Other studies seem to confirm our findings. In fact, it has been observed that the incidence of death was higher in obese subjects and heavy smokers [5]. This study observed also combined effects of smoking and obesity; a very high risk of death was found in obese heavy smokers. Also, another study observed that a very high proportion of people with intellectual disabilities and asthma were also current smokers and/or obese [6], confirming that both smoking and obesity are involved in the development of asthma and associated with worse disease outcomes.

On the contrary, CAZZOLA *et al.* [7] recently found that an increase in BMI was frequently associated with the diagnosis of COPD or asthma, but they did not find any further increase in asthma diagnosis in current smokers when compared to never or former smokers. Yet, for the majority of their patients, the diagnosis was mainly clinical and this may have influenced their results.

Smoking and BMI-induced inflammation may be the cause of a higher BHR in overweight/obese smokers. Obesity is considered as a state of chronic systemic inflammation resulting from interactions between adipocytes and adipose tissue macrophages that are recruited by obese adipose tissue. This inflammation, particularly obesity-related changes in tumour necrosis factor-α, leptin and adiponectin, may contribute to airway hyperresponsiveness in obesity [4]. However, persistent exposure to cigarette smoking, combined with asthmatic inflammation, may induce important changes in the asthma endotype with a predominance of activated macrophages and neutrophils in sputum, airways and lung parenchyma, as in early chronic obstructive pulmonary disease, causing a progressive decline in lung function over time [8]. Thus, it may be speculated that persistent exposure to cigarette smoke, associated with an obesity status, drives additive or synergistic inflammatory and remodelling responses in the asthmatic airways, thus explaining the increased risk for a more severe BHR in these subjects. Assessment of smoking habits and overweight/obesity in subjects with BHR is extremely important.

@ERSpublications
When associated, overweight/obesity and smoking can have additive/synergic effects on bronchial hyperresponsiveness http://ow.ly/q5Gms

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From the authors:

We thank B. Sposato and M. Scalese for their comments on our paper on smoking and bronchial hyperresponsiveness (BHR) [1], and we appreciate their interest for discussing the important, and complex, topic about determinants of BHR. Our paper was focused on the effects of smoking on BHR, a topic that has been under discussion for decades. Already in the very early, large scale, population studies, such as the Dutch Vlagtwedde-Vlaardingen Study [2], evidence was indicated concerning the effects of smoking on

BHR. Our contribution was that, in a general population study setting, we could demonstrate a dose-dependent association of smoking on BHR. This effect remained after the adjustment of effects concerning the level of lung function variables and a number of possible confounders.

B. Sposato and M. Scalese interestingly point out the effects of an increased body mass index (BMI) and obesity on BHR and suggest that our data could verify the interaction between smoking and BMI on BHR found in their study. Several studies have addressed the relationship between obesity and asthma, and less studies the association between obesity and BHR. Population-based studies using clinical methods, including BHR testing, have found an association between obesity and incident asthma among both males and females [3], while studies based on asthma cohorts have mostly found this association to be attributed to females [4]. In our current study setting, the association between BMI and BHR was addressed [5]. However, no statistically significant association was found in univariate analyses, why the odds ratio of increased BMI in multivariate settings was not reported in the paper (BMI $\geqslant$30 yielded nonsignificant odds ratios from 1.45 to 1.60 for a provocative dose of histamine inducing a 15% fall in forced expiratory volume in 1 s $\leqslant$1.6 mg histamine in multiple logistic regression analyses). A probable explanation is lack of statistical power due to the limited sample size of the subjects who underwent BHR testing in our study, and thus interaction analyses of smoking and BMI were not meaningful. Interestingly, the magnitude of the odds ratio for increased BMI is similar to what B. Spolato and M. Scalese have found.

Differences in outcomes can be explained by the large differences in sample sizes of subjects who underwent BHR testing in the study by B. Sposato and M. Scalese and in our study, and further by the different study populations. The study by B. Sposato and M. Scalese was based on almost 4000 asthma patients (approximately 2000 were hyperreactive) from their outpatient department, while our study reflected the adult general population of Helsinki, Finland.

Investigating selected patient populations may cause bias when studying associations between, for instance, obesity and BHR. In the 1980s DODGE *et al.* [6] had already pointed out problems with selection bias, *i.e.* that smoking subjects with respiratory symptoms were mostly classified as having bronchitis, while nonsmokers with similar symptoms were diagnosed as having asthma. It would be an advantage if the interesting results by B. Sposato and M. Scalese could be verified in studies based on the general population.

@ERSpublications
A dose-dependent association effect of smoking on BHR remained after the adjustment of a number of possible confounders http://ow.ly/qvglo

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