Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study

A A Litonjua, D Sparrow, J C Celedon, D DeMolles, S T Weiss

Background: The rising prevalence of asthma in developed nations may be associated with the rising prevalence of obesity in these same nations. The relationship between body mass index (BMI) and the development of an objective marker for asthma, methacholine airway hyperresponsiveness (AHR), was investigated in adult men.

Methods: Sixty one men who had no AHR at initial methacholine challenge testing but who developed AHR about 4 years later and 244 matched controls participated in the study. The effects of initial BMI and change in BMI on development of AHR were examined in conditional logistic regression models. Results: Initial BMI was found to have a non-linear relationship with development of AHR. Compared with men with initial BMI in the middle quintile, men with BMI in the lowest quintile (BMI=19.8–24.3 kg/m²) and those with BMI in the highest quintile (BMI >29.4 kg/m²) were more likely to develop AHR: OR=7.0 (95% CI 1.8 to 27.7) and OR=10.0 (95% CI 2.6 to 37.9), respectively. These results remained significant after controlling for age, smoking, IgE level, and initial FEV₁. In addition, there was a positive linear relationship between change in BMI over the period of observation and the subsequent development of AHR.

Conclusions: In this cohort of adult men, both a low BMI and a high BMI were associated with the development of AHR. For men with a low initial BMI the increased risk for development of AHR appears to be partly mediated by a gain in weight. The effect of BMI on AHR may suggest mechanisms in the observed associations between obesity and asthma.
output by weight methacholine based on previous determination of nebuliser methacholine (equivalent to a cumulative dose of 16.8 µmol postsaline value at or before one inhalation of 25 mg/ml methacholine (equivalent to a cumulative dose of 8.58 µmol methacholine).

Univariate relationships between dependent and independent variables were explored using t tests for normally distributed variables, non-parametric Wilcoxon rank sum test for skewed variables, and χ² tests for categorical variables. To deal with the matching of cases and controls, univariate and multivariable conditional logistic regression models were created using the NLIN procedure in SAS. All analyses were performed with the SAS statistical software package (SAS Institute Inc, Cary, NC, USA).

RESULTS

Sixty one men were identified with a negative initial methacholine challenge test and a positive methacholine challenge test (AHR) on subsequent testing. Two hundred and forty four controls who had negative methacholine challenge tests both at the initial and follow up examinations were matched to the cases on the basis of the date of the initial examination. The mean time between initial and follow up examinations did not differ between cases and controls (mean (SD) 3.78 (1.63) years and 3.72 (1.53) years, respectively; p>0.05). Baseline characteristics of the study subjects are shown in table 1. Cases had lower initial lung function and higher initial BMI than controls. The prevalence (current smokers) and intensity (in pack years) of smoking was greater in cases than in controls, although these differences were not statistically significant.

Table 2 shows the results of univariate and multivariable conditional logistic regression models evaluating the relationship between initial BMI and incident AHR. This relationship is non-linear, with the lowest and highest quintiles representing the greatest risk for AHR compared with the middle quintile. This relationship was maintained even after controlling for age, smoking (both prevalence and intensity), log₁₀ IgE (log transformed serum IgE levels), and initial FEV₁ values. We considered whether the association between initial BMI and development of AHR could be mediated by level of lung function. As shown in table 3, there were no statistically significant differences in percentage predicted values of either FEV₁ or forced vital capacity (FVC) between quintiles of BMI in cases or controls. In fact, cases in the lowest quintile of initial BMI had somewhat higher lung function than those in the second, third, and fifth quintiles.

Figure 1 shows the relationship between the mean change in BMI/year (in quintiles) and incident AHR. Although not

### Table 1: Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Quintiles of baseline BMI (kg/m²)</th>
<th>No (%) of cases</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariable OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24.3</td>
<td>16 (26.2%)</td>
<td>7.0 (1.8 to 27.7)</td>
<td>7.5 (1.3 to 44.7)</td>
</tr>
<tr>
<td>24.3–25.9</td>
<td>11 (18.0%)</td>
<td>3.9 (1.0 to 15.0)</td>
<td>4.1 (0.7 to 25.0)</td>
</tr>
<tr>
<td>25.9–27.3</td>
<td>3 (5.9%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>27.3–29.4</td>
<td>11 (18.0%)</td>
<td>4.2 (1.0 to 16.9)</td>
<td>3.6 (0.7 to 18.5)</td>
</tr>
<tr>
<td>≥29.4</td>
<td>20 (32.8%)</td>
<td>10.0 (2.6 to 37.9)</td>
<td>7.5 (1.5 to 37.8)</td>
</tr>
</tbody>
</table>

*Model adjusted for age, smoking status (current, former, and never smoker), pack years of smoking, log₁₀ IgE, and initial FEV₁.
one of the changes in BMI/year quintiles was statistically significant on its own compared with the third quintile (change in BMI/year=0.0–0.2), the relationship was strongly positive and linear. Incorporating a categorical variable for quintiles of change in BMI/year in the model as a test for a linear trend was statistically significant (p=0.02), so there was increasing risk for AHR with increasing BMI. These results were unchanged when adjusted for age, baseline BMI, smoking, log10 IgE, and initial FEV1 values.

Table 4 shows the relationship between initial BMI and change in BMI. For all quintiles except the middle quintile, the relationship between BMI/year and log10 IgE was strongly positive and linear. Incorporating a categorical variable for quintiles of change in BMI/year=0.0–0.2, the relationship was strongly positive and linear. Among the cases in the lowest quintile of initial BMI, there was a statistically significant increase in the risk for asthma compared with the third quintile. The risk increased for each quintile of BMI compared with the lowest quintile. Although the investigators observed an increased risk for asthma in the highest quintile, this was not statistically significant. Because of the cross sectional nature of these studies, it is difficult to say whether obesity increases the risk for asthma. However, the relationship between obesity and asthma was investigated in a prospective analysis among nurses participating in the Nurses Health Study. The risk for incident asthma over the 4 year follow up period increased in a linear fashion with increasing BMI measured at the start of follow up, and subjects who gained weight after the age of 18 were at increased risk for developing asthma. However, the limitation of these clinical and epidemiological studies remains the difficulty in objectively measuring asthma.

An alternative to defining asthma is to use an associated objective marker such as AHR. Studies in children and adolescents have shown that both obese asthmatic and obese non-asthmatic subjects have greater degrees of exercise induced bronchospasm than their non-obese counterparts. To date, no other studies have investigated this phenotype in adults.

We found a U-shaped relationship between baseline BMI and the development of methacholine AHR. Our results are consistent with a previous Italian survey that investigated BMI and the prevalence of chronic diseases. Using data on 72 284 individuals aged 15 or over from the 1983 Italian National Health Survey, Negri et al found that men with BMI <20 kg/m² had an associated relative risk for asthma of 1.42 (95% CI 1.15 to 1.76) compared with men with BMI of 20–24.9 kg/m². The risk was also increased for men with BMI ≥30 kg/m² (RR 1.70, 95% CI 1.42 to 2.02). For women the association between BMI and asthma was more linear, consistent with previous findings among women. Interestingly, for both men and women in this study the association between BMI and emphysema or respiratory insufficiency was also found to be U-shaped. Nutritional factors may play a role in the development of methacholine AHR in older adult men. Our results also suggest that weight gain over this same time interval may be associated with an increased risk for the development of methacholine AHR, and this weight gain among cases in the lowest quintile of initial BMI may partly explain the increased risk associated with having a low BMI.

Over the past few years there have been increasing numbers of reports documenting the relationship between obesity and asthma across several age groups. In children the prevalence of asthma and wheeze were found to be greater in children who are overweight and obese. In adults two studies have found a relationship between obesity and reported asthma in women, but these studies did not find a significant relationship in men. The first study was a survey of 19 126 Dutch adults ranging in age from 20 years to over 65 years. Severely overweight women (BMI ≥30) were found to be 1.8 times more likely than women in the reference category (BMI=20.0–24.9) to have asthma. A second study was performed on 8960 adults aged 26 years who were part of the 1970 British Cohort Study and an increasing risk for asthma was observed for each quintile of BMI compared with the lowest quintile in women. Although the investigators observed an increased risk for asthma in the highest quintile in the men, this was not statistically significant. Because of the cross sectional nature of these studies, it is difficult to say whether obesity increases the risk for asthma or whether subjects became obese after their asthma became active. The relationship between obesity and asthma was investigated in a prospective analysis among nurses participating in the Nurses Health Study. The risk for incident asthma over the 4 year follow up period increased in a linear fashion with increasing BMI measured at the start of follow up, and subjects who gained weight after the age of 18 were at increased risk for developing asthma. However, the limitation of these clinical and epidemiological studies remains the difficulty in objectively measuring asthma.

An alternative to defining asthma is to use an associated objective marker such as AHR. Studies in children and adolescents have shown that both obese asthmatic and obese non-asthmatic subjects have greater degrees of exercise induced bronchospasm than their non-obese counterparts. To date, no other studies have investigated this phenotype in adults.

We found a U-shaped relationship between baseline BMI and the development of methacholine AHR. Our results are consistent with a previous Italian survey that investigated BMI and the prevalence of chronic diseases. Using data on 72 284 individuals aged 15 or over from the 1983 Italian National Health Survey, Negri et al found that men with BMI <20 kg/m² had an associated relative risk for asthma of 1.42 (95% CI 1.15 to 1.76) compared with men with BMI of 20–24.9 kg/m². The risk was also increased for men with BMI ≥30 kg/m² (RR 1.70, 95% CI 1.42 to 2.02). For women the association between BMI and asthma was more linear, consistent with previous findings among women. Interestingly, for both men and women in this study the association between BMI and emphysema or respiratory insufficiency was also found to be U-shaped. Nutritional factors may play a role in the development of methacholine AHR in older adult men. Our results also suggest that weight gain over this same time interval may be associated with an increased risk for the development of methacholine AHR, and this weight gain among cases in the lowest quintile of initial BMI may partly explain the increased risk associated with having a low BMI.

Over the past few years there have been increasing numbers of reports documenting the relationship between obesity and asthma across several age groups. In children the prevalence of asthma and wheeze were found to be greater in children who are overweight and obese. In adults two studies have found a relationship between obesity and reported asthma in women, but these studies did not find a significant relationship in men. The first study was a survey of 19 126 Dutch adults ranging in age from 20 years to over 65 years. Severely overweight women (BMI ≥30) were found to be 1.8 times more likely than women in the reference category (BMI=20.0–24.9) to have asthma. A second study was performed on 8960 adults aged 26 years who were part of the 1970 British Cohort Study and an increasing risk for asthma was observed for each quintile of BMI compared with the lowest quintile in women. Although the investigators observed an increased risk for asthma in the highest quintile in the men, this was not statistically significant. Because of the cross sectional nature of these studies, it is difficult to say whether obesity increases the risk for asthma or whether subjects became obese after their asthma became active. The relationship between obesity and asthma was investigated in a prospective analysis among nurses participating in the Nurses Health Study. The risk for incident asthma over the 4 year follow up period increased in a linear fashion with increasing BMI measured at the start of follow up, and subjects who gained weight after the age of 18 were at increased risk for developing asthma. However, the limitation of these clinical and epidemiological studies remains the difficulty in objectively measuring asthma.

An alternative to defining asthma is to use an associated objective marker such as AHR. Studies in children and adolescents have shown that both obese asthmatic and obese non-asthmatic subjects have greater degrees of exercise induced bronchospasm than their non-obese counterparts. To date, no other studies have investigated this phenotype in adults.

We found a U-shaped relationship between baseline BMI and the development of methacholine AHR. Our results are consistent with a previous Italian survey that investigated BMI and the prevalence of chronic diseases. Using data on 72 284 individuals aged 15 or over from the 1983 Italian National Health Survey, Negri et al found that men with BMI <20 kg/m² had an associated relative risk for asthma of 1.42 (95% CI 1.15 to 1.76) compared with men with BMI of 20–24.9 kg/m². The risk was also increased for men with BMI ≥30 kg/m² (RR 1.70, 95% CI 1.42 to 2.02). For women the association between BMI and asthma was more linear, consistent with previous findings among women. Interestingly, for both men and women in this study the association between BMI and emphysema or respiratory insufficiency was also found to be U-shaped. Nutritional factors may play a role in the development of methacholine AHR in older adult men. Our results also suggest that weight gain over this same time interval may be associated with an increased risk for the development of methacholine AHR, and this weight gain among cases in the lowest quintile of initial BMI may partly explain the increased risk associated with having a low BMI.

Over the past few years there have been increasing numbers of reports documenting the relationship between obesity and asthma across several age groups. In children the prevalence of asthma and wheeze were found to be greater in children who are overweight and obese. In adults two studies have found a relationship between obesity and reported asthma in women, but these studies did not find a significant relationship in men. The first study was a survey of 19 126 Dutch adults ranging in age from 20 years to over 65 years. Severely overweight women (BMI ≥30) were found to be 1.8 times more likely than women in the reference category (BMI=20.0–24.9) to have asthma. A second study was performed on 8960 adults aged 26 years who were part of the 1970 British Cohort Study and an increasing risk for asthma was observed for each quintile of BMI compared with the lowest quintile in women. Although the investigators observed an increased risk for asthma in the highest quintile in the men, this was not statistically significant. Because of the cross sectional nature of these studies, it is difficult to say whether obesity increases the risk for asthma or whether subjects became obese after their asthma became active. The relationship between obesity and asthma was investigated in a prospective analysis among nurses participating in the Nurses Health Study. The risk for incident asthma over the 4 year follow up period increased in a linear fashion with increasing BMI measured at the start of follow up, and subjects who gained weight after the age of 18 were at increased risk for developing asthma. However, the limitation of these clinical and epidemiological studies remains the difficulty in objectively measuring asthma.

An alternative to defining asthma is to use an associated objective marker such as AHR. Studies in children and adolescents have shown that both obese asthmatic and obese non-asthmatic subjects have greater degrees of exercise induced bronchospasm than their non-obese counterparts. To date, no other studies have investigated this phenotype in adults.

We found a U-shaped relationship between baseline BMI and the development of methacholine AHR. Our results are consistent with a previous Italian survey that investigated BMI and the prevalence of chronic diseases. Using data on 72 284 individuals aged 15 or over from the 1983 Italian National Health Survey, Negri et al found that men with BMI <20 kg/m² had an associated relative risk for asthma of 1.42 (95% CI 1.15 to 1.76) compared with men with BMI of 20–24.9 kg/m². The risk was also increased for men with BMI ≥30 kg/m² (RR 1.70, 95% CI 1.42 to 2.02). For women the association between BMI and asthma was more linear, consistent with previous findings among women. Interestingly, for both men and women in this study the association between BMI and emphysema or respiratory insufficiency was also found to be U-shaped. Nutritional factors may play a role in the development of methacholine AHR in older adult men. Our results also suggest that weight gain over this same time interval may be associated with an increased risk for the development of methacholine AHR, and this weight gain among cases in the lowest quintile of initial BMI may partly explain the increased risk associated with having a low BMI.
in the risk for AHR and obstructive airway disease among those with a low BMI. In animal models, protein and calorie restriction during the prenatal and early postnatal periods can result in permanent abnormalities in lung structure and function, including emphysema-like lesions.\textsuperscript{17,18} In humans, experiments on volunteers showed a negative effect of starvation on various indices of ventilatory function.\textsuperscript{19} AHR was not measured in these early studies, and we are not aware of any other study which has reported an association between low BMI and AHR. Although we are quite certain that none of the men in our study was on a starvation diet, it may be that undernourishment in itself could have an effect on respiratory function. However, based on this analysis, at least part of the risk mechanism has been proposed to explain the association between weight gain and BMI, and not just low BMI, in the lowest quintile. Thus, we hypothesise that the mechanism(s) for the development of AHR in lean men may be different from the mechanisms occurring in obese men, leading to a non-linear association. This non-linear association between BMI and AHR in men may be one reason why many studies have found associations between BMI and asthma in women but not in men.

Our results also suggest that weight gain may be associated with an increased risk for development of AHR. Various mechanisms have been proposed to explain the association between weight gain and AHR and/or asthma. Weight gain resulting in obesity has been shown to result in reductions in lung volumes\textsuperscript{20} resulting in decreased airway calibre, which is a known factor in AHR.\textsuperscript{21} As a further mechanical consequence of obesity, breathing at lower tidal volumes leads to greater contractile responses of airway smooth muscle.\textsuperscript{22} The argument has also been made that obesity is a marker for decreased physical activity, a sedentary lifestyle and spending more time indoors,\textsuperscript{23,24} resulting in greater exposure to indoor allergens. Another plausible link could be with diet, especially with recent data suggesting that an increase in dietary fat may be associated with both AHR\textsuperscript{25} and asthma.\textsuperscript{26} There is emerging recognition that systemic inflammation occurs in the obese state, as evidenced by increased levels in the circulation of acute phase reactants\textsuperscript{27} and of proinflammatory cytokines.\textsuperscript{28} These proinflammatory cytokines are known to contribute to airway inflammation in asthma\textsuperscript{29} and provide a possible mechanism by which obesity may predispose to AHR or asthma. Additionally, the finding that leptin, the protein of the putative OB gene, upregulates inflammatory immune responses in a murine model\textsuperscript{30} strengthens the plausibility of this hypothesis. Whether or not significant inflammation occurs in formerly lean individuals who gain some weight is not known. Other potential mechanisms include autonomic pathways\textsuperscript{31} which may be common to both obesity and asthma, and genetic factors such as β adrenergic receptor polymorphisms\textsuperscript{32} that may predispose an individual to have both conditions. More studies are needed to clarify the mechanisms involved in this association.

Several limitations are recognised in this study. The number of cases that we were able to identify was relatively small. However, despite this, we were able to detect significant effects of BMI on the development of AHR. We also recognise that there may be variability in the response to methacholine, and going from a negative test to a positive test at a cumulative dose of 16.8 µmol methacholine may be part of this variability. However, restricting the analysis to a stricter definition of a positive test (cumulative dose of 8.58 µmol methacholine) yielded similar results. Another limitation was the fact that the second measurements of BMI and methacholine AHR occurred at the same examination at the end of the time interval of interest. Thus, for the cases the onset of AHR may have occurred at any time during the interval and may have preceded weight gain. Because of the relatively short time interval between observations, however, we feel that, for most of the cases, the onset of AHR occurred close to the time of the second examination. In addition, since no measures of physical activity or diet were used, we are unable to comment on the role of these exposures in the current analysis. The participants in our study were all middle aged to older white men with adult onset AHR; our findings may not be generalisable to younger men or to those of non-white ethnic origin.

In conclusion, we have shown that baseline BMI is associated with development of methacholine AHR in older men and that this association is non-linear. This finding may be one reason why previous studies, while finding linear associations between BMI and asthma in women, have not found significant associations between obesity and asthma in men. We have also shown a strong positive linear relationship between weight gain over the period of observation and development of AHR.

\begin{center}
\textbf{Authors' affiliations}
\end{center}

\begin{itemize}
\item A Litonjua, J C Celedon, S T Weiss, Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA
\item D Sparrow, Pulmonary Center, Boston University School of Medicine, Boston, Massachusetts, USA
\item D Sparrow, D DeMolles, Veterans Administration Medical Center, Boston, Massachusetts, USA
\end{itemize}

Grant support: KOB-HL03870 from the National Institutes of Health; HL34645 and HL03870 from the National Heart, Lung, and Blood Institute.

\textbf{Dr Litonjua is a recipient of an American Lung Association Research Grant RG-024-N.}

\textbf{Dr Sparrow is a Research Career Scientist of the Medical Research Service of the Department of Veterans Affairs.}

The Normative Aging Study is supported by the Cooperative Studies Program/ERIC of the US Department of Veterans Affairs and is a component of the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC).

\begin{thebibliography}{99}
\bibitem{5} Wilson MM, Irwin RS. The association of asthma and obesity. \textit{Arch Intern Med} 1999;\textit{159}:2513–4.
\bibitem{6} Bell B, Rose CI, Damon D. The Normative Aging Study: an interdisciplinary and longitudinal study of health and aging. \textit{Aging Hum Dev} 1972;\textit{3}:5–17.
\bibitem{8} Farris BG Jr. Epidemiology standardization project. \textit{Am Rev Respir Dis} 1976;\textit{118}:1–88.
\end{thebibliography}


Aging Study

hyperresponsiveness in men: the Normative Development of Methacholine Airway

A A Litonjua, D Sparrow, J C Celedon, D DeMolles and S T Weiss

Thorax 2002 57: 581-585
doi: 10.1136/thorax.57.7.581

Updated information and services can be found at:
http://thorax.bmj.com/content/57/7/581

These include:

References
This article cites 26 articles, 9 of which you can access for free at:
http://thorax.bmj.com/content/57/7/581#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Asthma (1782)
- Health education (1223)
- Smoking (1037)
- Tobacco use (1039)
- Obesity (public health) (197)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/