)	0.094
H2-blockers	955 (20%)	3982 (21%)	0.176

COPD, chronic obstructive pulmonary disease; PPI, Proton pump inhibitors; AChEIs, acetylcholine esterase inhibitors; BZDRs, benzodiazepines and related drugs.

TABLE 2 Hip fracture risk estimates for of PPI use compared to non-use

PPI use	Cases N = 4818	Controls N = 19 235	OR crude (95% CI), *P* value	OR adjusted (95% CI),[a] *P* value
Current use	973 (20%)	3274 (17%)	1.24 (1.15-1.35), <0.0001	1.12 (1.03-1.22), 0.010
Past use	104 (2%)	335 (2%)	1.30 (1.04-1.63), 0.022	1.19 (0.95-1.50), 0.131
Duration of current use				
<1 y	543 (11%)	1,673 (9%)	1.36 (1.22-1.51), <0.0001	1.23 (1.10-1.37), 0.0002
Long-term use[b]				
1-2 y	189 (4%)	717 (4%)	1.11 (0.94-1.30), 0.233	0.97 (0.81-1.15), 0.696
2-3 y	115 (2%)	353 (2%)	1.36 (1.09-1.68), 0.006	1.20 (0.96-1.49), 0.115
3-4 y	56 (1%)	227 (1%)	1.04 (0.77-1.40), 0.821	0.96 (0.71-1.31), 0.815
>4 y	70 (1%)	304 (2%)	0.97 (0.73-1.25), 0.791	0.90 (0.68-1.17), 0.426
Ever user	2321 (48%)	9066 (47%)	1.19 (1.10-1-30), <0.0001	1.08 (0.99-1.18), 0.094
Cumulative use				
<1 y	1358 (28%)	5377 (28%)	1.03 (0.96-1.11), 0.415	0.98 (0.91-1.06), 0.631
1-2 y	330 (7%)	1228 (6%)	1.10 (0.97-1.25), 0.156	0.96 (0.84-1.11), 0.601
2-3 y	218 (5%)	756 (4%)	1.17 (1.00-1.37), 0.047	1.03 (0.87-1.22), 0.716
3-4 y	136 (3%)	532 (3%)	1.05 (0.86-1.27), 0.653	0.90 (0.74-1.11), 0.327
4-5 y	91 (2%)	401 (2%)	0.93 (0.74-1.17), 0.528	0.82 (0.65-1.05), 0.116
5-6 y	52 (1%)	245 (1%)	0.87 (0.64-1.18), 0.367	0.79 (0.58-1.08), 0.132
6-7 y	48 (1%)	171 (1%)	1.15 (0.83-1.59), 0.393	0.99 (0.71-1.39), 0.970
7-8 y	34 (<1%)	118 (<1%)	1.18 (0.80-1.74), 0.399	1.08 (0.73-1.62), 0.695
8-9 y	27 (<1%)	104 (<1%)	1.07 (0.70-1.63), 0.770	0.87 (0.56-1.36), 0.539
9-10 y	25 (<1%)	118 (<1%)	0.87 (0.56-1.34), 0.513	0.73 (0.47-1.15), 0.174

PPI, proton pump inhibitors; OR, odds ratio; CI, confidence interval.
[a]Adjusted by age, sex, socioeconomic position; ≥90 hospital days during the follow-up; cardiovascular diseases, diabetes, asthma/chronic obstructive pulmonary disease, glaucoma, rheumatoid arthritis, epilepsy; previous fracture, stroke, cancer, depression or bipolar syndrome, schizophrenia, substance abuse; use of acetylcholine esterase inhibitors, memantine, oral corticosteroids, bisphosphonates, antipsychotics, antidepressants, benzodiazepines and related drugs, opioids, antithrombotics, H2-blockers.
[b]Long-term use ≥1 year: crude OR 1.12 (95% CI 1.00-1.25), *P* value 0.058; adjusted OR 1.00 (95% CI 0.89-1.13), *P* value 0.946.

TABLE 3 PPI drug substances and hip fracture risk estimates at the index date

	Cases N = 4818	Controls N = 19 235	OR adjusted (95% CI),[a] *P* value
Pantoprazole	407 (8%)	1384 (7%)	1.12 (0.98-1.25), 0.075
Esomeprazole	174 (4%)	662 (3%)	0.94 (0.79-1.24), 0.495
Omeprazole	170 (4%)	521 (3%)	1.20 (1.00-1.44), 0.053
Lansoprazole	123 (3%)	451 (2%)	1.07 (0.87-1.32), 0.528
Rabeprazole	5 (0%)	9 (0%)	2.09 (0.68-6.40), 0.199

PPI, proton pump inhibitors; OR, odds ratio; CI, confidence interval.
[a]Adjusted by age, sex, socioeconomic position; ≥90 hospital days during the follow-up; cardiovascular diseases, diabetes, asthma/chronic obstructive pulmonary disease, glaucoma, rheumatoid arthritis, epilepsy; previous fracture, stroke, cancer, depression or bipolar syndrome, schizophrenia, substance abuse; use of acetylcholine esterase inhibitors, memantine, oral corticosteroids, bisphosphonates, antipsychotics, antidepressants, benzodiazepines and related drugs, opioids, antithrombotics, H2-blockers.

4 | DISCUSSION

Long-term or cumulative PPI use was not associated with risk of hip fracture among community-dwelling persons with Alzheimer's disease. Current PPI use was modestly associated with an increased risk of hip fracture. While the risk was evident in short-term current use, no association was found for longer duration of use. No differences were found in risk of hip fracture between drug substances.

Possible mechanism for the association between PPIs and fractures is still unclear.[38] Our results do not support the previous hypothesis that long-term PPI use would increase the risk of hip fracture by bone loss due to decreased calcium absorption,[39] because the increased risk was not found in long-term PPI use. Duration of current use was assessed in 1 year categories until 4 years of use and duration of cumulative use until 10 years. Furthermore, it is unlikely that other suggested mechanisms for association, such as hypomagnesaemia, myopathy and vitamin B12 deficiency, could increase the fracture risk during less than 1 year of use.[23-25,38,40] In addition, the evidence of these mechanisms is contradictory.[17,20]

Our results are in contrast with two studies that found an increased risk of hip fracture in long-term use.[17,25] A study of Targownik et al was conducted among persons aged 50 years or older and found an increased risk only for over 5 years of PPI use.[17] Study population of Lewis et al were women, and the main finding was the

increased risk in long-term (≥1 year) use.[25] Contrary to the previous studies reporting risk estimates varying 1.30-2.11 for hip fracture and cumulative PPI use,[12,14,41] we found no consistent association between cumulative PPI use and risk of hip fracture. Thus, based on our results, pharmacological mechanism between the association of PPI use and hip fracture seems to be unlikely. In addition, Targownik et al,[22] found no changes in bone mineral density with long-term PPI use.

Our finding concerning short-term current PPI use and increased risk of hip fracture, is in line with previous case-control studies conducted among general population,[13,15,16] which all reported the slightly increased risk in current use but no significant risk in long-term or cumulative use. In addition, the study of Adams et al, which was restricted to men only, reported the highest risk at the beginning of the treatment which is consistent with our results.[42] The highest risk during short-term PPI use might be explained so that PPIs are prescribed to persons with high risk for falling because of their unstable health condition. Current PPI users had more comorbidities and used more frequently fall-risk increasing drugs. Although the analysis was adjusted for several diseases and drug use, it is possible that these adjustments did not fully capture the severity and symptoms of the possible underlying health conditions influencing PPI use. This is supported by findings of previous studies, which reported that PPIs are used as gastroprotection for reducing the adverse effects caused by drugs or exacerbation of diseases.[7,43]

Our study found no differences between drug substances and risk of hip fracture. Three previous studies have reported differences between drug substances.[16,42,44] Two found an increased risk associated with omeprazole use[16,42] compared to non-use of omeprazole, and one found no significant differences.[44]

Psychotropic drugs, which have been previously shown to be associated with an increased risk of hip fractures[35-37] were more commonly used by persons with hip fracture than their controls. Consistent to previous studies,[41,45] persons with hip fracture were more likely to have epilepsy or previous fracture or stroke, which are also risk factors for falling.[11] Opioids were used more commonly among hip fracture cases compared to controls, which indicates that pain was more prevalent among cases and may be one reason for falling and fracture.

Our study had strengths and limitations. A large, qualified, nationwide data allowed an extensive study including information of diagnoses, drug purchases, special reimbursements, hospital stays and socioeconomic position and combining the information personally with Personal Identification Numbers. Drug use periods were modelled with PRE2DUP model, which has been validated against self-reported drug use from interview to expert-opinion based evaluation.[31,32] Controls were matched with cases according to time since Alzheimer's disease diagnoses which was the best available proxy for the stage of Alzheimer's disease, which is a major risk factor for falling and therefore, fractures. Validity of hip fracture diagnoses in Hospital Discharge Register is proven to be good.[46] However, we lacked information on lifestyle factors, such as nutrition, physical activity or limitations, smoking or alcohol use, which are associated with falling risk.[11] In addition, we had no information of indications for drug use, laboratory test results such as serum B12-vitamin levels, severity of diseases or Over the Counter drug use. As PPI users seem to have several comorbidities and medications, residual confounding cannot be ruled out and may partly explain the association between short-term PPI use and hip fracture.

There was no risk increase for long-term or cumulative PPI use and thus, our findings do not support previous assumptions that long-term PPI use would be associated with an increased risk of hip fractures. The risk of hip fracture was modestly increased during current short-term PPI use, which may be partly explained by other diseases and medications. At least in terms of hip fracture, long-term use of PPI can be considered among persons with Alzheimer's disease if the treatment is necessary.

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AUTHORSHIP

Guarantor of the article: Sanna Torvinen-Kiiskinen (STK).

Author contributions: STK, SH and HT performed the research; STK, AMT, MK and HT analysed the data; STK, SH, HT designed the research study and STK wrote the paper; and all authors contributed to the design of the study. All authors have critically revised the manuscript and approved the final version of the manuscript.

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