Relationship between exhaled nitric oxide and body mass index in children and adolescents

To the Editor:

We read with interest the report by de Winter-de Groot et al[1] on the association between body mass index (BMI) and exhaled nitric oxide (eNO) in healthy adults. Their results and conclusions prompted us to investigate a pediatric population.

We measured the eNO by using the single-breath online method with NIOX (Nitric Oxide Monitoring System; Aerocrine AB, Solna, Sweden) according to published criteria[2] in 40 nonatopic children with no history of respiratory tract disease (15 boys; median age, 11 y; range, 6.1-18 y; 22 [55%] showing signs of initial or advanced pubertal stage). None of the subjects took medications or food before the measurement. BMI was calculated for each participant. Since BMI is age-dependent and sex-dependent, BMI *z* scores were also computed according to published standards.[3]

Mean (SD) eNO was 10 (4.2) ppb. Mean (SD) BMI and BMI *z* score were 19.5 (3.3) kg/m^2 and 0.5 (0.9) kg/m^2, respectively. Thirteen subjects were overweight (BMI > 85th percentile) and 4 obese (BMI > 95th percentile). Correlation tests including the Spearman rank coefficient (ρ) and the Kendall τ-b revealed that eNO levels were related to age ($r = 0.6$; $P = .0001$) and BMI ($r = 0.4$; $P = .02$; Fig 1, *A*), but not to BMI *z* score ($r = -0.01$; $P = .9$; Fig 1, *B*) and sex ($r = 0.1$; $P = .4$).

An increase of eNO with age has been reported by Franklin et al[4] and was recently confirmed by Buchvald et al[5] in a large multicenter study of healthy children. It has been questioned whether age per se affects eNO. Several age-related variables, including developmental and maturational changes of the airways or changes in nitric oxide production as a result of different levels of inducible nitric oxide synthase activity, have been proposed as possible explanations.[5]

The primary aim of our investigation was to assess whether any relationship between eNO and adiposity exists. We observed a positive association between eNO and BMI that was explained by the strong correlation found between eNO and age. In fact, when we used the BMI *z* score, which is age-independent and sex-independent, this relationship was not further confirmed. Therefore, unlike in adults, the relationship between adiposity measures and pulmonary indices in children always needs to be controlled for age.

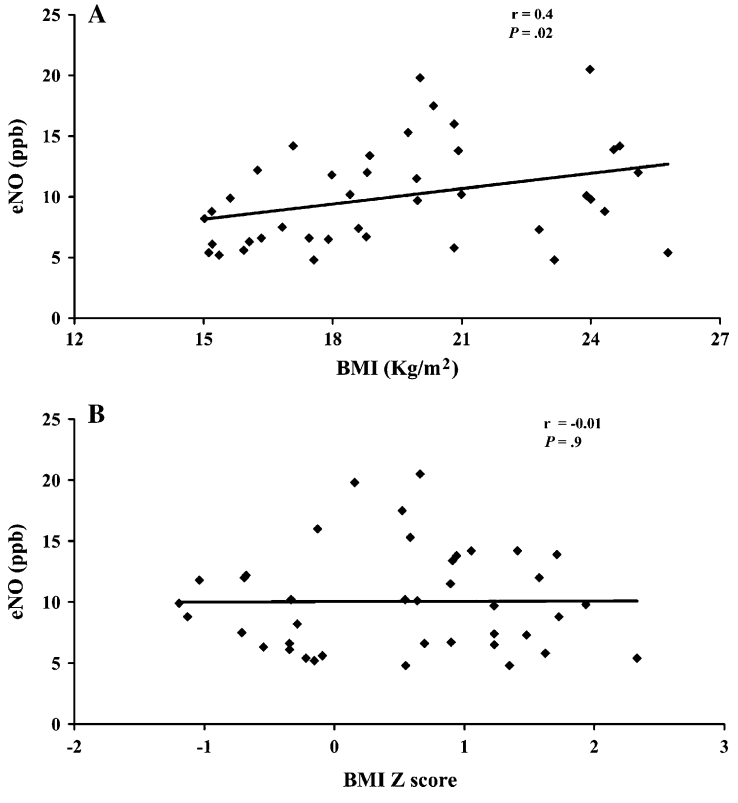

FIG 1. Relationship between eNO levels and **(A)** BMI or **(B)** BMI *z* score.

The only pediatric study examining the relationship between eNO and adiposity indices was performed in Hong Kong and failed to find any association between these variables in both 92 subjects with asthma and 23 controls.[6] Authors used an age-independent adiposity index (the weight-for-height z score) as well. However, the z score of −0.12 (0.88) in healthy subjects indicates that the score range shifted toward lower values, revealing that only few subjects were frankly obese. This might represent a drawback for the correct interpretation of the lack of relationship between eNO and obesity. Because our local population included 42% overweight or obese subjects, as usually occurs in the Italian pediatric population,[7] our results extend the findings from the former study, suggesting that no relationship exists between eNO and BMI z score.

The comparative analysis of the data among adult and pediatric studies seems to indicate that children, unlike adults, do not have a significant rise in eNO levels with increasing adiposity. We cannot provide a rational explanation for this. Overweight is associated with a low-grade systemic inflammation due to increased adipokines synthesis by fat tissue.[1] Even though no data on the enhancement of airways inflammation are available in obese adults or children, we speculate that adults, compared with children, might be exposed to high adipokines levels for a longer period. This might explain the positive relationship between overweight indices and eNO in adulthood.

Further studies should be implemented in both children and adults for clarifying the mechanisms linking adiposity to airway inflammation. Ideally, these studies would help explain the relationship between asthma and obesity.

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Reply

To the Editor:

Santamaria et al[1] describe a lack of association between exhaled nitric oxide (eNO) and body mass index z scores in healthy children. Recently we described a significant association between levels of eNO and body mass index in healthy adults[2] and suggested that obesity might result in upregulation of inflammatory mechanisms in the airways. Such a relationship in healthy adults was also described by Tsang et al[3] and was recently confirmed by Kazaks et al[4] in the Journal.

The discrepancy with the data from adults is intriguing. Although the dataset of Santamaria et al[1] is rather small, their findings are confirmed by 2 recent large studies in children[5,6] and therefore seem to be relevant.

One can speculate on the reasons for the observed differences between children and adults. Santamaria et al[1] suggest that differences in lung volumes between children and adults might cause differences in eNO levels. The relationship between lung volumes and gasses from alveolar origin like carbon monoxide is clear.[7] However, regarding eNO, which originates from the bronchi, such a relationship is lacking. In our study population,[2] no relationship was found between eNO and forced vital capacity (Spearman $r = 0.19$; $P = .36$), FEV_1 ($r = 0.13$; $P = .55$), total lung capacity ($r = 0.16$; $P = .46$), or residual volume ($r = -.07$; $P = .73$).

Buchvald et al[5] described an increase in eNO levels of 5% per annum in both boys and girls. If this increase is not caused by growing lung volumes, it might be speculated whether aging itself is related to a physiological rise in nitric oxide production. These findings underline the need for longitudinal studies from childhood to adulthood. Besides genetic and environmental factors, physiologic changes during aging will have an effect on the phenotype of chronic diseases like asthma and obesity and on their mutual relationships.

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