problematic for the developing young child. Importantly, remodeling and airway changes typical of asthma can occur in children between 1 and 3 years of age.[9] The partial postbronchodilator reversibility seen in the recurrent exacerbation group in our study suggests that these children might not yet have fixed obstruction; however, it will be interesting to longitudinally assess for progressive loss of lung function in these children with early recurrent exacerbations.

A limitation of this study is the lack of baseline lung function measurements from the first several years of life, preventing us from definitively determining whether these severe wheezing episodes caused progressive loss of lung function, were due to an initial low baseline lung function, or both. However, data from the Tucson Children's Respiratory Study suggest that abnormalities in lung function might not be present during the first year of life but develop during early childhood in children with persistent wheezing.[3]

Our findings highlight the importance of close follow-up for children with histories of severe exacerbations during early life and suggest that preventing additional severe wheezing episodes could affect subsequent morbidity caused by loss of lung function. Thus novel strategies for the prevention of wheezing exacerbations, particularly in preschool children, are sorely needed.

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Obesity is not linked to increased whole-body mast cell burden in children

To the Editor:

Obesity is clearly associated with insulin resistance and chronic low-grade inflammation.[1,2] Macrophages appear to be especially important in this relationship because they infiltrate adipose tissue and produce a variety of inflammatory cytokines.[1] Exploring the contribution of other immune cells to the development of obesity, Liu et al[3] described a role for mast cells in the development of obesity and diabetes in mice. Using genetically modified mice and pharmacologic stabilizers of mast cells, they demonstrated that mast cells and mast cell–mediated protease expression can promote the growth of white adipose tissue. Importantly, the idea that mast cells might function in a similar manner in human obesity was suggested by the finding of increased numbers of mast cells in human white adipose tissue from obese compared with lean subjects in their study. Furthermore, mean serum tryptase levels were higher in obese (13.1 ng/mL) than lean (7.7 ng/mL) subjects, as determined by using an in-house tryptase assay. We attempted to replicate these data by comparing serum tryptase levels in obese, overweight, and lean subjects from a pediatric population.

Because the serum total tryptase level, which is comprised primarily of α and β protryptases, seems to correlate with the whole-body burden of mast cells,[4] we measured levels of this protein in subjects 8 to 18 years old recruited through newspaper advertisement for research participation. The cohort contained a diverse group of children and adolescents with and without obesity, impaired glucose tolerance, and/or diabetes mellitus (Fig 1, *A*, and see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). Because the body mass index (BMI) is age and sex specific in children and teens,[5] we divided the subjects based on the BMI percentiles by age and sex into those who were of healthy weight (BMI ≥5th to <85th percentile), overweight (BMI ≥85th to <95th percentile), and obese (BMI ≥95th percentile). Comparisons were made by using the nonparametric Kruskal-Wallis test because the data were not normally distributed after standardization to percentiles. No statistical difference in the

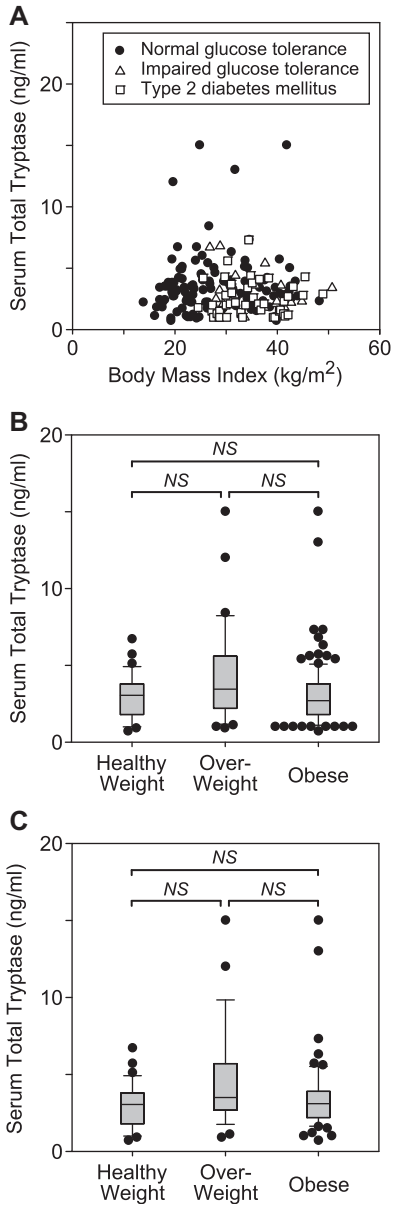

FIG 1. Serum total tryptase levels in healthy-weight, overweight, and obese pediatric patients. **A,** Serum total tryptase levels were measured in a cohort of pediatric patients with varying degrees of body fat, as approximated here by BMI. Subjects with normal glucose tolerance, impaired glucose tolerance, and overt type 2 diabetes mellitus are indicated by *solid circles*, *open triangles*, and *open squares*, respectively. **B,** Serum total tryptase levels were compared among all healthy-weight (n = 34), overweight (n = 26), and obese (n =117) subjects, as defined by BMI percentile. **C,** Serum total tryptase levels were compared among only those healthy-weight (n = 34), overweight (n = 21), and obese (n = 59) subjects, as defined by BMI percentile, with normal glucose tolerance. Box plots (Fig 1, *B* and *C*) demonstrate the medians and 10th, 25th, 75th, and 90th percentiles, with all outliers (those data outside the 10th through 90th percentiles) plotted as *solid circles*. *NS*, No significant difference.

median serum tryptase level was seen among the groups (3.1, 3.5, and 2.7 ng/mL, respectively; $P = .068$; Fig 1, *B*). Although the BMI varies with age and sex in pediatric patients, the raw values still accurately reflect total-body fatness[5] and thus should directly correlate with the serum tryptase levels according to the data presented by Liu et al.[3] Therefore to directly compare our results with those of Liu et al, lean subjects (BMI, <26 kg/m^2) were compared with overweight (BMI, ≥26 but <32 kg/m^2) and obese (BMI, ≥32 kg/m^2) subjects; these data were normally distributed. Again, no statistical difference among the groups was observed by means of 1-way ANOVA ($P = .449$; see Fig E1, *A*, in this article's Online Repository at www.jacionline.org).

Because some of the subjects in the cohort demonstrated impaired glucose tolerance or overt type 2 diabetes mellitus, the above comparisons were repeated with data from only those subjects with normal glucose tolerance. Once again, no statistical difference was seen between lean, overweight, and obese subjects, as defined either by BMI percentile ($P = .138$, Kruskal-Wallis test; Fig 1, *C*) or by BMI alone ($P = .386$, ANOVA; see Fig E1, *B*).

Finally, multiple linear regression analysis was performed on the entire cohort to determine the association of multiple different obesity-related parameters (BMI, BMI percentile, age, race, height, weight, fat mass, percentage of body fat, waist circumference, hip circumference, waist/hip ratio, visceral adipose tissue, percent visceral adipose tissue, subcutaneous adipose tissue, percent subcutaneous adipose tissue, and total adipose tissue) with serum tryptase levels. The combined model was unable to significantly predict serum tryptase levels ($R^2 = 0.043$ and $P = .997$ for all subjects and $R^2 = 0.110$ and $P = .974$ for only subjects with normal glucose tolerance). Moreover, none of the individual parameters were found to significantly correlate with serum tryptase levels.

We did not perform histologic examination of the adipose tissue, and thus we cannot comment on the numbers of mast cells within the adipose tissue. It is quite possible that they are indeed increased, as in the Liu et al[3] report. However, despite any possible increase in mast cell numbers in the adipose tissue, our data indicate that obese youth do not have a significantly increased whole-body mast cell burden that would manifest as an increased serum total tryptase level. There are several potential reasons for the conflicting results, the most obvious being the age difference of the subjects: in our study ages ranged from 8 to 18 years, whereas in the Liu et al[3] report, ages ranged from 20 to 66 years. Another recent study involving subjects aged 15 to 69 years showed a positive correlation between BMI and serum tryptase level (median tryptase level, 3.3 ng/mL [BMI, 18.5 to <25 kg/m^2], 3.8 ng/mL [BMI, 25 to <30 kg/m^2], and 4.3 ng/mL [BMI, ≥30 kg/m^2]),[6] albeit with a more modest effect than in the report by Liu et al.[3] In that same study age was also found to correlate with serum tryptase levels, with greater than 3 times the standardized effect of BMI. However, the link between obesity and chronic low-grade systemic inflammation has been established in children and adults, with similar immunologic mechanisms and cytokine profiles found in both populations.[7,8] Therefore one should expect that similar mechanisms for mast cell recruitment and activation should be present in both age groups, although this does not seem to be the case.

Another potential cause for the difference in findings is unintentional selection bias. Although Liu et al[3] attempted to exclude those with evidence of infection or inflammatory disease, the significantly increased serum tryptase levels seen in the obese group (up to 73 ng/mL) suggest that 1 or more of the subjects might have had an undiagnosed clonal mast cell disorder, such as systemic mastocytosis.[9] We would also note that the tryptase assay used by Liu et al[3] has been used in a limited number of studies and thus might not be well characterized or validated in a clinical

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