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DR BRIGHT NWARU (Orcid ID : 0000-0002-2876-6089)

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Pubertal BMI change and adult-onset asthma in men: population-based cohort study in Sweden

Bright I. Nwaru,^{1,2} Claes Ohlsson,³ Maria Bygdell,³ Jari Martikainen,⁴ Jenny M Kindblom,³

¹Krefting Research Centre, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden

²Wallenberg Centre for Molecular and Translational Medicine, Institute of Medicine, University of Gothenburg, Sweden

³Centre for Bone and Arthritis Research, Institute of Medicine, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

⁴Bioinformatics Core Facility, the Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Corresponding author:
Bright Nwaru, PhD,
Krefting Research Centre
Institute of Medicine
University of Gothenburg
P.O. Box 424
SE-405 30 Gothenburg
Sweden
bright.nwaru@gu.se
Phone: +46 760 642 614

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62 **ABSTRACT**

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64 **Background:**

65 The role of pubertal BMI change in adult-onset concomitant asthma and allergic rhinitis is unknown.

66

67 **Objective:**

68 We investigated the association of childhood and young adult BMI, and pubertal BMI change with adult-
69 onset asthma, allergic rhinitis, and concomitant asthma and rhinitis in Swedish men.

71 **Methods:**

72 The BMI Epidemiology Study in Gothenburg, Sweden, comprised of height and weight measures taken
73 from school health records (6.5-9.5 years) and during military conscription (17.5-22 years) for all men born
74 1945-1961 (n=37,652). Age-adjusted childhood BMI centred at 8 years and young adult BMI at 20 years
75 were linked to high quality data on asthma and allergic rhinitis diagnoses from the Swedish National
76 Patient Register.

78 **Findings:**

79 High BMI (4th quartile vs the two median quartiles) at 8 years was associated with increased risk of
80 concomitant asthma and allergic rhinitis (HR 1.45; 95%CI 1.00-2.11). Overweight (HR 1.45; 95%CI 1.12-
81 1.89) and obesity (HR 1.95; 95%CI 1.08-3.54) at 20 years were associated with increased risk of asthma
82 without concomitant allergic rhinitis as main or auxiliary diagnosis. Pubertal BMI change showed a non-
83 linear association, so that both low (1st quartile vs the two median quartiles) and high pubertal BMI change
84 were associated with increased risk of asthma (low: HR 1.36; 95%CI 1.11-1.68; high: HR 1.32; 95%CI
85 1.07-1.63) and asthma without concomitant allergic rhinitis (low: HR 1.33; 95%CI 1.04-1.69; high: HR
86 1.36; 95%CI 1.07-1.74) as a main diagnosis.

88 **Conclusions and clinical relevance:**

89 Both low and high pubertal BMI change are predictors of adult-onset asthma in men, particularly asthma
90 without concomitant allergic rhinitis. Primary prevention of adult-onset asthma requires monitoring of
91 changes in BMI during puberty.

96 **Keywords:** asthma, allergic rhinitis, body mass index, cohort study, men, obesity, pubertal BMI change,
97 Sweden

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INTRODUCTION

The increase in asthma during the second half of the past century paralleled key lifestyle changes, including a rise in obesity.^{1,2} Studies in children and adults have consistently shown obesity to be a risk factor for asthma.^{1,2} However, it is unclear whether obesity is a cause or consequence of asthma. In obese individuals, increased breathing workload exerts direct impact on mechanics of the respiratory system through altering the lung volume, airway calibre, respiratory muscle strength, and functional residual capacity.^{3,4} On the other hand, factors associated with asthma, such as reduced or absence of physical activity and systemic pharmacological treatments, may lead to weight gain and obesity.^{3,4} This uncertainty was heightened by the fact that several early studies were cross-sectional in design or had short follow-up. Nevertheless, subsequent cohort studies and meta-analyses have largely supported findings from previous studies, indicating that obesity and measures of adiposity are associated with incident asthma and its clinical outcomes.^{1,2} In studies on weight loss, based on behavioural changes and surgical interventions, obese asthma patients who lose weight may have considerable improvements.^{1,6}

Some studies using body mass index (BMI) as a composite measure of fat and lean mass demonstrate dose-response associations with asthma incidence, so that increasing BMI scores increased asthma risk.^{7,8} However, both low and high BMI have also been linked to increased risk of asthma.^{9,10} These associations may differ between men and women.⁷ Beyond assessment of BMI at a single time point, changes in BMI scores over time may equally be important.¹ There are no data evaluating association of pubertal weight change with adult-onset asthma, and whether this association differs between asthma with and without

concomitant allergic rhinitis. We have previously demonstrated that increase in BMI during puberty is a risk factor for cardiovascular mortality,¹¹ stroke,¹² heart failure,¹³ and type 2 diabetes¹⁴ in men. In the current study, we investigated whether childhood and young adult body weight (BMI, overweight and obesity) and pubertal BMI change are associated with adult-onset asthma in a large cohort of Swedish men, and evaluated any differential association with asthma with and without concomitant allergic rhinitis.

METHODS

Study population

The study population was derived from the BMI Epidemiology Study (BEST), a population-based cohort study undertaken in Gothenburg, Sweden.¹¹⁻¹⁴ We collected data on birthweight and directly measured height and weight from centrally archived School Health Care records for all men born 1945-1961. The school health care program has been ongoing for almost 100 years, and assesses the general health and wellbeing of all Swedish children (nationwide coverage $\approx 98.5\%$) throughout the school years (from age 7 years).¹⁵ Trained school nurses performed vaccinations and measured height and weight. Height was measured using a wall-mounted stadiometer and weight was measured in light clothing. Additional height and weight data were derived from the tests undertaken during military conscription, which was mandatory until 2008 for all Swedish men. Using the unique personal identification numbers (PINs) assigned to all Swedish residents, the study data were linked to national population registers held by the National Board of Health and Welfare and Statistics Sweden. Overall, the study population included 37,652 men, constituting participants with complete data to calculate both childhood BMI (8 years) and young adult BMI (20 years), who were alive and resided in Sweden at age 20 years and who had not been diagnosed with asthma or allergic rhinitis before age 20. The study subjects were followed from the age 20 years until diagnosis of asthma or allergic rhinitis, censoring due to death, emigration, or until 31st of December 2016, whichever came first. Subjects who received an asthma or allergic rhinitis diagnosis in the National Patient Register (NPR) before age 20 years were excluded. The ethics committee of the University of Gothenburg approved the study and waived the requirement for written informed consent.

Exposure assessment

Described in detail elsewhere,¹¹⁻¹⁴ childhood BMI was calculated by using all paired height and weight measurements between 6.5 and 9.5 years of age and age-adjusted to age 8 years using a linear regression model. Similarly, young adult BMI was calculated using all paired height and weight measurements between 17.5 and 22 years of age and age-adjusted to age 20 years using a linear regression model. The age-dependent change was assumed to follow the slope of the model and BMI was estimated using the slope of the fitted model.¹¹⁻¹⁴ Childhood underweight ($<13.8 \text{ kg/m}^2 - 5^{\text{th}}$ percentile), overweight ($\text{BMI} \geq 17.9$

kg/m²) and obesity (BMI $\geq$ 20 kg/m²) were defined using the Centers for Disease Control and Prevention's cut-offs at age 8 years. Young adult underweight, overweight and obesity were defined as <18.5 kg/m², BMI $\geq$ 25 kg/m² and BMI $\geq$ 30 kg/m², respectively. Pubertal BMI change was defined as the difference between young adult BMI and childhood BMI.

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176 **Outcomes**

Outcomes were asthma and allergic rhinitis, which were identified from the NPR, defined according to the International Classification of Diseases (ICD) coding. During the study period, ICD-8 was used 1969-1986; ICD-9 1987-1996; and ICD-10 since 1997. For asthma, we used J45 (ICD-10) and 493 (ICD-9 and ICD-8). For allergic rhinitis, we used J30 (ICD-10) and 477.0, 477.2, and 477.9 (ICD-9); there were no applicable ICD-8 codes for allergic rhinitis. For both outcomes, we extracted data on the first recorded diagnosis after age 20 years. We defined two asthma outcomes: (1) asthma as the main or auxiliary diagnosis, and (2) asthma as the main diagnosis. We also defined concomitant asthma and allergic rhinitis –as those having both asthma and allergic rhinitis; non-concomitant asthma and allergic rhinitis as those having asthma but not allergic rhinitis.

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187 **Confounding variables**

From the BEST cohort, we collected information on participants' birthweight and from Statistics Sweden, we collected information on participants' and parents' country of birth, participants' year of birth and educational level. These variables were adjusted in the analyses.

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192 **Statistical analysis**

For descriptive analysis, we used means and frequency tables for continuous and categorical variables, respectively. We calculated birth period incidence rates and their corresponding 95% confidence intervals (95% CI) of asthma and allergic rhinitis for the following birth periods: 1945-1949; 1950-1954; 1955-1959; and 1960-1961. Birthweight, childhood BMI, and young adult BMI values were log-transformed. We used Kaplan-Meier survival curves to describe the cumulative risk of the outcomes over time, separately comparing the first quartile versus the two median quartiles (as the reference) as well as the last quartile versus the two median quartiles.

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We used Cox proportional hazards regression to study the associations between the exposures and incident asthma and allergic rhinitis. The assumption of proportionality was confirmed for all variables. We first used the log-transformed continuous forms of the BMI exposures in relation to the outcomes. Then a quadratic term was included to evaluate non-linear associations. We observed a statistical significance for the quadratic term ($p<0.05$) with regards to childhood BMI, young adult BMI, and BMI change during

puberty, hence we categorized all BMI exposure variables into quartiles (the two median quartiles were combined and used as reference). As a post-hoc assessment of non-linear associations, we applied a restricted cubic spline for the associations between pubertal BMI change and the outcomes. We placed three knots at different percentiles of pubertal BMI change. Using the Akaike Information Criterion (AIC), we evaluated the different placement of the knots: whilst all models gave similar curves, the smallest AIC value was found for placement of knots at percentiles 5, 20, and 95 for asthma and at percentiles 5, 80, and 95 for allergic rhinitis. Cox regression was also used to study the association between the exposure variables and concomitant asthma and allergic rhinitis, using the age of onset of asthma to estimate the time to event in each case. The analyses considering childhood BMI, overweight, and obesity were adjusted for pubertal BMI change, while the analyses considering pubertal BMI change, young adult BMI, overweight, and obesity were adjusted for childhood BMI. All models were adjusted for birth year and country of birth; the adjusted models additionally included education level and birthweight. Test of proportionality assumption, graphing of the Kaplan-Meier survival curves and restricted cubic splines were undertaken in R using the 'survival' and 'rms' packages. Other analysis were carried out in SPSS version 22.

RESULTS

Characteristics of the study population

Of all participants ($N=37,652$) with data for calculating both childhood BMI (at 8 years) and young adult BMI (at 20 years), data on birthweight was available for 35,643 individuals (95%). At both 8 and 20 years, average BMI was below the cut-offs for overweight. At 8 years, about 4% and 6% were underweight and overweight, respectively. At 20 years, about 9% and 7% were underweight and overweight, respectively. Most participants were born in Sweden. The cumulative incidence of asthma was only above 1% as main diagnosis, but above 2% as a main or auxiliary diagnosis. Similarly, only about 1% of the study population was diagnosed with allergic rhinitis. Concomitant asthma and allergic rhinitis was uncommon. Participants with and without data on birthweight were similar, except that those with data on birthweight were slightly more obese and more likely to be born in Sweden than those without data on birthweight (Table 1). Total follow-up for each outcome was over 1.5 million person-years (Table 2). Within each birth cohort, the incidence rate for each outcome was below one per 1000 person-years. There was a slight increase in incidence rates by decreasing birth period, so that the incidence rates were slightly lower in older than in younger birth cohorts (Table 2).

BMI at 8 years, childhood overweight, obesity and risk of asthma and rhinitis

BMI at 8 years, childhood overweight and obesity were not significantly associated with any asthma and allergic rhinitis (Table 3). The upper quartile of childhood BMI (compared to median quartiles) was

borderline statistically significantly associated with an increased risk of asthma (as main or auxiliary diagnosis) and concomitant allergic rhinitis (Table 4).

BMI at 20 years, young adult overweight, obesity and risk of asthma and rhinitis

Young adult BMI and obesity at 20 years were not significantly associated with any asthma or allergic rhinitis, but young adult overweight was associated with increased risk of asthma as main or auxiliary diagnosis and borderline significantly associated with asthma as main diagnosis (Table 3). Young adult BMI was not associated with asthma (with or without concomitant allergic rhinitis), but both overweight and obesity were associated with significantly increased risk of asthma (as main or auxiliary diagnosis) without concomitant allergic rhinitis (Table 4).

Pubertal BMI change and risk of asthma and rhinitis

Both lower and upper quartiles of pubertal BMI change (compared to combined median quartiles) were associated with significantly increased risk of asthma (both as main diagnosis and as main or auxiliary diagnosis; the association between lower quartile of pubertal BMI change and asthma as main or auxiliary diagnosis was however at borderline statistical significance), but not with allergic rhinitis (Table 3). Both lower and upper quartiles of BMI change were associated with asthma without concomitant allergic rhinitis, but not with asthma with concomitant allergic rhinitis (Table 4). The restricted cubic spline confirmed that this association was non-linear (Figure 1). The Kaplan-Meier survival curves showed that both lower and upper quartiles were at increased risk of developing asthma when compared to the median quartiles. For allergic rhinitis, while the lower quartile appeared to be slightly at increased risk compared to the two middle quartiles, the upper quartile was at a decreased risk (Figure 2). Stratifying the results by period of birth (1945-53 and 1954-61), the results were largely similar between the two birth periods, except for some differences in the associations between upper quartile of pubertal BMI change and asthma as a main diagnosis and asthma without concomitant allergic rhinitis (data not shown).

DISCUSSION

With over 1.5 million person-years of follow-up of this large population of Swedish men, both low and high pubertal BMI change were associated with an increased risk of adult-onset asthma, particularly asthma without concomitant allergic rhinitis. High childhood BMI was associated with an increased risk of asthma with concomitant allergic rhinitis. Young adult overweight and obesity were associated with an increased risk of any asthma and asthma without concomitant allergic rhinitis. Restricted cubic spline confirmed a non-linear association between pubertal BMI change and asthma risk.

275 The BEST cohort is a well-defined cohort with large sample size that provides sufficient power to detect
276 even small putative associations between pubertal BMI change and adult-onset asthma. The study
277 population is representative of the background population of men of the same age in Gothenburg,
278 Sweden.¹¹ As the cohort constitutes only men, we cannot draw inference regarding women. Through
279 linkage of the BEST cohort data to high quality patient registers, we had an exhaustive collection of
280 inpatient data for all study participants. The registers in Sweden are continuously used to implement
281 important public health and clinical studies across different disease conditions. The patient register is a
282 valid source for defining asthma and allergy outcomes in epidemiological research.^{16,17} Whilst the NPR
283 came into full national coverage across Sweden in 1987, it achieved full coverage in Gothenburg already
284 from 1972, indicating that most asthma and allergic rhinitis cases would probably have been captured in
285 our study. Individuals who moved out of Gothenburg to other places in Sweden might have however ended
286 up residing in areas where coverage came much later than in Gothenburg, and thus asthma among these
287 people could have been missed. For individuals born as early as 1945-61, as in our study, the childhood
288 years are not well covered in any national register in Sweden. However, as some asthma and allergic
289 rhinitis cases have been recorded in the NPR before the age of 20, we did exclude these individuals from
290 the analysis so that we would have a better chance of capturing only adult-onset disease. On the other hand,
291 the fact that the study participants were born as early as 1945-61 gave us a unique long-term follow-up.
292 Since the NPR is based on inpatient admissions treated in hospital health care and not on primary care
293 managed by general practitioners, the asthma cases may reflect those with more severe than mild disease.
294 That out asthma cases may constitute more severe cases is manifested in the fact that while the cumulative
295 incidence of asthma (1.4% to 2.4%) observed in our study compare quite closely with reports from
296 previous Swedish studies,¹⁸⁻²⁰ the incidence rates in our study is lower than those observed in previous
297 studies. Whilst previous studies validating the asthma definition by the NPR have shown low sensitivity,
298 validation for allergic rhinitis has not been previously evaluated. Nevertheless, the low sensitivity of the
299 NPR-defined asthma should be similar across childhood and young adult BMI categories, thus the observed
300 risk estimates should not be substantially different if the sensitivity was high. The concomitance of asthma
301 and allergic rhinitis may not reflect allergic and non-allergic asthma phenotypes, as the typical definition
302 requires IgE-mediated hyper-responsiveness to environmental inhalant allergens. Nevertheless, allergic
303 rhinitis manifests through a similar mechanism as IgE-mediated hyper-responsiveness.²¹⁻²³ Recent advances
304 have proposed a unified management of allergic asthma and allergic rhinitis.²¹ This therefore gives some
305 merit to our definition of concomitance of asthma and allergic rhinitis. Due to data unavailability, we were
306 only able to adjust for a limited panel of potential confounders, which can introduce residual confounding.
307 We ensured temporality of the associations by including asthma and allergic rhinitis occurring for the first
308 time after age 20 years.

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310 A systematic review by Egan and colleagues reported that both childhood overweight and obesity were
311 associated with increased risk of physician-diagnosed asthma, similarly for boys and girls.²⁴ The meta-
312 analysis by Chen et al. showed a dose-response association between elevated BMI and asthma onset in
313 childhood, but with boys having greater risk than girls.⁷ High BMI at age 7 years was associated with
314 incident asthma after age 21 years in an Australian cohort, but this was evident only in women but not
315 men.²⁵ Several other previous studies have also reported an increased risk of incident asthma and asthma-
316 related symptoms during young adulthood as a consequence of elevated weight during the prenatal,
317 childhood, and adolescent periods.²⁶⁻²⁸ A recent Danish study reported that high BMI between 7 and 13
318 years was associated with increased asthma risk in young adult women, but low BMI was overall
319 borderline significantly associated with an increased risk among men.²⁹ However, by focusing on ages 7 to
320 13, that study did not cover the entire spectrum of the pubertal period. In our study, high BMI at 8 years
321 was associated with adult-onset asthma with concomitant allergic rhinitis in men, but not with any asthma
322 and allergic rhinitis. Furthermore, BMI at 20 years showed a non-linear association with adult-onset
323 asthma, and both overweight and obesity at the same age were associated with an increased risk of asthma.
324 A meta-analysis showed that elevated BMI, overweight and obesity were associated with adult-onset
325 asthma in a dose-response manner.⁸

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327 Changes in body weight over time may reflect equally an important aspect of consideration. In a cohort of
328 Norwegian middle age men and women, a change in self-reported BMI over a 5-year period was associated
329 with incident asthma in a dose-response manner.³⁰ In Canadian men, gaining weight during a 6-year follow-
330 up was associated with a decline in lung function.³¹ Whilst the role of pubertal BMI change in asthma onset
331 in adults has not been previously studied, our results show that this association is non-linear, so that both
332 least and highest pubertal BMI change equally increased the risk of adult-onset asthma. A similar non-
333 linear association between adult BMI and asthma and methacholine airway hyper-responsiveness in adult
334 men and women has also been reported previously.^{9,10}

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336 Puberty is an important developmental milestone and is accompanied by complex biological and
337 physiological changes, including growth spurt and maturation of secondary sexual characteristics and
338 fertility.³² Puberty is initiated when the anterior pituitary is stimulated to secrete follicle stimulating
339 hormone and luteinizing hormone, the main regulators of testicular function, i.e., secretion of testosterone
340 and spermatogenesis.³³ The pubertal processes and environmental exposures established during this period
341 have been consistently linked to several disease conditions later in adulthood.^{11-14,34} Our results imply that
342 primary prevention of adult-onset asthma will benefit from close monitoring of pubertal BMI changes.
343 Although not with respect to pubertal BMI change and adult-onset asthma, a previous Swedish study of
344 men conscripted into the Swedish military service found that the risk for both allergic and non-allergic

345 asthma were increased among those with low BMI and those with high BMI.³⁵ Two other studies, one in
346 children³⁶ and one in adults³⁷ found that, although adiposity was associated with increased risk of allergic
347 and non-allergic asthma, the risk was greater for non-allergic asthma.

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349 We did not observe any putative association between low BMI at 8 and 20 years and asthma, instead both
350 lowest and highest pubertal BMI change were associated with increased risk of onset of asthma. Whilst the
351 underlying mechanism for these observations is unclear, it suggests probably that changes in body mass
352 during puberty may be more important than body mass at a single time point. The mechanism underlying
353 the impact of low BMI on adult-onset asthma may differ from those of high BMI. For low BMI, foetal and
354 early life protein and calorie restriction may cause long-lasting abnormalities in the structure and function
355 of the lung.^{38,39} Reduced weight gain during early life may inhibit lung growth, reduce airway calibre, and
356 heighten susceptibility to environmental insults; these in turn may increase asthma risk later in life.^{9,40} The
357 impact of high BMI on the risk of adult-onset asthma may operate both through mechanical and molecular
358 pathways. Mechanically, the effect of adiposity on asthma may result from the effect expiratory flow
359 limitations has on smooth muscle remodelling and function, which may lead to increased hyper-
360 reactivity.^{3,4} Overweight or obese individuals have a restrictive physiology and decreased tidal volumes,
361 which result from reduction in the expansion of the chest as a result of increased weight on the chest, as
362 well as impact of abdominal weight on the diaphragms.³ Continuous breathing at low lung volumes can
363 lead to a restrictive lung pattern and has been linked to increased airway hyper-responsiveness.³ Asthmatics
364 have intrinsic impairment to stretch airway smooth muscle.³ The molecular aspect suggests that metabolic
365 mediators produced by adipose tissue may play a role here.³ In the visceral fat of asthmatics, there is an
366 increase in mediators of adipose tissue metabolic inflammation, which may have direct effect on the airway
367 to the extent that they can increase airway inflammation.^{3,4} In a previous study, we showed that a high
368 pubertal BMI change is associated with increased amount of visceral adipose tissue at young adult age.⁴¹
369 Leptin, a peptide hormone produced mainly by adipose cells, has been linked to pathogenesis of obesity-
370 related asthma through its multiple effects on the lung, including reduction in lung volume and alveolar
371 surface area and decreased proliferation of the tracheal epithelium.^{42,43} Consequently, leptin has been
372 considered as a pro-inflammatory cytokine that govern inflammatory processes modulating the activities of
373 T-helper cells in the cellular immune response.^{42,43}

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375 CONCLUSIONS

376 Both low and high pubertal BMI changes may be risk factors for adult-onset asthma in adult men. The
377 increased risk for both low and high pubertal BMI changes may have potential underlying biological
378 plausibility. Primary prevention of adult-onset asthma may benefit from monitoring of pubertal BMI

379 changes to ensure maintenance of normal weight trajectory between childhood and young adulthood, and
380 avoidance of the extremes of low and high weight gain.

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391 of Gothenburg.

392

393 **AUTHORS' CONTRIBUTION**

394 BN, CO, and JMK designed the study. CO, MB and JMK performed the data collection and BN, JM and
395 JMK performed the data analyses and BN, CO and JMK performed the data interpretation. BN and JMK
396 drafted the manuscript. CO, MB and JM critically revised the manuscript for intellectual content and all
397 authors approved the final version.

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399 **CONFLICT OF INTEREST**

400 None to declare

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403 **DATA AVAILABILITY STATEMENT**

404 Research data are not shared.

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Table 1. Participants' characteristics by availability of data on birthweight

Characteristic	All	With data on	Without data on

	<i>N</i> = 37,652	birthweight <i>n</i> = 35,643	birthweight <i>n</i> = 2,009
Exposure variables			
Childhood BMI (8 years; kg/m ²)* , mean (SD)	15.7 (1.4)	15.7(1.4)	15.7(1.4)
Young adult BMI (20 years; kg/m ²)**, mean (SD)	21.4 (2.5)	21.4(2.5)	21.2(2.4)
ΔpBMI(20- 8 years; kg/m ²) , mean (SD)	5.6 (2.0)	5.7(2.0)	5.4(1.9)
Birthweight (kg), mean (SD)	3.6 (0.6)	3.6(0.6)	Not applicable
Childhood overweight (8 years), <i>n</i> (%)	2,357 (6.3)	2,233(6.3)	124(6.2)
Childhood obesity (8 years), <i>n</i> (%)	504 (1.3)	480(1.3)	24(1.2)
Young adult overweight (20 years), <i>n</i> (%)	2,788 (7.4)	2,654(7.4)	134(6.7)
Young adult obesity (20 years), <i>n</i> (%)	327 (0.9)	318(0.9)	9(0.4)
Country of birth, <i>n</i> (%)			
Sweden	31,391 (83.4)	29,862(83.8)	1,529(76.1)
Other	6,261 (16.6)	5,781(16.2)	480(23.9)
Education level <i>n</i> (%)			
Elementary school	6,641 (17.6)	6,267(17.6)	374(18.6)
Secondary education	16,208 (43.0)	15,378(43.1)	830(41.3)
Post-secondary education	13,704 (36.4)	12,977(36.4)	727(36.2)
No information	1,099 (2.9)	1,021 (2.9)	78(3.9)
Outcome variables (cumulative incidence)			
Asthma (main or auxiliary diagnosis)	922 (2.4)	875(2.5)	47(2.3)
Asthma (main diagnosis)	515 (1.4)	483(1.4)	32(1.6)
Allergic rhinitis	572 (1.5)	537(1.5)	35(1.7)
Asthma (main or auxiliary diagnosis) <i>AND</i> allergic rhinitis	158 (0.4)	150(0.4)	8(0.4)
Asthma (main diagnosis) <i>AND</i> allergic rhinitis	124 (0.3)	118(0.3)	6(0.3)
Asthma (main or auxiliary diagnosis) <i>BUT NOT</i> allergic rhinitis	764 (2.0)	725(2.0)	39(1.9)
Asthma (main diagnosis) <i>BUT NOT</i> allergic rhinitis	391 (1.0)	365(1.0)	26(1.3)

548 BMI = Body Mass Index

549 ΔpBMI = BMI change during puberty

550 SD= standard deviation.

551 *Childhood overweight and obesity at 8 years defined as BMI ≥ 17.9 kg/m² and 20.0 kg/m² respectively
552 **Young adult overweight and obesity at 20 years defined as BMI ≥ 25 kg/m² or 30 kg/m², respectively
553 Significance test using chi-square (2-sided): p<0.05 for young adult obesity, p<0.001 for country of birth.
554 Using Student's t (independent samples) p<0.001 for young adult BMI and BMI change during puberty. All
555 other comparisons not significant.

556

557

Table 2. Person-years of follow-up and incidence rates for asthma and allergic rhinitis by birth period

Birth period	Frequency n (%) ¹	Asthma (main or auxiliary diagnosis)			Asthma (main diagnosis)			Allergic rhinitis		
		<i>n</i>	Person-years of follow-up	Incidence rate ² (95% CI)	<i>n</i>	Person-years of follow-up	Incidence rate ² (95% CI)	<i>n</i>	Person-years of follow-up	Incidence rate ² (95% CI)
1945-1949	9,895 (26.3)	269	443,334	0.61 (0.54-0.68)	131	444,358	0.29 (0.25-0.35)	122	445,140	0.27 (0.23-0.33)
1950-1954	12,120 (32.2)	312	497,304	0.63 (0.56-0.70)	164	498,513	0.33 (0.28-0.38)	176	498,938	0.35 (0.30-0.41)
1955-1959	12,898 (34.3)	279	474,623	0.59 (0.52-0.66)	174	475,550	0.37 (0.31-0.42)	225	475,338	0.47 (0.41-0.54)
1960-1961	2,739 (7.3)	62	91,163	0.68 (0.53-0.87)	46	91,327	0.50 (0.38-0.67)	49	91,307	0.53 (0.41-0.71)
Total	37,652 (100)	922	1,506,424	0.61 (0.57-0.65)	515	1,509,748	0.34 (0.31-0.37)	572	1,510,724	0.38 (0.35-0.41)

¹n=number of those born within each birth period; %=n/N*100; N=37,652

²Incidence rate per 1000 person-years; calculated as the number of cases per person-years follow-up in strata

Table 3. Estimates of association between BMI in childhood, young adulthood, and BMI change during puberty and risk of developing asthma and allergic rhinitis: hazard ratio (HR) and 95% confidence interval (95% CI)

	Asthma (main or auxiliary diagnosis) HR (95% CI) <i>n</i> = 922		Asthma (main diagnosis) HR (95% CI) <i>n</i> = 515		Allergic rhinitis HR (95% CI) <i>n</i> = 572	
	Base model (<i>n</i> =922)	Adjusted (<i>n</i> =916)	Base (<i>n</i> =515)	Adjusted (<i>n</i> =511)	Base (<i>n</i> =572)	Adjusted (<i>n</i> =572)
BMI at 8 years ¹ (mean [range], kg/m ²)						
1 st quartile (15.8 [10.4-14.8])	1.11(0.95-1.30)	1.12(0.95-1.31)	1.15(0.93-1.41)	1.15(0.93-1.41)	0.95(0.78-1.16)	0.95(0.77-1.16)
2 nd & 3 rd quartile (15.6 [14.8-16.4])	Reference	Reference	Reference	Reference	Reference	Reference
4 th quartile (15.9 [16.4-33.3])	1.06(0.91-1.25)	1.07(0.91-1.26)	1.02(0.83-1.27)	1.03(0.83-1.27)	0.97(0.80-1.19)	0.96(0.78-1.17)
Childhood overweight ¹	1.16(0.90-1.49)	1.17(0.91-1.51)	1.06(0.75-1.51)	1.08(0.76-1.53)	1.12(0.82-1.55)	1.10(0.80-1.51)
Childhood obesity ¹	1.17(0.69-1.98)	1.20(0.71-2.03)	1.02(0.48-2.15)	1.04(0.50-2.20)	0.77(0.35-1.72)	0.74(0.33-1.65)
BMI at 20 years ² (mean [range], kg/m ²)						
1 st quartile (19.2 [13.5-19.7])	1.00(0.85-1.17)	0.98(0.82-1.16)	1.09(0.88-1.34)	1.05(0.83-1.32)	0.89(0.73-1.09)	0.92(0.74-1.14)
2 nd & 3 rd quartile (21.0 [19.7-22.6])	Reference	Reference	Reference	Reference	Reference	Reference
4 th quartile (24.2 [22.6-44.1])	1.00(0.85-1.17)	0.98(0.82-1.17)	1.01(0.82-1.25)	1.01(0.80-1.27)	0.79(0.64-0.97)	0.78(0.62-0.97)
Young adult overweight ²	1.41(1.14-1.75)	1.44(1.14-1.83)	1.32(0.98- 1.77)	1.40(1.01-1.93)	0.96(0.70-1.31)	0.98(0.70-1.38)
Young adult obesity ²	1.77(1.02-3.06)	1.71(0.97-3.02)	1.63(0.77-3.43)	1.68(0.78-3.65)	1.01(0.42-2.45)	1.08(0.44-2.65)
BMI change (20-8 years) ² (mean [range], kg/m ²)						

1 st quartile (3.4 [-5.6 to 4.3])	1.18(1.01-1.38)	1.17(1.00-1.37)	1.36(1.11-1.68)	1.36(1.10-1.68)	1.14(0.93-1.38)	1.14(0.94-1.38)
2 nd & 3 rd quartile (5.5 [4.3-6.7])	Reference	Reference	Reference	Reference	Reference	Reference
4 th quartile (8.3 [6.7-23.5])	1.22(1.05-1.43)	1.22 (1.04-1.43)	1.32(1.07-1.63)	1.32(1.07-1.63)	0.84(0.68-1.03)	0.86(0.70-1.07)

¹ All models (including base model) adjusted for birth year and country of birth. Adjusted model is further adjusted for BMI change during puberty and education level

² All models (including base model) adjusted for birth year and country of birth. Adjusted model is further adjusted for childhood BMI and education level

****Boded values are statistically significant**

Table 4. Estimates of association between BMI in childhood, young adulthood, and BMI change during puberty and risk of concomitant and non-concomitant asthma and allergic rhinitis: hazard ratio (HR) and 95% confidence interval (95% CI)

	Asthma (main or auxiliary diagnosis) <i>AND</i> allergic rhinitis Adjusted model HR (95% CI) <i>n</i> = 158	Asthma (main or auxiliary diagnosis) <i>BUT NOT</i> allergic rhinitis Adjusted model HR (95% CI) <i>n</i> = 758	Asthma (main diagnosis) <i>AND</i> allergic rhinitis Adjusted model HR (95% CI) <i>n</i> = 124	Asthma (main diagnosis) <i>BUT NOT</i> allergic rhinitis Adjusted model HR (95% CI) <i>n</i> = 387
BMI at 8 years ¹				
1 st quartile	1.37(0.94-2.01)	1.07(0.90-1.27)	1.34(0.88-2.05)	1.09(0.86-1.39)
2 nd & 3 rd quartile	Reference	Reference	Reference	Reference
4 th quartile	1.45(1.00-2.11)	1.00(0.84-1.19)	1.30(0.85-2.00)	0.94(0.73-1.21)
Childhood overweight ¹	1.43(0.83-2.48)	1.11(0.84-1.48)	1.14(0.58-2.26)	1.05(0.70-1.57)
Childhood obesity ¹	0.91(0.23-3.69)	1.26(0.71-2.23)	⁴	1.40(0.66-2.97)
BMI at 20 years ²				
1 st quartile	1.08(0.72-1.64)	0.96(0.79-1.16)	1.15(0.734-1.81)	1.02(0.78-1.33)
2 nd & 3 rd quartile	Reference	Reference	Reference	Reference
4 th quartile	0.78(0.51-1.20)	1.03(0.85-1.24)	0.85(0.52-1.38)	1.06(0.82-1.39)
Young adult overweight ²	1.40(0.79-2.47)	1.45(1.12-1.89)	1.35(0.69-2.64)	1.41(0.98-2.04)
Young adult obesity ²	0.69(0.09-5.14)	1.95(1.08-3.54)	⁴	2.20(1.00-4.82)

BMI change (20-8 years) ²				
1 st quartile	1.24(0.85-1.80)	1.16(0.97-1.38)	1.46(0.96-2.21)	1.33(1.04-1.69)
2 nd & 3 rd quartile	Reference	Reference	Reference	Reference
4 th quartile	0.98(0.66-1.46)	1.28(1.07-1.52)	1.18(0.76-1.84)	1.36(1.07-1.74)

¹Adjusted model is adjusted for birth year, BMI change during puberty, country of birth, and education level

²Adjusted model is adjusted for birth year, childhood BMI, country of birth, and education level

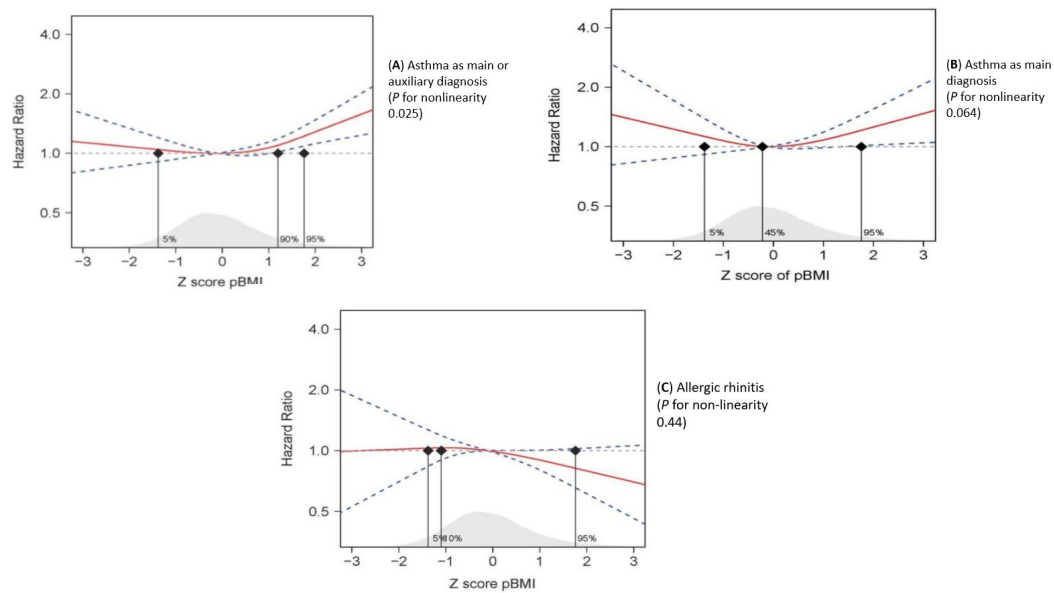
⁴Inestimable due to no cases among obese individuals

****Bolded values are statistically significant**

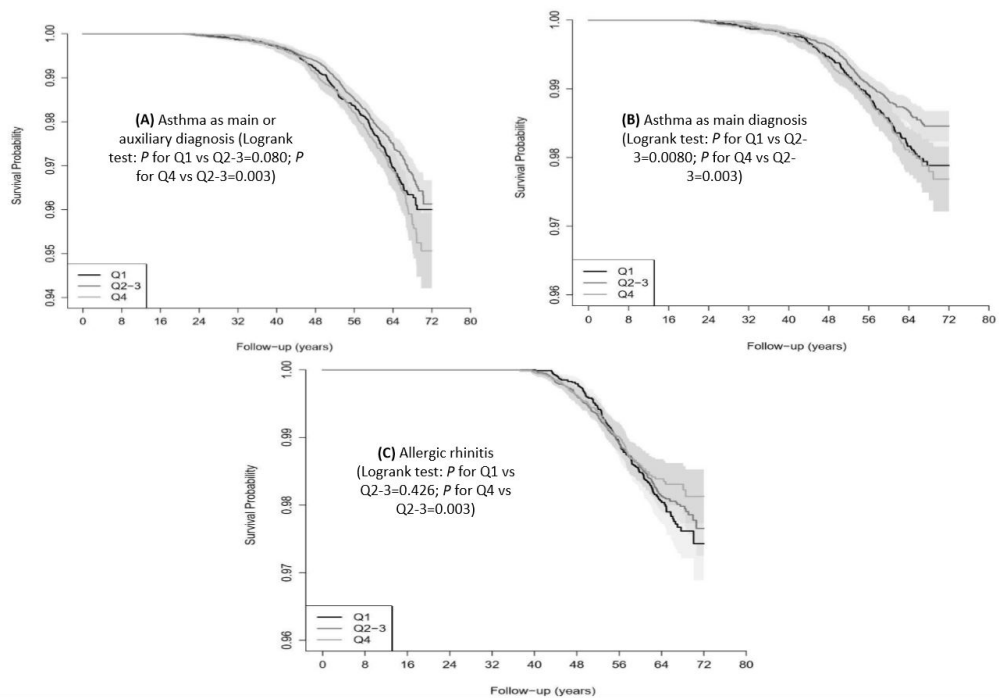
FIGURE LEGENDS:

Figure 1. Smoothed restricted cubic spline plots evaluating non-linear association between BMI change during puberty (kg/m^2) and (a) Asthma as main or auxiliary diagnosis, (b) Asthma as main diagnosis, (c) Allergic rhinitis

Figure 2. Kaplan-Meier curves comparing asthma- and allergic rhinitis-free survival times between subjects in lower and upper quartiles of BMI change during puberty vs subjects in median quartiles



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