Impact of lifetime body mass index trajectories on the incidence and persistence of adult asthma

Gulshan Bano Ali[1], Adrian J. Lowe[1,2], Jennifer L. Perret[1,3], E. Haydn Walters[1,4], Caroline J. Lodge[1], David Johns[4], Alan James[5,6], Bircan Erbas[7], Garun S. Hamilton[8,9], Gayan Bowatte[1], Richard Wood-Baker[4], Michael J. Abramson[10], Dinh S. Bui[1,11] and Shyamali C. Dharmage[1,2,11]

[1]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia. [2]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia. [3]Institute for Breathing and Sleep (IBAS), Melbourne, Australia. [4]School of Medicine, University of Tasmania, Hobart, Australia. [5]Dept of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Australia. [6]Medical School, University of Western Australia, Perth, Australia. [7]School of Psychology and Public Health, La Trobe University, Melbourne, Australia. [8]Dept of Lung and Sleep, Sleep Medicine Research at Monash Medical Centre, Clayton, Australia. [9]School of Clinical Sciences, Monash University, Clayton, Australia. [10]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia. [11]D.S. Bui and S.C. Dharmage are equal senior authors.

Corresponding author: Shyamali C. Dharmage (s.dharmage@unimelb.edu.au)

Shareable abstract (@ERSpublications)
Individuals belonging to "child average-increasing" and "high" BMI trajectories from childhood to middle age of life may be at risk of adult incident asthma and bronchial hyperresponsiveness; the risk was up to 4-fold for the high group https://bit.ly/3ovbX2P

Cite this article as: Ali GB, Lowe AJ, Perret JL, *et al*. Impact of lifetime body mass index trajectories on the incidence and persistence of adult asthma. *Eur Respir J* 2022; 60: 2102286 [DOI: 10.1183/13993003.02286-2021].

Received: 19 Aug 2021
Accepted: 30 Jan 2022

Abstract

Background High body mass index (BMI) trajectories from childhood to adulthood are associated with the development of some chronic diseases, but whether such trajectories influence adult asthma has not been investigated to date. Therefore, we investigated associations between BMI trajectories from childhood to middle age (5–43 years) and incidence, persistence and relapse of asthma from ages 43 to 53 years.

Methods In the Tasmanian Longitudinal Health Study (n=4194), weight and height were recorded at eight time-points between 5 and 43 years of age. BMI trajectories were developed using group-based trajectory modelling. Associations between BMI trajectories and asthma incidence, persistence and relapse from age 43 to 53 years, bronchial hyperresponsiveness (BHR) at age 50 years, and bronchodilator responsiveness at age 53 years were modelled using multiple logistic and linear regression.

Results Five distinct BMI trajectories were identified: average, low, child high-decreasing, child average-increasing and high. Compared with the average trajectory, child average-increasing and high trajectories were associated with increased risk of incident asthma (OR 2.6, 95% CI 1.1–6.6 and OR 4.4, 95% CI 1.7–11.4, respectively) and BHR in middle age (OR 2.9, 95% CI 1.1–7.5 and OR 3.5, 95% CI 1.1–11.4, respectively). No associations were observed for asthma persistence or relapse.

Conclusions Participants with child average-increasing and high BMI trajectories from childhood to middle age were at higher risk of incident adult asthma. Thus, encouraging individuals to maintain a normal BMI over the life course may help reduce the burden of adult asthma.

Introduction

Asthma is a major global health problem [1], affecting more than 339 million people [2]. It is a leading cause of disability across all ages, accounting for 23.7 million global disability-adjusted life years [3]. Its effects peak during older age, which may be due to age-related increases in asthma incidence and persistence. Therefore, potentially modifiable risk factors for adult asthma are current research interests, intending to identify interventions to reduce its burden [4].

Adult asthma is a complex health condition associated with various risk factors, with obesity being considered a significant risk factor [5]. However, only few studies have assessed this association

longitudinally [6]. Some studies have reported a higher risk of late-onset adult asthma among obese and overweight individuals [7]. In contrast, others have proposed that asthma symptoms over a lifetime increase body weight, which results in obesity and overweight during adult life [6]. Thus, the longitudinal associations between obesity and adult asthma incidence and persistence in adults remain uncertain. One possible reason for the inconsistent associations could be that most studies measure body mass index (BMI) at one time-point only, limiting inferences about causality [8].

BMI at a single time-point does not capture dynamic changes in weight gain, *i.e.* age of onset of obesity and its progress over time, which may impact various health outcomes [9], including asthma. Similarly, growth itself may change in a nonlinear way over time, resulting in diverse patterns [10]. BMI measured at multiple time-points and expressed as a variable that changes over time (BMI trajectories) may allow a better understanding of pathophysiological variations associated with obesity [9], and its impact on incidence and persistence of asthma during adulthood. Studies investigating associations between BMI trajectories and other chronic diseases have highlighted that a high BMI pattern from childhood to adulthood has a particularly strong impact on poor health outcomes in later life [11].

Given it is currently unknown if BMI trajectories play a role in predicting the risk of asthma in later life, we investigated the associations between different patterns of BMI trajectories from childhood (5 years) to middle age (43 years) and the incidence, persistence and relapse of asthma from age 43 to 53 years.

Methods

Study design and population

The current study used data from the Tasmanian Longitudinal Health Study (TAHS), a population-based longitudinal study of respiratory health outcomes. A detailed description of the methodology has been published elsewhere [12] (for details on measurements, see supplementary material and supplementary figure S1).

BMI trajectories

The current analysis included participants whose weights and heights were recorded from childhood to middle age. Weights and heights were measured at baseline and all follow-ups. Previously, their weights and heights were measured and recorded regularly in school medical records by school nurses, and these data were extracted. Thus, we had data available for analyses at ages 7, 13, 20, 31 and 43 years collected in the study follow-ups, and at ages 5–6, 10–11 and 14–15 years from the school medical records, giving a total of eight time-points. BMI (weight/height^2) was converted into age and sex-specific BMI z-scores, based on the observed values within this cohort, as there were no standard equations for an Australian adult population.

Definitions of asthma

Asthma was defined using data from the baseline study at age 7 years as reported by parents, and at 2002–2006 follow-up (mean age 43 years) and at 2012–2016 follow-up (mean age 53 years) as reported by participants (see supplementary material for questions used and supplementary figure S2 for asthma status change from age 43 to 53 years). Participant's self-reported asthma status at age 43 years was corrected using parent-reported asthma at age 7 years to avoid misclassification due to recall bias [13].

Using this information, we defined asthma status at both 43 and 53 years of age in three levels: 1) "current asthma" as having had any symptoms of asthma or specific asthma medication use in the past year, 2) "remitted asthma" as having had episodes of asthma in the past but no current asthma and 3) "never asthma" as having never had any episodes of asthma.

We investigated the association between trajectories and change in asthma status from 43 to 53 years of age. The outcomes were defined as: 1) current incident asthma: never asthma by age 43 years and current asthma by age 53 years (control group: never asthma at age 43 and 53 years), 2) persistent asthma: current asthma at age 43 years and current asthma at age 53 years (control group: current asthma at age 43 years, but remitted at age 53 years) and 3) relapsed asthma: remitted asthma at age 43 years (prior history of asthma, but no current asthma at age 43 years) and current asthma at age 53 years (control group: remitted asthma at age 43 years and remitted at age 53 years).

Bronchial responsiveness

"Direct" bronchial responsiveness was measured at age 50 years using increasing doses of inhaled methacholine [14]. Bronchial hyperresponsiveness (BHR) was defined as a cumulative dose of

methacholine provoking a 20% fall in forced expiratory volume in 1 s (FEV_1) from post-saline FEV_1 (PD_{20} FEV_1) ⩽2 mg.

Bronchodilator responsiveness

Using pre- and post-bronchodilator lung function measures at age 53 years, bronchodilator responsiveness (BDR) was defined as a continuous variable, *i.e.* percentage change in lung function (FEV_1 and/or forced vital capacity (FVC)) from pre-bronchodilator ((post-bronchodilator–pre-bronchodilator)/pre-bronchodilator×100). We were unable to analyse BDR as a categorical variable due to small numbers fulfilling the condition of >12% change from pre-BD and >200 mL absolute increase (in FEV_1: n=88 and in FVC: n=27) at 53 years [15]. Pre- and post-bronchodilator spirometry was done according to American Thoracic Society/European Respiratory Society guidelines [16].

Potential confounders and effect modifiers

We constructed a diagram depicting the possible causal relationships between BMI and other factors from childhood to adulthood (supplementary figure S3). Variables were selected based on the current literature [17]. Information on a range of potential confounders and effect modifiers relevant to our associations of interest was prospectively collected *via* questionnaires or direct measurement (see supplementary material for definitions).

Statistical analysis

We analysed internally derived BMI z-scores at eight time-points (mean ages 5, 7, 10, 13, 15, 20, 30 and 43 years). We further defined 5-year BMI by grouping 5–6 years, 10-year BMI by grouping 10–11 years and 15-year BMI by grouping 14–15 years data to maximise the number of observations extracted from school medical records. The sample for the analysis was restricted to those with BMI available for at least three time-points, of which two were from childhood and one from adulthood. We developed BMI trajectories using group-based trajectory modelling (GBTM), a finite mixture modelling approach using maximum likelihood to identify groups of individuals following similar growth patterns over time [18]. We conducted logistic regression to investigate the association of BMI trajectories with change in asthma outcomes: 1) incident asthma *versus* no asthma, 2) persistent asthma *versus* remitted asthma and 3) relapsed asthma *versus* completely remitted asthma. All associations were adjusted for the minimum set of confounders. All analyses were conducted using Stata version 16 (StataCorp, College Station, TX, USA) (see supplementary material for details on statistical analysis, minimum set of confounders and BMI trajectory model building).

Results

Of 8583 TAHS participants, 4194 (48.9%) had BMI data available to be included in this analysis.

BMI trajectories

We identified five distinct BMI trajectories: average, low, child high-decreasing, child average-increasing and high. These trajectories were labelled based on their shapes over time (figure 1). The average trajectory was considered the reference trajectory, comprising 50.3% (2109 out of 4194) participants who had a mean BMI z-score around the study population average (z-score 0) at all ages. The low trajectory included 26.7% (1120 out of 4194) participants with a mean BMI z-score between −1 and −0.5 at all time-points. The child high-decreasing trajectory included 14.1% (592 out of 4194) participants whose mean BMI z-score started at 1 and ended at 0. The child average-increasing trajectory comprised 5.8% (245 out of 4194) participants who began with a mean BMI z-score of 0 and ended at 2. Finally, the high trajectory included 3.1% (128 out of 4194) participants whose mean BMI z-score was between 2 and 3 at all time-points. Confidence intervals and mean BMI at each time-point for all of the trajectories are presented in supplementary figures S4 and S5.

Early-life characteristics related to BMI trajectories

The proportion of maternal smoking and maternal asthma was higher in the child average-increasing and high trajectories (table 1). In addition, the prevalence of small for gestational age was higher in the low trajectory. Participants in the average-increasing and high BMI trajectories may have had a lower social class. They had a lower proportion of parents who were managers/professional workers and a higher proportion whose parents were labourers. Distributions of sex, childhood asthma, childhood food allergy, bronchitis and the number of siblings were similar across all five trajectories.

Respiratory characteristics associated with BMI trajectories at age 43 and 53 years

The proportions of participants with current hay fever, current cough without cold, current bronchitis, current wheeze, current wheeze without a cold, current nocturnal shortness of breath, emphysema and

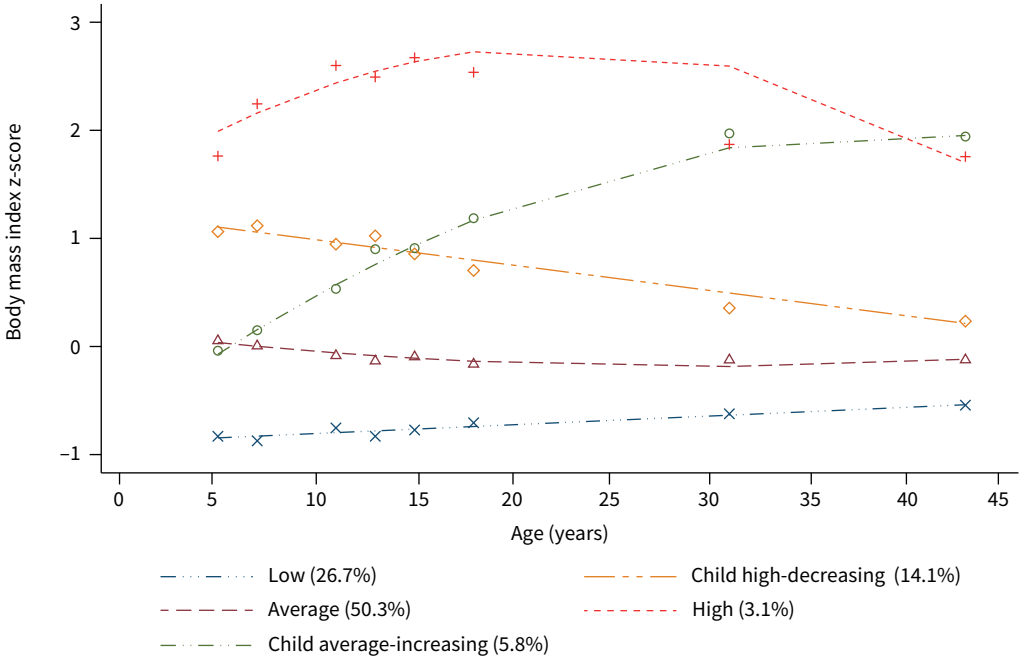

FIGURE 1 Body mass index (z-score) trajectory classes across ages from 5 to 43 years of age.

chronic obstructive pulmonary disease at age 43 years were higher in the child average-increasing and high trajectories compared with the other BMI trajectories (table 2). However, these differences were only statistically significant for cough without a cold, bronchitis and wheeze.

Similarly, at age 53 years, proportions of individuals with these respiratory characteristics were higher in the child average-increasing and high trajectories. In addition, we found high proportions of individuals

TABLE 1 Early-life characteristics of the body mass index trajectory groups

	Average (n=2109)	Low (n=1120)	Child high-decreasing (n=592)	Child average-increasing (n=245)	High (n=128)
Female*	47.2 (995)	50.0 (560)	47.3 (280)	57.1 (140)	50.0 (64)
Pre-term#,**	11.3 (119)	15.9 (94)	15.2 (42)	5.7 (7)	9.09 (6)
Low birthweight#,***	5.5 (66)	8.6 (58)	2.2 (7)	9.7 (14)	2.7 (2)
Small for gestational age#,***	20.5 (189)	36.2 (147)	12.2 (29)	24.5 (27)	24.1 (14)
Childhood food allergy	7.2 (148)	7.5 (83)	7.2 (42)	9.1 (22)	7.9 (10)
Childhood asthma	17.5 (364)	15.5 (171)	18.8 (111)	19.9 (46)	14.8 (19)
Childhood bronchitis	50.9 (1060)	47.4 (524)	46.0 (271)	53.1 (129)	52.3 (67)
Siblings, n	2.5±1.75	2.4±1.67	2.4±1.62	2.4±1.64	2.4±1.87
Parental social class					
Managers/professional	22.1 (447)	21.5 (230)	25.9 (147)	16.4 (38)	16.8 (20)
Tradespersons/advanced clerical	6.8 (138)	6.6 (71)	5.8 (33)	6.0 (14)	6.7 (8)
Intermediate clerical/ production	30.5 (617)	30.5 (327)	26.8 (152)	30.2 (70)	26.1 (31)
Elementary clerical	28.6 (579)	27.7 (297)	27.2 (154)	29.7 (69)	29.4 (35)
Labourers/related workers	11.8 (239)	13.4 (144)	14.1 (80)	17.6 (41)	21.0 (25)
Mother's smoking**	33.9 (680)	31.1 (332)	34.0 (193)	35.7 (83)	48.3 (60)
Father's smoking	56.4 (1109)	59.5 (622)	59.8 (331)	62.2 (140)	62.8 (76)
Mother's asthma	10.9 (219)	9.9 (106)	11.1 (63)	15.9 (37)	12.9 (16)
Father's asthma	11.2 (222)	9.4 (99)	10.8 (60)	10.8 (24)	9.8 (12)

Data are presented as % (n) or mean±SD. #: gestational age was known for 2100 participants, birthweight for 2391 participants and small for gestational age for 1855 participants (406 were small for gestational age) out of the total sample (n=4194). For continuous variables, we used ANOVA; for categorical variables, we used the Chi-squared test. *: p<0.05; **: p<0.01; ***: p<0.001.

TABLE 2 Respiratory characteristics of the participants in each body mass index trajectory group at age 43 and 53 years

	Average (n=2109)	Low (n=1120)	Child high-decreasing (n=592)	Child average-increasing (n=245)	High (n=128)
Age 43 years					
Hay fever	49.6 (1038)	51.0 (569)	47.4 (297)	54.1 (132)	53.9 (69)
Cough without a cold***	16.7 (350)	15.1 (168)	16.5 (97)	25.7 (63)	27.3 (35)
Bronchitis**	12.5 (260)	10.9 (122)	13.4 (79)	17.9 (44)	19.5 (25)
Emphysema	0.9 (18)	0.5 (5)	0.5 (3)	0.8 (2)	2.4 (3)
COPD	0.8 (14)	0.8 (9)	0.7 (4)	0.8 (2)	1.6 (2)
Wheeze***	23.3 (490)	20.4 (228)	23.9 (142)	30.2 (74)	36.7 (47)
Wheeze without a cold	73.5 (358)	70.4 (159)	68.3 (97)	72.9 (54)	78.7 (37)
Shortness of breath	9.0 (189)	7.7 (86)	8.4 (49)	10.7 (26)	11.7 (15)
Age 53 years					
Hay fever	74.4 (518)	69.9 (268)	70.8 (131)	78.1 (57)	84.6 (33)
Rhinosinusitis	5.4 (67)	7.2 (49)	5.1 (18)	6.2 (8)	8.8 (6)
Wheeze**	20.1 (249)	16.9 (114)	23.2 (82)	28.7 (37)	27.5 (19)
Wheeze without cold	67.8 (173)	72.4 (84)	69.9 (58)	70.3 (26)	80.0 (16)
Shortness of breath*	4.6 (57)	4.5 (31)	4.4 (16)	11.5 (15)	7.4 (5)
Bronchitis	53.3 (662)	55.3 (375)	58.4 (208)	63.1 (82)	63.8 (44)
Chest illness	24.5 (303)	23.7 (160)	23.6 (84)	29.5 (38)	36.2 (25)
Pneumonia	4.75 (50)	3.58 (21)	5.63 (17)	5.7 (6)	9.26 (5)
Incident asthma at age 53 years[#,**]	5.6 (41)	5.9 (25)	4.8 (10)	13.3 (8)	17.9 (7)
Persistent asthma at age 53 years[#]	54.8 (142)	47.1 (72)	50.6 (40)	58.3 (21)	52.6 (10)
Relapse of asthma at age 53 years[#]	26.9 (34)	18.6 (13)	25 (10)	13.3 (2)	50 (3)
BDR: %ΔFEV_1[¶]	4.05±6.9	3.84±5.8	3.61±4.7	3.29±4.6	3.57±5.2
BDR: %ΔFVC[¶]	0.70±4.0	0.64±4.5	0.22±3.5	0.53±3.9	0.99±4.4
BHR at age 50 years[#,**]	19.7 (57)	24.2 (36)	26.5 (22)	44.4 (12)	50 (7)

Data are presented as % (n) or mean±SD. COPD: chronic obstructive pulmonary disease; BDR: bronchodilator responsiveness; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BHR: bronchial hyperresponsiveness. [#]: percentages calculated from different subgroups of asthma participants at age 43 years; [¶]: BDR was measured as %Δ=(post-bronchodilator–pre-bronchodilator)/pre-bronchodilator×100. For continuous variables, we used ANOVA; for categorical variables, we used the Chi-squared test. *: p<0.05; **: p<0.01; ***: p<0.001.

with current chest illness, current pneumonia, incident asthma and BHR at age 50 years in these same trajectories. However, the proportions were significantly different only for wheeze, incident asthma and BHR (table 2).

BMI trajectories and incident asthma

Of the 1461 participants without asthma by age 43 years, 6.2% had developed incident asthma by age 53 years. Those belonging to the child average-increasing (OR 2.64, 95% CI 1.05–6.63) and high (OR 4.41, 95% CI 1.71–11.37) trajectories were at significantly higher risk of developing incident asthma at age 53 years compared with those in the average trajectory, after adjusting for the minimum set of confounders (figure 2a and supplementary table S1). Additional adjustment for small for gestational age did not change the associations in a subset with data available for small for gestational age (supplementary table S2).

BMI trajectories and persistent asthma

Of all participants with asthma at age 43 years (n=546), 285 (52.2%) had persistent asthma to age 53 years. None of the trajectories were significantly associated with an increased risk of persistent asthma (figure 2b and supplementary table S3). Adjustment for the minimum set of confounders or additional adjustment for small for gestational age did not change the association in a subset analysis (supplementary table S4).

BMI trajectories and relapsed asthma

Of the 257 participants with past asthma at age 43 years, 24.1% had relapsed by age 53 years. No BMI trajectory was associated with asthma relapse and the associations were imprecisely measured with wide confidence intervals, particularly for the high trajectory group (figure 2c and supplementary table S5).

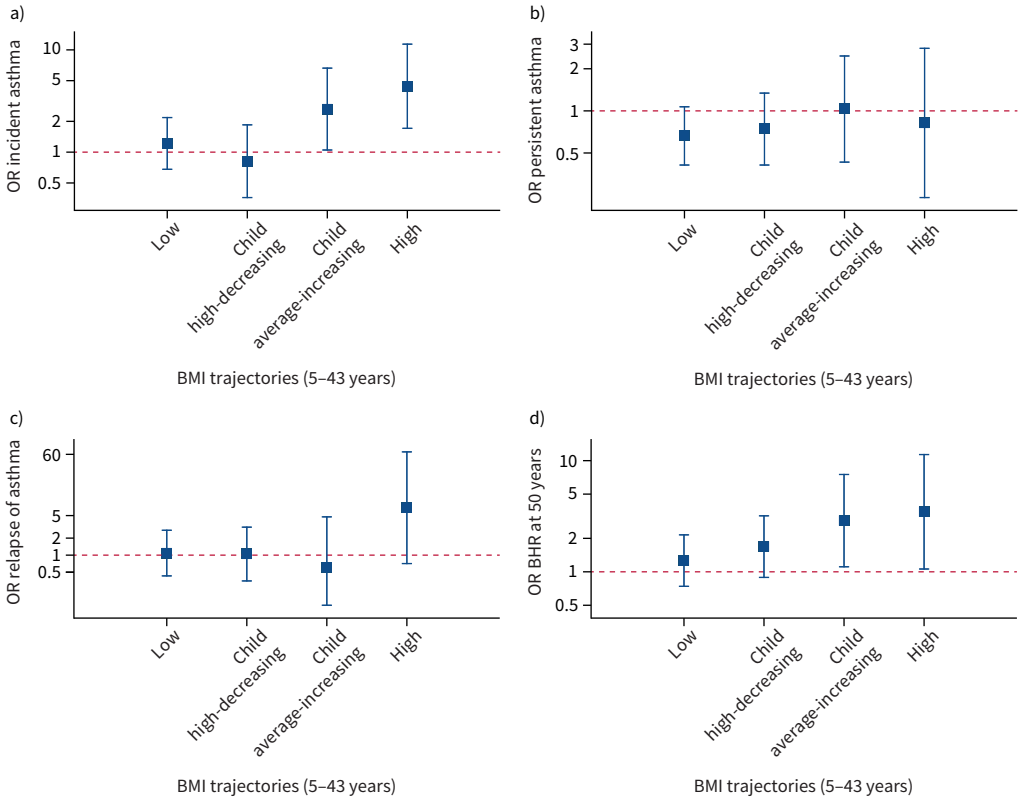

FIGURE 2 Association (OR (95% CI)) between body mass index (BMI) trajectories and a) incident, b) persistent and c) relapse asthma from 43 to 53 years of age, and d) bronchial hyperresponsiveness (BHR) at age 50 years. Adjusted for sex, type of feeding in the first 3 months, number of siblings, chest illness, tonsillectomy, pneumonia, childhood food allergy, bronchitis, social class during childhood, mother's employment, mother's age, mother's asthma, mother's smoking, father's asthma, father's smoking, adulthood education, adulthood food allergy, smoking and current employment.

Additional adjustment for small for gestational age did not change this (results not shown). Sex, current smoking or current BMI did not modify any of the associations observed (supplementary table S6).

BMI trajectories, BHR and BDR

Both child average-increasing and high trajectories showed significant associations with BHR (OR 2.89, 95% CI 1.11–7.51 and OR 3.47, 95% CI 1.06–11.35, respectively) compared with the average trajectory (figure 2d and supplementary table S7). However, we did not find any associations between BMI trajectories and BDR (supplementary table S8).

Discussion

This is the world's first study investigating the association between BMI trajectories from childhood to middle age and subsequent development, persistence and relapse of asthma in middle age. Using anthropometric data collected over the first five decades of life and GBTM, we identified five distinct BMI trajectories, with 50% of the participants being in the average trajectory. Compared with this average trajectory, child average-increasing and high trajectories were associated with an increased risk of incident asthma from age 43 to 53 years and increased BHR at age 50 years. While BMI trajectories were not associated with either persistent or relapsed asthma from age 43 to 53 years or BDR at age 53 years, these associations were imprecisely measured due to small sample sizes. These findings are novel, and they provide an understanding of trends in weight gain relative to height and their role in adult asthma.

Although no previous studies investigated BMI trajectories from childhood to middle age and adult asthma, our results are consistent with previous studies investigating the association between BMI trajectories from childhood to adulthood and other chronic diseases [11, 19, 20]. A population-based longitudinal study (n=7289) that identified three BMI trajectories from age 20 to 50 years reported a higher

risk of incident diabetes in older individuals in medium-increasing and high-increasing BMI trajectories compared with the low-increasing BMI trajectory [20]. Another population-based study identified six distinct BMI trajectories from age 9 to 45 years: stable normal, resolving, progressively overweight, progressively obese, rapidly overweight/obese and persistent increasing overweight/obese. All the higher BMI trajectories were associated with cardiometabolic risk factors compared with the stable normal group [11]. Together, these studies provide evidence that lifetime high BMI trajectories carry significant long-term health risks.

A small number of studies have investigated this research question in children and adolescents [10, 21–23]. Previously, we identified five BMI trajectories in the first 2 years of life, and found that "early-low and catch-up" and "persistently high" trajectories were associated with asthma at age 18 years [21]. Ziyab *et al*. [10] identified four BMI trajectories from 1 to 18 years of age with a persistent early obesity group associated with increased risk of asthma at age 18 years. Chen *et al*. [22] reported four BMI trajectories in children aged 6–11 years and found that the persistently overweight trajectory was associated with an increased risk of incident asthma in adolescents. Overall, our findings are consistent with these studies, that high BMI trajectories may carry a higher risk of subsequent development of asthma, if it persists over time.

Our findings on the impact of child average-increasing and high BMI trajectories on asthma risk were further supported by the observation that these two BMI trajectories were at an increased risk of BHR at age 50 years, a hallmark physiological feature of asthma disease activity. Furthermore, we observed that those in the child average-increasing and high BMI trajectories were at greater risk of having other respiratory morbidities at both 43 and 53 years of age. This suggests that there could be an ongoing physiological abnormality in high BMI trajectories. In contrast, the child high-decreasing trajectory showed low proportions of these adverse respiratory outcomes at both 43 and 53 years of age. This suggests that early-life adiposity does not carry a risk alone unless it persists from early life to adulthood. Nevertheless, this may have clinical significance in suggesting that remediation is possible through weight loss at a strategic time. Furthermore, the proportion of females was higher in the child average-increasing trajectory in the current study, suggesting a greater problem with adult-onset obesity among females; however, overall, sex was not shown to be acting as an effect modifier when examined.

Furthermore, small for gestational age was high in the low BMI trajectory. We did not find any evidence of a special risk of asthma in the low BMI trajectory, which carried a high prevalence of small for gestational age compared with other trajectories. We have found previously in the same cohort that small for gestational age was significantly associated with incident asthma [24]. Therefore, we additionally adjusted for small for gestational age in a subset where data were available for each asthma outcome (for incident *versus* never asthma n=652, persistent *versus* remitted asthma from age 43 years n=267 and relapsed *versus* completely remitted asthma n=125) and did not find any differences in the outcomes before or after this adjustment, which suggests that small for gestational age was not acting as a confounder in this analysis.

The importance of the approach of using trajectories was supported by the lack of association between BMI measured only at age 43 years (categorisation: underweight (BMI <18.5 $kg \cdot m^{-2}$), normal (BMI 18.5–24.9 $kg \cdot m^{-2}$), overweight (BMI 25–29.9 $kg \cdot m^{-2}$) and obese (BMI $\geqslant$30 $kg \cdot m^{-2}$)) and the asthma outcomes in our study (see supplementary table S9). Our BMI trajectories have provided an opportunity to clarify the associations of interest, while taking lifetime variation in BMI into account. For example, we found those who had an average BMI during childhood but who progressively increased to being high in adulthood were at increased risk for the development of incident asthma. Hence, all the children with average BMI during childhood could not be considered a risk-free group. In contrast, studies which have had just one time-point for BMI have reported the lowest risk of adult asthma for those with an average BMI during childhood and used "average" as the childhood reference group [25]. This might explain the conflicting results between child obesity and adult-onset asthma. Even so, the current study did show that the risk of incident asthma was almost double for those with persistent obesity compared with those who only have obesity during adult life.

Evidence is limited regarding a specific underlying pathophysiological mechanism for the association between obesity and asthma, but some potential mechanisms have been suggested. Fatty tissue in obese individuals is responsible for the secretion of various immunologically active factors [26, 27]. These cytokines, adipokines and chemokines stimulate the release of tumour necrosis factor-α and interleukins resulting in increased airway responsiveness [27]. Although human studies on the potential role of adipose tissue cytokines in the link between obesity and asthma are limited, animal studies suggest that these

cytokines may modulate BHR through airway inflammation [28]. Another potential mechanism could be the effect of body weight on lung volumes and airway mechanics. Obese individuals have lower expiratory reserve volume, functional residual capacity and tidal volume due to increased inspiratory loads on the chest wall and diaphragm [29]. These alterations reduce the compliance of the whole respiratory system [30]. Other possible mechanisms are genetic and epigenetic influences and oxidative stress mechanisms [31]. Given no established mechanism to explain the link between obesity over time and adult asthma, further investigations are needed to explore this area for translation into therapeutic options.

Our study provides unique insights into long-term patterns of change in BMI from childhood to middle age. BMI is a good proxy marker for adiposity, given its high correlation with subcutaneous fat [32]. Importantly, our findings showed that BMI patterns diverged markedly over time. Previous studies have reported different numbers and shapes of the BMI trajectories, with the number of trajectories mostly ranging between three and six trajectories [11, 23]. It appears likely that these trajectories and the proportion of participants belonging to a specific trajectory may vary from population to population due to variations in age, ethnicity, number of time-points for which BMI is available, sample size and modelling methods used. However, all the studies, irrespective of sample size and patterns of trajectories, have concluded that those with the high BMI trajectories carry more risk for various adverse health outcomes [11, 19, 20, 22].

Strengths and limitations

Our study has many strengths. The current study was conducted on a population-representative sample with a relatively large cohort size and long follow-up over five decades. Thus, we had anthropometric measurements from childhood to middle age, which enabled robust classification of BMI trajectories over a long time. Bodyweight and height were measured repeatedly throughout childhood and adolescence, which allowed capture of the BMI trajectory transition during the early rapid growth period. The exposure information was assessed from childhood to age 43 years and outcomes were evaluated from 43 to 53 years of age to avoid reverse causation.

However, this study also has several limitations. Weight and height were measured at ages 5, 7, 10, 13, 15 and 20, but self-reported at ages 30 and 43 years. However, studies suggest that the discrepancy between actual and self-reported weight has been declining since the late 1980s [33]. We used two datasets to increase the BMI time-points. Weights and heights in both data sources were measured by trained staff. School health nurses measured the weights and heights and recorded them in school medical records. The trained TAHS study staff measured the data in TAHS follow-ups. Furthermore, to address the potential methodological issue with using the different data sources, we assessed the correlation between the data collected by school nurses and TAHS trained researchers at 7 years of age. The correlation between the two data sources in a sample of 669 participants was strong and statistically significant (r_s=0.75, p<0.001). Given the two sources of measurements for each participant were not measured at the same time in the two datasets, less than perfect correlation between the two sets is expected. Similarly, the correlation between self-reported data at age 43 years and measured data at age 45 years (n=1360) was strong and significant (r_s=88, p<0.001). Therefore, we believe that the use of two data sources at both time-points did not influence our findings. The potential for attrition bias is minimal as neither BMI trajectories nor asthma at age 43 years were associated with attrition in our analysis. We compared the BMI trajectories and asthma at age 43 years between those who continued from the 43-year to the 53-year follow-up and those who dropped out over this time, and observed no differences in the distribution of the BMI trajectories and asthma diagnosis at age 43 years. In addition, baseline age 7 years characteristics were similar between those included in the development of BMI trajectories and the remainder of the cohort. Therefore, it is unlikely that attrition bias has influenced our findings (supplementary tables S10–S12). Although we used self-reported asthma outcomes at age 43 and 53 years, we corrected these using prospectively collected 7-year asthma status reported by parents to avoid misclassification related to recalling past asthma status. Although self-reported asthma can introduce potential misclassification, all of the questions used in the study were standardised questions used in the previous literature [34, 35]. The TAHS-specific asthma questions were previously validated in the same population against respiratory physicians' diagnoses [36]. We also tested the agreement between reported self-reported asthma with doctor-diagnosed asthma at age 43 years and found a high agreement between the two variables with a weighted κ=0.74 (95% CI 0.71–0.76). These additional analyses suggest that the likelihood of misclassification is minimal. We did not have information on birthweight or gestational age for the whole sample, but we adjusted for them in a subsample and found results to remain consistent. Another possible limitation is that information on some essential confounders, including maternal obesity, participant's diet and physical activity, was not available. This might impact the associations due to residual confounding.

Conclusions

We identified five distinct BMI trajectories from early childhood to middle age in a population-representative cohort. Those with high BMI or persistently increasing BMI over time were at higher risk of incident asthma and increased BHR in middle age. Our findings have both clinical and public health implications. Encouraging individuals to maintain a normal BMI over the life course may well help reduce the burden of new-onset asthma in adulthood. It could be helpful to develop weight management programmes and encourage changing behaviour (diet and physical activity) that focus on critical times and intensity of obesity. Visual presentation of BMI trajectories could help educate people about the risks of being in the high BMI trajectory groups. We believe that having anthropometric growth record registries or charts over the lifetimes of individuals instead of only during earlier life could be useful for assessing the population at risk and identifying the best time to intervene with an individual at risk. Such an approach will help improve adult respiratory health, and should figure more in asthma clinical guidelines and also research agendas to provide an evidence base for these presumptions. This study also provides the impetus for further investigation in this field, focusing on possible underlying biological mechanisms.

Acknowledgements: The authors thank all the investigators of the Tasmanian Longitudinal Health Study for their involvement in the study design, funding and study conduct over a long period with multiple follow-ups. We also thank Mark Jenkins (Centre for Epidemiology and Biostatistics, University of Melbourne, Melbourne, Australia) and Iain Feather (Gold Coast Hospital, Southport, Australia) for their assistance with obtaining funds and data collection as TAHS investigators, but not involved in the current study. We thank all of the study participants for their participation and ongoing support for this study, and the project staff who collected data at each follow-up. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaires.

Author contributions: Study concept and design: S.C. Dharmage, E.H. Walters, M.J. Abramson, D.S. Bui and A.J. Lowe. Acquisition of data: S.C. Dharmage, E.H. Walters, J.L. Perret, G. Bowatte and D.S. Bui. Analysis and interpretation of data: G.B. Ali, S.C. Dharmage, D.S. Bui and A.J. Lowe. Drafting of the manuscript: G.B. Ali, S.C. Dharmage, D.S. Bui and A.J. Lowe. Critical revision of the manuscript for important intellectual content: G.B. Ali, S.C. Dharmage, D.S. Bui, A.J. Lowe, J.L. Perret, E.H. Walters, C.J. Lodge, D. Johns, A. James, B. Erbas, G.S. Hamilton, G. Bowatte, R. Wood-Baker and M.J. Abramson. Statistical analysis: G.B. Ali, S.C. Dharmage, D.S. Bui and A.J. Lowe. Obtained funding: S.C. Dharmage, E.H. Walters and M.J. Abramson.

Conflicts of interest: M.J. Abramson holds investigator-initiated grants for unrelated research from Pfizer, Boehringer Ingelheim and Sanofi; has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi; and has also received a speaker's fee from GSK. The other authors included in this study declare that they have no competing interests. All authors declare no support from any organisation or no financial relationship with any organisation that could appear to have influenced the submitted work.

Support statement: Tasmanian Asthma Foundation supported the baseline 1968 study. Subsequent follow-ups have received funding from several sources. Funding bodies have included the National Health and Medical Research Council of Australia (grants 299901, 454425, 566931, 628513 and 1021275); NHMRC European collaborative grant scheme 1101313; the Australian Lung Foundation; Victorian, Queensland and Tasmanian Asthma Foundations; Clifford Craig Medical Research Trust of Tasmania; University of Melbourne; Royal Hobart Hospital Research Foundation; Helen Macpherson Smith Trust; and GlaxoSmithKline. None of the funding bodies that supported the establishment and ongoing follow-ups of the Tasmanian Longitudinal Health Study had any role in the study design, collection, analysis, interpretation of the data or writing this article. Therefore, the study design, results, conclusion and implications reported in this article are those of the authors involved in this study.

References

1 Bateman ED, Hurd S, Barnes P, *et al.* Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008; 31: 143–178.
2 Ehteshami-Afshar S, FitzGerald J, Doyle-Waters M, *et al.* The global economic burden of asthma and chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis* 2016; 20: 11–23.
3 Global Asthma Network. The Global Asthma Report 2018. 2018. http://globalasthmareport.org/resources/Global_Asthma_Report_2018.pdf Date last accessed: 8 February 2021.
4 Scott HA, Wood LG, Gibson PG. Role of obesity in asthma: mechanisms and management strategies. *Curr Allergy Asthma Rep* 2017; 17: 53.
5 Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018; 141: 1169–1179.
6 Holguin F, Bleecker ER, Busse WW, *et al.* Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011; 127: 1486–1493.

7 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007; 175: 661–666.
8 Fukutomi Y, Taniguchi M, Nakamura H, *et al.* Association between body mass index and asthma among Japanese adults: risk within the normal weight range. *Int Arch Allergy Immunol* 2012; 157: 281–287.
9 Ferreira I, Stehouwer CD. Obesity paradox or inappropriate study designs? Time for life-course epidemiology. *J Hypertens* 2012; 30: 2271–2275.
10 Ziyab AH, Karmaus W, Kurukulaaratchy RJ, *et al.* Developmental trajectories of body mass index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health* 2014; 68: 934–941.
11 Buscot M-J, Thomson RJ, Juonala M, *et al.* Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk. *Eur Heart J* 2018; 39: 2263–2270.
12 Matheson MC, Abramson MJ, Allen K, *et al.* Cohort profile: the Tasmanian Longitudinal Health Study (TAHS). *Int J Epidemiol* 2017; 46: 407–408i.
13 Burgess JA, Walters EH, Byrnes GB, *et al.* Who remembers whether they had asthma as children? *J Asthma* 2006; 43: 727–730.
14 Crapo RO, Casaburi R, Coates AL, *et al.* Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med* 2000; 161: 309–329.
15 Pellegrino R, Viegi G, Brusasco V, *et al.* Interpretative strategies for lung function tests. *Eur Respir J* 2005; 26: 948–968.
16 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
17 Williamson EJ, Aitken Z, Lawrie J, *et al.* Introduction to causal diagrams for confounder selection. *Respirology* 2014; 19: 303–311.
18 Jones BL, Nagin D. A note on a Stata plugin for estimating group-based trajectory models. *Sociolog Methods Res* 2013; 42: 608–613.
19 Fan B, Yang Y, Dayimu A, *et al.* Body mass index trajectories during young adulthood and incident hypertension: a longitudinal cohort in Chinese population. *J Am Heart Assoc* 2019; 8: e011937.
20 Lv J, Fan B, Wei M, *et al.* Trajectories of early to mid-life adulthood BMI and incident diabetes: the China Health and Nutrition Survey. *BMJ Open Diabetes Res Care* 2020; 8: e000972.
21 Ali GB, Bui DS, Lodge CJ, *et al.* Infant body mass index trajectories and asthma and lung function. *J Allergy Clin Immunol* 2021; 148: 763–770.
22 Chen Y-C, Liou T-H, Chen P-C, *et al.* Growth trajectories and asthma/rhinitis in children: a longitudinal study in Taiwan. *Eur Respir J* 2017; 49: 1600741.
23 Rzehak P, Wijga AH, Keil T, *et al.* Body mass index trajectory classes and incident asthma in childhood: results from 8 European Birth Cohorts – a Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol* 2013; 131: 1528–1536.
24 Matheson MC, D'Olhaberriague AL-P, Burgess JA, *et al.* Preterm birth and low birth weight continue to increase the risk of asthma from age 7 to 43. *J Asthma* 2017; 54: 616–623.
25 Black MH, Zhou H, Takayanagi M, *et al.* Increased asthma risk and asthma-related health care complications associated with childhood obesity. *Am J Epidemiol* 2013; 178: 1120–1128.
26 Farah CS, Salome CM. Asthma and obesity: a known association but unknown mechanism. *Respirology* 2012; 17: 412–421.
27 Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004; 89: 2548–2556.
28 Sood A, Shore SA. Adiponectin, leptin, and resistin in asthma: basic mechanisms through population studies. *J Allergy* 2013; 2013: 785835.
29 Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J Appl Physiol* 2005; 98: 512–517.
30 Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018; 12: 755–767.
31 Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respir Med* 2013; 107: 1287–1300.
32 Nadeem B, Bacha R, Gilani SA. Correlation of subcutaneous fat measured on ultrasound with body mass index. *J Med Ultrasound* 2018; 26: 205–209.
33 Stommel M, Osier N. Temporal changes in bias of body mass index scores based on self-reported height and weight. *Int J Obes* 2013; 37: 461–467.
34 Bowatte G, Lodge CJ, Knibbs LD, *et al.* Traffic related air pollution and development and persistence of asthma and low lung function. *Environ Int* 2018; 113: 170–176.
35 Bui DS, Burgess JA, Lowe AJ, *et al.* Childhood lung function predicts adult chronic obstructive pulmonary disease and asthma–chronic obstructive pulmonary disease overlap syndrome. *Am J Respir Crit Care Med* 2017; 196: 39–46.
36 Jenkins MA, Clarke JR, Carlin JB, *et al.* Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996; 25: 609–616.