Prevalence of childhood asthma over 40 years in Greece: is the changing trend a result of diagnostic fashion?

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Abstract

Background: A series of repeated questionnaire surveys among 8- and 9-year-old schoolchildren in the city of Patras, Greece, demonstrated a continuous rise in the prevalence of wheeze/asthma from 1978 to 2003, with a plateau between 2003 and 2008. We further investigated wheeze/asthma trends within the same environment during the last decade. Methods: Two further identical cross-sectional surveys were conducted in 2013 (N=2554) and 2018 (N=2648). Physician-diagnosed wheeze and asthma were analysed separately and in relation to their occurrence (recent-onset: solely within the last two years; non-current: prior to the last two years; persistent: both before and within the last two years). In addition, in 2018, spirometry was performed in participants reporting relevant symptoms and in a random sample of healthy controls. Results: The prevalence of current wheeze/asthma declined from 6.9% in 2008 to 5.2% in 2013 and 4.3% in 2018. The persistent and non-current wheeze/asthma groups (both including children with symptoms at preschool age) followed this overall trend, while the prevalence of recent-onset wheeze/asthma remained unchanged. Persistent and non-current wheezers were also more frequently diagnosed with asthma, in contrast to those with recent-onset wheeze. Children with recent-onset wheeze/asthma and a considerable fraction of those with persistent symptoms had lower lung function. Conclusions: The prevalence of childhood wheeze/asthma has declined significantly during the last decade in Greece. Our analysis suggests that the reversing trend is most likely attributed to changing asthma perceptions among physicians and/or parents, especially in the case of preschool children with troublesome respiratory symptoms.

Introduction

Ample evidence exists that there has been a dramatic increase in the prevalence of childhood asthma through the 1980s and 1990s in westernised countries. Many spoke of an 'asthma epidemic' and there has been broad discussion on the underlying causes and the burden of the disease on patients and society[1-7]. However, studies conducted in the first two decades of the 21st century suggested that asthma prevalence may have reached a plateau or even be declining[8-15]. In the initial phase of the International Study of Asthma and Allergies in Childhood (ISAAC I), particularly high asthma rates were reported in English speaking countries[16]. But in ISAAC III, 5-10 years later, these countries showed a significant decline, despite the slight worldwide increase in the prevalence of childhood asthma[17]. This was also the case in a study based on 2001-2013 data from the USA[18] and in the Aberdeen surveys that cover a period of 50 years (1964-2014)[14,15]. In contrast to the 'asthma epidemic', however, the reversing trend in the prevalence of childhood asthma is difficult to explain[12,15,18].

The Patras respiratory school surveys[6,7,19], a series of repeated questionnaire-based studies of 8-9-year-old schoolchildren in the city of Patras, Greece, demonstrated a continuous rise in the prevalence of

wheeze/asthma from 1978 to 2003[6,7], followed by a plateau phase between 2003 and 2008[19]. Two identical follow-up surveys were conducted in 2013 and 2018, while in the latter study spirometry was also performed in children with a positive history of wheeze/asthma and in a random sample of negative controls. Here, we present the results of the last two surveys, aiming to provide data on the prevalence trends of childhood asthma over a period of 40 years (1978-2018) in an urban environment in Greece.

Methods

Questionnaire surveys

The methodology of 2013 and 2018 studies was identical to that of the previous surveys of 1978, 1991, 1998, 2003 and 2008[6,7,19]. Standard asthma parental questionnaires were distributed during January and February 2013 and 2018 to third- and fourth-grade schoolchildren (i.e. aged 8-9 years, range 7-10 years) from 44 out of 50 public primary schools of Patras, a coastal city of Western Greece with a metropolitan area of approximately 214.000 inhabitants. The target population represented approximately 89.8% of the local population within the respective age range in 2013, and 91.2% in 2018 (National Census 2011 data). The same 44 schools were surveyed in 1998, 2003 and 2008.

The exact wording of the questionnaire and the definitions used for wheeze and asthma have remained constant since 1991 and are presented in E-table 1. Briefly, the questionnaire consisted of two questions on current (i.e. within two years from the survey year) physician-diagnosed wheeze (two or more episodes) and asthma, and two questions on non-current (i.e. prior to but not within two years of the survey) physician-diagnosed wheeze and asthma. A positive answer to any of these questions was termed 'lifetime wheeze/asthma'. Physician-diagnosed wheeze with or without asthma within the last two years but not earlier, was termed 'recent-onset' wheeze/asthma, while wheeze/asthma that occurred both prior to and within the last two years was termed 'persistent wheeze/asthma'. A positive answer to a question on asthma premised a positive answer to the respective (current or non-current) question on wheeze. Conflicting answers were resolved by telephone call; elsewise, they were not included in the analysis.

The methodology used in the distribution and collection of the questionnaires has been described previously[6,7,19]; a relevant scheme is presented in E-figure 1. All positive responders (at least one positive response) and an approximately equal number of randomly selected negative responders were approached by telephone contact to confirm their answers (validation process).

Spirometry

In the 2018 study, all participants who were contacted for response confirmation were invited for spirometry at the Pediatric Respiratory Unit of the University Hospital of Patras. Measurements were performed from June 18 to September 7, 2018 using a Micro 5000 spirometer (Medisoft, Sorinnes, Belgium) according to the established guidelines[20,21]. All children who performed spirometry were free of respiratory symptoms and had interrupted asthma medication for at least four weeks. Forced expiratory volume at 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}) values were assessed according to Global Lung Initiative normative data[22].

Ethics

Formal approval was obtained for both surveys from the Ethics Committee of the University Hospital of Patras, the Regional Directorate of Primary Education and the Greek Ministry of Education. Parental written informed consent forms were distributed and collected with the questionnaires. Spirometry was performed after additional parental written consent and child's verbal assent.

Statistics

The prevalence of wheeze/asthma was calculated as the ratio of cases to total number of responders. The Mantel-Haenzel extension of chi-square test for trends was applied to evaluate prevalence tendency among surveys. Prevalence rate ratios (i.e. prevalence rate changes) between consecutive surveys were calculated by logistic regression analysis with adjustment for sex. Spirometric parameters were compared with one-way

ANOVA with Tukey's post-hoc test for multiple comparisons. Statistical analyses were performed in IBM SPSS version 25 (IBM Corp., Armonk, NY).

Results

In 2013, 3086 questionnaires were distributed, 2643 were collected and, after those with missing or inconsistent data were excluded (N=89; 2.9%), 2554 questionnaires were analyzed. Telephone confirmation was achieved in 88.2% of the 254 positive responders and in 260 controls. Of the 3135 distributed questionnaires in 2018, 2719 were collected and 2648 were analyzed (questionnaires with missing or inconsistent data N=71; 2.3%). Telephone confirmation was achieved in 96% of the 174 positive responders and in 180 negative controls. The flow charts of the 2013 and 2018 surveys are presented in Figure 1. The overall sample included 285 children of non-Greek ethnic origin (11.2%; 8.8% Albanian) in 2013, and 270 in 2018 (10.2%; 7.6% Albanian).

Prevalence trends of current (persistent and recent-onset) and non-current wheeze/asthma are presented in Table 1 and in E-figure 2. A decreasing trend in the prevalence of current, persistent, and non-current wheeze/asthma was noted after 2008 (P for trend <0.001), while the prevalence of recent-onset wheeze/asthma during the same period remained stable (P for trend 0.964). The sex-adjusted prevalence rate ratio for current wheeze/asthma was 0.76 (95% CI 0.61-0.96) between 2008 and 2013, and 0.82 (0.64-1.06) between 2013 and 2018. The 2008-2013 and 2013-2018 prevalence rate ratios were significant for persistent and non-current wheeze/asthma, but not for the recent-onset symptoms (Figure 2).

The rates of children with physician-diagnosed asthma among those with physician-diagnosed wheeze are presented in Figure 3. Similar to the previous surveys, a diagnosis of recent-onset asthma was given to a smaller percentage of children with recent-onset wheeze (35.5% in 2013 and 37.2% in 2018), as compared to their counterparts with persistent asthma (65% of persistent wheeze in 2013 and 70% in 2018) or non-current asthma (87.4% of non-current wheeze in 2013 and 83.3% in 2018) (Figure 3, E-table 2. E-figure 3).

In 2018, 119 (68.4%) of the positive responders (65.1% of those with recent-onset wheeze/asthma, 69% of those with persistent wheeze/asthma, and 70% of those with non-current wheeze/asthma) as well as 85 controls (negative responders) underwent spirometry. The characteristics of these children are presented in E-table 3. Participants with recent-onset wheeze/asthma had lower FEV_1 and FEF_{25-75} compared with their non-current wheeze/asthma counterparts or healthy controls (Figure 4, E-table 4). Children with persistent wheeze/asthma had lower FEV_1/FVC but comparable FEV_1 and FEF_{25-75} with those with non-current wheeze/asthma or healthy controls (Figure 4, E-table 4). Of the participants with resent-onset and persistent wheeze/asthma, 32.1% and 22.4%, respectively, had FEV_1 z-score less than –1 (Figure 5).

Discussion

After a continuous rise in the prevalence of wheeze/asthma since 1978 and a phase of stabilization from 2003 to 2008, the sixth (2013) and seventh (2018) follow-up surveys of Patras epidemiological study showed a continuing decline in wheeze/asthma rates among 8- and 9-year-old schoolchildren in Greece.

Interestingly, persistent and non-current wheeze/asthma followed this overall trend, while the prevalence of recent-onset disease remained essentially unchanged. In our surveys, both the persistent and the non-current group included children in whom wheeze/asthma was diagnosed more than two years prior to the survey, whereas the recent-onset group consisted of children with symptoms that were manifested more recently (i.e. solely within the last two years). It seems, therefore, that the prevalence trends of childhood wheeze/asthma in Patras were primarily determined by changes in the dissemination of wheeze/asthma diagnosis at younger ages (i.e. to children younger than 6-7 years).

It is worth noting that the diagnosis of asthma was also particularly applied to persistent and non-current wheezers (Figure 3), i.e., to children in whom the onset of wheeze occurred at preschool age. Conversely, asthma was reported at significantly lower rates in children with recent-onset wheeze. These findings suggest that Greek paediatricians tend to assign the diagnosis of asthma to preschoolers with troublesome respiratory symptoms, thus resulting in transfer of asthma diagnosis towards younger ages. Conversely, asthma may be

underdiagnosed and therefore undertreated in older children with recent-onset symptoms. Our spirometric findings of lower FEV_1 and FEV_1/FVC in recent-onset wheezers/asthmatics (see below) reinforce the above assumption.

Many studies from Europe, North America and other parts of the world have reported an increase in the prevalence of asthma through the late 1990s[1-7,13,18]. However, studies of the last 20 years have shown that the 'asthma epidemic' has reached a peak and may even be declining in high prevalence societies[8-18]. A series of repeated surveys from 1964 to 2014 in the city of Aberdeen, Scotland, indicate a continuing decline in asthma prevalence after 2004 among the 5-12-years-old schoolchildren[14,15]; after its peak in 2004 (29.5%), the prevalence of lifetime asthma (i.e. ever-had asthma) declined to 22.7% in 2009 and to 18.6% in 2014, i.e. lower than the 1994 levels (19.5%)[14,15]. Data from the National Health Interview Survey also indicate a decrease in the prevalence of current childhood asthma in the USA, from 9.6% in 2009 to 8.4% in 2017[18,23].

The Patras epidemiological study is one of the longest worldwide (40 years; second only to the Aberdeen study) that has captured the prevalence of childhood asthma at several time points by using identical methodology. The two most recent surveys of 2013 and 2018, showed -for the first time- a decline in wheeze/asthma prevalence: from 6.9% in 2008 to 5.2% in 2013 and 4.3% in 2018 for current wheeze/asthma, and from 12.6% in 2008 to 9.6% in 2013 and 6.6% in 2018 for lifetime wheeze/asthma. These rates are two- to almost four-fold lower than those reported in the Aberdeen and other studies[14,15,18,24], which may be attributed to the more 'restrictive' phrasing of our questionnaire (i.e. physician-diagnosed wheeze/asthma) and the prompting of parents to respond with a negative answer if in doubt. Nevertheless, the relative prevalence changes between Patras surveys (Figure 2) are comparable to those of the Aberdeen[19].

In contrast to the 'asthma epidemic' of the 1980s and 1990s, the reversed trends in the prevalence of childhood asthma are difficult to explain. Although the decline has been generally attributed to lifestyle changes or/and to improved diagnostic and management practices[12,15,25], such causal relationships have not been proven to date. Our study was not designed to evaluate the influence of various risk factors on asthma prevalence. However, it is highly unlikely that lifestyle and environmental parameters (allergen exposure, viral epidemics, nutrition, overweight/obesity, physical activity, atmospheric pollution, etc)[26] have shifted during the last decade in a manner that would favor a substantial decline in asthma prevalence. The increase in disease awareness in association with the broad dissemination of pediatric asthma guidelines and the establishment of controller therapy, may have led to the significant reduction of asthma admissions since the early 1990s in Athens, Greece,[27] i.e. in an urban environment similar to ours. However, the decrease in admission rates occurred almost two decades before the decline in asthma prevalence that we report herein and was noted in a period during which childhood asthma rates were in fact still increasing.

Based on our analysis, we maintain that the course of childhood asthma prevalence over the past decades largely reflects the changing perceptions regarding the disease among the physicians and/or parents[28], especially in the case of younger children with troublesome respiratory symptoms. The diagnostic transfer at younger ages most likely reflects the 'asthma fashion' of the last two decades of the 20^{th} century[29], when broad dissemination of asthma guidelines among physicians occurred[30]. To the best of our knowledge, the present study is the only one to evaluate physician-diagnosed wheeze and asthma, both separately and in relation to their onset and duration (i.e., recent-onset, non-current, and persistent) over a period of three decades. Furthermore, in the 2018 study, all children with at least one positive answer to wheeze/asthma questions (recent-onset, persistent, and non-current wheezers/asthmatics) and a random sample of those with negative responses (healthy controls) were invited to perform spirometry. Participants with recent-onset wheeze/asthma had significantly lower FEV_1 and FEV_1/FVC (i.e. an obstructive spirometric pattern) as compared to all other groups; their FEF_{25-75} values were also lower than those of healthy controls. These results, together with the fact that the diagnosis of asthma was less frequently assigned to recent-onset wheezers, suggest that asthma which occurs at late preschool age may have been underdiagnosed and thus remained under suboptimal treatment in our population. On the other hand, children with persistent wheeze/asthma also had lower FEV_1/FVC compared to healthy controls, although the FEV_1 did not differ between the two groups. However, the distribution of FEV_1 values in the persistent wheeze/asthma group was wide, thus

including many cases with low FEV_1 (Figure 4). Indeed, when only children with relatively low FEV_1(i.e. less than -1 z-score) were considered, we found that both persistent and recent-onset wheezers/asthmatics were overrepresented. The latter finding is important, because it suggests that a considerable percentage of preschool wheezers in whom the symptoms persist at school age may exhibit decreased lung function. The cross-sectional design of our study does not permit to draw further conclusions on the trajectories of lung function in relation to the natural history of wheeze/asthma in this group.

The limitations of studies based on written asthma questionnaires have been addressed repeatedly; still, such studies remain the single most useful tool to obtain information from large numbers of participants[13,19,24,31,32], It has also been established that the understanding of the term 'wheeze' differs greatly between parents and physicians[33,34]. In our surveys, however, parents were asked to report not on the symptom as perceived by themselves but on wheeze diagnosed by a physician. The reporting of physician-diagnosed asthma was almost always accompanied by reporting of physician-diagnosed wheeze; equivocal answers were resolved by telephone contact and, if still doubtful, they were excluded from analysis. Cough was not included in our questionnaire; it is our conviction that in order to maintain the results between surveys comparable the phrasing of the previous set of questions (1991, 1998, 2003, 2008) should not be altered. Moreover, the inclusion of persistent or recurrent cough without wheeze in the diagnosis of childhood asthma has been challenged[35,36].

In conclusion, the results of seven identical surveys over a 40-year period show that the prevalence of childhood wheeze/asthma in Greece declines continuously since its peak during the 2003-2008 period. This reversing trend is most likely the result of changing asthma perceptions among physicians and/or parents, especially in the case of preschool children with troublesome respiratory symptoms. Concurrently, however, true asthma may be underdiagnosed and thus remain under suboptimal treatment. The lower lung function of children with recent-onset wheeze/asthma and of a considerable fraction of those with persistent disease, further strengthens the above hypothesis.

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Authors Contributions

Conceptualization and design: SF, MBA. Project Administration: SF, MBA, GD, KNP. Data collection and curation: AN, IG, PL, AV, EGK, SM. Data analysis: SF, GD. Data interpretation: SF, MBA, KNP, GD. Writing – original draft: AN, IG, PL. Witting – review and editing: AV, EGK, SM, KNP, GD, MBA, SF. Final Approval: AN, IG, AV, EGK, SM, KNP, GD, MBA, SF

References

1. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ 1992; 304:873-875.
2. Omran M, Russell G. Continuing increase in respiratory symptoms and atopy in Aberdeen schoolchildren. BMJ 1996; 312:34.
3. Devenny A, Wassall H, Ninan T, Omran M, Khan SD, Russell G. Respiratory symptoms and atopy in children in Aberdeen: questionnaire studies of a defined school population repeated over 35 years. Br Med J 2004; 329:489-490.
4. Downs SH, Marks GB, Sporik R, Belosouva EG, Car NG, Peat JK. Continued increase in the prevalence of asthma and atopy. Arch Dis Child 2001; 84:20-23.
5. Burr ML, Wat D, Evans C, Dunstan FDJ Doull IJM. British Thoracic Society Research Committee. Asthma prevalence in 1973, 1988 and 2003. Thorax 2006; 61:296-299.
6. Anthracopoulos M, Karatza A, Liolios E, Triga M, Triantou K, Priftis K. Prevalence of asthma among schoolchildren in Patras, Greece: tree surveys over 20 years. Thorax 2001; 56: 569-571.
7. Anthracopoulos MB, Liolios E, Panagiotakos DB, Triantou K, Priftis K. Prevalence of asthma among

schoolchildren in Patras, Greece: four questionnaire surveys during 1978-2003. Arch Dis Child 2007; 92:209-212.
8. Ronchetti R, Villa MP, Barreto M, Rota R, Pagani J, Martella S, Falasca C, Paggi B, Guglielmi F, Ciofetta G. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. Eur Respir J 2001; 17:881-886.
9. Zöllner IK, Weiland SK, Piechotowski I, Gabrio T, von Mutius E, Link B, Pfaff G, Kouros B, Wuthe J. No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992-2001. Thorax 2005; 60:545-548.
10. Zilmer M, Steen N, Zachariassen G, Duus T, Kristiansen B, Halken S. Prevalence of asthma and bronchial hyperreactivity in Danish schoolchildren: no change over 10 years. Acta Paediatr 2011; 100:385-389.
11. Hicke-Roberts A, Åberg N, Wennegren G, Hesselmar B. Allergic rhinoconjunctivitis continued to increase in Swedish children up to 2007, but asthma and eczema levelled off from 1991. Acta Paediatr 2017; 106:75-80.
12. van Schayck CP, Smit HA. The prevalence of asthma in children: a reversing trend. Eur Respir J 2005; 26:647-650.
13. Anderson RH, Gupta R, Strachan PD, Limb SE. 50 years of asthma: UK trends from 1955 to 2004. Thorax 2007; 62:85-90.
14. Osman M, Tagiyeva N, Wassall HJ, Ninan TK, Devenny AM, McNeill G, Helms PJ, Russell G. Changing trends in sex specific prevalence rates for childhood asthma, eczema, and hay fever. Pediatr Pulmonol 2007; 42:60-65.
15. Barnish MS, Tagiyeva N, Devereux G, Aucott L, Turner S. Diverging prevalence and different risk factors for childhood asthma and eczema: a cross-sectional study. BMJ Open 2015; 5:008446.
16. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the international study of asthma and allergies in childhood (ISAAC). Eur Respir J 1998; 12:315-335.
17. Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C; ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2007; 62:758-766.
18. Akinbami L, Simon AE, Rossen LM. Changing trends in asthma prevalence. Pediatrics 2016; 137:1-7.
19. Anthracopoulos MB, Pandiora A, Fouzas S, Panagiotopoulou E, Liolios E, Priftis KN. Sex-specific trends in prevalence of childhood asthma over 30 years in Patras, Greece. Acta Paediatr 2011; 100:1000-1005.
20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005; 26:319-38.
21. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky DA, McCarthy K, McCormack MC, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med 2019; 200:e70-e88.
22. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MS, Zheng J, et al; ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40:1324-43.
23. Centers for Disease Control and Prevention. National Center for Health Statistics. Health, United States 2018: Current asthma among children under age 18 years, by race and Hispanic origin: United States, 2007–2017. Available at:*https://www.cdc.gov/nchs/data/hus/2018/fig09.pdf.* Assessed on 16 March 2021.
24. Wennegren G, Ekerljung L, Alm B, Eriksson J, Lötvall J, Lundbäck B. Asthma in late adolescence – farm childhood is protective and the prevalence increase has levelled off. Pediatr Allergy Immunol 2010; 21:806-813.
25. Koshy G, Delpisheh A, Brabin BJ. Trends in prevalence of childhood and parental asthma in Mersey-

side, 1991-2006. J Public Health (Oxf) 2010; 32:488-95.
26. Priftis KN, Mantzouranis EC, Anthracopoulos MB. Asthma symptoms and airway narrowing in children growing up in an urban versus rural environment. J Asthma 2009; 46:244-251.
27. Priftis KN, Paliatsos AG, Panagiotopoulou-Gartagani P, Kotsonis K, Tapratzi-Potamianou. Decrease in childhood asthma in Athens, Greece from 2001 to 2005. Acta Paediatr 2007; 96:924-925.
28. Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. BMJ 2004; 328:386-7.
29. Kälvesten L, Bråbäck L. Time trend for the prevalence of asthma among school children in a Swedish district in 1985-2005. Acta Paediatr 2008; 97:454-458.
30. Kroegel C, Wirtz H. History of guidelines for the diagnosis and management of asthma: from opinion to control. Drugs 2009; 69:1189-204.
31. Pekkanen J, Pearce N. Defining asthma in epidemiological studies. Eur Respir J 1999; 14:951-957.
32. Magnus P, Jaakkola JJ. Secular trend in the occurrence of asthma among children and young adults: critical appraisal of repeated cross-sectional surveys. BMJ 1997; 314:1795-1799.
33. Cane RS, Ranganathan SC, McKenzie SA. What do parents of wheezy children understand by "wheeze"? Arch Dis Child 2000; 82:327-332.
34. Elphick HE, Ritson S, Rogers H, Everard ML. When "wheeze is not a wheeze: acoustic analysis of breath sounds in infants. Eur Respir J 2000; 16:593-597.
35. Chang AB. Isolated cough: probably not asthma. Arch Dis Child 1999; 80:211-213.
36. Donnelly D, Everard ML. 'Dry' and 'wet' cough: how reliable is parental reporting? BMJ Open Respir Res 2019; 6:e000375.

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