

### Sex differences in asthma morbidity associated with obesity in a representative population sample

To the Editor:

The association between obesity and asthma morbidity remains contentious. The results of the few studies that have investigated the impact of obesity on asthma control or morbidity have been inconsistent, and these studies have limitations in sampling and size.<sup>1,2</sup> Adipose tissue secretes a number of proinflammatory mediators,<sup>3</sup> which may provide a link between the 2 inflammatory states of asthma and obesity. Central/abdominal obesity may also have a greater modifying effect on airway smooth muscle function by mechanical factors.<sup>3</sup> Our aim was to determine the modifying effect of obesity and the relative effects of fat distribution on asthma morbidity in the North West Adelaide Health Study, a representative biomedical population study of adults (age 18 years) from Adelaide, South Australia (population 1.2 million).<sup>4</sup>

North West Adelaide Health Study participants were recruited from households selected at random from the electronic White Pages directory. Of the eligible sample of 8213, a total of 5850 (71%) completed the initial interview. Of these, 4060 (69%) attended the clinic for the biomedical examination. Respondents completed surveys and underwent clinic assessment, including measurement of spirometry (according to American Thoracic Society criteria), weight, and waist circumference. The study was approved by the institutional ethics committees of the North West Adelaide Health Service, and all subjects gave written informed consent.

This study was conducted in 563 (14.1%) people with asthma, identified by self-reported physician-diagnosed asthma or demonstration of a significant bronchodilator response of at least 9% predicted FEV<sub>1</sub> in the absence of a doctor's diagnosis of asthma. To avoid confusion with chronic obstructive pulmonary disease (COPD), we excluded 47 men (19.7%), and 30 women (9.4%;  $P < .01$ ) with persistent airways obstruction (postbronchodilator FEV<sub>1</sub>/forced vital capacity [FVC] ratio  $< 0.70$ ) from the analyses assessing the relationships among obesity and asthma morbidity, quality of life, and lung function in the remaining 482 subjects (192 men [12.3% of the population], 290 women [15.8%];  $P < .01$ ).  $\beta_2$ -Agonist medication use was identified through data linkage to the Australian Government's Pharmaceutical Benefit Scheme records. Participants completed questionnaires on smoking status, health service use, and demographics. Respiratory symptoms were assessed with the validated Chronic Lung Disease Index and physical health-related quality of life with the Short Form 36 (SF-36) Physical Health Component Summary (PCS) scores.

Data were weighted to census data by region, age group, sex, and probability of selection in the household to provide population representative estimates. Data were analyzed by using SPSS (Version 13.0; SPSS Inc, Chicago, Ill). Sex-specific multivariate ANOVA was used to calculate the means of continuous variables (eg, % predicted FEV<sub>1</sub>, decline in FEV<sub>1</sub>, and SF-36 PCS scores) in relation to body mass index (BMI) or waist circumference (WC) category, adjusted for baseline covariates including smoking status and age. Mean decline in percent predicted FEV<sub>1</sub> was

calculated in relation to follow-up BMI or WC category with adjustment for baseline BMI or WC. Because there was a significant interaction between sex and obesity for asthma morbidity, sex-specific multiple logistic regression models adjusted the adiposity-related risk of respiratory symptoms, airway obstruction, health service use, and  $\beta_2$ -agonist use for confounders including age and smoking (including former smoking). Separate models assessed asthma morbidity in relation to obesity because WC and BMI demonstrated significant collinearity when included in the same model in men and women.

The median ages of men and women with asthma were 52.0 (18-89 years) and 46.0 (18-80 years), respectively. Smoking rates (current and former) were not significantly different between women (42.2%) and men (47%). Overall, 71% ( $n = 345$ ; men, 77%; women, 61%) of the asthma sample without COPD at stage 1 was available at follow-up (mean, 3.5 years; SD, 0.6 years).

In men, obesity as assessed by WC (Table I) and BMI (see this article's Table E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)) was demonstrated in 35.4% and 24.5%, respectively (Pearson correlation,  $r = 0.89$ ). Compared with those with normal levels of the adiposity measures, obese WC and BMI were significantly associated with increased likelihood of moderate to severe respiratory symptoms,  $\beta_2$ -agonist use, frequent primary care visits in the previous 12 months, and significantly reduced lung function and quality of life, after adjustment for age and smoking. Obese men also demonstrated a decline in percent predicted FEV<sub>1</sub>, which was not statistically significant. When men with obstruction were included in the analysis, those with central obesity (but not BMI  $\geq 30$  kg/m<sup>2</sup>) also had an increased likelihood of demonstrating airway obstruction that bordered on significance.

In women, obesity as assessed by WC (Table I) and BMI (Table E1) was demonstrated in 43.4% and 46.4%, respectively (Pearson correlation,  $r = 0.91$ ). Only reduced quality of life and increased use of primary care providers were significantly associated with obesity. However, an overweight level of WC was significantly associated with increased likelihood of reporting symptoms and health service use. We observed an increased likelihood of airways obstruction with central obesity, but this was not statistically significant.

In this representative sample of urban adults with asthma, both central and generalized obesity was significantly associated with increased morbidity in men after adjusting for confounders. In contrast, centrally overweight women with asthma experienced the burden of excess morbidity. We excluded participants with airway obstruction from the analyses to avoid the observed morbidity being attributable to COPD. Furthermore, to address suggestions that asthma is overdiagnosed in obese subjects, we have demonstrated that obesity does not inversely associate with undiagnosed asthma.<sup>5</sup>

The only published study to assess asthma severity in relation to obesity with a large ( $n = 3095$ ) unselected sample used self-reported height and weight, and showed obesity was associated with several measures of asthma severity and that these associations were not modified by sex.<sup>6</sup> The misclassification of BMI because of the use of self-reported measures<sup>7</sup> has been reported to affect the association of obesity with asthma in men.<sup>8</sup> It is possible that self-reported measures may also affect the association of obesity with measures of asthma morbidity or severity and

**TABLE I.** Prevalence (%) and likelihood (odds ratio [OR] and 95% CI) of asthma morbidity, and mean (SE) pulmonary function, in relation to levels of WC in men and women with asthma

|                                               | Men (n = 192)      |                        |                   | Women (n = 290)     |                        |                    |
|-----------------------------------------------|--------------------|------------------------|-------------------|---------------------|------------------------|--------------------|
|                                               | Normal<br>(n = 80) | Overweight<br>(n = 44) | Obese<br>(n = 68) | Normal<br>(n = 111) | Overweight<br>(n = 53) | Obese<br>(n = 126) |
| Moderate to severe symptoms                   |                    |                        |                   |                     |                        |                    |
| Percent                                       | 9.2                | 13.6                   | 25.8              | 20.0                | 43.1                   | 19.4               |
| OR (95% CI)                                   | 1.00               | 1.52 (0.5-4.8)         | 2.58 (1.0-7.0)    | 1.00                | 3.00 (1.4-6.3)         | 0.92 (0.5-1.8)     |
| $\beta_2$ -Agonist use                        |                    |                        |                   |                     |                        |                    |
| Percent                                       | 2.3                | 27.3                   | 21.6              | 18.8                | 25.0                   | 19.3               |
| OR (95% CI)                                   | 1.00               | 32.6 (2.6-407)         | 25.5 (2.1-305)    | 1.00                | 0.80 (0.2-2.6)         | 0.58 (0.2-1.5)     |
| ≥1 Emergency department visit                 |                    |                        |                   |                     |                        |                    |
| Percent                                       | 13.6               | 15.6                   | 17.6              | 13.5                | 25.9                   | 16.7               |
| OR (95% CI)                                   | 1.00               | 1.33 (0.4-4.0)         | 1.96 (0.7-5.6)    | 1.00                | 2.80 (1.2-6.8)         | 1.79 (0.8-3.9)     |
| ≥6 Primary care provider visits               |                    |                        |                   |                     |                        |                    |
| Percent                                       | 22.2               | 27.3                   | 50.0              | 35.1                | 59.3                   | 57.1               |
| OR (95% CI)                                   | 1.00               | 1.02 (0.4-2.5)         | 2.64 (1.2-5.8)    | 1.00                | 2.60 (1.3-5.2)         | 2.34 (1.3-4.1)     |
| SF-36 PCS score                               |                    |                        |                   |                     |                        |                    |
| Mean (SE)                                     | 50.1 (1.1)         | 49.9 (1.5)             | 45.0 (1.2)        | 48.6 (1.0)          | 46.7 (1.3)             | 44.1 (0.9)         |
| ANOVA <i>P</i>                                | <.01               |                        |                   | <.01                |                        |                    |
| Postbronchodilator FEV <sub>1</sub> /FVC <70% |                    |                        |                   |                     |                        |                    |
| Percent                                       | 12.0               | 25.4                   | 24.4              | 5.1                 | 15.9                   | 10.0               |
| OR (95% CI)*                                  | 1.0                | 2.22 (0.92-5.3)        | 2.20 (0.98-4.9)   | 1.0                 | 3.81 (1.3-11.3)        | 2.29 (0.8-6.5)     |
| Postbronchodilator lung function              |                    |                        |                   |                     |                        |                    |
| % Predicted FEV <sub>1</sub>                  |                    |                        |                   |                     |                        |                    |
| Mean (SE)*                                    | 100.7 (1.7)        | 100.5 (2.2)            | 92.2 (1.8)        | 105.2 (1.4)         | 101.6 (2.0)            | 100.0 (1.3)        |
| ANOVA <i>P</i>                                | <.01               |                        |                   | .03                 |                        |                    |
| % Predicted FVC                               |                    |                        |                   |                     |                        |                    |
| Mean (SE)*                                    | 100.2 (1.6)        | 100.6 (2.1)            | 91.7 (1.7)        | 105.4 (1.4)         | 104.6 (2.0)            | 101.0 (1.3)        |
| ANOVA <i>P</i>                                | <.01               |                        |                   | NS                  |                        |                    |
| Decline in % predicted FEV <sub>1</sub> ‡     |                    |                        |                   |                     |                        |                    |
| Mean (SE)†                                    | 8.5 (1.8)          | 9.1 (1.6)              | 12.0 (1.4)        | 7.6 (1.6)           | 5.2 (1.4)              | 9.1 (1.0)          |
| ANOVA <i>P</i>                                | NS                 |                        |                   | NS                  |                        |                    |

NS, Not significant.

Waist circumference (cm): men: normal, ≤94 cm; overweight, 95-101 cm; obese, ≥102 cm; women: normal, ≤80 cm; overweight, 80-87 cm; obese, ≥88 cm.

Data are adjusted for age and smoking unless indicated otherwise.

\*Adjusted for smoking.

†Adjusted for smoking and baseline WC category.

‡At follow-up (mean, 3.5 years): Men—normal, n = 45; overweight, n = 33; obese, n = 62. Women—normal, n = 49; overweight, n = 42; obese, n = 107.

this accounts for the differences with our study. Previous evidence from selected samples may have limited generalizability to unselected samples. For example, Varraso et al<sup>2</sup> reported asthma severity was related to BMI in women only in a sample with low mean BMI (male subjects, 24.1; female subjects, 22.4 kg/m<sup>2</sup>) compared with our sample (27.9 kg/m<sup>2</sup>).

Consideration of measures of central adiposity in addition to BMI is important because of the potential effects of mass loading on the airways by central obesity.<sup>3</sup> Despite the similar effects of BMI and WC exerted on symptoms,  $\beta_2$ -agonist use, lung function, and quality of life in men, central but not generalized obesity was associated with persistent airways obstruction in male subjects. Other studies reporting an association between obstruction and generalized obesity have not examined the effects of central obesity.<sup>1</sup> Inconsistencies in the relationship between high BMI and airway hyperresponsiveness have led to suggestions of overdiagnosis or misdiagnosis,<sup>3</sup> without consideration of the effect of different obesity phenotypes. Determining the importance of fat

distribution will require measures of airway and systemic inflammation in longitudinal population samples with asthma for 2 reasons. First, the regional differences in adipokine production by visceral and abdominal subcutaneous fat<sup>9</sup> may also exist between peripheral subcutaneous fat and central fat deposits. Second, it is likely that statistical models will not identify the contribution of central or generalized obesity to asthma morbidity given their lack of statistical independence from each other.

The strengths of this study include our large representative population sample with longitudinal follow-up and the use of measured rather than self-reported adiposity measures, which have been shown to underestimate the prevalence of obesity.<sup>7</sup> Spirometry measures also enabled us to consider the effects of obesity on lung function. Limitations include the cross-sectional nature of our study and the relatively short follow-up time of the cohort that may have prevented the demonstration of statistically significant decline in lung function related to obesity in men.

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## Direct activation of natural killer T cells induces airway hyperreactivity in nonhuman primates

### To the Editor:

We and others recently demonstrated that the development of allergen-induced airway hyperreactivity (AHR) in mice requires the presence of a novel type of T cell, called invariant natural killer T (iNKT) cells.<sup>1,2</sup> iNKT cells represent a distinct lineage of T cells that express characteristics of both conventional T cells and natural killer cells and express a highly conserved T-cell receptor (TCR)  $\alpha$  chain: V $\alpha$ 14-J $\alpha$ 18 in mice and V $\alpha$ 24-J $\alpha$ Q in human subjects.<sup>3</sup> Unlike conventional T cells, which recognize protein antigens, iNKT cells recognize glycolipid antigens presented by the nonpolymorphic MHC class I-like molecule CD1d.<sup>3</sup> Although a critical role for iNKT cells has been clearly demonstrated in murine models of asthma, it is not yet certain whether iNKT cells play a similarly vital role in human subjects in the development of AHR, a cardinal feature of asthma.

We therefore examined the function of iNKT cells in asthma in primates by challenging cynomolgus monkeys with the

exquisitely specific iNKT cell-activating agent  $\alpha$ -galactocylceramide ( $\alpha$ -GalCer).  $\alpha$ -GalCer directly activates iNKT cells by specifically binding to the invariant TCR of iNKT cells in mice and human subjects<sup>3</sup> and, when administered into the lungs, causes AHR in wild-type but not in iNKT cell-deficient mice.<sup>4</sup> Because  $\alpha$ -GalCer is extraordinarily specific in directly activating iNKT cells, but not T<sub>H</sub>2 cells, airway epithelial cells, or smooth muscle cells (it has no effects in natural killer T cell-deficient mice),  $\alpha$ -GalCer is extremely useful in studying the role of iNKT cells in isolation of T<sub>H</sub>2 cells. Furthermore, monkeys provide a very useful model for studying human asthma because monkeys and human subjects are closely related in terms of their genomes, respiratory physiology, and immune responses<sup>5</sup> and because airway challenge of human subjects with  $\alpha$ -GalCer at this time poses unacceptable risks.

We challenged 4 monkeys with  $\alpha$ -GalCer or vehicle using a crossover design (approved by the animal care and use committees at the Children's Hospital Boston and the Charles River Laboratory), which minimized the effects of genetic variation and the differing past histories in each of the outbred monkeys. In particular, because each monkey served as its own control animal, the crossover design allowed us to normalize the different baseline levels of AHR that each monkey possessed and thus minimized the number of animals required for generating statistically significant results. Each adult cynomolgus monkey was anesthetized, intubated, and challenged with nebulized  $\alpha$ -GalCer or vehicle. For safety reasons and to avoid any possible toxic effects of  $\alpha$ -GalCer that might cause AHR, a dose-escalation approach was used, starting with a very low dose of  $\alpha$ -GalCer (150  $\mu$ g/m<sup>2</sup>) similar to the lowest doses used intravenously in phase I safety studies in human subjects with solid tumors. Only one dose of  $\alpha$ -GalCer was administered to the monkeys before evaluation of AHR because after activation with  $\alpha$ -GalCer, iNKT cells become anergic temporarily.<sup>6</sup> Twenty-four hours after challenge, the monkeys were reintubated and assessed for AHR by measuring lung resistance in response to increasing concentrations of methacholine.

Surprisingly, with the first very low inhaled dose of  $\alpha$ -GalCer (150  $\mu$ g/m<sup>2</sup>), 3 of the 4 monkeys had significantly increased AHR compared with that seen after challenge with vehicle control (Fig 1, A, monkeys A, C, and D). The fourth monkey (monkey B), which did not respond to the first dose of  $\alpha$ -GalCer, had a significant AHR response after later receiving a higher dose of  $\alpha$ -GalCer (600  $\mu$ g/m<sup>2</sup>; Fig 1, A, monkey B). When combined, data for the 4 monkeys showed that  $\alpha$ -GalCer inhalation induced a significantly higher percentage change in lung resistance from baseline compared with that after vehicle control ( $P = .0003$ , paired *t* test comparing results at the highest dose of methacholine used after  $\alpha$ -GalCer treatment; Fig 1, B). Although the primary outcome of the study (enhanced AHR in response to methacholine) was achieved, secondary outcomes (increased eosinophils, neutrophils, iNKT cells, and IL-4 levels in the bronchoalveolar lavage fluid in response to  $\alpha$ -GalCer), while trending toward an increase, did not reach statistical significance, possibly because the dose of  $\alpha$ -GalCer was too low due to safety considerations or due to the small sample size.

Nevertheless, these data clearly demonstrate that direct activation of pulmonary iNKT cells with  $\alpha$ -GalCer in monkeys resulted in the development of significant AHR. Furthermore, these results are consistent with observations in mice demonstrating that iNKT cells are required for the development of

**TABLE E1.** Prevalence (%) and likelihood (odds ratio [OR] and 95% CI) of asthma morbidity, and mean (SE) pulmonary function, in relation to levels of BMI in men and women with asthma

|                                                      | Men (n = 192)      |                        |                   | Women (n = 290)     |                        |                   |
|------------------------------------------------------|--------------------|------------------------|-------------------|---------------------|------------------------|-------------------|
|                                                      | Normal<br>(n = 48) | Overweight<br>(n = 97) | Obese<br>(n = 47) | Normal<br>(n = 113) | Overweight<br>(n = 88) | Obese<br>(n = 89) |
| Moderate to severe symptoms                          |                    |                        |                   |                     |                        |                   |
| Percent                                              | 9.1                | 10.4                   | 34.8              | 29.5                | 17.9                   | 23.0              |
| OR (95% CI)                                          | 1.0                | 0.96 (0.3-3.2)         | 3.98 (1.2-12.9)   | 1.0                 | 0.48 (0.2-0.98)        | 0.65 (0.3-1.3)    |
| β <sub>2</sub> -Agonist use                          |                    |                        |                   |                     |                        |                   |
| Percent                                              | 9.4                | 4.9                    | 31.0              | 23.9                | 12.5                   | 21.1              |
| OR (95% CI)                                          | 1.0                | 0.61 (0.1-4.1)         | 4.83 (1.1-20.5)   | 1.0                 | 0.24 (0.1-0.8)         | 0.46 (0.2-1.2)    |
| ≥1 Emergency department visit                        |                    |                        |                   |                     |                        |                   |
| Percent                                              | 16.3               | 10.4                   | 23.4              | 17.9                | 17.2                   | 15.9              |
| OR (95% CI)                                          | 1.0                | 0.88 (0.3-2.6)         | 2.03 (0.7-6.2)    | 1.0                 | 1.10 (0.5-2.4)         | 1.18 (0.5-2.5)    |
| ≥6 Primary care provider visits                      |                    |                        |                   |                     |                        |                   |
| Percent                                              | 26.5               | 27.1                   | 53.2              | 45.1                | 48.3                   | 53.9              |
| OR (95% CI)                                          | 1.0                | 1.27 (0.5-3.0)         | 3.35 (1.3-8.5)    | 1.0                 | 1.02 (0.6-1.8)         | 1.34 (0.8-2.4)    |
| SF-36 PCS score                                      |                    |                        |                   |                     |                        |                   |
| Mean (SE)                                            | 51.0 (1.4)         | 49.2 (1.0)             | 43.4 (1.4)        | 48.0 (0.9)          | 47.6 (1.0)             | 42.6 (1.0)        |
| ANOVA P                                              | <.01               |                        |                   | <.01                |                        |                   |
| Postbronchodilator FEV <sub>1</sub> /FVC <70%        |                    |                        |                   |                     |                        |                   |
| Percent                                              | 21.0               | 21.1                   | 14.5              | 13.2                | 5.4                    | 8.2               |
| OR (95% CI) <sup>†</sup>                             | 1.0                | 0.79 (0.4-1.7)         | 0.57 (0.2-1.5)    | 1.0                 | 0.42 (0.1-1.2)         | 0.57 (0.2-1.4)    |
| Postbronchodilator lung function                     |                    |                        |                   |                     |                        |                   |
| % Predicted FEV <sub>1</sub>                         |                    |                        |                   |                     |                        |                   |
| Mean (SE)*                                           | 98.5 (2.1)         | 100.7 (1.5)            | 90.3 (2.1)        | 103.5 (1.4)         | 101.9 (1.6)            | 101.4 (1.6)       |
| ANOVA P                                              | <.01               |                        |                   | NS                  |                        |                   |
| % Predicted FVC                                      |                    |                        |                   |                     |                        |                   |
| Mean (SE)*                                           | 97.0 (2.1)         | 100.9 (1.5)            | 90.3 (2.1)        | 103.7 (1.4)         | 105.2 (1.6)            | 101.2 (1.6)       |
| ANOVA P                                              | <.01               |                        |                   | NS                  |                        |                   |
| Decline in % Predicted FEV <sub>1</sub> <sup>‡</sup> |                    |                        |                   |                     |                        |                   |
| Mean (SE) <sup>†</sup>                               | 9.1 (2.7)          | 9.7 (1.1)              | 11.8 (2.1)        | 7.9 (1.6)           | 7.1 (1.2)              | 8.6 (1.4)         |
| ANOVA P                                              | NS                 |                        |                   | NS                  |                        |                   |

NS, Not significant.

BMI (kg/m<sup>2</sup>): normal, ≤24.9; overweight, 25.0-29.9; obese: ≥30.0.

Data are adjusted for age and smoking unless indicated otherwise.

\*Adjusted for smoking.

<sup>†</sup>Adjusted for smoking and baseline BMI category.

<sup>‡</sup>At follow-up (mean, 3.5 years): Men—normal, n = 27; overweight, n = 69; obese, n = 45. Women—normal, n = 66; overweight, n = 55; obese, n = 78.