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Comorbidities of asthma during childhood: possibly important, yet poorly studied

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ABSTRACT: Asthma in adults is associated with comorbidities such as obesity, gastro-oesophageal reflux, dysfunctional breathing and mental disorders. Herein, we provide an overview of the current state of evidence on these comorbidities in childhood asthma. The prevalence, known mechanisms and possible treatment options for each comorbid condition will be discussed.

Obesity is an increasing health problem in children, but its relationship with asthma remains unclear. Allergic rhinitis is a very common comorbidity in asthma, both in children and in adults, but its effect on childhood asthma severity has not been studied. The prevalence and treatment options of dysfunctional breathing, a known comorbidity in adult asthma, have not yet been studied in paediatric asthma. Food allergies appear to cause more severe reactions in patients with asthma. Depressive disorders are more prevalent in childhood asthma than in healthy children, but seem to be poorly recognised and treated in children. Although gastro-oesophageal reflux is commonly thought to be a comorbid disease complicating asthma, it remains uncertain whether treatment improves asthma control.

In conclusion, knowledge of asthma comorbidities in childhood is sparse. Further studies are urgently needed to identify the prevalence, and, more importantly, the effects of these comorbidities and their treatment on the degree of asthma control in children.

KEYWORDS: Asthma, childhood, comorbidity prevalence, diagnosis, treatment

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The guidelines on the diagnosis and management of asthma focus on achieving and maintaining asthma control as the key goal in asthma treatment [1, 2]. Asthma control can be defined as the extent to which various manifestations of asthma have been reduced or resolved by treatment [3].

In clinical studies of children with asthma, reported in guidelines and reviews, satisfactory asthma control can be achieved and maintained in most patients by regular treatment with inhaled corticosteroids (ICS) [4, 5]. Large population-based surveys, however, consistently show that poor asthma control is common in many children with asthma, despite ICS treatment [6–8]. In the 17 yrs since the inception of the first international asthma guidelines, hospitalisation rates, emergency department visits and deaths from asthma have remained stable in the USA [9]. The situation in Europe is more complex. Studies from Scandinavia between 1980 and 2000 have shown a decrease in asthma hospitalisation days and a trend towards fewer admissions for childhood asthma [10–15]. In Greece, however, hospitalisations for asthma increased during the same study period [16].

The reasons for this striking paradox between ICS efficacy in clinical trials and the ongoing morbidity in asthmatic children treated with ICS in daily practice remain largely unclear. Only recently have investigators started to explore its potential contributing factors. It appears that poor inhalation technique [17], poor adherence to ICS [18]

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and low parental expectations of the benefit of ICS treatment [8, 19] are associated with unsatisfactory asthma control despite ICS maintenance treatment. Conversely, correct inhalation technique and high adherence have been shown to contribute to achieving and maintaining good asthma control [17, 20, 21]. Observational evidence suggests that control of exposure to environmental triggers, such as tobacco smoke and relevant inhalant allergens [2, 20, 22], and comprehensive, repeated education and ongoing follow-up [23, 24] may help to improve asthma control. In fact, many children with ''problematic severe asthma'' [25] can achieve complete asthma control by improving adherence and correct inhalation technique [17], and by eliminating exposure to environmental triggers [20].

It seems likely, therefore, that achieving and maintaining asthma control should be possible in the large majority of children with asthma if a number of issues are consequently and comprehensively addressed in its management.

Although a considerable body of evidence is available on interventions to reduce exposure to environmental trigger factors, poor adherence to maintenance therapy and poor inhalation technique in children with asthma [23, 26–33], the issue of comorbidities in childhood asthma and their influence on asthma control has received relatively little attention in paediatric literature to date. In problematic severe asthma especially, the presence of comorbidities should be evaluated. In this article, we review the published evidence on the impact of comorbid medical conditions on the severity and control of childhood asthma.

METHODS

Studies were identified in PubMed, EMBASE and the Cochrane Library. The following keywords were used: ''comorbidity'', ''asthma'', ''obesity'', ''allergic rhinitis'', ''food allergy'', ''dysfunctional breathing'', ''mental disorder'', ''anxiety'', ''depression'', ''GERD'' or ''gastro-oesophageal reflux disease'', ''treatment'' and ''diagnosis''. The search was limited to ''all child''. The references in retrieved articles were scanned to find additional relevant papers. Because asthma in children <4 yrs of age is a different entity [3, 34], we focused on studies in children between the age of 5 and 18 yrs. Comorbidity was defined as the presence of one or more disorders (or diseases) in addition to the primary disease asthma.

RESULTS

Allergic rhinitis

The prevalence of allergic rhinitis has increased in children over the past decades, and it now varies from 0.8% to 39.7%, depending on country and age [35, 36]. The majority of asthmatic children also have allergic rhinitis. Nevertheless, allergic rhinitis commonly goes unrecognised and undertreated in children with asthma [37].

The reported prevalence of allergic rhinitis in children with asthma is substantially higher than that in the general population, and ranges from 60% to 80% [37, 38]. SIMONS [39] stated that it is likely that asthma and allergic rhinitis frequently coexist because of their similarities in anatomy, physiology and immunopathology (table 1). Most patients with allergic rhinitis have symptoms, such as nasal itching, sneezing, increased nasal secretions and nasal obstruction. However, general symptoms such as lassitude, cough and sleepiness may also occur. If these are the presenting symptoms, the diagnosis of allergic rhinitis may be missed if the patient and parents are not actively questioned about the presence of nasal symptoms [35]. For example, in a recent study at Princess Amalia Children's Clinic (Isala Klinieken, Zwolle, The Netherlands) of 61 children referred for nonspecific cough and breathlessness, 13 (21%) were diagnosed with allergic rhinitis [40].

Treatment of allergic rhinitis with intranasal corticosteroids is the first choice of therapy in adults [41, 42]. Literature regarding children is sparse. The few studies on intranasal steroids for allergic rhinitis in children show short-term improvement of nasal (sneezing, rhinorrhoea, obstruction and itching) and ocular symptoms [43, 44]. It is reasonable to assume, therefore, that treatment of concurrent allergic rhinitis in children with asthma will reduce rhinitis symptoms. More challenging is the question as to whether treatment of allergic rhinitis also improves asthma control. In adults, the use of nasal corticosteroids was associated with a significantly reduced risk of asthma-related emergency room treatments and hospitalisations (adjusted OR 0.75 (95% CI 0.62–0.91) and 0.56 (95% CI 0.42–0.76), respectively) [37, 45]. This has not yet been studied in children. Indirect evidence for poorer control of asthma in children with allergic rhinitis may come from greater health service utilisation and costs. It has been shown that asthmatic children with allergic rhinitis have more frequent emergency department visits and hospital admissions than children with asthma without allergic rhinitis [46]. Although this suggests that treatment of allergic rhinitis in children with asthma could improve asthma control, this hypothesis requires confirmation in a randomised controlled trial.

Food allergy

Food allergy is defined as an adverse immunological response to food that is reproducible under blinded conditions [47]. Previous studies suggest that the prevalence of food allergies in the general population is ~8% in children aged <3 yrs, and ~2% in adults [48, 49]. The incidence, reported in a study, of confirmed food-induced respiratory reactions is estimated to be between 2% and 8% in children and adults with asthma [50]. As

TABLE 1 Similarities in anatomy, physiology and immunopathology in asthma and allergic rhinitis

Anatomy	Chronology of embryological development.
	Respiratory epithelium extends from the nasal fossa throughout the nasopharynx, larynx, trachea, bronchi and bronchioles
Physiology	Nasal and bronchial hyperresponsiveness to environmental and chemical stimuli
	Nasobronchial reflex from environmental stimuli
Immunopathology	Immediate hypersensitivity and allergic responses and persistent allergic inflammation, characterised by eosinophilia occuring in upper and lower airways
	There is a systemic immune response to airborne allergens

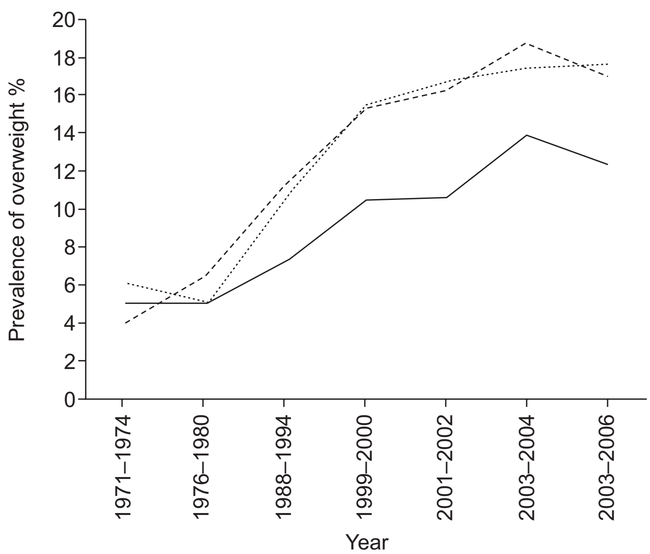

FIGURE 1. Increase in obesity in children in the USA as reported in the National Health and Nutrition Surveys. Modified from [54–56] with permission from the publisher. —: children aged 2–5 yrs; ---: children aged 6–11 yrs; ···: children aged 12–19 yrs.

food allergy and asthma are both atopic diseases they may coexist, but asthma as the only manifestation of food allergy is rare and atypical [47, 48, 50]. Fatal or near fatal reactions (anaphylaxis) are more common in patients with asthma [48]. SICHERER *et al.* [51] showed that patients with asthma were more likely to have a severe reaction to food allergens than patients without asthma (33% *versus* 21%; $p<0.0001$). In the UK, all children ($n=8$) with fatal anaphylaxis had a history of asthma [52]. In a retrospective study in children with asthma and food allergy, peanut and milk allergies were both associated with an increased number of hospitalisations for asthma [53].

Therefore, it seems that comorbid asthma in food allergy increases the risk of severe reactions, and that comorbid food allergy in asthma reduces asthma control.

Obesity

Overweight in children has become a major public health problem. Since the 1970s, prevalence rates have more than quadrupled in the USA in children aged 6–11 yrs, and have also sharply increased in children young than school age and adolescents (fig. 1) [57]. No pan-European data could be found although several studies from individual European countries report a similar rise in prevalence. For example, in the Netherlands in 1997, 8.8% of boys and 11.8% of girls (5–17 yrs) were obese. This increased to 13.5% for boys and 16.7% for girls in 2002–2004 [58]. In Spain, overweight increased in both boys and girls from 4.4% and 2.9%, respectively, in 1992 to 10.1% and 7.6%, respectively, in 2004 [59]. Similarly, overweight in 12-yr-old Finnish children increased from 12.8% in 1986 to 23.6% in 2006 [60]. Explanations for the rise in obesity in children include a decrease in physical activities, an increase in sedentary activities (watching television and playing computer games), an increase in food portions and the increased consumption of calorie-dense convenience foods [57].

Several studies show higher rates of asthma in children who are overweight [61–63]. A high body mass index (BMI) at 1–2 yrs was significantly associated with a higher prevalence of asthma symptoms at 3 yrs (OR 1.40 (95% CI 1.12–1.73); $p=0.003$), and a high BMI at 3–5 yrs was significantly associated with a higher prevalence of asthma symptoms at 6 yrs (OR 1.36 (95% CI 1.03–1.79); $p=0.03$) [63]. This effect was particularly strong in females. For example, girls who became overweight or obese between 6–11 yrs of age were seven times more likely to develop new asthma symptoms at the age of 11 or 13 yrs ($p<0.01$) [55]. Other studies found an association of overweight with exercise-induced cough and wheeze, visits to the emergency department (39% *versus* 31%; $p=0.04$) and missed school days [64, 65]. Although the majority of studies have found an association between asthma and obesity, some did not find such a relation [66–68]. A possible explanation is that obese children could have asthma-like symptoms (shortness of breath) without having asthma. In addition, differences in the definition of asthma severity could play a role [67].

The possible mechanisms of the effect of obesity on asthma have been discussed in depth in a recent review, and are summarised in table 2 [69].

In a 12-yr follow-up study of very low birth-weight children, leptin was thought to play a role in the pathogenesis of both asthma and obesity [70]. Leptin levels were considerably higher in the overweight than in the non-overweight children (median value 18.1 *versus* 2.8 $ng \cdot mL^{-1}$; $p<0.001$). In the overweight children, current asthmatics had leptin levels that were twice as high as children without current asthma (median value 30.8 *versus* 14.3 $ng \cdot mL^{-1}$; $p=0.14$), which was not the case in the non-overweight children [70]. The association of obesity with serum leptin levels has been confirmed [71].

Suboptimal response to controller therapy (ICS) is a possible mechanism explaining why asthma could be more severe in obesity. In adults, an altered response to ICS has been shown in obese asthma patients. Elevated BMI was associated with blunted *in vitro* response to ICS in overweight and obese patients whilst this could not be shown in obese patients without asthma [72].

The association between obesity and asthma may also be partly explained by the influence of asthma on obesity. Exercise-induced asthma may lead to avoidance of physical activity that can increase weight gain [73]. Thus, asthma and obesity can worsen each other [57]. A recent Norwegian study, however,

TABLE 2 Possible mechanisms of the effect of obesity on asthma

Reduced lung volume and tidal volume in obesity that promote narrowing of the airways
Low grade of inflammation may act on the lungs to exacerbate symptoms
Obesity-related changes in hormones
Dyslipidaemia
Gastro-oesophageal reflux
Sleep-disordered breathing
Type-2 diabetes
Hypertension

showed that adolescents with and without asthma did not differ in physical activity and energy intake [74]. In adults, there is evidence that weight reduction in obese asthmatic patients improves lung function, symptoms, morbidity and health status [75]. In children, the relationship between obesity and more severe asthma has not been demonstrated as clearly. Also dynamic mechanical factors are postulated to be involved. In obese individuals, breath frequency is increased and tidal volumes are reduced compared with non-obese individuals [76]. A forced extension of airway smooth muscle is provided by spontaneous tidal breathing which has been shown to have a bronchodilatory action [77]. Obese individuals without this bronchodilatory mechanism would be, as reported recently, expected to experience increased airway hyperresponsiveness [78]. Further research should improve our understanding on the relationship between asthma and obesity in children. Although it has not been shown conclusively that body weight reduction improves asthma control in obese children, this should not discourage physicians from trying to achieve weight loss in these patients, as the importance of weight control in overweight children has been clearly reviewed [79, 80].

Dysfunctional breathing

Dysfunctional breathing is defined as chronic or recurrent changes in breathing pattern, causing respiratory and non-respiratory complaints [81]. Symptoms of dysfunctional breathing include dyspnoea with normal lung function, chest tightness, chest pain, deep sighing, exercise-induced breathlessness, frequent yawning and hyperventilation [82]. Hyperventilation or dysfunctional breathing has been reported in childhood [83–88], but its prevalence is unknown. There is no accepted gold standard of the diagnosis of dysfunctional breathing beyond the clinical description, but the Nijmegen Questionnaire is a symptom checklist (table 3) that can be used to discriminate dysfunctional breathers from normal individuals in adults [89]. In a random sample of 300 adults without asthma from the medical records of a UK semirural general practice, 8% of patients showed positive screening scores for dysfunctional breathing [90]. In the same study, 29% of asthmatics showed positive screening scores for dysfunctional breathing [90]. This indicates that dysfunctional breathing is more prevalent in adults with asthma than in healthy controls. Approximately one third of females and a fifth of males with asthma had scores suggestive of dysfunctional breathing (table 4) [91].

TABLE 3 Nijmegen Questionnaire symptom checklist

Chest pain
Feeling tense
Blurred vision
Dizzy spells
To be confused, losing touch with environment
Accelerated or deepened breathing
Shortness of breath
Constricted chest
Bloated abdominal sensation
Tingling fingers
Unable to breath deeply
Stiffness of fingers or arms
Tightness around the mouth
Cold hands or feet
Palpitations
Feeling of anxiety

Each item scores 0 (never) to 4 (very often) points. When the Nijmegen Questionnaire score is $\geqslant$23, the diagnosis of dysfunctional breathing is 80% certain. Modified from [65] with permission from the publisher.

In a randomised controlled trial in adults with symptoms suggestive of dysfunctional breathing, a clinically relevant improvement in quality of life was found following a brief physiotherapy intervention. This improvement was maintained for 6 months after the intervention in 25% of patients [82].

The application of the Nijmegen Questionnaire in the context of asthma in children requires further exploration [81]. It has been described, both by us and by others, that there are children with troublesome breathlessness during or after exercise, in whom lung function remains normal during exercise testing [86–88, 92]. It has been our experience that most of these patients benefit from physiotherapy aimed at relaxation and at maintaining a normal breathing pattern [93]. These preliminary observations need confirmation and further exploration in rigorously designed further studies.

Vocal cord dysfunction

Vocal cord dysfunction (VCD) syndrome is a functional disorder of the vocal cords [94], characterised by the inappropriate adduction of the vocal cords during inspiration. Two phenotypes of VCD syndrome have been described [95]. One type occurs spontaneously, with the patient experiencing dyspnoea and inspiratory stridor (often described as ‘‘wheezing’’) at various and often unpredictable times, thus mimicking asthma. The other phenotype only occurs with exercise. Flexible fiberoptic endoscopy while the patient is symptomatic is the gold standard for the diagnosis of VCD. The prevalence of VCD in children is unknown. Vocal cord dysfunction should be evaluated as a possible comorbid condition in difficult asthma.

Mental disorders

Childhood depressive illnesses, including major depressive disorder and dysthymia, are recurrent, often chronic conditions with significant morbidity and mortality [96, 97]. Population studies of children and adolescents in the USA and in Europe have reported prevalence rates of depression ranging between 0.14% and 2.5% in children and 0.45 to 8.3% in adolescents [96–98]. KATON *et al.* [99] interviewed 781 subjects aged 11–17 yrs who were diagnosed with asthma and

TABLE 4 Adults with positive scores for dysfunctional breathing by age and sex

	Aged <40 yrs	Aged >40 yrs	Total
Males	7/25 (28)	10/62 (16)	17/87 (20)
Females	14/38 (37)	32/94 (34)	46/132 (35)
Total	21/63 (33)	42/165 (27)	63/219 (29)

Data are presented as n/N (%).

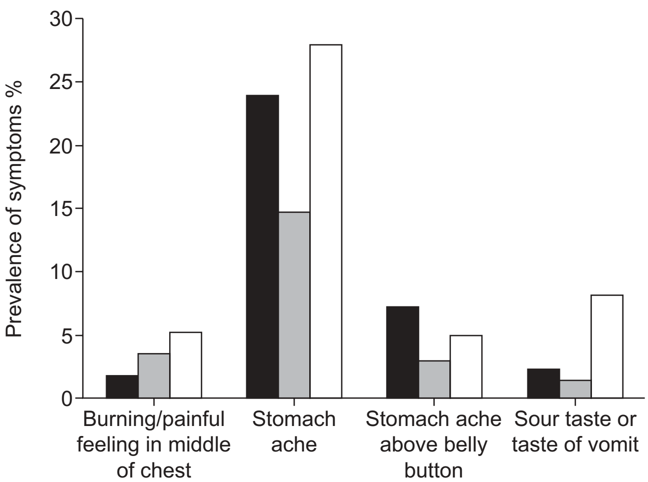

FIGURE 2. Percentage of reported gastro-oesophageal reflux symptoms in the past week. (adapted from NELSON *et al.*) [106]. ■: reported by parents of children aged 3–9 yrs (n=566); ■: reported by parents of children aged 10–17 yrs (n=584); □: reported by children aged 10–17 yrs (n=615).

compared them to a group of matched non-asthmatics. They found that 16.3% of the children with asthma met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for one or more anxiety or depressive disorders in the previous 12 months, compared with 8.6% of those without asthma ($p<0.01$). Higher trait anxiety has been associated with increased perception of asthma symptoms in children, especially in mild asthma [100]. Both over perception of asthma symptoms and blunted perception of symptoms may play a role in maintaining poor asthma control, and hamper successful management [100]. In adults, increasing levels of depression have been associated with increased emergency department visits, hospitalisations, and unscheduled healthcare visits for asthma [101, 102]. In children, negative affect scores are related to asthma symptom scores in a dose-dependent fashion [19].

The scanty literature on depressive disorders in children with asthma suggests that it may commonly go unrecognised and untreated. For example, even if mental disorders are recognised in the assessment of children with asthma, only one in five of these patients received an adequate dosage and duration of antidepressant medication, and only one in six received an adequate number of psychotherapy sessions [103]. More children should be identified as at risk and prevented or treated for this co-morbidity [104].

Gastro-oesophageal reflux

The prevalence of gastro-oesophageal reflux disease (GERD) has been poorly studied in children [105]. One cross-sectional survey in the USA in children aged 3–17 yrs of age showed that 1–18% of children had symptoms of GERD, depending on the severity or frequency queried (fig. 2) [106]. GUSTAFSSON *et al.* [107] showed that oesophageal dysfunction occurred more frequently in 8–19-yr-old asthmatics than in controls (60% *versus* 14%; $p<0.01$), and that acid reflux was found in 50% of these asthmatic teenagers [108]. A systematic review on the prevalence of GERD in children with asthma reported prevalence rates ranging from 19.3% to 65% [109]. These findings were supported in a recent study in 30 children with non-atopic asthma, 21 (70%) of which showed GERD using extended oesophageal pH monitoring [110]. One study compared the prevalence of asthma in 1,980 children >2 yrs of age with GERD to 7,920 controls without GERD. The prevalence of diagnosed asthma in children with GERD was twice the prevalence of that in controls (13.2% *versus*. 6.8%; $p<0.0001$) [111].

Although asthma and GERD in children appear to be related, a causal relationship between the two disorders has not yet been established. Whether it is asthma that causes reflux, reflux that causes asthma, or is there no clinically relevant relationship remains unclear. An oral challenge with 200 mL diluted HCl in children with asthma increased histamine sensitivity ($p=0.001$), although baseline peak flow did not change [112]. A population-based birth cohort showed that the association between reflux symptoms and respiratory symptoms in young adults was independent of BMI [113]. Overweight did not explain the higher frequency of GERD in asthma patients [114].

Very few studies have examined the effect of GERD therapy on asthma [106]. One short-term study (12 weeks) in children showed no improvement in asthma symptoms [115]. In another study, a reduction in asthma exacerbations was found in children with asthma and GERD when treated with proton pump inhibitor and pro-kinetic agents for 12 months compared with treatment with ranitidine alone (0.33 *versus* 2.2 exacerbations·patient^{-1}; $p<0.05$) [116]. KHOSHOO *et al.* [110] found a reduction in bronchial hyperreactivity after 2 yrs of GERD treatment in a group of non-atopic asthma patients, but no control group was used. Similarly, in children with asthma and GERD, a modest reduction in nocturnal asthma symptoms was observed during ranitidine treatment [117]. A recent review on treatment of GERD in asthma did not identify additional high quality studies [118]. Further high-quality randomised controlled trials on the treatment of GERD in asthma in children are needed before any firm conclusion can be drawn on the usefulness of such therapy in children with asthma.

CONCLUSION

As in adults, comorbidities are present in children with asthma. Although the evidence of the impact of comorbidities on childhood asthma is poor, clinicians should be aware of the high likelihood of comorbid disorders in children with asthma, and should actively screen asthmatic children, in particular those with troublesome or uncontrolled asthma, for the presence of overweight, allergic rhinitis, dysfunctional breathing, depressive disorders and, perhaps, gastro-oesophageal reflux. When comorbid conditions are recognised and treated adequately, better asthma control may be obtained.

STATEMENT OF INTEREST

A statement of interest for E.J. Duiverman can be found at www.erj.ersjournals.com/misc/statements.dtl

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