

To the Editors:

We read with interest the recent report by KORNUM *et al.* [1] investigating the link between community-acquired pneumonia and obesity in a large cohort of Danish patients. The authors observed that the increased risk of pulmonary infection no longer existed for obesity when other major chronic diseases were included in the regression model. Cohort studies that describe comorbid associations become more meaningful when one can assign an underlying pathophysiological process. In this context, we would suggest that there are a number of plausible mechanisms that are confounders with obesity. Insulin resistance and hyperglycaemia are more prevalent amongst obese individuals. Airway surface fluid glucose is normally strictly maintained at low levels, which may be as much as 20 times lower than that of plasma, by means of a process of active transport. Elevation of glucose in airway surface fluid, which can occur with even mild hyperglycaemia, promotes bacterial growth within the airway in a dose-dependent manner and predisposes to pneumonia [2].

It was also suggested that gastro-oesophageal reflux related to obesity increases the risk of community-acquired pneumonia by the aspiration of gastric contents into the lung. The situation may be rather more complex, as gastric contents by nature of their acidity are usually sterile. However, the use of acid-suppressing drugs, such as proton pump inhibitors and, to a lesser extent, H<sub>2</sub>-antagonists, raise gastric pH and promote the survival and growth of bacteria colonising the aerodigestive tract [3]. Use of the more potent proton pump inhibitors has increased in obese patients [4] and this group of drugs is strongly associated with the development of community-acquired pneumonia. One may also consider other drugs that are more frequently prescribed in the obese; for example, the statins. This class of drug may be beneficial in both preventing and reducing the severity of community-acquired pneumonia, thus decreasing the need for hospitalisation [5]. Improving the outcome of community-acquired pneumonia will require exploration of these and other mechanisms where plausible risk factors are identified by cohort studies.

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**Statement of Interest:** None declared.

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From the authors:

We thank our colleagues for their interest in our recent study in the *European Respiratory Journal* on the risk of pneumonia hospitalisation in obese individuals [1].

I. Schreter and colleagues present interesting data on body mass index (BMI) as a predictor of pneumonia in a cohort of patients hospitalised with influenza. Their findings suggest that increased BMI (reference value not stated) is related to higher odds for the presence of pneumonia among hospitalised influenza patients, after adjustment for age, sex and comorbidity. Pneumonia was present at the time of admission in most influenza patients with pneumonia, suggesting that obesity may have worsened the pre-hospital course of influenza. This association may be biological, *i.e.* due to impaired immune response, risk of aspiration, or an altered ventilation pattern in obesity. However, it may also be that obese persons are, on average, less likely to seek timely medical advice and antiviral medication treatment. The challenge in such observational epidemiological studies (including our own) is the risk of uncontrolled confounders associated with being obese, such as a less healthy lifestyle, a possible increase in substance abuse, fewer immunisations, and altered healthcare-seeking behaviour.

C.D. Hingston and colleagues suggest two pathophysiological mechanisms that may have increased the risk of pneumonia in our obese study participants: hyperglycaemia leading to bacterial growth in airway surface fluid, and acid-suppressing drug use leading to bacterial growth in the gastric contents that may be aspirated. Unfortunately, there were no available medication data in our dataset to examine the latter mechanism. However, we observed a higher occurrence of gastro-oesophageal reflux diagnoses in severely obese individuals (3% among those with a BMI  $\geq 35$  kg·m<sup>2</sup>) than in normal-weight participants (1% of those with a BMI 22.5–24.9). Concerning hyperglycaemia, we observed that 17% of severely obese *versus* only 1% of normal-weight participants in our study developed new uncomplicated diabetes during follow-up, and 6% *versus* 0.3%, respectively, developed complicated diabetes. Development of any comorbidity was a strong predictor of subsequent pneumonia in our cohort (hazard ratio (HR) 4.4 (95% CI 4.0–4.8) for a Charlson comorbidity index score of 1–2, and HR 11.5 (95% CI 9.4–14.2) for a Charlson index score of  $\geq 3$ ), and associations between baseline obesity and pneumonia risk vanished when adjusting for subsequent comorbidity [1]. Diabetes is known to increase pneumonia risk by 25–75%, particularly when long-term glycaemic control is poor [2]. We therefore find it likely that diabetes mediated some of the effect of obesity in our study, perhaps by the mechanisms suggested by C.D. Hingston and

colleagues. With regard to the use of statins, in a previous study we reported on their potential role in decreasing pneumonia severity [3], and we agree that differences in statin and other drug use may have caused some unmeasured confounding in our study.

The issue of obesity and infection in general is complicated. A certain degree of mild obesity or being slightly overweight might even be beneficial to withstanding infection [4] or when admitted with critical disease to the intensive care unit [5]. Based on our own results and those of others, including those noted during the recent influenza A (H1N1) pandemic, we believe that severe obesity (perhaps in particular abdominal obesity) increases the risk of severe influenza and pneumonia, as also reflected in the current immunisation guidelines [6]. We believe there is less evidence that mild obesity or being slightly overweight predicts severe respiratory tract infections, particularly where it is not associated with obesity-related comorbidities such as cardiovascular disease or diabetes [1].

We wholeheartedly agree with the remarks by I. Schreter and colleagues that, given the globally rising prevalence of obesity, we need to improve our understanding of the biological association between obesity and infections. This task requires joint efforts from epidemiologists and clinical and laboratory researchers within endocrinology, infectious diseases, respiratory medicine and related specialties.

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# The effect of nanoparticles on airway allergy in mice

*To the Editors:*

We read with great interest a recent experimental (*in vivo*) study by HUSSAIN *et al.* [1] and would like to comment on that article. First of all, we were very interested in the overall results that a single airway exposure to relatively low dose ( $16 \mu\text{g}\cdot\text{mouse}^{-1}$ ) of nanoparticles facilitates allergic airway inflammation. We have previously examined several types of nanoparticles/nanomaterials on ovalbumin-induced airway inflammation [2–5]. However, the doses were higher ( $25\text{--}100 \mu\text{g}\cdot\text{mouse}^{-1}$  administered weekly a total of seven times) and provoked a more moderate increase in the number of inflammatory leukocytes into bronchoalveolar spaces in the absence of allergen than that in the present study by HUSSAIN *et al.* [1]. Thus, their study is valuable in terms of promoting the effect of relatively realistic dose of nanoparticles on allergic inflammation, although sensitivity against nanoparticles seems to depend on mouse strains (we used ICR mice). We have recently shown that single intratracheal instillation of carbon black nanoparticles (CBNPs) (14 nm) at a dose of  $10 \mu\text{g}\cdot\text{mouse}^{-1}$  aggravates bleomycin-induced pulmonary fibrosis (unpublished data); thus, taking these studies into consideration, it is

confirmed at the animal model (*in vivo*) level that exposure to trace doses of some nanoparticles exacerbates several types of pulmonary inflammatory conditions.

Consistent with the study by HUSSAIN *et al.* [1], we have found that effects of nanoparticles/nanomaterials on airway hyper-responsiveness depend on the characteristics of these materials: two sizes (14 and 56 nm) of carbon nanoparticles significantly enhanced airway resistance [2]; in contrast, two types (single- and multiwalled) of carbon nanotubes [3, 4] and two sizes (25 and 100 nm) of latex nanoparticles did not ([5] and unpublished data). Indeed, some previous reports have implicated the independency of airway hyperresponsiveness from airway inflammation [6, 7]; thus, the theory might be applied to the impacts of nanoparticles/nanomaterials on the allergic trait in the study by HUSSAIN *et al.* [1].

Regarding factors contributing to inflammatory cell infiltration in the airway, impacts of immune modulators on the T-helper cell (Th) milieu should be important to assess allergic reactions. In particular, Th2 (*e.g.* interleukin (IL)-5) and Th17 (*e.g.* IL-17A) cytokines are reportedly crucial for eosinophil