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REVIEW

# Use of acid-suppressive drugs and risk of fracture in children and young adults: a meta-analysis of observational studies

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## Abstract

**Background** Acid-suppressive drugs (ASDs) are being used by increasing number of children and young adults. However, evidence for a relationship between ASD use and the risk of fracture in these groups of patients is conflicting. We conducted a meta-analysis to evaluate the risk of fracture in children and young adults exposed to ASDs.

**Methods** A literature search was performed using the PUBMED, EMBASE, and Cochrane Library databases from inception to November 2020. Pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated to determine the relationship of ASD use with fracture risk in children and young adults.

**Results** Six studies reporting the outcomes of more than 900,000 children and young adults with ASD use were included in the meta-analysis. The pooled RR for fracture with the use of proton pump inhibitors (PPIs) versus non-use of these medications was 1.17 (95% CI = 1.1–1.25; $P < 0.001$) in children and 1.2 (95% CI = 0.87–1.65; $P = 0.272$) in young adults. By contrast, the use of histamine H2-receptor antagonists (H2RAs) was not significantly associated with fracture risk in children (RR, 1.08, 95% CI = 0.99–1.17; $P = 0.083$) or young adults (RR, 1.08, 95% CI = 0.82–1.42; $P = 0.589$). Significant statistical and clinical heterogeneity among studies were determined for the main analysis and most of the subgroup analyses.

**Conclusions** Our study provides evidence linking PPI use to an increased risk of fracture in children. Thus, the use of PPIs in these patients should be carefully considered. However, randomized controlled studies are needed to determine causality and the role of unmeasured/residual confounding factors in this association.

**Keywords** Acid suppression medications · Bone fracture · Pediatric · Reflux

## Introduction

Acid-suppressive drugs (ASDs), including proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs), are commonly prescribed for treatment of gastric ulcer, gastroesophageal reflux, eosinophilic esophagitis, and Helicobacter pylori infection [1]. The use of ASDs doubled from 2004 to 2008 [2] and tripled from 2002 to 2009 [3]. Also, this increase occurred in infants, children, and young adults, despite concerns regarding the safety of these drugs in such individuals. Several adverse events have been associated with ASDs, such as *Clostridium difficile* infection [4], pneumonia [5], dementia [6], and hypomagnesemia [7].

The link between ASD use in adults and fracture risk has been examined extensively. A previous meta-analysis [8] of studies on two types of ASDs, PPIs, and H2RAs concluded that PPIs but not ASDs are associated with an increased risk of fracture, irrespective of the dose (high or typical). Recently, Poly et al. [9] published a meta-analysis focusing on hip fracture, and reported a higher risk of fracture in short- and long-term PPI users. Since then, several studies [10–15] have investigated the relationship between the use of ASD use and fractures in children and young adults. In a case–control study, Freedberg et al. [10] reported that PPI use in young adults was associated with an increased risk of fracture; however, in another study [11], the use of PPI and H2RA was not associated with an increased risk of fracture in young adults. In several studies, pediatric ASD exposure [12–14] was also shown to increase the risk of fracture later in life, but the results were inconsistent in a subgroup

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analysis based on ASD type. However, a recent large pediatric cohort study [15] found a moderate association between PPIs and any bone fracture. Thus, the relationship between ASD exposure in children and young adults and the risk of fracture is unclear. In this study, we conducted a systematic literature review and meta-analysis to assess this association. However, since the various factors associated with ASD exposure (i.e., duration, age of exposure, and ASD type) may differentially affect the risk of fracture, these must still be analyzed separately.

## Methods

This meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. This systematic review was not registered in PROSPERO or INPLASY.

### Literature search

We conducted a comprehensive literature search of the Cochrane Library, PubMed, and EMBASE databases (inception to December 2020) using keywords related to ASDs and fracture risk. The search was performed using the terms: "H2 blocker OR histamine-2 receptor antagonists OR H2RA OR cimetidine OR ranitidine OR famotidine OR nizatidine OR proton pump inhibitors OR proton pumps OR omeprazole OR Nexium OR lansoprazole OR rabeprazole OR pantoprazole OR esomeprazole" AND "osteoporosis or osteopenia or fracture or bone health or bone metabolism or bone mineral density" AND "infant OR child OR children OR pediatric OR adolescent OR young adult." Reference lists of potential articles were manually searched for additional eligible articles.

### Study selection

Two of the authors independently evaluated the eligibility of all relevant articles found in the databases based on the selection criteria. Full texts were retrieved after reading the titles and abstracts. Any discrepancies were resolved by discussion with a third author. Peer-reviewed studies were included if they met the following (PICO) criteria. Types of studies: randomized controlled trials (RCTs), cohort, nested case control, and case–control studies; types of participants: children and young adults (aged < 29 years at the time of fracture); types of interventions: the experimental intervention was ASD use (PPIs or H2RAs; at least one prescription) before the development of fracture, with either a no-ASD treatment or placebo control group; and types of outcome measures: a list of fracture outcomes reported in the studies, including the adjusted odds ratios (ORs), relative risks (RRs), and 95% confidence interval (CIs) or other appropriate data, was compiled to estimate risk.

### Data extraction and quality assessment

The following data were extracted: first author, publication year, study design, study location, age, ascertainment of ASD exposure, assessment of fracture, number of participants, statistical adjustments, and study quality. The most adjusted effect-size estimate was included in the analysis if more than one estimate was presented. We assessed the methodologic quality of the included studies using the Newcastle–Ottawa Scale (NOS) as recommended by the Cochrane Collaboration [17]. A score of > 7 points was suggestive of a high-quality study.

### Main and subgroup analyses

The association between the use of ASDs and risk of fracture was investigated in adjusted analyses. A sensitivity analysis was conducted to investigate the influence of single studies on the overall risk estimate, by omitting the studies on an individual basis. In addition, subgroup analyses were performed, based on study quality (high vs. low), the number of variables adjusted for (≥ 5 vs. < 5), the type of agent (PPI vs. H2RA), fracture outcome (upper limb vs. lower limb vs. other fracture), sex (male vs. female), and exposure during 1 year of life. Subgroup analyses based on age range were also conducted between children (aged < 18 years) and young adults (aged 18–29 years).

### Statistical analysis

Based on the assumption that the RRs approximated the ORs, study estimates were combined irrespective of which measure of association was reported, because the incidence of the outcomes of interest was low in all populations. A random-effects model was used to pool the obtained effect estimates, accounting for between-study variance. The heterogeneity of the results across studies was determined using Higgins' $I^2$. An $I^2$ value at 0–25%, 25–50%, 50–75%, and more than 75% represents very low, low, medium, and high heterogeneity, respectively [18]. Splitting one study to several estimates leads to substantially more weight being assigned to that study in the meta-analysis, especially in a random-effects model. Therefore, we used a fixed-effects model to produce a pooled RR if more than three estimates from one study were provided, and this pooled RR was included in the meta-analysis [19]. Publication bias was not assessed because the meta-analysis included fewer than 10 studies [20]. Stata SE software (version 10.0; Stata Corp, College Station, TX) was used to perform the statistical analysis.

## Results

### Search results

Searches of three databases yielded 597 potentially eligible articles. Duplicate ($n=565$) and ineligible articles were excluded after reading the titles and abstracts; 32 citations were left for full-text screening. Finally, six studies [10–15] were included in the meta-analysis. Figure 1 shows the number of articles excluded at each stage of the eligibility assessment, together with the reasons for exclusion.

### Characteristics of the included studies

The characteristics of the included studies are listed in Table 1. Five [11–15] were cohort studies and one [10] was a nested case–control study. The publication year ranged from 2015 to 2020, and the patient cohort included in the studies was as early as 1994. The sample size of the included studies varied from 65,432 to 2,490,526; the pooled total was 4,690,968. Among the six studies, two [14, 15] evaluated PPI only; four [10–13] evaluated PPI and H2RA separately.

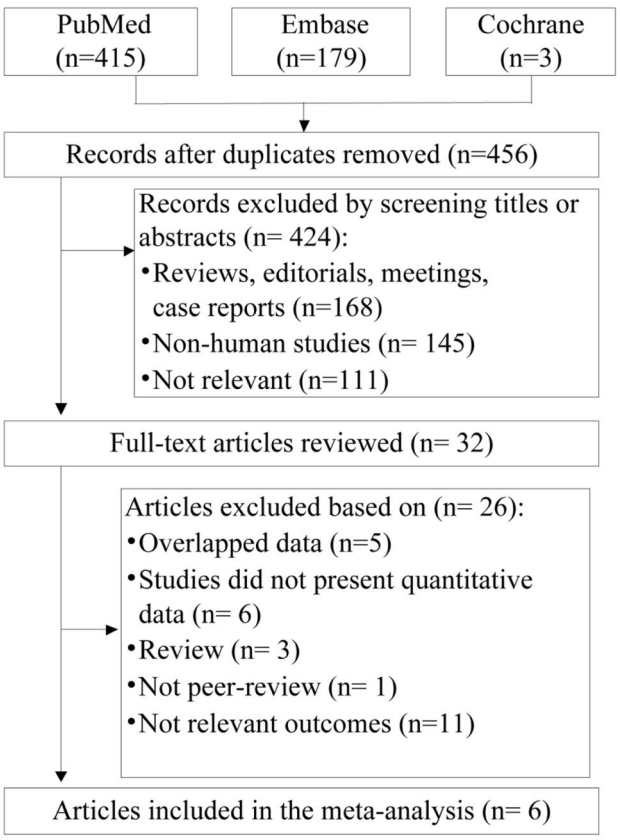


**Fig. 1** Flow chart of the studies considered and finally selected for review

Four studies [12–15] evaluated fracture risk in children, one in young adults [11], and the remaining one [10] in children and young adults separately. All six studies involved Western populations (three [12–14] in the USA, one [11] in Israel, and two [10, 15] in Europe). The extent of adjustment for potential clinical risk factors varied considerably among the studies, and four [11, 12, 14, 15] studies adjusted for more than five important potential confounders.

Based on the methodological quality assessment scores, four studies were of high quality; the breakdown of the scores is provided in Tables S1 and S2 (see Supplemental Content).

### Meta-analysis

#### PPI use and fracture risk

All analyses results are shown in Table 2. According to our meta-analysis of six studies featuring 12 estimates, exposure to PPIs was associated with an increased risk of fracture in children and young adults (RR, 1.2, 95% CI = 1.18–1.29; $P<0.001$). High heterogeneity was observed among the studies ($I^2=66.8\%$). Sensitivity analysis revealed no substantial change in the pooled risk estimates upon exclusion of any single study; the pooled RRs for fracture ranged from 1.18 to 1.22.

In a subgroup analysis by age range, a significant association was observed in children (RR, 1.17, 95% CI = 1.1–1.25; $P<0.001$; $I^2=55.4\%$) (Fig. 2A). However, no increased risk of fracture was detected in young adults (RR, 1.2, 95% CI = 0.87–1.65; $P=0.272$; $I^2=46.3\%$) (Fig. 2B).

In a subgroup analysis by type of study quality, a significant association was observed in high quality studies (RR, 1.18, 95% CI = 1.1–1.28; $P<0.001$; $I^2=62.7\%$). A non-significant effect toward an increased risk of fracture was detected in low quality studies (RR, 1.21, 95% CI = 1–1.46; $P=0.051$; $I^2=62.7\%$).

Regarding the number of adjustment variables revealed a significantly increased fracture risk in those adjusting for at least 5 variables (RR, 1.32, % CI = 1.11–1.57; $P=0.002$; $I^2=80.6\%$) and for fewer than 5 variables (RR, 1.16, 95% CI = 1.08–1.23; $P<0.001$; $I^2=37.6\%$).

Subgroup analyses by sex showed no significant association between PPI use and hip fracture risk in male (RR, 1, 95% CI = 0.75–1.34; $P=0.989$; $I^2=39\%$). In contrast, we found significant association in female (RR, 1.13, 95% CI = 1.07–1.2; $P<0.001$; $I^2=0\%$).

When we grouped studies by fracture outcome, we found a significant positive association between PPI use and upper limb fracture risk (RR, 1.08, 95% CI = 1.04–1.13; $P<0.001$; $I^2=0\%$) and lower limb fracture risk (RR, 1.24, 95% CI = 1.08–1.42; $P=0.002$; $I^2=0\%$), whereas there was no significant association between PPI use and the risk of

**Table 1** Characteristics of the included studies

| Author, year | Location, setting | Study design/born period of the children | Age at the fracture event | Type of ASD | Ascertainment of ASD exposure | Outcome measurement | Number of participants | Confounding adjusted (yes/no) | Follow-up | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| Freedberg et al. 2015 [10] | UK, population-based | Nest case–control, 1994–2013 | 4–29 years (children: 4–18 years; young adults: 18–29 years old) | PPI and H2RA | Health Improvement Network primary | Read code system | 124,799 cases 605,643 controls | Prior use of H2RA, antiepileptic drugs, opiates, and oral glucocorticoids | > 1 year | 6 |
| Wagner et al. 2018 [13] | USA, population-based | Cohort, 2009–2010 | < 5 years | PPI and H2RA | Civilian and military outpatient pharmacy records | ICD-9-CM | Exposed 1047 Non-exposed 64,385 | Male sex, gestational age, comorbidities, and medication use | > 5 years | 8 |
| Fedida et al. 2019 [11] | Israel, population-based | Cohort, 2007–2017 | 18–25 years | PPI and H2RA | Medication prescription data | ICD-9 | Exposed 1216 Non-exposed 487,719 | Age, BMI, education level, ethnicity, military occupation, and duration of follow-up | > 1 year | 6 |
| Malchodi et al. 2019 [12] | USA, population-based | Cohort, 2001–2013 | 3.6–9.1 years | PPI and H2RA | Civilian and military outpatient pharmacy records | ICD-9-CM | Exposed 754,345 Non-exposed 97,286 | Male sex, preterm birth, LBW, obesity and/or overweight, anti-epileptics, fracture before 1 year of age, and time when indicated | > 2 years | 9 |
| Fleishman et al. 2020 [14] | USA, hospital-based | Cohort, 2011–2015 | 6 months-15.5 years | PPI | Pediatric Health Information System database | Diagnostic codes | Exposed 32,001 Non-exposed 32,001 | Propensity-matched analysis | > 2 years | 9 |
| Wang et al. 2020 [15] | Sweden, population-based | Cohort, 2006–2016 | < 18 years | PPI | The Prescribed Drug Register | ICD-10 | Exposed 117,234 Non-exposed 2,373,292 | Propensity-matched analysis | > 5 years | 9 |

*ASD* acid-suppressive drug, *BMI* body mass index, *H2RA* H2-receptor antagonists, *ICD* international classification of diseases, *PPI* proton pump inhibitor

**Table 2** Meta-analysis for studies included in the analysis

| Subgroup analysis | Number of studies | Number of estimates | Pooled RR (95% CI), $I^2$ statistics (%), $P$ value for the heterogeneity $Q$ test | Model used |
|---|---|---|---|---|
| PPI [10–15] | 6 | 12 | 1.2 (1.12–1.29); $I^2=66.8\%$, $P<0.001$ | Random effects |
| Age range | | | | |
| Children (< 18 years old) [10, 12–15] | 5 | 6 | 1.17 (1.1–1.25); $I^2=55.4\%$, $P=0.038$ | Random effects |
| Young adults (≥ 18 years old) [10, 11] | 2 | 5 | 1.2 (0.87–1.65); $I^2=46.3\%$, $P=0.114$ | Random effects |
| Study quality | | | | |
| High quality [12–15] | 4 | 6 | 1.18 (1.1–1.28); $I^2=62.7\%$, P = 0.02 | Random effects |
| Low quality [10, 11] | 2 | 6 | 1.21 (1–1.46); $I^2=64.8\%$, $P=0.014$ | Random effects |
| No. of adjustment variables | | | | |
| < 5 [10, 13] | 2 | 3 | 1.32 (1.11–1.57); $I^2=80.6\%$, $P=0.006$ | Random effects |
| ≥ 5 [10–12, 14, 15] | 4 | 9 | 1.16 (1.08–1.23); $I^2=37.6\%$, $P=0.018$ | Random effects |
| Gender | | | | |
| Male [11, 15] | 2 | 3 | 1 (0.75–1.34); $I^2=39\%$, $P=0.194$ | Random effects |
| Female [11, 15] | 2 | 3 | 1.13 (1.07–1.2); $I^2=0\%$, $P=0.405$ | Random effects |
| Fracture type | | | | |
| Upper limb [14, 15] | 2 | 2 | 1.08 (1.04–1.13); $I^2=0\%$, $P=0.59$ | Random effects |
| Lower limb [14, 15] | 2 | 2 | 1.24 (1.08–1.42); $I^2=42.2\%$, $P=0.188$ | Random effects |
| Other fracture [14, 15] | 2 | 4 | 1.38 (0.98–1.96); $I^2=82.7\%$, $P=0.001$ | Random effects |
| Exposure during 1 year of life [12, 13] | 2 | 2 | 1.34 (1.08–1.65); $I^2=68.6\%$, $P=0.075$ | Random effects |
| H2RA [10–13] | 4 | 8 | 1.09 (1–1.18); $I^2=55.8\%$, $P=0.027$ | Random effects |
| Age range | | | | |
| Children (< 18 years old) [10, 12, 13] | 3 | 5 | 1.08 (0.99–1.17); $I^2=61.5\%$, $P=0.034$ | Random effects |
| Young adults (≥ 18 years old) [10, 11] | 2 | 3 | 1.08 (0.82–1.42); $I^2=49\%$, $P=0.041$ | Random effects |
| Study quality | | | | |
| High quality [12, 13] | 2 | 4 | 1.05 (0.99–1.1); $I^2=16.1\%$, $P=0.311$ | Random effects |
| Low quality [10, 11] | 2 | 4 | 1.19 (1–1.41); $I^2=42.9\%$, $P=0.154$ | Random effects |
| No. of adjustment variables | | | | |
| < 5 [10, 13] | 2 | 3 | 1.2 (1.09–1.33); $I^2=34.3\%$, $P=0.218$ | Random effects |
| ≥ 5 [11, 12] | 2 | 5 | 1.03 (0.98–1.08); $I^2=0\%$, $P=0.515$ | Random effects |
| Exposure during 1 year of life [12, 13] | 2 | 2 | 1.06 (0.99–1.13); $I^2=35.2\%$, $P=0.214$ | Random effects |

other fractures (RR, 1.38, 95% CI = 0.98–1.96; $P=0.069$; $I^2=82.7\%$).

When we limited our analysis to studies reporting PPI exposure during 1 year of life, a significant positive association between PPI use and subsequent fracture risk was observed (RR, 1.34, 95% CI = 1.08–1.65; $P=0.008$; $I^2=68.6\%$).

### H2RA use and fracture risk

According to our meta-analysis of four studies featuring 8 estimates, exposure to H2RAs was associated with an increased risk of fracture in children and young adults (RR, 1.09, 95% CI = 1–1.18; $P<0.038$). High heterogeneity was observed among the studies ($I^2=58.8\%$). Sensitivity analysis revealed no substantial change in the pooled risk estimates upon exclusion of any single study; the pooled RRs for fracture ranged from 1 to 1.17.

In a subgroup analysis by age range, no increased risk of fracture was detected in children (RR, 1.08, 95% CI = 0.99–1.17; $P=0.083$; $I^2=61.5\%$) (Fig. 3A) or young adults (RR, 1.08, 95% CI = 0.82–1.42; $P=0.589$; $I^2=49\%$) (Fig. 3B).

In a subgroup analysis by type of study quality, a significant association was observed in low quality studies (RR, 1.19, 95% CI = 1–1.41; $P=0.047$; $I^2=42.9\%$). A non-significant effect toward an increased risk of fracture was detected in high quality studies (RR, 1.05, 95% CI = 0.99–1.1; $P=0.089$; $I^2=16.1\%$).

Regarding the number of adjustment variables revealed a significantly increased fracture risk in those adjusting for fewer than 5 variables (RR, 1.2, % CI = 1.09–1.33; $P<0.001$; $I^2=34.3\%$). In studies adjusting for at least 5 variables, there was no association between H2RA use and fracture risk (RR, 1.03, 95% CI = 0.98–1.08; $P=0.222$; $I^2=0\%$).

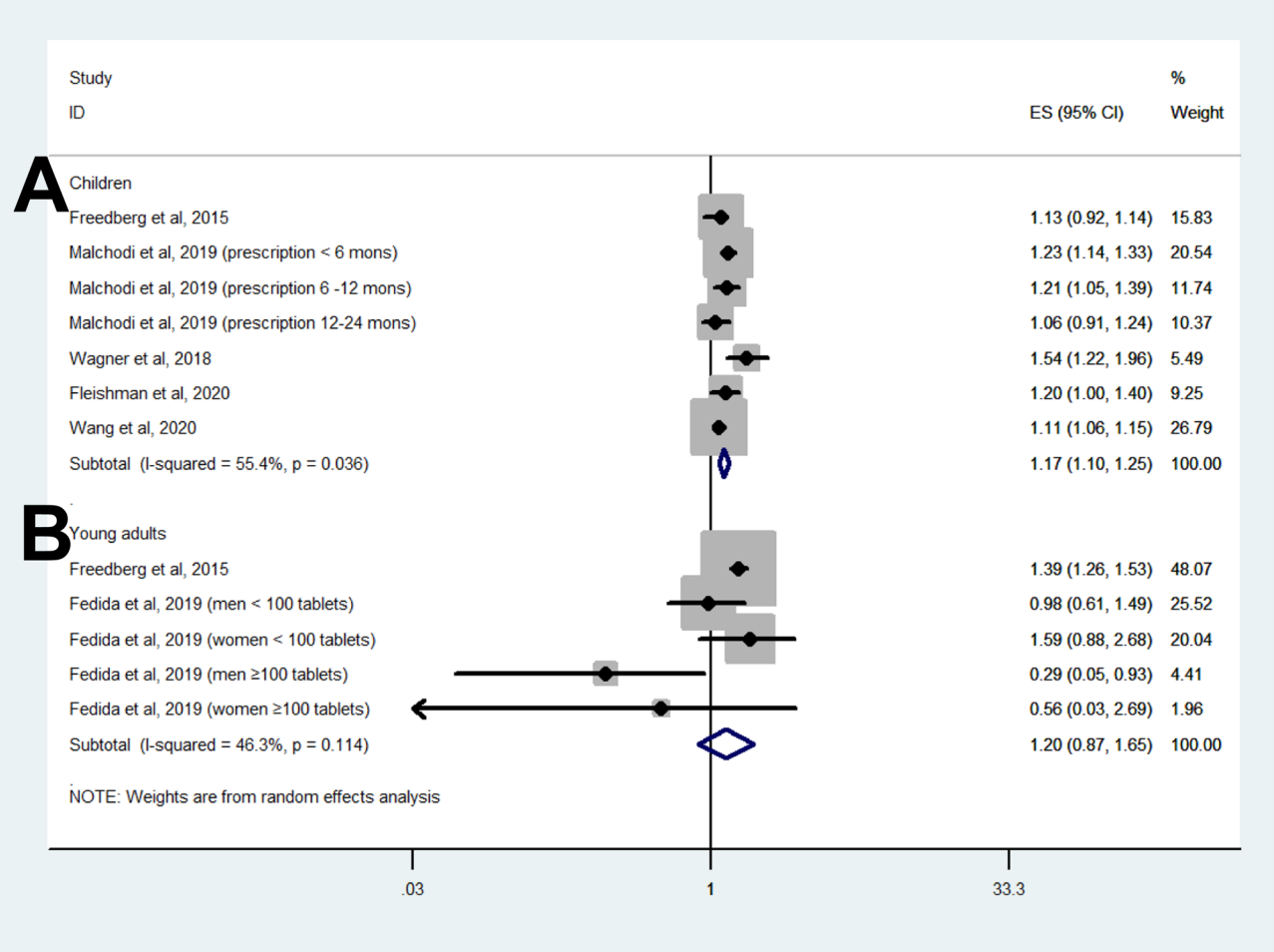


**Fig. 2** Relative risk of fracture in children (**A**) and young adults (**B**) exposed to PPIs

When we limited our analysis to studies reporting H2RA exposure during 1 year of life, a non-significant effect toward an increased risk of fracture was detected between H2RA use and subsequent fracture risk was observed (RR, 1.06, 95% CI = 0.99–1.13; $P = 0.071$; $I^2 = 35.2\%$).

## Discussion

Compared to non-use, PPI use in children, but not young adults, was associated with an increase in the risk of fracture, according to the pooled estimate. By contrast, there was no evidence that H2RA use was significantly associated with an increased risk of fracture in children or young adults. However, confidence in the results was reduced by the considerable heterogeneity and small number of studies analyzed.

The biological mechanisms underlying the relationship between ASD exposure and the subsequent risk of fracture are unclear. ASD may interfere with calcium absorption in the small intestine by increasing the pH [21]. Calcium solubility is believed to be important for its absorption and an acidic gastric environment is necessary for the release of ionized calcium from insoluble calcium salts [22]. High-dose PPIs blocked calcium absorption and thereby decreased bone mineral density in rat [23]. Furthermore, insufficient calcium absorption might lead to compensatory secondary hyperparathyroidism [24], increasing the rate of osteoclastic bone resorption and decreasing bone mineral density. In addition, PPIs are reported to impair osteoclast function and enhance their apoptosis by inhibiting osteoclastic vacuolar H + /K + ATPase activity [25]. Under such conditions, old bone is not replaced.

Although these modifying effects are biologically plausible, the included studies reported conflicting results, and there was significant heterogeneity in our meta-analysis. This could be partly explained by differences in study quality, sex, fracture outcome, and age range, although other possible sources of variability could not be thoroughly explored due to the small number of included studies. The presence

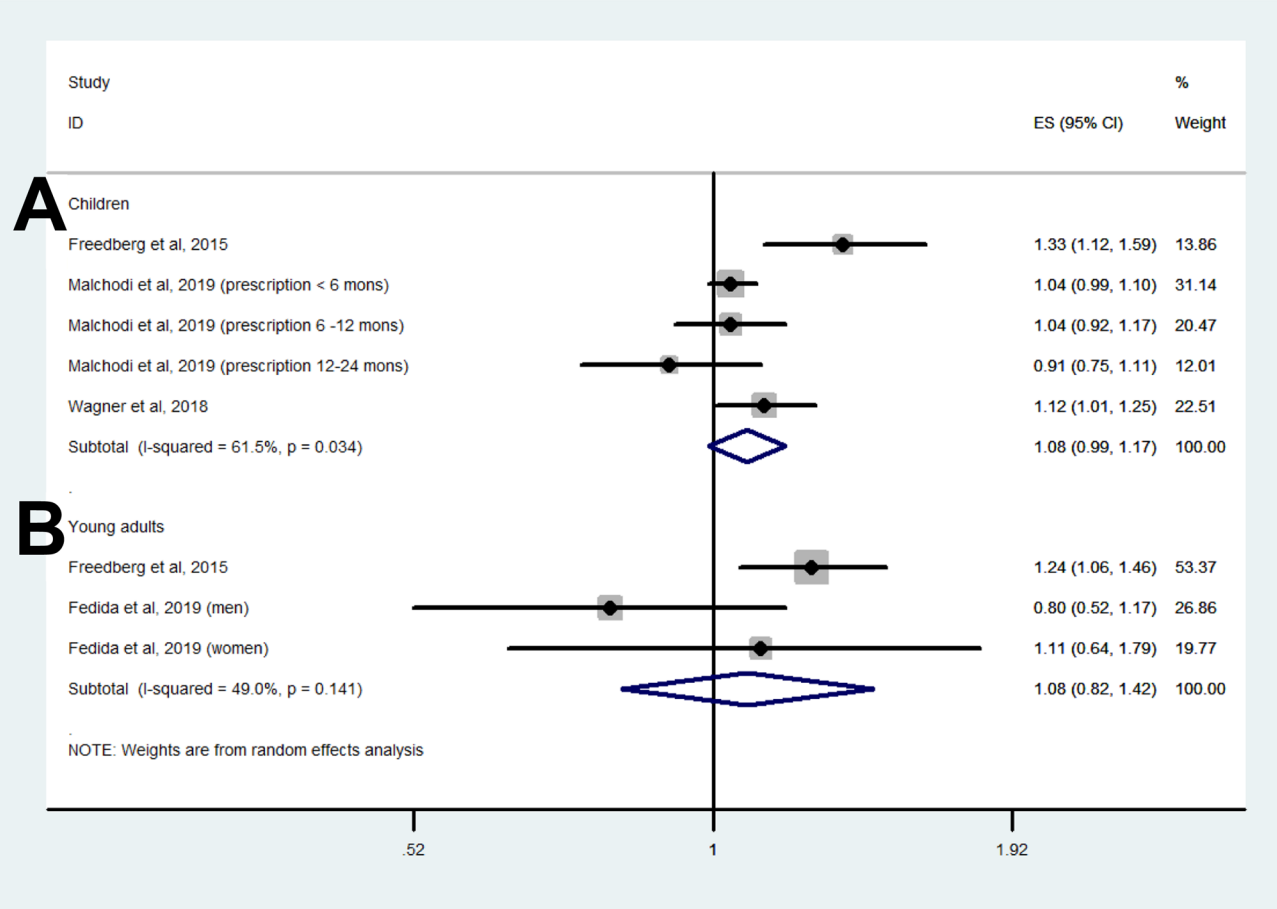


**Fig. 3** Relative risk of fracture in children (**A**) and young adults (**B**) exposed to H2RAs

of clinical heterogeneity would be expected to lead to some degree of heterogeneity in the statistical results.

Children, particularly very young ones, are more vulnerable to drug toxicity because of their physiological immaturity and a slower rate of drug clearance and drug metabolism [26]. Therefore, children and young adults may be at higher risk of fracture for physiological reasons. In our analyses stratified by age, PPI use was associated with an increased fracture risk among children, whereas there was no significant association between PPI or H2RA use and the risk of fracture in young adults. The highest risk (RR = 1.34) of fracture was seen in children with PPI exposure during the first year of life. This implies that age may modulate the effect of ASD on fracture risk. However, our results are limited by the small sample size. Further investigation is required to confirm the link and identify its underlying mechanism.

The various types of ASDs may have different effects on the risk of fracture. PPIs inhibit acid production by about 90%, compared to 60–70%, for H2RAs, suggesting that PPIs result in a greater reduction in calcium absorption. A previous meta-analysis [8] of 11 studies demonstrated a modest association between PPI use and risk of fracture in adults, but no association for H2RA use. Although our overall analysis showed associations of both PPI and H2RA use with fracture risk in children and young adults, subgroup analyses by age suggested a link only between PPI exposure and fracture risk in children. In the only included study [15] that directly compared PPI and H2RA use, there was no difference in fracture risk. However, the authors noted that the absence of a significant association should be interpreted with caution due to residual confounding factors and limited statistical power of the study.

Third, ASDs increase fracture risk by reducing calcium absorption, suggesting an effect of ASD exposure duration on fracture risk. A previous meta-analysis [27] showed that shorter duration of PPI use was associated with an increased risk of hip fracture, whereas there was no significant increase in the risk of hip fracture in long-term PPI users. If such an association exists, it may be attributable to a mechanism other than calcium absorption. The cut-off of cumulative duration was inconsistent among the included

studies, which hindered subgroup analysis based on treatment duration. Freedberg et al. [10] found a dose–response effect with increased total exposure to PPIs in young adults, but not in children. In contrast, Wang et al. [15] demonstrated higher risk with a longer cumulative duration of PPI use in children. However, there has been no direct comparison between short- and long-term uses. Additional research on the effect of ASD treatment duration on the risk of fracture in children and young adults is needed before definite conclusions can be reached.

Residual confounders may have been a source of heterogeneity in our study. Interestingly, subgroup analyses based on the number of variables adjusted for showed lower risks of fracture in association with both PPI and H2RA use when the data were adjusted for at least five variables. This finding is consistent with the associations seen in the subgroup analysis based on study quality.

Finally, the different degrees of acid-suppression by ASDs may modulate the risk of fracture. Fleishman et al. [14] reported no correlation between fracture risk and individual PPIs (but data not shown in their manuscript), whereas Wang et al. [15] concluded that only omeprazole was associated with an increased risk of any fracture. We were unable to analyze drug-related differences because only the study of Wang et al. provided data on individual PPIs. Further studies are needed on the association between individual ASDs and fracture risk in children and young adults.

To our knowledge, this systematic review and meta-analysis is the first to evaluate the effect of ASD use on fracture risk in children and young adults. The main strength of this meta-analysis lies in stratification of the data. Nevertheless, this work had several limitations. First, the number of included studies was small and the types of analyses differed. Thus, the subgroup analysis was limited by the sample size and further investigation is needed. Second, as in all meta-analyses of observational studies, uncontrolled confounding variables may have affected the results. Third, there were insufficient data on the cumulative dose of ASD used in the included studies; therefore, we could not determine whether this parameter is associated with fracture risk. Fourth, publication bias was not evaluated, due to the limited number of studies; tests for publication bias typically have low power when there are few studies.

In conclusion, this systematic review and meta-analysis suggested an association between PPI use and the risk of fracture in children. To confirm our results, randomized controlled studies are needed.

**Supplementary information** The online version contains supplementary material available at https://doi.org/10.1007/s00228-021-03245-3.

**Author contributions** JY and DNB conceived the study and revised the manuscript critically for important intellectual content. TJZ and JY made substantial contributions to its design, acquisition, analysis, and interpretation of data. All authors read and approved the final manuscript.

## Declarations

**Ethics approval and consent to participate** No ethical approval was required for this review as all data were already published in peer-reviewed journals.

**Conflict of interest** The authors declare no competing interests.

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