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ORIGINAL RESEARCH

Gender-specific presentations for asthma, allergic rhinitis and eczema in primary care

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Abstract:
Aim: To identify age- and gender-specific prevalence rates for physician-diagnosed asthma, allergic rhinitis (AR) and eczema across a whole lifespan.
Method: Presentations of asthma, allergic rhinitis and eczema were identified in individuals aged 0 to 65 who consulted their general practitioner at least once in 1998-99 from a population sample of 266,733 in Scotland, and in 1991-95 for asthma and allergic rhinitis in 6,836,063 person years at risk in England and Wales.
Results: In both sexes asthma presentations peak at 4-6 years whilst eczema peaks in infancy. A second asthma peak occurs during adolescence, earlier in females, at a time when a female predominance for all three atopic diseases is established. Female predominance of eczema presentations are limited to the reproductive period of 15-49 years.
Conclusion: The patterns of presentations for asthma, allergic rhinitis and eczema by age and gender suggest important gender-specific differences in disease predisposition and diagnosis.

Introduction

The prevalence of asthma is highest in childhood and has a male predominance that reverses during adolescence.[1,2] There is also a suggestion of a similar gender difference in the expression of allergic rhinitis in limited cross-sectional surveys; surveys in the north-east of England restricted to children aged 6-7 and 13-14 years found a higher

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prevalence of rhinitis in pre-pubertal males, with a relatively higher prevalence among adolescent girls.[3,4] A similar study in Belgium also found a higher prevalence of asthma, allergic rhinitis and eczema in 6-7 year old boys, but it was only asthma that had a higher prevalence in older boys aged 13-14 years.[5] The gender differences for eczema presentation across the human life span are not well characterised and it is not clear if eczema exhibits a reversal in gender distribution around adolescence.

We hypothesised that since asthma, allergic rhinitis and eczema are often associated, a similar pattern and timing of gender differences might be expected. If on the other hand disease mechanisms, detection or perceptions differ by gender or condition, a dissimilar course would be seen in disease presentation to physicians across the human life span. We therefore examined age- and gender-specific prevalence for physician-diagnosed asthma, allergic rhinitis and eczema using information from two large independent whole population UK primary care databases. Some of the preliminary findings were presented at the 2002 British Thoracic Society meeting in London and at the 2004 European Respiratory Society meeting in Glasgow.

Methods

Scottish data on patient consultations for asthma, allergic rhinitis and eczema were obtained from 47 General Practices participating in the Scottish Continuous Morbidity Recording (CMR) project for all patients registered in April 1998 to April 1999. These CMR practices are representative of the age/gender and rural/urban mix of the Scottish population, with 266,733 patients registered in the year of study.[6] CMR uses a system whereby every face-to-face doctor-patient contact is recorded. Information is collected on the index condition and up to 10 concomitant medical problems. Each diagnosis is given a Read code[7] along with an appropriate modifier of 'first', 'recurrent' or 'persistent'. Patient consultation rates for asthma (Read code H33 and below), allergic rhinitis (Read code H17, Hyu2) or eczema (Read code M11, M12z) within the year were used as a measure of period prevalence.[7] Repeat consultations were excluded.

To examine how consistent these observations were, a comparison was made with data from the General Practice Research Database (GPRD) for 1991-1995, originally derived for a respiratory epidemiology project funded by the English Department of Health. The GPRD is one of the largest sources of information on primary care in the UK and covered between 3-6% of the population of England & Wales over the study period. The GPRD holds data on both diagnoses and prescriptions but does not use a Problem Orientated Medical Record.[8] The GPRD data for diagnosis only, relating to person consultations within a calendar year, were used to enable a direct comparison with the CMR data. Comparisons were based on the average yearly patient consultation rates for asthma (excluding patients who also had a diagnosis of COPD) and allergic rhinitis (OXMIS codes used available on request from the authors). Eczema presentations had not been extracted from this data set. GPRD rates were based on 264,258 consultations for asthma and 176,766 consultations for allergic rhinitis, relating to 6,836,063 person years at risk.[9]

The rates for each condition were examined by age and sex from birth to 65 years of age and expressed as 'per thousand registered patients' in each age group. Rates for older patients, aged 65 years or more, were excluded because of the difficulty in distinguishing between asthma and chronic obstructive lung disease (COPD) in later life.[10] The male:female ratio for each condition was calculated using odds ratios in five-year age bands. Ninety-five percent confidence intervals are presented for the odds ratios to allow for sampling variation.

Results

The prevalence of asthma (Figure 1 shows the GPRD data and the CMR data) was highest in childhood with a peak at 4-6 years of age in Scotland (CMR), England and Wales (GPRD). A second peak occurred for both CMR and GPRD data (Figure 1) with its apex at around 12 years for males and 14 years for females. Following the second peak there was a steep decline in consultations for both males and females. The more rapid decline in male consultation rates after this second peak resulted in a reversal of the male:female ratios seen in early childhood. By age 15 years the consultations had reversed to a female predominance. Following the switch to a female predominance in adolescence the gender bias in favour of females was maintained throughout adulthood, albeit with a small rise in consultations after the fourth decade, particularly in males. Male:female odds ratios were approximately 1.5:1 in early childhood for asthma for both the CMR and GPRD data (Table 1), falling gradually to ratios in adulthood that were

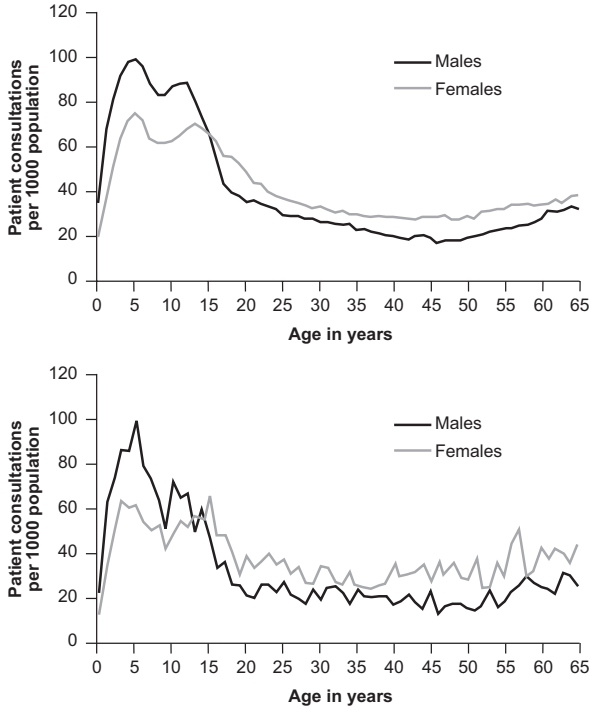

Figure 1 Patient consultation rates for asthma by single year of age for ages 0-65 years in the GPRD (General Practice Research Database) 1991-1995 and in the CMR (Continuous Morbidity Recording) 1998-99.

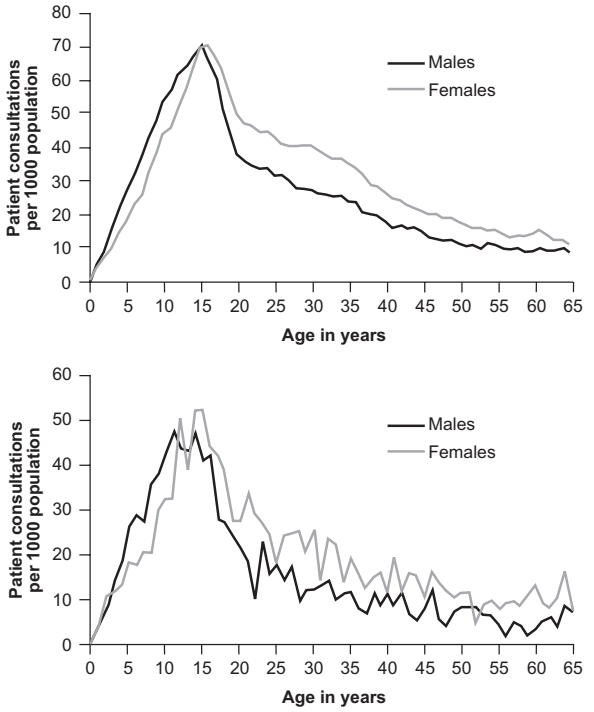

Figure 2 Patient consultation rates for asthma by single year of age for ages 0-65 years in the GPRD (General Practice Research Database) 1991-1995 and in the CMR (Continuous Morbidity Recording) 1998-99.

approximately the reverse of those seen in infancy, i.e. a female predominance.

Although less clearly defined in the CMR than the GPRD data, the age- and gender-related pattern for allergic rhinitis was generally similar to asthma presentations in the timing of the peaks in adolescence and in the differences between males and females (Figure 2 shows the GPRD and CMR data, and Table 1 the odds ratios). Presentations of allergic rhinitis increased progressively during childhood reaching a peak at 16 years (Figure 2). Following this peak, consultation rates fell with increasing adult age for males and females, initially steeply and then more gradually. A significant male predominance was noted up to adolescence after which, from age 15, a female predominance emerged which was sustained throughout adult life.

Presentations for eczema (Figure 3) were only available from the Scottish CMR data, where the peak occurred between birth and 2 years of age, with a sharp decline to age 6 years and with steady levels during the remainder of childhood. For males, presentations for eczema fell during adolescence and remained stable from the age of 20 years. However, for females, presentations rose

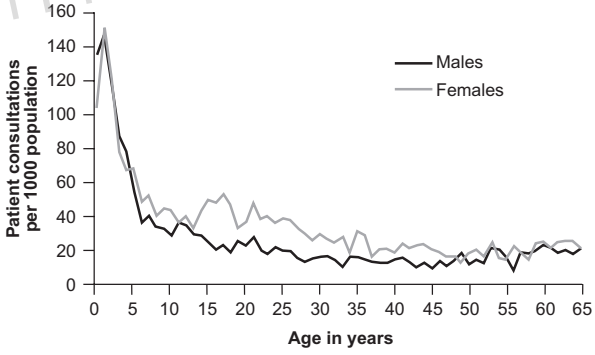

Figure 3 Patient consultation rates for eczema by single year of age for ages 0-65 years in the CMR (Continuous Morbidity Recording) 1998-99.

during adolescence and were approximately twice as common as those seen in adult males. The female predominance emerged from the age of 15 years and persisted until ages 45-49 years, when rates declined to the same level as that seen in males (Figure 3). The changing male:female odds ratios are shown in Table 1 where the consistent and significant female predominance from 15 to 49 years of age can be seen.

Table 1 Male:female odds ratios for patient consultations for asthma, allergic rhinitis and eczema by five year age-groups with 95% confidence intervals for CMR and GPRD data

Age	Asthma		Allergic rhinitis		Eczema
Groups	CMR	GPRD	CMR	GPRD	CMR
00-04	1.55 (1.27, 1.92)	1.52 (1.47, 1.57)	1.13 (0.64, 2.02)	1.48 (1.35, 1.61)	1.10 (0.97, 1.25)
05-09	1.41 (1.20, 1.65)	1.35 (1.31, 1.39)	1.55 (1.17, 2.07)	1.36 (1.30, 1.43)	0.81 (0.67, 0.99)
10-14	1.26 (1.07, 1.49)	1.26 (1.22, 1.30)	1.14 (0.93, 1.40)	1.15 (1.11, 1.19)	0.81 (0.65, 1.01)
15-19	0.76 (0.63, 0.93)	0.82 (0.79, 0.85)	0.80 (0.65, 0.99)	0.90 (0.87, 0.94)	0.44 (0.34, 0.57)
20-24	0.68 (0.52, 0.87)	0.80 (0.77, 0.84)	0.67 (0.50, 0.89)	0.76 (0.73, 0.79)	0.57 (0.43, 0.73)
25-29	0.71 (0.56, 0.91)	0.83 (0.80, 0.86	0.67 (0.49, 0.91)	0.73 (0.70, 0.76)	0.53 (0.40, 0.69)
30-34	0.76 (0.60, 0.97)	0.82 (0.79, 0.86	0.65 (0.48, 0.88)	0.69 (0.66, 0.72)	0.49 (0.36, 0.65)
35-39	0.83 (0.65, 1.06)	0.77 (0.73, 0.80)	0.61 (0.43, 0.86)	0.69 (0.66, 0.72)	0.64 (0.47, 0.85)
40-44	0.64 (0.49, 0.82)	0.70 (0.67, 0.74)	0.63 (0.43, 0.92)	0.70 (0.66, 0.74)	0.56 (0.41, 0.77)
45-49	0.56 (0.43, 0.73)	0.65 (0.61, 0.68)	0.60 (0.39, 0.90)	0.68 (0.64, 0.72)	0.71 (0.50, 0.99)
50-54	0.59 (0.45, 0.77)	0.70 (0.66, 0.74)	0.90 (0.57, 1.40)	0.67 (0.62, 0.72)	0.85 (0.62, 1.17)
55-59	0.62 (0.46, 0.81)	0.73 (0.69, 0.77)	0.45 (0.23, 0.81)	0.73 (0.67, 0.80)	0.89 (0.61, 1.30)
60-64	0.72 (0.55, 0.95)	0.88 (0.84, 0.93)	0.47 (0.24, 0.84)	0.72 (0.65, 0.78)	0.76 (0.54, 1.06)

CMR = Continuous Morbidity Recording for data from Scotland
GPRD = General Practice Research Database for data from England and Wales

Discussion

Although the importance of gender in the evolution of wheezing illness and asthma has been previously reported,[1,11,12] to our knowledge the present study is the first in which the presentations of asthma, allergic rhinitis and eczema have been compared simultaneously in large whole populations from birth to late adulthood. Consultation rates for asthma peaked at 4-6 years in both sexes, with a second peak in adolescence. Male predominance for asthma and allergic rhinitis was found in childhood with a switch to a female predominance after adolescence. Whereas the female predominance for both asthma and allergic rhinitis was evident throughout adult life, the female predominance for eczema was only evident during the female reproductive period.

The strength of the present study lies in the recording of population data gathered prospectively from two independent Primary Care databases, CMR

and GPRD, with consistent results. The use of routinely acquired data from primary care is likely to reflect the impact of significant disease at the whole population level. As similar patterns were seen in two large primary care datasets in the UK it is likely that these patterns would also be seen in whole population prospective cohorts.

The smaller CMR dataset is considered representative of the Scottish population.[6] Although broadly representative of the English and Welsh population, the GPRD data set is under-representative of general practices in inner city areas and of single-handed practices and may therefore have a small bias to higher socio-economic groups[9] — which may lead to an underestimation of consultation rates[13] but which should not invalidate the findings with respect to age and gender. The time periods sampled for CMR and GPRD data sets were also different, albeit only separated by 3-7 years, a time period during which secular trends in disease prevalence and diagnostic labelling could have occurred. However, despite these potential biases and the differences in timing of ascertainment, the observed patterns of consultations were remarkably similar, thus increasing confidence in the generalisability of the results to the whole UK population.

We used patient consultations of diagnosed cases as a proxy for population prevalence. Prevalence reflects the incidence and duration of disease, both of which influence the timing and magnitude of changes in gender-specific prevalence rates. While incidence can be more readily related to disease aetiology and onset, use of this measure would not have captured pubertal influences on already established disease. Use of patient consultations is likely to be a proxy for active disease, although not all sufferers seek medical attention — thus reducing the sensitivity of this method as a measure of true population prevalence. However, no method of disease ascertainment is without its problems, since questionnaire surveys are subject to recall bias and misinterpretation of symptoms by those completing them.[14,15]

Accuracy of the recording and coding systems in general practice is important to consider. A review of patients' notes and a questionnaire validated against bronchial hyper-responsiveness used in patients aged 16-55 has shown that in a general practice database a person labelled with asthma is likely to be correctly labelled almost 90% of the time.[16] In the same study there was little evidence of under-reporting of asthma assessed against symptoms and when comparing computer records with the general practice notes.

The focus of this paper is to examine the variations in prevalence patterns with respect to age and gender. The system of coding and the way this is interpreted by differing general practices may affect the recorded consultation rate but this is unlikely to vary systematically by age and gender so should not preclude examination of prevalence patterns. However, it may be affected by known systematic differences in diagnosis and consultation patterns depending on the age and gender of the patient. For example, there are problems with the diagnosis of asthma in the preschool age group due to heterogeneous presentations which may vary from classical atopic asthma to subtypes of viral associated wheeze, previously labelled as wheezy bronchitis.[17] The peak of asthma prevalence at age 5 and subsequent fall may reflect entry to school or behaviour of parents with different aged children. Consultation rates for children up to the age of 16 may be affected simply by the fact that consultations occur when the children's parents decide that they have a problem.[18]

There are also diagnostic problems at the other extreme of life, and although we chose not to collect data relating to patients over the age of 65 we could not exclude the possibility that the rise in asthma prevalence in late adult life could reflect the difficulties of separating asthma from chronic obstructive pulmonary disease (COPD).[19] It is difficult to quantify this misclassification, but one UK study found only 5% misclassification of COPD as 'asthma' in patients aged 40-80 years presenting to general practice with an exacerbation of COPD.[20]

The observation that male and female patient consultation rates reverse during late childhood and adolescence may in part be explained by changes in illness perception and health behaviour during and after puberty. Consultations for other health related issues are also likely to be different, with consultations for contraceptive advice, genitourinary conditions and monitoring of pregnancy increasing doctor-patient contacts with the female population, thereby increasing the opportunity for recording other conditions. In support of this argument similar changes from male to female predominance in consultation rates in teenage years have also been documented for several other conditions.[21] However, despite these potential influences on health and illness behaviour it is unlikely that these would explain all the age- and gender-specific features reported here.

These prospective data from presentations in primary care are consistent with surveys conducted in specific age groups.[1,3-5] The timing of the gender reversal in asthma prevalence has

generally been reported to occur between 10-20 years of age in most studies, with exceptions locating the switch beyond 20 years.[2] The switch in gender-specific presentations occurred between 15-16 years of age in our study, slightly later than that found in a survey of 27,000 schoolchildren aged 11-16 years in Nottingham from the same time period (1996) and where the switch occurred at age 13.[1]

Findings using the ISAAC protocols are consistent with the present observations for allergic rhinitis in that self- or parent-reported symptoms were commoner for males at 6-7 years,[3] but for females at 13-14 years.[4,5] 'Ever eczema' was higher for females in school children aged 12-14 years.[4] Our study showed no significant gender differences in eczema in childhood with the female predominance becoming apparent from the age of 14 years.

The disease-specific patterns we observed are likely to reflect differences in the natural courses of these three conditions, in terms of both incidence and remission, and gender-specific differences in the interpretation of symptoms and their impact on the individual.

The first peak in asthma presentations, at around 5 years of age (Figure 1), is likely to reflect the rise and subsequent fall in transient early wheezing. The observed male predominance in early childhood may be explained by the relative male disadvantage in terms of airway function[22] and possible reduced adaptive immunity during this early period of life.[23] School entry could also influence this peak, through increased exposure to respiratory infections resulting in more wheezing episodes and a greater likelihood of primary care consultations. Rhinitis presenting in early childhood is more likely to be infectious rather than allergic, and the higher prevalence in boys gives further support to a contribution from the suggested gender-specific reduced adaptive immunity in young boys.[23] The high rates of eczema in early childhood may be influenced by increased recording associated with routine child health surveillance. However, since only a minority of children present to their General Practitioner with concerns relating to allergic reactions and anaphylaxis whilst the vast majority are managed by community staff, it seems very unlikely that universal vaccination, which occurs through to school age, is related to physician diagnosis of eczema.

The differences in the timing of peak presentations for asthma and eczema and their corresponding sex differences suggest a dissociation of asthma and atopy in the preschool age group. Eczema has its highest prevalence in infancy reflecting possible *in utero* programming or exposures soon after birth. The rapid decline in early childhood could reflect the waning of these influences on disease expression.

The coincidence of peak asthma prevalence in girls and boys at 4-6 years and the later gender-specific secondary adolescence peaks could reflect the established different ages of pubertal onset and completion between boys and girls (girls enter puberty and complete pubertal development ahead of boys). Studies have concluded that the overall risk of asthma is not influenced by puberty per se.[2,24] After puberty, males acquire larger lung volumes for a given age and stature, changes associated with increased muscularity of the chest wall and increased respiratory reserve.[24] Changes in baseline lung function could therefore be responsible for the observed gender switch in presentations. These gender-specific differences may also suggest a specific sex hormonal contribution in disease expression in the transition from childhood to adulthood.[2,25]

The increased prevalence of eczema during adolescence in females and the two-fold predominance throughout the reproductive period (Figure 3) would also support a role for hormonal influences on the expression of allergic disease. In this regard there is evidence for the immunostimulatory effects of the female sex steroids, oestrogens and progesterone.[26] The observation that reactivity to allergens increases in women during mid-menstrual cycle also points to important modulation of immune responses by the balance of, and level of, sex steroids.[27]

Factors other than biological influences on the underlying diseases mechanisms also need to be considered. Gender-specific changes in prevalence may reflect socio-cultural attitudes and possible differences in the threshold for seeking medical advice and/or attitudes of physicians to respiratory illnesses in females.[28] In this regard, gender differences in physician diagnosis of asthma have been shown, since adolescent females with the same level of symptoms and greater degree of bronchial hyper-responsiveness are less likely to be given the label of asthma than males with similar signs and symptoms. However, our observations indicate that the reverse may be true from adolescence. The present findings might also be explained by gender-specific differences in severity or by differences in the perception of symptoms. Environmental contributors could also compound the gender-specific patterns of disease. From teenage years there are likely to be increasing gender-specific environmental lifestyle exposures, such as exposure to cosmetics and cigarette smoking.

Oestrogen has pro-inflammatory effects and testosterone has anti-inflammatory effects.[25,26] Thus far these findings have been applied in the field of auto-immunity research. However, these properties of sex steroids may shed light on the significant sex differences and reversals that have been demonstrated in asthma and atopy — particularly as the gender reversal in prevalences occurs at the time of hormonal pertubations. It may be that during the reproductive years, particularly during puberty, higher levels of female sex hormones increase the expression of an atopic predisposition in females. Conversely male hormones may have a protective effect. These influences may not all be immune mediated since sex steroids have multiple biological effects and with regards to asthma the potential consequences on airway and lung development and maturation may be more relevant. Gender differences in asthma and atopy provide an opportunity to research into the factors that are responsible for the initiation and remission of disease with the possibility of fresh insights. The changes in the sex distribution of asthma and atopic diseases may prove to be informative in understanding the basis for changes in the expression of disease.

In conclusion, the observed consultations for these conditions by age and gender are, in part, likely to reflect gender-specific differences in disease mechanisms, diagnosis and interpretation of related symptoms. There may also be important environmental determinants underlying these gender-specific presentations.

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Conflict of interest

There are no conflicts of interest to declare.

References

1. Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ* 1998;**316**(7149):1945-6.
2. Zannolli R, Morgese G. Does puberty interfere with asthma? *Med Hypotheses* 1997;**48**(1):27-32.
3. Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema: the north east study. *Arch Dis Child* 1999;**81**(4):313-17.
4. Shamssain MH, Shamsian N. Prevalence and severity of asthma, rhinitis, and atopic eczema in 13- to 14-year-old schoolchildren from the northeast of England. *Ann Allergy Asthma Immunol* 2001;**86**(4):428-32.
5. Wieringa MH, Weyler JJ, Van Bever HP, Nelen VJ, Vermeire PA. Gender differences in respiratory, nasal and skin symptoms: 6-7 versus 13-14-year-old children. *Acta Paediatr* 1999;**88**(2):147-9.
6. Simpson CR, Helms PJ, Taylor MW, Baxter-Jones A. Respiratory morbidity in Primary Care: A population based study using practices from the Scottish Continuous Morbidity Recording Reseach Database. *Health Bull* (Edinb) 2001;**60**:488-95.
7. Stuart-Buttle CD, Read JD, Sanderson HF, Sutton YM. A language of health in action: Read Codes, classifications and groupings. *Proc AMIA Annu Fall Symp* 1996;75-9.
8. Carey IM, Cook DG, De Wilde S, *et al*. Implications of the problem orientated medical record (POMR) for research using the electronic GP databases: a comparison of the Doctors Independent Network (DIN) and the General Practice Research Database (GPRD). *BMC Fam Prac* 2003;**4**:14.
9. Hansell A, Hollowell J, NT, McNiece R, Strachan D. Use of the General Practice Research Database (GPRD) for respiratory epidemiology: a comparison with the 4th Morbidity Survey in General Practice (MSGP4). *Thorax* 1999;**54**:413-19.
10. Dodge R, Cline MG, Burrows B. Comparisons of asthma, emphysema, and chronic bronchitis diagnoses in a general population sample. *Am Rev Respir Dis* 1986;**133**(6):981-6.
11. Gissler M, Jarvelin MR, Louhiala P, Hemminki E. Boys have more health problems in childhood than girls: follow-up of the 1987 Finnish birth cohort. *Acta Paediatr* 1999; **88**(3):310-14.
12. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996; **312**(7040):1195-9.
13. Saxena S, Majeed A, Jones M. Socioeconomic differences in childhood consultation rates in general practice in England and Wales: prospective cohort study. *BMJ* 1999; **318**(7184):642-6.
14. Kabesch M, Mutuis E. Epidemiology and public health. In Silverman M, ed. Childhood Asthma and other Wheezing Disorders, *Chapman & Hall Medical* 2002. Chapter 2 p. 9-22.
15. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? *Arch Dis Child* 2000;**82**:327-32.
16. Ward DG, Halpin DM, Seamark DA. How accurate is diagnosis of asthma in a general practice database? A review of patients' notes and questionnaire-reported symptoms. *Br J Gen Pract* 2004;**54**:753-8.
17. Wilson NM. Wheezy bronchitis revisited. *Arch Dis Child* 1989;**64**(8):1194-9.
18. Bruijnzeels MA, Foets M, van der Wouden JC, van den Heuvel WJ, Prins A. Everyday symptoms in childhood: occurrence and general practitioner consultation rates. *Br J Gen Pract* 1998;**48**:880-4.
19. Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980;**122**(4):567-75.
20. O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000;**55**:635-42.
21. Anna McCormick, Douglas Fleming, John Charlton. Morbidity Statistics from General Practice. *Fourth*

national study 1991-1992 1995. London, HMSO.
22. Rosenthal M, Bain SH, Cramer D, *et al*. Lung function in white children aged 4 to 19 years: I--Spirometry. *Thorax* 1993;**48**(8):794-802.
23. Michaels RM, Rogers KD. A sex difference in immunologic responsiveness. *Pediatrics* 1971;**47**(1):120-3.
24. Nicolai T, Illi S, Tenborg J, Kiess W, Mutius E. Puberty and prognosis of asthma and bronchial hyper-reactivity. *Pediatr Allergy Immunol* 2001;**12**(3):142-8.
25. Osman M. Therapeutic implications of sex differences in asthma and atopy. *Arch Dis Child* 2003;**88**(7):587-90.
26. Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. Science 1999;**283**(5406):1277-8.
27. Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen. *Clin Exp Allergy* 1995;**25**(5):461-6.
28. Henriksen AH, Holmen TL, Bjermer L. Gender differences in asthma prevalence may depend on how asthma is defined. *Respir Med* 2003;**97**(5):491-7.

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