Bronchial hyperresponsiveness and obesity in middle age: insights from an Australian cohort

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Airway closure is important, measurable and remediable in the obesity and bronchial hyperresponsiveness relationship http://ow.ly/J79u30dMh8N

Cite this article as: Burgess JA, Matheson MC, Diao F, *et al*. Bronchial hyperresponsiveness and obesity in middle age: insights from an Australian cohort. *Eur Respir J* 2017; 50: 1602181 [https://doi.org/10.1183/13993003.02181-2016].

ABSTRACT The association between obesity and bronchial hyperresponsiveness (BHR) is incompletely characterised. Using the 2006 follow-up of the Tasmanian Longitudinal Health Study, we measured the association between obesity and BHR and whether it was mediated by small airway closure or modified by asthma and sex of the patient.

A methacholine challenge measured BHR. Multivariable logistic regression measured associations between body mass index (BMI) and BHR, adjusting for sex, asthma, smoking, corticosteroid use, family history and lung function. Mediation by airway closure was also measured.

Each increase in BMI of 1 $kg \cdot m^{-2}$ was associated with a 5% increase in the odds of BHR (OR 1.05, 95% CI 1.01–1.09) and 43% of this association was mediated by airway closure. In a multivariable model, BMI (OR 1.06, 95% CI 1.00–1.16) was associated with BHR independent of female sex (OR 3.26, 95% CI 1.95–5.45), atopy (OR 2.30, 95% CI 1.34–3.94), current asthma (OR 5.74, 95% CI 2.79–11.82), remitted asthma (OR 2.35, 95% CI 1.27–4.35), low socioeconomic status (OR 2.11, 95% CI 1.03–4.31) and forced expiratory volume in 1 s/forced vital capacity (OR 0.86, 95% CI 0.82–0.91). Asthma modified the association with an increasing probability of BHR as BMI increased, only in those with no or remitted asthma.

An important fraction of the BMI/BHR association was mediated *via* airway closure. Conflicting findings in previous studies could be explained by failure to consider this intermediate step.

Introduction

Many regard bronchial hyperresponsiveness (BHR) as an essential component of asthma [1], yet not all asthma patients exhibit BHR [2] and BHR is found in other respiratory conditions [3] and the apparently healthy [4]. BHR is related to airway inflammation and remodelling due to bronchial smooth muscle thickening, increased vascularity and mucosal thickening [5], and airway geometry can modulate the response to a provocative stimulus [6]. BHR is important clinically because of its role as a risk factor for, and a possible intermediary in, the development of asthma and chronic obstructive pulmonary disease (COPD) [7]. BHR increases the detrimental effect of smoking such that as much as 60% of COPD risk in smokers has been attributed to BHR [8].

Obesity has been studied as a risk factor for BHR [9] with conflicting results. Chinn *et al.* [10] found an association between obesity and BHR in the first European Community Respiratory Health Survey, and this association was found to be stronger in men than in women. Celedon *et al.* [11] reported an association between under-/overweight and BHR in high-risk Chinese adults. Sood *et al.* [12] found an association between overweight or obesity and symptomatic BHR in women only , while Bustos *et al.* [13] found a negative association between BMI and BHR. Paradoxically, Schacter *et al.* [14] reported increased odds of BHR in underweight, but not overweight or obese, subjects , although the underweight group may have included undertreated asthmatics. Finally, Juusela *et al.* [15] found no association between BMI or sex of the patient and BHR.

An association between obesity and BHR might be part explained by small airway closure. Small airway closure occurs in healthy lungs between functional residual capacity (FRC) and residual volume towards the end of expiration [16]. Furthermore, obesity reduces FRC [17] and the exponential relationship between BMI and FRC results in an FRC decrease in very obese patients [18]. In obese subjects, airway closing volume was closer to FRC than in non-obese subjects, suggesting that airway closure during tidal breathing was more likely in the obese patient group [19]. With reduced lung volumes, there is a reduction in peripheral airway diameter that has the potential to increase airflow obstruction and BHR [20]. Chapman *et al.* [21] reported that airway closure and BMI were predictors of airway responsiveness in obese subjects, yet BMI appeared to protect against BHR after correcting for airway closure, suggesting that airway closure might lie on a causal pathway between obesity and BHR.

We investigated the association between obesity and BHR in middle age using Tasmanian Longitudinal Health Study (TAHS) data. We further investigated whether sex or asthma modified this association and measured a possible causal role for airway closure in this association.

Methods

We performed an inhalational methacholine (MCh) challenge in a stratified subset of middle-aged adults who had taken part in the laboratory phase of the 2004–06 follow-up TAHS survey.

Study sample

The TAHS commenced in 1968 when parents of 8583 Tasmanian children (probands) born in 1961 and attending school in Tasmania (98.9% of those eligible) completed a questionnaire on their children's respiratory health. Each child underwent lung function tests, and height and weight were measured. The methodology has been reported elsewhere [22]. The fifth-decade follow-up study started in 2004 when probands had a mean age of 49.6±0.61 years. We traced 7296 (85.0%) of the original 1968 cohort and achieved a response from 5729 (78.5%) to a postal survey. A subgroup, enriched for a history of asthma or cough, was invited to participate in a detailed laboratory study. Of the 2387 invited, 1397 (58.6%) completed a full laboratory visit, 354 (14.8%) completed a telephone questionnaire or laboratory visit only, and 636 (26.6%) withdrew. The BHR study was conducted on the laboratory attendees. Of the 1397 eligible for the BHR study, 794 (56.8%) completed a full laboratory visit, 36 (2.6%) completed a telephone questionnaire only, 7 (0.5%) completed a laboratory visit only, 283 (20.2%) withdrew, and 247 (17.7%)

Received: Nov 06 2016 | Accepted after revision: June 02 2017

Support statement: The study was supported by the National Health and Medical Research Council of Australia; Clifford Craig Medical Research Trust, Tasmania; Royal Hobart Hospital Research Foundation; and Asthma Australia. The funding agencies had no direct role in the conduct of the study, the collection, management, statistical analysis, and interpretation of the data, preparation, or approval of the manuscript. J. Burgess is the guarantor of the content of the manuscript, including the data and analysis. Funding information for this article has been deposited with the Crossref Funder Registry.

Conflict of interest: Disclosures can be found alongside this article at erj.ersjournals.com

could not be continued in the study. Some had either died (n=12, 0.9%) or had withdrawn from the TAHS cohort before the BHR study began (n=18, 1.3%) (figure 1).

Of the 697 who completed the MCh challenge, 90 (12.9%) had no history of asthma or cough; 63 (9.1%) only had an asthma history, of whom 22 (34.9%) were current asthmatics; 283 (40.6%) only had a history of cough; and 260 (37.4%) had a history of both asthma and cough. The fifth-decade follow-up and the BHR study were approved by the Human Research Ethics Committee of the University of Melbourne (HREC Ref. number 040375.1). All participants provided written informed consent.

Definitions

Bronchial hyperresponsiveness (BHR) was identified by 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)$\leqslant$2 mg.

Baseline FEV_1/FVC ratio was derived from the best values for FEV_1 and forced vital capacity (FVC) following the inhalation of the diluent (saline), the first step in the methacholine challenge.

Airway closure (%ΔFVC) was the percentage change in FVC from baseline to the end of the methacholine challenge [23].

Childhood asthma was identified in 1968 by the parent's affirmative response to: "Has your child at any time in his/her life suffered from asthma or wheezy breathing?"

Asthma ever was self-reported by the participants in the 2010 laboratory study by an affirmative response to: "Have you at any time in your life suffered from asthma or wheezy breathing?" Participants who reported no asthma ever in 2010 were recorded as "having asthma ever" if their parent had given an affirmative response to the childhood asthma question in earlier surveys.

Asthma status was a three-level variable derived from responses to the modified "asthma ever" question and to a separate question: "Have you had an attack of asthma within the last 12 months?" Those with an affirmative response to both were classed as "current asthma". Those with an affirmative response to the asthma-ever question and a negative response to the "attack in the last 12 months" question were classed as "remitted asthma". Those with a negative response to the asthma-ever question were classed as "never asthma".

Cough was identified by an affirmative response to: "Have you at any time in your life suffered from cough with phlegm in the chest?"

Inhaled corticosteroid (ICS) use was self-reported in the 2010 laboratory study by an affirmative response to: "Have you ever used inhaled steroids to help your breathing?".

Body mass index (BMI) of each participant was calculated as weight (kg) divided by square of the height (m^2) measured in the laboratory.

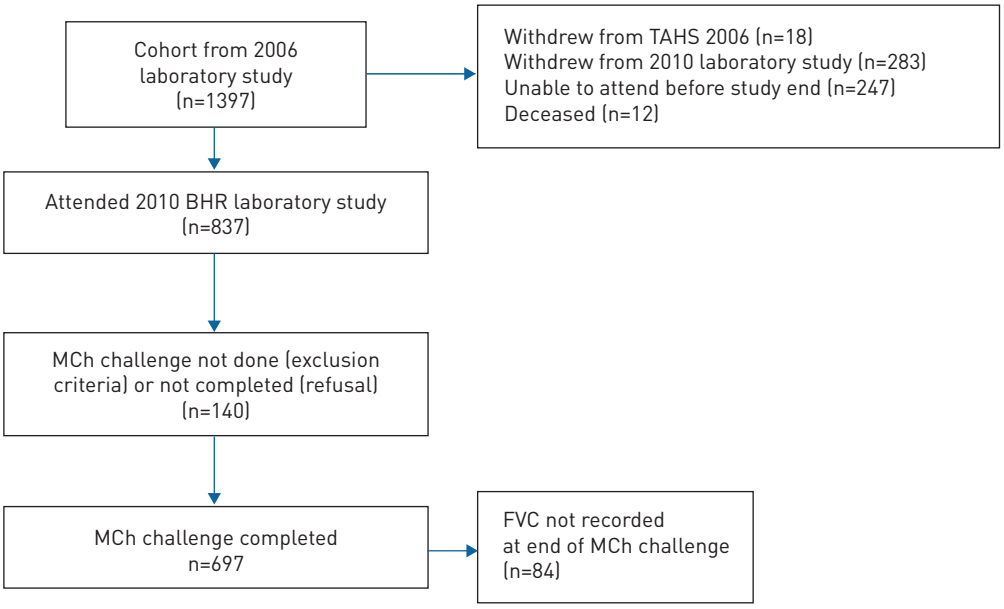

FIGURE 1 A flow chart showing the development of the study sample.

Smoking was self-reported by the participants in 2010 as lifetime smoking of at least 100 cigarettes and classed as "never", "former" and "current" smoking.

Atopy was identified by one or more positive skin-prick tests (wheal diameter ⩾3 mm greater than the negative control) for any aeroallergen.

Socioeconomic status (SES) was defined by the participant's occupation and coded according to the Australian Standard Classification of Occupations (ASCO) [24]. These four-digit codes were then grouped into five major skill groups: 1) managers/professionals; 2) tradespersons and advanced clerical; 3) intermediate clerical and production; 4) elementary clerical; and 5) labourers and related workers.

Statistical methods

A directed acyclic graph determined which covariates should be included in regression models for both association and mediation analyses. A role for %ΔFVC as a mediator between BMI and BHR was examined following the steps recommended by Kenny using the "bivariate mediation" module of Stata software [25]. Using multiple logistic regression models, relationships between BMI and BHR were explored while adjusting for sex, baseline lung function, atopy, asthma, smoking, family history of asthma, SES, and ICS use, with the results presented as an odds ratio with a 95% confidence interval. Prevalence estimates and regression models were reweighted using the known sampling fractions derived from the 1968, 1974 and 2004 surveys [26]. Interactions between BMI and sex and between BMI and asthma were estimated and examined further if the interaction p-value was ⩽0.10. All analyses were performed using Stata Statistical Software: Release 13.1 (StataCorp, College Station, TX, USA).

Results

Characteristics of attendees and non-attendees are shown in table 1. Non-attendees were more likely to be current smokers, less likely to be atopic, and marginally more obese than attendees.

BHR prevalence was 19.3% (95% CI 16.3%–22.7%), greater in females than males (24.5%, 95% CI 19.8–29.9 *versus* 14.0%, 95% CI 10.7–18.2; p=0.001). Mean±SD BMI did not differ between males (28.4±4.39 $kg \cdot m^{-2}$) and females (28.5±6.36 $kg \cdot m^{-2}$) (p=0.71).

TABLE 1 Characteristics of those attending and not attending the laboratory study (of a total of 1397 who were invited to attend)

Characteristic	Attended laboratory (n=837)	Did not attend laboratory (n=560)	p-value
Age# years	44.83±0.996	44.79±0.934	0.39
Sex			
Male	412 (49.2)	297 (53.0)	
Female	425 (50.8)	263 (47.0)	0.16
BMI $kg \cdot m^{-2}$	28.19 (5.93)	28.85 (6.82)	0.06
Smoking status			
Never	367 (44.2)	215 (38.9)	
Former	258 (31.2)	152 (27.5)	
Current	204 (24.6)	186 (33.6)	0.001
Asthma			
Never	265 (31.9)	205 (36.9)	
Remitted	298 (35.9)	188 (33.8)	
Current	268 (32.2)	163 (29.3)	0.15
Social class			
Level 1	262 (31.7)	134 (24.3)	
Level 2	103 (12.4)	63 (11.5)	
Level 3	171 (20.7)	106 (19.2)	
Level 4	143 (17.3)	107 (19.5)	
Level 5 (lowest)	148 (17.9)	140 (25.5)	0.002
Atopy			
No	345 (41.9)	268 (48.7)	
Yes	478 (58.1)	282 (51.3)	0.013
Family history of asthma			
Neither parent	589 (74.5)	400 (76.9)	
One or both parents	202 (25.5)	120 (23.1)	0.17

Data are presented as mean±SD or n (%), unless otherwise stated. BMI: body mass index. #: At the 2006 laboratory study.

Table 2 shows the univariable associations with BHR. Female sex, the lowest stratum of social class, atopy, current smoking, ever inhaled corticosteroid use, current or remitted asthma, %ΔFVC and BMI, and having at least one parent with asthma, were associated with BHR. Baseline FEV_1/FVC was negatively associated with BHR.

A mediation analysis [25] with adjustment for baseline FEV_1/FVC, asthma status, SES, sex of patient and smoking determined the proportion of the association between BMI and BHR that passed*via* %ΔFVC (table 3).

The proportion of the total effect of BMI on BHR mediated *via* %ΔFVC was 43% (0.0741/0.1724).

Two logistic regression models (table 4) were then fitted to the data. Model 1 included BMI as the sole predictor of BHR. Model 2 included each of the variables from table 1 except %ΔFVC. Model 2 also included interaction terms between BMI and current asthma (p=0.006) and BMI and remitted asthma (p=0.10). There was no interaction between BMI and sex (p=0.25). BMI was significantly associated with BHR only in those with no asthma (Model 2).

The analyses were repeated using waist circumference and waist-to-hip ratio as alternative measures of obesity and the results did not change (not shown).

The predicted probability of BHR with increasing BMI in those with current asthma, remitted asthma and no asthma is shown in figures 2 and 3.

The probability of BHR was significantly greater in the current asthma group than the never asthma group for values of BMI in the normal and overweight range, but there was no difference in the probability of BHR between current and remitted or remitted and never asthma groups (figure 2). As BMI increased (figure 3), the probability of BHR in the never-asthma group increased from 2% to 73%, while in the remitted asthma group the probability increased from 14% to 42%. For the current asthma group, the probability of BHR fell slightly from 43% to 34% with increasing BMI.

A sensitivity analysis was conducted using "subject-reported and doctor-confirmed" current and remitted asthma in place of subject-reported asthma.

There were minor changes to the point estimates in Model 2 but no change to their direction or significance (not shown). In figures 2 and 3 there were minor alterations to the slope of the plot lines for current and remitted asthma, no change to the slope of the plot line for the never-asthma group, and no change to the interpretation of the plots.

There were 19 subjects who were self-reported non-asthmatics, obese ($BMI \geqslant 30\ kg \cdot m^{-2}$), and had documented BHR, for whom we examined the responses to questions about "asthma-like" symptoms. Of the 19, one (5%) reported cough without a cold and shortness of breath after exercise, and another three (16%) reported wheeze and cough without a cold and shortness of breath after exercise. A sensitivity analysis was conducted by reclassifying these four persons as having current asthma and re-analysing the data. There were minor changes to the point estimates in Model 2, but not to their direction or significance (not shown). There was no change to figures 2 and 3.

Discussion

We found an independent association between BMI and BHR in middle age, confirming findings from other studies. Asthma modified the association between BMI and BHR such that the association between BMI and BHR was significant only in those with no history of asthma, a finding also reported by Sood *et al.* [27] from a retrospective review of medical records. We confirmed previously reported associations between female sex, poorer lung function [15], atopy [28] and BHR. We found an increased risk of BHR in current and former smokers that was not statistically significant, whereas at least one previous study found an independent and significant association [29]. Other studies [10, 12] found that the association between obesity and BHR was modified by the patient's sex, but we did not confirm this.

We found that airway closure mediated the relationship between BMI and BHR with almost half of the presumed causal pathway between BMI and BHR passing *via* airway closure. This finding, together with effect modification by asthma of the BMI/BHR association, suggested that to understand the effect of obesity on bronchial hyperresponsiveness, one needs to take account of both asthma status and the amount that airway closure might contribute to BHR. Previous studies have commented on the role of airway closure in the association between obesity and BHR [21]. However, to our knowledge, this is the first study to provide an actual measurement of any contribution made to BHR by airway closure.

There were differing relationships between BMI and BHR in the never, remitted and current asthma groups. The risk of BHR in non-asthmatics increased markedly with increasing BMI, but less so in remitted asthma. However, the risk of BHR in the current asthma group did not increase with increasing

TABLE 2 Univariable relationships with bronchial hyperresponsiveness (BHR)

Exposure	BHR		
	OR	95% CI	p-value
BMI (n=683)	1.05	1.01–1.09	0.03
Female sex (n=340)	1.99	1.32–3.01	0.001
%ΔFVC (n=599)	1.33	1.23–1.44	<0.001
Asthma status			
Never asthma (n=370)	1.00		
Remitted asthma (n=160)	3.53	2.08–6.02	<0.001
Current asthma (n=151)	8.40	5.01–14.08	<0.001
Smoker			
Never (n=322)	1.00		
Former (n=249)	0.91	0.57–1.46	0.70
Current (n=112)	1.87	1.09–3.20	0.02
Social class			
Level 1 (highest) (n=230)	1.00		
Level 2 (n=83)	0.84	0.42–1.68	0.61
Level 3 (n=144)	0.73	0.39–1.35	0.31
Level 4 (n=111)	1.09	0.59–2.04	0.78
Level 5 (n=113)	2.16	1.21–3.84	0.01
Atopy (n=674)	2.37	1.49–3.72	<0.001
ICS use (n=678)	3.81	2.32–6.25	<0.001
Baseline FEV_1/FVC (n=683)	0.89	0.85–0.94	<0.001
Family history of asthma			
Neither parent (n=481)	1.00		
Either or both parents (163)	1.78	1.12–2.85	0.02

BMI: body mass index; (Δ)FVC: (change in) forced vital capacity; ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 s.

BMI. This suggested that the mechanism underlying BHR in these contexts may be different and not additive.

Possible mechanisms

Obesity can facilitate small airway closure because of its mechanical effect on airway diameter with increase in elastic load [30]. Increased chest and abdominal fat mass seen in obesity can lead to lower FRC [31] and smaller tidal volumes [32], resulting in compressed airways, and hence BHR from geometric effects. There may also be less surfactant available at these low volumes to stabilise small airways. The increasing risk of BHR in non-asthmatics as BMI increased may be understood as the result of the combination of these physiological and mechanical effects leading to small airway closure. This is supported by studies showing a favourable effect of bariatric surgery on airway responsiveness [33].

Increased serum and tissue levels of obesity-related pro-inflammatory adipokines could also modulate bronchial responsiveness by altering pulmonary surfactant structure and function [34], increasing surface tension at the air–liquid interface of small airways and promoting closure [35].

However, other mechanisms could also be important. Diet in obese individuals is often unhealthy, containing fewer antioxidants and omega-3 fatty acids, which are known to have beneficial effects on lung function [36]. Further investigation of dietary factors in studies of BHR may clarify this.

TABLE 3 The relationship between body mass index and bronchial hyperresponsiveness showing the mediating effect of airway closure (percentage change in forced vital capacity (FVC) from baseline to the end of the methacholine challenge)

	Coefficient	Standard error	p-value	95% CI
Indirect effect	0.0741	0.0301	0.014	0.0152–0.1331
Direct effect	0.0983	0.0434	0.024	0.0132–0.1833
Total effect	0.1724	0.0554	0.002	0.0638–0.2810

Model adjusted for baseline forced expiratory volume in 1 s to FVC ratio, asthma status, socioeconomic status, sex and smoking.

TABLE 4 Crude and adjusted models for the association between body mass index (BMI) and bronchial hyperresponsiveness

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
BMI	1.05** (1.01–1.09)	#1.17** ([1.05–1.31) ¶1.05 (0.98–1.13) +0.99 (0.93–1.04)
Interaction term		
BMI×remitted asthma		0.90 (0.79–1.02); p=0.10
BMI×current asthma		0.84 (0.71–0.95); p=0.006
Never asthma		
Remitted asthma		
Current asthma		
Female sex		3.69*** (2.18–6.26)
Atopy		2.40*** (1.38–4.16)
Never smoker		1.00
Former smoker		1.11 (0.60–2.04)
Current smoker		1.74 (0.88–3.42)
Socioeconomic status		
Level 1		1.00
Level 2		1.03 (0.43–2.48)
Level 3		0.86 (0.42–1.78)
Level 4		1.02 (0.46–2.26)
Level 5 (lowest)		2.17* (1.07–4.41)
ICS use		1.05 (0.57–1.96)
Baseline FEV_1/FVC ratio		0.86*** (0.81–0.91)
Family history of asthma		
Neither parent		1.00
Either or both parents		1.21 (0.66–2.24)
Observations	683	628

*: p<0.05; **: p<0.01; ***: p<0.001. #: estimate for a 1-unit increase in BMI for "never asthma"; ¶: estimate for a 1-unit increase in BMI for "remitted asthma"; +: estimate for a 1-unit increase in BMI for "current asthma". ICS: inhaled corticosteroid; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Whatever the mechanisms, our findings suggest that inconsistent findings from earlier studies of obesity and airway responsiveness, particularly in non-asthmatic subjects, could be explained by failure to consider the effect of obesity on vulnerability to airway closure.

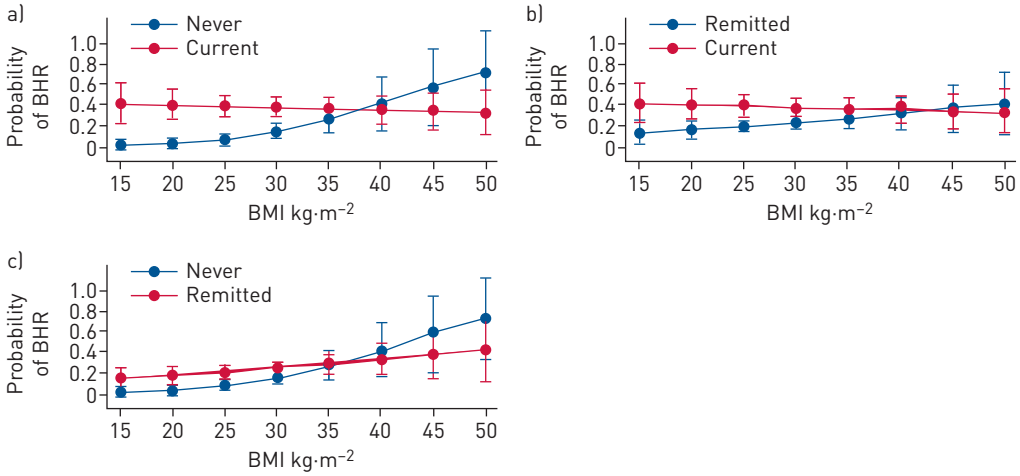

FIGURE 2 The relationship between body mass index (BMI) and bronchial hyperresponsiveness (BHR) when comparing across current, remitted and never asthma groups.

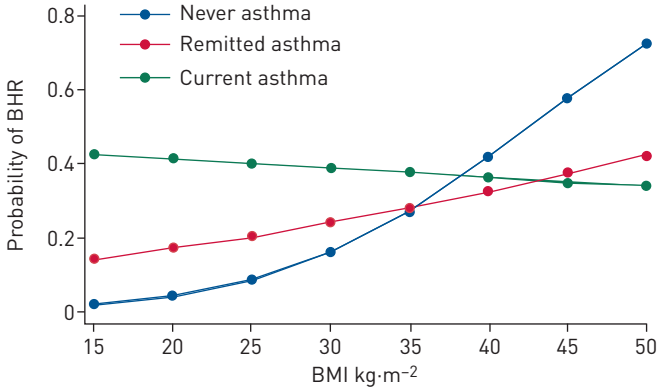

FIGURE 3 The relationship between body mass index (BMI) and bronchial hyperresponsiveness (BHR) for each of current, remitted and never asthma groups separately.

Strengths and limitations

The main strength of our study is its large sample size and objective measures of adiposity, avoiding self-reporting bias.

A limitation is the cross-sectional nature of these data, preventing any conclusion regarding causality. Further, our study sample was selected based on a history of asthma and cough, and our findings are not representative of a more general population. In addition, the methacholine challenge used deep inspiration rather than tidal breathing to administer the agent and it is possible that the consequent bronchodilator effect could have lessened the response to methacholine. However, if this were true, the effect estimates would be drawn towards the null.

A possible limitation is the use of %ΔFVC to measure airway closure. We acknowledge that airway closure can be measured more precisely by radionuclide studies or nitrogen washout, but neither of these was available. Previous studies have used %ΔFVC to measure airway closure [21, 23, 37, 38], and the use of %ΔFVC for this purpose is accepted in the scientific literature.

In addition, we used self-report to identify asthma, not doctor-diagnosis. However, self-reported asthma is commonly used in epidemiological studies [39] and has been found to be valid and reliable as a measure of asthma [40].

Another possible limitation was potential misclassification of asthma status among those participants who self-reported never asthma, were obese and had BHR. We identified only four such participants who reported asthma-like symptoms that could be considered as identifying misclassification. The sensitivity analysis conducted with these four participants reclassified as current asthma patients made no change to the estimates, suggesting that any such misclassification was not likely to be important.

BMI has been criticised as a poorer measure of intra-abdominal fat than waist circumference or waist-to-hip ratio. However, our analyses where waist circumference and waist-to-hip ratio were used gave similar results to those where BMI was used, and we believe that the use of BMI to measure adiposity is justifiable.

Conclusions

Although our study is not the first to document a relationship between obesity and BHR in non-asthmatic subjects, there are novel aspects. We have expanded on previous research by quantifying in our study population the degree of BHR (43%) mediated through airway closure in obese individuals. This important contribution to BHR may be modifiable. As BHR is a known risk factor for progression to poorer lung function, our findings support vigorous public health measures to tackle the current obesity epidemic.

Further studies of obesity and BHR with attention to lung mechanics, dietary factors and serum adipokine levels are required. Elucidation of risk factors for middle age BHR can translate into clinical practice by expanding understanding of its pathophysiology and hence its prevention. Also requiring further clinical research is the relevance of the two phenotypes of BHR and BMI; namely, that seen in those with defined asthma and that seen in those with a non-asthmatic "obesity-BHR syndrome". We suggest that weight loss is likely to be more effective in reducing BHR and possible loss of lung function in the latter group. Our findings emphasise the importance of taking care to avoid a misdiagnosis of allergic asthma in obese middle-aged persons with BHR who might otherwise be treated unnecessarily with inhaled corticosteroids.

Acknowledgements

We acknowledge the TAHS study participants and previous investigators Heather Gibson, Bryan Gandevia, Harold Silverstone and Norelle Lickiss. We thank Mark Jenkins, Centre for Epidemiology and Biostatistics, University of Melbourne, who is a TAHS investigator but not a co-author of this manuscript for his assistance with data collection and obtaining funds. We also acknowledge and thank all the study site coordinators and respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland and New South Wales; the research interviewers and data entry operators; and the organisational roles of Cathryn May and Desiree Mészáros.

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