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Title:

Associations between asthma status and radiologically confirmed fracture in children: A data-linkage study

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Abstract

Aim: Worldwide, ~14% of children have prevalent asthma. As most bone accrual occurs in childhood, and data suggest a detrimental role on bone from asthma and/or medications, we investigated whether asthma was associated with radiologically-confirmed fractures in a large cohort of children.

Methods: Data from the Barwon Asthma Study (BAS) (2005), a population-based, cross-sectional survey of all children attending 91 primary schools in the Barwon Statistical Division (BSD), were linked to the Geelong Osteoporosis Study Fracture Grid (2006-2007), a fracture register encompassing the BSD (n=16,438; 50.5% boys; aged 3.5-13.6yr). Asthma, ascertained from parent-reported symptoms using the International Study of Asthma and Allergies in Childhood questionnaire, was categorised as: (a) *recent wheeze*, and number of (b) *recent wheezy episodes*, (c) *doctor visits for wheeze symptoms* and (d) *doctor visits for asthma check-ups*. Using logistic regression analyses, stratified by sex and adjusted for age and medication use, we determined whether asthma was associated with radiologically-confirmed fractures.

Results: In total, 961 fractures were observed among 823 BAS participants (5.9% of total sample; 61.1% boys). *Recent wheeze* and 1-3 *recent wheezy episodes* were associated with increased odds of fracture in boys (OR 1.26, 95%CI 1.03–1.55; OR 1.40, 95%CI 1.12–1.77, respectively), but not girls (OR 1.03, 95%CI 0.78-1.37; OR 0.67, 95%CI 0.38-1.19). Results were independent of age, and sustained after adjustment for medication.

Conclusions: Independent of age, asthma was associated with fracture for boys, but not girls. There is an imperative for strategies to promote bone health among children with asthma.

Keywords: asthma, fracture, children

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What is already known on this topic

- Asthma, an inflammatory condition, may directly affect bone health and susceptibility to fracture.
- Inhaled corticosteroids, a commonly prescribed treatment for asthma, have been associated with decreased bone mineral density in children.
- The role of inhaled corticosteroids on fracture risk is controversial: most likely due to studies having small sample sizes and investigating self-reported fractures.

What this paper adds

- This is the largest study in children, to date, to investigate associations between asthma severity and radiologically-determined fractures.
- Boys, but not girls, with a *recent wheeze* or who had 1-3 *recent wheezy episodes*, were more likely to fracture.
- The observed associations between asthma and fracture were independent of medication use, including inhaled corticosteroids.

Introduction

Worldwide, asthma is characterized by chronic suffering, disability and preventable deaths (1), with recent prevalence estimates exceeding 334 million people (2). For children aged 5-14 years, asthma is reported to be among the top 10 causes of disability-adjusted life years (2). Approximately 14% of children are estimated to have asthma symptoms (1): with boys having the highest prevalence of all children aged <10 years of age, and girls having the highest prevalence in children aged over 10 years (3-5).

Inhaled corticosteroids (ICS), a commonly-prescribed medication to treat persistent asthma (6), have been associated with decreased bone mineral density (BMD) in children (7). However, the effect of ICS on fracture risk is controversial, for instance, whilst ICS use was associated with increased fracture incidence in boys in one population-based study (n=279; all hand fractures) (8), a meta-analysis of 18 randomised controlled trials (RCTs) found no association between long-term use of ICS and fracture in children or adults (9).

Asthma, an inflammatory condition, may also directly affect bone health and susceptibility to fracture. In one population-based study encompassing 683 general practices in the United Kingdom, asthma severity was more clearly associated with increased fracture risk in children aged 4–17 years than use of ICS (10). Similarly, an Australian study of children aged 0–17 years (2001–2004) showed an increased number of self-reported injuries (including fractures) associated with self-reported asthma status, however, the impact of ICS was not assessed (11). Only small studies (e.g. n=313) (12) have included measures of radiologically-confirmed, rather than self-/parent-reported, fractures.

The aim of this study was to investigate the association between asthma and radiologically-confirmed fractures in primary school aged children by linking two large datasets from a single geographic region.

Materials and Methods

This study was performed using the Barwon Asthma Study (BAS) and the Geelong Osteoporosis Study Fracture Grid (GOSFracGrid) fracture register, both of which cover the Barwon Statistical Division (BSD) in south-eastern Australia.

The BAS (13) was conducted in 2005. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (14) was distributed to parents of children attending one of the 91 primary schools located in the BSD (13). Parents were requested to complete the ISAAC questionnaire regarding their child's respiratory symptoms and medication use (n=16,977; 76% response). Children with parent-reported asthma symptoms were divided into four categories (Table 1).

The GOSFracGrid captures all radiologically-confirmed (all-cause) fractures sustained by residents of the BSD (15), the methodology for which has previously been validated (16). For the current study, we extracted all fractures that occurred in children, resident in the BSD, during 2006–2007. Skeletal site of fractures were coded according to the International Classification of Diseases, Ninth Revision (ICD–9) (17).

The BAS dataset was electronically linked to the GOSFracGrid using: surname, first name, date of birth (DOB) and residential address of the child. Among 16,977 BAS participants who had provided responses, 539 children could not be electronically linked to the GOSFracGrid due to missing information (surname, first name or DOB); this left 16,438 participants to be included in this study (50.5% male; age range 3.5–13.6 years). For analyses, participants were categorised into four age groups: (i) 3.5–6.9 years, (ii) 7.0–8.9 years, (iii) 9.0–10.9 years and (iv) 11.0–15.0 years.

Asthma-related medication use was categorised as a binary variable (yes/no) for each of the following categories: (i) no medication, (ii) inhaled steroid, (iii) bronchodilator, (iv) a combination of inhaled steroid and bronchodilator, (v) oral steroid, and (vi) other.

Statistical Analyses

Differences between those with asthma compared to without asthma symptoms were tested using chi-square or Kruskal-Wallis. Logistic regression analyses were used to calculate odds ratios (OR) with 95% confidence interval (95%CI) to investigate associations between each definition of asthma status and incident fracture. Sex-specific models were adjusted for age, with subsequent adjustment for medication use. Interaction terms were investigated for effect modification and, where confirmed, data were reported within strata. All statistical analyses were performed using Minitab 16 (Version 16.0; Minitab, State College, PA), and a p value < 0.05 was considered statistically significant.

Results

Table 2 presents the characteristics of the study sample. During 2006–2007, 961 fractures were sustained by 823 participants (5.9% of total sample; 61.1% fractures in boys). Girls were less likely than boys to have *recent wheeze* and had fewer numbers of *recent wheezy episodes*, *doctor visits for wheeze symptoms* and *doctor visits for asthma check-ups* (p value < 0.0001 for each). Girls were also less likely to use inhaled steroids, or a combination of inhaled steroids and bronchodilators. Bronchodilators were the most commonly used medication type in both sexes (boys=18.3%; girls=13.7%). Wrist fractures accounted for 52.3% of all fractures observed.

Tables 3 and 4 present the associations between *recent wheeze* and 1-3 *recent wheezy episodes* and incident fracture in children. In boys, independent of age, both *recent wheeze* and 1-3 *recent wheezy episodes* were associated with increased odds of an incident fracture (OR 1.26, 95%CI 1.03–1.55; OR 1.40, 95%CI 1.12–1.77, respectively) compared to those without a *recent wheeze*. These associations persisted, albeit partially attenuated, after adjustment was made for medication use. No associations were observed in girls, and no associations were observed between four or more *recent wheezy episodes* and fracture in either sex. For boys, in the multivariable models, older age was associated with an increased odds of incident fracture. Compared to those in the youngest age group (3.5-6.9 years), boys aged 9–11 years were almost twice as likely to sustain a fracture, whilst those aged 11-15

years had a 2.5-fold increased odds (all $p < 0.0001$). These associations were sustained after adjustment for medication.

Similar associations were observed as reported above for alternate categories of asthma status (Online Supplementary Tables 1 and 2).

Discussion

We present, in the largest study to date, the associations between asthma and radiologically-confirmed incident fractures in children. Findings from this data linkage study suggest that boys, but not girls, with a *recent wheeze* or who had 1-3 *recent wheezy episodes*, were more likely to fracture, independent of age, and medication use.

Severe asthma is characterised by daily asthmatic episodes, with substantial underlying lung inflammation (3, 18). In one population-based study encompassing 683 general practices around the United Kingdom, the severity of asthma was associated with fracture risk in children aged 4–17 years, independent of glucocorticoid use (10). These data suggested that the underlying disease processes of asthma may negatively influence bone development in children. Inflammation can lead to bone loss by interfering with mechanisms in bone formation and resorption processes (19, 20). Thus, it is plausible that recurrent and persistent inflammation among children with asthma may have a detrimental effect on bone health.

We observed that adjustment for medication types partially, but not fully, explained the associations between asthma and fracture. This aligns with the results of a New Zealand study of 313 children, in which ICS use did not influence the age of first fracture (11). However, the contribution of ICS to fracture risk among children with asthma remains controversial; for instance, some (8, 10), but not all (9, 21), studies report associations between corticosteroids and fracture in children.

We observed older age to be independently associated with fracture in both sexes; however, boys were more likely to fracture than girls, and the peak of fractures in boys occurred at an

older age than girls. These observations have been previously reported by other smaller studies (8, 15, 22-24): associations that appear biologically plausible. The sex-specific associations between asthma and fracture may relate to sexual maturation, as girls enter puberty at a younger age than boys. Consistent with this, girls have the greatest bone mass accrual aged 11–15 years whilst for boys this occurs between 14–15 years of age (25). Given this, associations between pubertal growth and increased fracture rate may relate to bone mineralisation lagging bone growth (22, 26). Finally, we speculate that boys may fracture more often than girls due to different lifestyle behaviours (15), such as the types of sports activities, and/or differences in risk-taking activities at certain ages (23, 24).

The strengths of this study include large sample size, high participation rates and the use of radiologically-confirmed fractures, a method that has been previously validated as the most reliable ascertainment of incident fracture (16), and enhances evidence from previous studies of asthma and fracture risk that relied on self-reported fractures. Limitations of this study include the use of parent-reported symptoms to define asthma status, and the lack of data regarding lifestyle behaviours and medication dosage. Further, we cannot exclude the possibility that fractures radiologically-assessed outside the BSD were not identified. In addition, we did not observe a dose-response between asthma and fracture, which defies causality, particularly given that the inflammatory processes of severe asthma are more extreme than in mild asthma. This lack of expected association may be explained by power issues, as our study population had fewer participants that reported have four or more wheeze episodes, compared to 1-3 wheeze episodes, during the previous 12 months (6.9% vs. 14.0% of total study population). An alternate speculation is that children with severe asthma may report fewer wheezy episodes due to their asthma symptoms being well-controlled, thereby masking the association between symptoms and fracture.

In conclusion, our findings suggest that asthma is associated with an increased likelihood of incident fracture in boys, but not girls. These data highlight the importance of strategies to promote bone health among children with asthma.

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**Associations between asthma status and radiologically-confirmed fracture in children:
A data-linkage study**

Original article

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