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Overweight in childhood and adolescence: Does it lead to airway hyperresponsiveness in adulthood?

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ABSTRACT

Background: Obesity is increasing worldwide among children and adolescents, and has been associated with an increased incidence of asthma. However, the mechanisms underlying this association are incompletely understood. **Objective:** In this cohort study we aimed to investigate whether being overweight in childhood and adolescence is associated with an increased risk of airway hyperresponsiveness (AHR), a hallmark of asthma, in early adulthood. **Methods:** Of 527 subjects from a random population sample of children and adolescents (7–17 years) examined at baseline, a total of 184 subjects completed the follow-up visit 20 years later and were included in the present analysis. Both visits included assessment of height and weight, case history and spirometry. At both visits, bronchial provocation tests were performed using either histamine (baseline) or methacholine (follow-up). In addition, fractional exhaled nitric oxide (FeNO) was measured at follow-up. **Results:** No significant difference in the prevalence of AHR at follow-up was found between subjects who were overweight or obese at baseline visit ($n = 26$) (pediatric definition, body mass index $\geq 85\%$ percentile) and normal weight subjects ($n = 158$) (positive bronchial provocation tests: 15.4% vs. 22.2%, respectively, $p = 0.35$). Likewise, follow-up FeNO levels did not differ significantly between subjects who were lean and those who were overweight or obese at baseline (geometric mean (95% confidence interval [CI]) 15.1 (13.7, 16.6) parts per billion (ppb) versus 13.0 (10.6, 15.9) ppb, $p = 0.23$). **Conclusion:** In children and adolescents, being obese or overweight seems not to be associated with an increased risk of AHR or increased FeNO levels in early adulthood.

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Introduction

Overweight among children and adolescents is an increasing challenge worldwide. Today, up to one in three children and adolescents in western countries are overweight and almost 10 percent are categorized as obese [1,2]. This has important implications for lung health, as birth cohort studies have indicated that gaining excessive weight during childhood is associated with increased incidence of asthma [3]. However, the mechanisms underlying this association are incompletely understood.

Airway hyperresponsiveness (AHR) is a hallmark of asthma and can be assessed with either physiological stimuli such as exercise or pharmacological provoking agents such as histamine, mannitol or methacholine [4–6]. The association between AHR and adiposity has been assessed in a number of population studies but the conclusions have been somewhat conflicting. Some studies have found that AHR increases with increasing

body mass index (BMI) [7], whereas others have found no correlation between AHR and adiposity [8,9]. Some investigators have observed that the association between asthma and BMI was modified by age of asthma onset [10] and sex [11], whilst others have found the association to be present only in non-asthmatic subjects [12]. Finally, in contrast to these findings, in one study adiposity was *negatively* associated with AHR [13].

Another marker of airway inflammation, fractional exhaled nitric oxide (FeNO), is closely associated with eosinophilic airway inflammation in asthma patients [14]. Eosinophilic airway inflammation is generally *not* associated with asthma in obese subjects [15], though some investigators have observed a positive association between BMI and eosinophilic airway inflammation. In one cross-sectional study, obese asthma patients had a significantly higher number of eosinophils in the bronchial submucosa than non-obese asthma patients [16], and in

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mice, obesity was found to enhance eosinophilic airway inflammation [17]. Moreover, it has been observed that the association between obesity and airway inflammation is sex-specific [18]. These observations underline the need for further studies.

Since cross-sectional studies cannot be used to determine causality, longitudinal studies are needed to assess the association between childhood adiposity and markers of lung pathophysiology in adult life. The aim of the present study is therefore to explore whether being overweight or obese during childhood and adolescence affects markers of airway pathophysiology including FeNO and AHR 20 years later, in early adulthood.

Methods

Participants

The present study is based on data from the Copenhagen Cohort Study, described in detail previously [19]. In summary, in 1986 a random sample was drawn from the civil registration list, consisting of 983 subjects born between 1969 and 1979, resident in Copenhagen, Denmark, and with a date of birth during the first 7 days of the month. Subjects were invited by letter every sixth year (in 1986, 1992, 1998 and 2006) to participate in a longitudinal survey. The present study includes data from the examinations conducted in 1986 (here termed “baseline visit”) and 2006 (here termed “follow-up visit”).

Case histories were obtained and validated in part by questionnaires and in part by semi-structured interviews performed by a trained physician at both visits. All participants or their parents filled out a questionnaire about asthmatic (see below) and allergic symptoms, i.e., rhinitis (sneezing, running or blocked nose not associated with a cold) and eczema (an itchy dry rash on face, arms or legs) and wheezy bronchitis in early childhood. Wheezy bronchitis in early childhood was defined as a history of breathing difficulties triggered by a respiratory tract infection before the age of 2. In addition, subjects were asked to answer if their mother and/or father had ever experienced one or more of the above-mentioned asthmatic or allergic symptoms and if their mother and/or father were smokers.

Asthma was defined on the basis of positive responses to one of the following questions: (1) “Does your breathing ever sound wheezy or whistling?”; (2) “Do you have attacks of shortness of breath with wheezing?”; (3) “Do you experience wheezing, chest tightness, cough, and breathlessness at rest, with exertion, with emotional stress, with exposure to cold air, or with chest infections or head cold?”; and (4) “Do you experience wheezing after exposure to dust, fumes, mold, pollen, food,

pets or drugs?” Current asthma was defined as symptoms of asthma within the preceding 12 months. The same questions about asthmatic and allergic symptoms were included in the questionnaires at baseline and at follow-up.

Baseline BMI-for-age percentiles and Z-scores were calculated from Centre for Disease Control growth charts [20]. The definition of normal weight was BMI < 85% percentile and overweight and obesity was defined as BMI ≥ 85% percentile.

All subjects gave written informed consent at each examination and the study was approved by the ethics committee of Copenhagen and Frederiksberg ((KF) 01318737).

Spirometry

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were assessed with spirometry performed on a 7-L dry wedge spirometer (Vitalograph®, Buckingham, UK) at both visits. In order to calculate FEV₁ in percent of predicted (FEV₁%pred) and FVC in percent of predicted (FVC%pred), we used spirometry reference material from Zapletal et al. [21] at baseline and the European Community for Coal and Steel (ECCS) [22] at follow-up. Established washout periods were followed for patients taking the following medication: short-acting β₂-agonist (6 hours), long-acting β₂-agonist (12 hours), leukotriene antagonist (24 hours) and theophylline (24 hours). Participants were allowed to continue the use of inhaled corticosteroid.

Bronchial provocation test

At baseline, bronchial challenge tests were performed using histamine as the provoking agent in accordance with the protocol described by Cockcroft et al. [5]. Aerosols of the test solution were generated by a Wright nebulizer (Aerosol Products Ltd; London, UK). The first aerosol was a saline solution (0.9%), followed by increasing concentrations of histamine of 0.075–8.0 mg/ml. A positive AHR test was defined as a fall in FEV₁ of 20% or more at a concentration of less than 8 mg/ml histamine.

At follow-up, bronchial challenge tests were performed using an inhalation-triggered dosimeter (Spira Respiratory Care Centre Ltd, Hämeenlinna, Finland). Subjects inhaled nebulized isotonic saline for baseline measurement followed by 1–5 incremental doses of nebulized methacholine. Two minutes after each inhaled dose, a spirometry measurement was performed. The test was stopped and considered positive when FEV₁ decreased by 20% or more, or at a cumulative dose of 8 μmol inhaled methacholine.

To assess AHR as a continuous variable, dose-response slopes for methacholine were calculated as the percentage fall in FEV₁ divided by the cumulative dose of inhaled methacholine. In order to avoid negative values of dose-response slopes, 3.1% was added to the percentage fall in FEV₁ in all subjects when dose-response slopes were calculated.

FeNO

FeNO levels were measured using a Nitric Oxide Analyzer (NIOX; Aerocrine AB, Solna, Sweden) in according to the American Thoracic Society guidelines [23]. Means of triplicate measures were calculated and reported.

Atopy

At baseline, a skin prick test for 9 aeroallergens was performed (birch [*Betula verrucosa*], grass [*Phleum pratense*] mugwort, horse, dog, cat [*Felis domesticus*], house dust mite [*D. pteronyssinus*], and fungi [*Alternaria* and *Cladosporium* species] (ALK-Abello, Hoersholm, Denmark)). Atopy was defined as a positive skin prick test (wheal diameter > 3 mm) to at least 1 of these 9 aeroallergens.

Statistical analyses

Data were stored and analyzed using the statistical software SPSS 23 (SPSS Inc. Illinois, USA).

Participants were categorized in two groups based on BMI levels at baseline: the normal weight group and the overweight/obese group with baseline BMI-Z scores < and ≥ 85% percentile, respectively. Unadjusted comparisons between the two groups for continuous variables were carried out using t-tests for normally distributed data and Mann-Whitney tests for data that was not normally distributed. Chi²-tests were used to compare categorical variables.

Pearson's correlation coefficient was used to analyze the association between baseline BMI and FeNO as well as AHR as a continuous variable at follow-up. After this, two multiple regression models were made in order to assess if baseline BMI Z-scores predicted AHR dose-response slopes and FeNO levels, respectively, at follow-up, when adjusted for age, sex, smoking history, asthma, use of inhaled corticosteroid (ICS), birth weight, baseline AHR and baseline measurements of height, atopy and FEV₁%pred.

FeNO values and AHR dose-response slopes were log-transformed for normality.

Values of $p < 0.05$ were considered statistically significant.

Table 1. Baseline characteristics of the 527 subjects who attended the baseline visit in 1986, divided by responder status at follow-up in 2006.

	Responders (n = 184)	Non- responders (n = 343)	p-value
Sex (% female)	56.5	46.0	0.02
Age (years)	12.3 (2.9)	12.1 (2.8)	0.49
BMI (kg/m ²)	19.0 (2.6)	18.7 (2.9)	0.39
Overweight or obese subjects (%) [§]	13.6	13.4	0.96
Wheezing in early childhood (%)	7.7	9.4	0.49
Pos. AHR (%)	4.4	8.9	0.06
FEV ₁ %predicted	98.6 (12.7)	96.8 (13.5)	0.13
Asthma (%)	3.3	6.5	0.12
Atopy (%) [†]	20.8	25.9	0.19
Rhinitis (ever) (%)	9.2	13.0	0.20
Eczema (ever) (%)	9.3	9.4	0.96

Values are given as % or mean (SD), unless otherwise indicated.

[†] Defined as a positive skin prick test response to at least 1 of 10 aeroallergens in a standard test panel.

[§] BMI-for-age ≥ 85% percentile.

Results

Of the 983 invited subjects, 527 agreed to participate in a baseline visit in 1986. Of these, 189 attended the follow-up visit in 2006 (338 were classified as non-responders). Five subjects were classified as underweight in 1986 (pediatric definition BMI-for-age <5% percentile) and were excluded from the analyses, leaving a total of 184 subjects in the cohort for this analysis. No significant differences were observed in age, height or weight or the proportion of overweight/obese subjects between the responders and the non-responders (Table 1). The proportion of females was slightly higher among the responders (57%) vs. non-responders (46%) ($p = 0.02$), and there was a non-significantly higher number of asthma patients among non-responders (6.5%) than among responders (3.3%), $p = 0.12$ (Table 1).

Cross-sectional results

Baseline

Of the included 184 participants, 158 were normal weight (BMI-for-age <85% percentile), and 26 were overweight or obese (BMI-for-age ≥ 85% percentile). Of these, 6 subjects (23%) had a BMI-for-age ≥ 95% percentile (pediatric definition of obese).

Baseline measurements showed that when compared to the lean group, overweight and obese subjects were significantly younger at cohort entry, but the prevalence of asthma and atopy did not differ between the two groups (Table 2). The subjects with asthma all had a positive AHR test. Two subjects (1 from the normal weight group and 1 from the overweight/obese group) had a positive AHR test but no respiratory symptoms, and were therefore *not* classified as asthmatic.

Table 2. Subjects' baseline (1986) characteristics by baseline adiposity status.

	Lean <i>n</i> = 158	Overweight/obese <i>n</i> = 26	<i>p</i> -value
Sex (% female)	58.2	46.2	0.25
Age [†]	13.0 (5)	10.0 (4)	<0.01
Height (cm)	153.9 (16.1)	145.0 (14.9)	<0.01
BMI Z-scores	−0.03 (0.63)	1.36 (0.27)	<0.001
FEV ₁ %pred	98.1 (12.4)	101.6 (14.6)	0.20
FVC%pred	92.1 (10.08)	95.8 (11.9)	0.11
FEV ₁ /FVC	0.90 (0.05)	0.89 (0.05)	0.24
Pos. AHR (%)	3.9	7.7	0.33
Asthma (%)	3.2	3.8	0.61
Atopy (%)	19.7	26.9	0.40
Rhinitis (%)	9.5	7.7	0.77
Eczema (%)	10.2	3.8	0.47
Wheezy bronchitis (%)	7.6	7.7	0.99
Birth weight (g)	3433 (567)	3445 (682)	0.92
Parent with allergy (%)	33.8	23.1	0.28
Parental smoking (%)	78.1	87.0	0.42

Values are given as % or mean (SD), unless otherwise indicated.

[†]Median (Interquartile range).

AHR, airway hyperresponsiveness.

The proportion of subjects with a positive AHR test did not differ significantly between the normal weight and the overweight and obese subjects (Table 2).

Follow-up

No association was observed between BMI at follow-up and levels of AHR (unstandardized $\beta = 0.005$, SE $\beta = 0.009$, $p = 0.58$). Likewise, follow-up BMI and levels of FeNO were not associated (unstandardized $\beta = 0.003$, SE $\beta = 0.004$, $p = 0.47$).

Longitudinal results

Spirometry and anthropometrics

Subjects who were overweight and obese at baseline had a significantly higher BMI at follow-up, compared to subjects who were normal weight at baseline. There was no significant difference in height at follow-up between the two groups, and likewise, FEV₁%pred, FVC and FEV₁/FVC did not differ significantly between the two groups (Table 3).

Asthma and AHR

The proportion of patients with asthma at the follow-up visit was not statistically different between subjects who were overweight or obese at baseline, and those who were normal weight (Table 3). Of the 24 subjects who had current asthma at follow-up, 16 subjects (66%) had a positive AHR test, and 8 subjects (one from the normal weight group and 7 from the overweight/obese group) had a negative test.

The overall prevalence of AHR at the follow-up visit was 21.2%. A total of 23 subjects (21 from the normal weight group and 2 from the overweight/obese group) had asymptomatic AHR and were therefore classified as

Table 3. Subjects' characteristics at follow-up (2006) divided by baseline (1986) adiposity status. Values are given as % or mean (SD), unless otherwise indicated.

	Lean <i>n</i> = 158	Overweight/obese <i>n</i> = 26	<i>p</i> -value
Age (years) [†]	33.5 (5)	31.0 (4)	<0.01
Height (cm)	173.4 (9.4)	174.3 (9.4)	0.67
BMI (kg/m ²)	24.9 (3.1)	30.9 (7.0)	<0.001
FEV ₁ %pred	104.0 (12.5)	104.4 (10.9)	0.89
FVC%pred	108.8 (12.5)	108.8 (11.2)	0.99
FEV ₁ /FVC	0.82 (0.06)	0.82 (0.05)	0.97
Pos. AHR (%)	22.7	15.4	0.35
AHR dose-response slope [§]	1.74 (1.44, 2.10)	1.76 (1.18, 2.63)	0.96
FeNO (ppb) [§]	15.1 (13.7, 16.6)	13.0 (10.6, 15.9)	0.23
Asthma (%)	13.3	11.5	0.55
Use of ICS (%)	3.8	7.7	0.32
Current smokers (%)	15.8	23.1	0.26

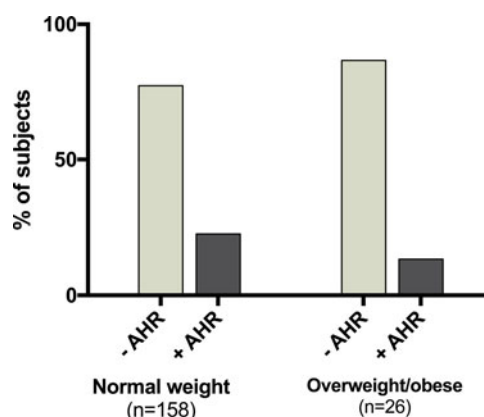
[†]Median (Interquartile range) [§]Geometric mean (95% CI).

AHR, airway hyperresponsiveness; FeNO, fractional exhaled nitric oxide (parts per billion); ICS, inhaled corticosteroids.

non-asthmatic. There was no difference in the prevalence of AHR at follow-up between subjects who were overweight or obese at baseline and subjects who were normal weight at baseline (positive bronchial provocation test: 15.4% vs. 22.2%, respectively, $p = 0.35$) (Table 3; Figure 1).

The degree of AHR at follow-up, measured as dose-response slopes for methacholine did not differ significantly between the subjects who were overweight or obese at baseline compared to normal weight subjects (dose-response slope (geometric mean (95% CI)) 1.76 (1.18, 2.63) vs. 1.74 (1.44, 2.10), $p = 0.96$) (Table 3; Figure 2).

No correlation was found between baseline BMI Z-scores and methacholine dose-response slopes at follow-up in the univariate analyses (Pearson's $r = 0.09$, $p = 0.24$; Figure 2). Furthermore, when adjusting for

**Figure 1.** The proportion of subjects who had a positive methacholine provocation test at follow-up divided by baseline adiposity status.

Normal weight: Pediatric definition, BMI $\geq$ 5% percentile and $<$ 85% percentile.

Overweight/obese: Pediatric definition, BMI $\geq$ 85% percentile.

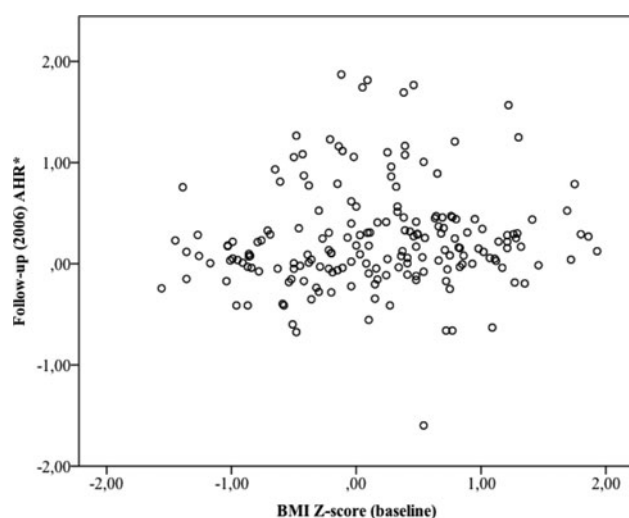


Figure 2. The association between baseline BMI Z-scores and AHR at follow-up. *Airway hyperresponsiveness (log dose-response slopes). R^2 linear = 0.008.

potential confounders (age, sex, smoking history, asthma, use of ICS, birth weight, baseline AHR and baseline measurements of height, atopy and FEV₁% predicted), baseline BMI Z-scores were not significantly associated with methacholine dose-response slopes at follow-up (unstandardized $\beta = 0.07$, SE $\beta = 0.05$, $p = 0.15$) (Table 4).

FeNO

FeNO levels at follow-up did not differ significantly between the subjects who were overweight and obese at baseline, compared with those who were normal weight (geometric mean (95% CI) 13.0 parts per billion (ppb) (10.6, 15.9) vs. 15.1 ppb (13.7, 16.6), $p = 0.23$) (Table 3). There was no association between BMI Z-scores at baseline and FeNO levels at follow-up in the univariate analysis (Pearson's $r = -0.09$, $p = 0.22$). When adjusting for potential confounders (age, sex, smoking history, asthma, use of ICS, birth weight, baseline AHR and baseline measurements of height, atopy and FEV₁%pred.) baseline BMI Z-scores were not significantly associated with

FeNO levels at follow-up (unstandardized $\beta = -0.03$, SE $\beta = 0.03$, $p = 0.35$) (Table 4).

Discussion

In this study we found no difference in the prevalence of AHR at age 27–37 between subjects who were overweight or obese at age 7–17, and subjects who were normal weight. The lack of association persisted after controlling for potential confounders. To our knowledge, this study is the first to describe the association between childhood and adolescence adiposity and development of adulthood AHR in a longitudinal study with a 20-year follow-up period.

Previous longitudinal studies have reported inconsistent results concerning the association between BMI and AHR development. Eneli et al. [24] found that in 557 children, being in the highest BMI quintile at the of age 4 and 7 did not predict AHR at the age of 10, and in fact the majority of the children who had developed AHR at the age of 10 were in the lowest BMI quintile. In contrast to this, Rasmussen et al. [25], found that in 272 14-year-old subjects, being in the highest BMI quintile increased the risk of developing AHR at age 20. Likewise, in the Normative Aging Study [26], a case-control study including 61 adult men who had developed AHR during a 4-year period and 244 healthy men who had *not* developed AHR, the men in the highest BMI tertile had a higher risk of having developed AHR.

The conflicting findings may be explained by a number of factors. Firstly, it can be that adiposity during childhood does not have as substantial an impact on the risk of AHR and airway inflammation later in life, as adiposity during adolescence and adulthood.

Secondly, it has been suggested that the association between obesity and AHR development is dose-dependent. In a cross-sectional study, Badier et al. [27] found that obese (BMI ≥ 30) and very obese subjects (BMI ≥ 35) had an increased prevalence of AHR, when compared to lean subjects, whereas this was not the case for subjects in the overweight category (≥ 25 BMI < 30). In our study, the majority of the subjects (77%) in the overweight/obese group were overweight, rather than obese, and the actual proportion of overweight or obese subjects was lower than in the majority of previous studies. This reflects the lower prevalence of excess weight and obesity among children and adolescences in Denmark, especially during the 1980's, when compared to for example the USA and Australia [2]. Perhaps, if a larger proportion of obese children and adolescents had been present in the current cohort, the association would have been different. Thirdly, studies have indicated that in non-obese subjects, BMI might not

Table 4. Adjusted correlation coefficients (β) between baseline BMI Z-scores and measurements of airway hyperresponsiveness and FeNO at follow-up.

	AHR (follow-up)			FeNO (follow-up)		
	β	S.E. (β)	p-value	β	S.E. (β)	p-value
BMI Z-score (baseline)	0.07 [§]	0.05	0.15	−0.03 [§]	0.03	0.35

[§]Unstandardized regression coefficient (β) adjusted for age, sex, smoking history, use of inhaled corticosteroids, birth weight, baseline AHR and baseline measurements of height, atopy and FEV₁% predicted.

be an optimal measure to assess adiposity, as it does not include information on body composition, i.e. fat percent. In support of this, Lazarus et al. [28] found that skinfold thickness, but not BMI, correlated with spirometry values in school-aged children. However, skinfold thickness was unfortunately not measured in our cohort. Finally, the use of different methodologies to assess AHR, for example the use of different provoking agents in previous studies, might contribute to the conflicting findings in the literature.

In the present study, FeNO levels, as a marker of eosinophilic airway inflammation at follow-up, did not differ significantly between the subjects who were overweight and obese at baseline, compared to those who were normal weight. In line with this, Uppalapati et al. [29] found that obese subjects had higher FeNO levels when compared to underweight subjects, but *not* when compared to those who were normal weight. Also, the impact of obesity on asthma risk has been found to be present only in subjects with low FeNO levels [30], which is consistent with findings from Scott et al. [31] who reported that eosinophilic airway inflammation was not associated with obesity in asthma patients. Likewise, in a large cross-sectional study by Singleton et al. [32], no association was observed between BMI and FeNO.

A number of studies have suggested that a U-shaped relationship between BMI and AHR exists, where being underweight [24] as well as obese increases the incidence of AHR [26], [33]. This could potentially obscure an association between adiposity and AHR in studies in unselected populations. However, in the present study, subjects who were underweight at baseline were excluded and our results are therefore unlikely to be influenced by this.

There are a number of limitations in our study. First of all, our sample size is limited. There are several factors known to promote AHR in humans, which could potentially blur the outcome of cohort studies with limited sample sizes [34]. Yet, conducting clinical studies with a follow-up period of 20 years can be a challenge, and our results can be compared to what have been achieved in other long-term follow-up studies within the same research field. Rasmussen et al. [25] were able to show a significant correlation between BMI at age 14 and AHR at age 20 among 272 included subjects. Our results, though based on a slightly smaller number of subjects, do not suggest a correlation, since the prevalence of AHR at follow-up was in fact slightly *higher* among subjects who were normal weight at baseline when compared to subjects who were overweight or obese. This does not indicate that our negative finding is caused by lack of statistical power. Another limitation is that we did not obtain information about subjects' home or working environments, which

could have been relevant as an increased prevalence of AHR has been documented in a variety of occupations associated with irritating or allergenic exposures [35].

The definition of asthma in our study was based solely on symptoms, despite the availability of lung function measurements. The reason for choosing this definition is that it had been used consistently in records throughout the Copenhagen Cohort Study [19,36]. It can be discussed if the definition should have been based on symptoms *plus* objective measures, i.e. a positive bronchial provocation test. At baseline, all subjects characterized as asthmatic had positive AHR, however, at follow-up, one-third of the subjects characterized as asthmatic had a negative test and there is therefore a risk that the reported asthma prevalence at follow-up was overestimated.

The long follow-up period in our study is a strength. However, a number of new test methods became available during the period from 1986 to 2006 i.e. methacholine provocation. The method used to assess AHR was therefore different between the two visits, as the equipment for histamine provocation was no longer available in the research facilities by the time of the 20-year follow-up visit. Still, the questionnaires used to assess asthma symptoms were the same, and the same spirometers were used at baseline and follow-up.

In conclusion, we found that being overweight or obese at age 7–17 was not associated with increased AHR or FeNO levels after 20 years. Though our sample size is modest, our findings do not support the hypothesis that elevated BMI in childhood and adolescence increases the risk of developing AHR and eosinophilic airway inflammation in adult life.

Declaration of interests

The authors have no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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