

From the authors:

We wish to thank R.J. Kurukulaaratchy and co-workers for their positive response to our article [1]. We were happy to see that our paper encouraged the Isle of Wight Birth Cohort (IOWBC) to assess the prognosis of early recurrent wheeze into the beginning adulthood. As the corresponding findings in the IOWBC, with its high 18-year follow-up rate of 90% [2], are in line with those from our Environment and Childhood Asthma Study, it strengthens the message that the longer term prognosis of early recurrent wheeze might not be as favourable as previously conceived [3, 4]. Furthermore, the findings underline the importance of long-running birth cohorts enabling studies where recall bias is limited. As recent retrospective reports suggest that adult chronic obstructive pulmonary disease may have an early-life origin [5, 6], the need for long-term prospective cohorts to address this specific question is obvious.

With the additional data now presented by R.J. Kurukulaaratchy and co-workers on the natural course of early life wheeze, we suggest a reconsideration of the possibility of diagnosing asthma in preschool children as well as caution when addressing the potential favourable long-term prognosis of early recurrent wheezy illness.



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We should reconsider diagnosing asthma in preschool children and be cautious with the prognosis of early wheeze <http://ow.ly/qkD5S>

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Received: June 18 2013 | Accepted: June 20 2013

Conflict of interest: None declared.

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Eur Respir J 2014; 43: 651 | DOI: 10.1183/09031936.00103313 | Copyright ©ERS 2014

Can overweight/obesity and smoking have combined effects on bronchial hyperresponsiveness?

To the Editor:

We read with interest the article by JUUSELA *et al*. [1], which showed a significant risk factor for bronchial hyperresponsiveness (BHR) with a dose-dependent pattern and which underlined that BHR severity increases with increased smoking (pack-years) in an adult sample of the general population. Unfortunately, in their study the authors did not analyse a possible additional influence of overweight/obese status on BHR. In fact, several researchers have shown that the overweight/obese condition may be a risk factor for BHR (adjusted for smoking), both in healthy subjects and, in particular, in asthmatics [2–4]. A fair amount

of subjects of the study of JUUSELA *et al.* [1] were most likely affected by asthma: most of them had a marked BHR, some had forced expiratory volume in 1 s (FEV₁) <80% and FEV₁ to forced vital capacity (FVC) ratio <70, others were allergic, others had had a history of wheezing or asthma in childhood, while others had elevated exhaled nitric oxide fraction values. To the best of our knowledge, there are no studies that have investigated the combined impact of body mass index (BMI) and smoking on BHR. Therefore, we tried to investigate such a possible influence by retrospectively analysing a sample of adults (aged >18 years) that performed a methacholine test for suspected asthma in our outpatient department. We recruited 3771 consecutive subjects (1842 (49.6%) males; 1929 (51.1%) hyperreactive patients; mean \pm SD age 38 \pm 15 years; FEV₁ 100.4 \pm 12.4%; FEV₁/FVC 85.1 \pm 6.9; BMI 25.1 \pm 4.6). Among them, 791 (21% of the total) were current smokers, whereas the remainder were nonsmokers. When we applied a multiple logistic multivariate regression analysis, current smoking status, corrected for sex, age, FEV₁, seasons and BMI, was a weak independent risk factor for BHR. In fact, only when a PD₂₀ (provocative dose producing a fall in FEV₁ of 20%) cut-off of 1600 μ g was used did the risk become statistically significant (OR 1.256, 95% CI 1.065–1.482; $p=0.007$), whereas no association was observed between smoking and marked BHR (400 μ g PD₂₀ cut-off). Conversely, only overweight and obesity status (reference: normal weight) were significant independent risk factors (corrected for sex, age, FEV₁, seasons and smoking) for BHR, both by using a 400 μ g and a 1600 μ g PD₂₀ cut-off value. In fact, odd ratios were 1.391 (95% CI 1.172–1.650) ($p<0.0001$) and 1.463 (95% CI 1.166–1.835) ($p<0.001$) in overweight and obesity status respectively, when we considered a lower cut-off, whereas, they were 1.196 (95% CI 1.021–1.401) ($p=0.027$) and 1.247 (95% CI 1.007–1.543) ($p=0.043$) when we considered a higher cut-off. At this point, multivariate logistic models (adjusted for age, sex, FEV₁ and seasons) were applied separately in smokers and nonsmokers to obtain odd ratios for four categories of BMI (underweight, normal weight, overweight and obese) with the purpose of examining the possible combined influence of smoking and weight status on BHR.

Our results, summarised in table 1, confirmed that overweight and obese status were significant risk factors for a marked BHR in nonsmokers. When we considered smokers, overweight and obesity status, compared to normal weight, were much higher risk factors for BHR, in particular for a marked BHR (table 1). Furthermore, we also investigated the possible interaction between BMI and smoking status by using a composite logistic model with all patients, including an interaction term for smoking status per weight status (reference: normal weight/nonsmoking condition). This analysis found a significant odds ratio only in overweight subjects, suggesting not only an additive, but also a synergistic, effect of smoking and weight for this category of subjects.

Therefore, according to our data and those of others, increased BMI can influence BHR [2–4]. Furthermore, even if overweight/obesity seems to determine a higher risk than smoking, the results of our study appear to confirm that overweight/obesity and smoking status together may have an additive (and perhaps also synergic) influence on BHR (and probably on asthma), rather than when they are present separately. This might suggest that a combination of different negative environmental conditions/exposures increases the risk of asthma. It must be underlined, however, that our patients were younger, selected differently and that the provocation test used was not the same as in the study of JUUSELA *et al.* [1].

TABLE 1 Adjusted[#] odd ratios with 95% confidence intervals for PD₂₀ \leq 400 μ g and PD₂₀ \leq 1600 μ g, according to smoking and body mass index and analysed by multivariate analysis

	Nonsmokers	Smokers	All [¶]
Subjects n	2920	791	3711
PD₂₀ \leq1600 μg			
Normal weight	1.00	1.00	1.00
Underweight	0.695 [0.395–1.221]	0.591 [0.255–1.373]	0.924 [0.339–2.522]
Overweight	1.169 [0.978–1.396]	1.279 [0.896–1.825]	1.119 [0.766–1.635]
Obese	1.235 [0.976–1.562]	1.440 [0.839–2.469]	1.218 [0.685–2.166]
PD₂₀ \leq400 μg			
Normal weight	1.00	1.00	1.00
Underweight	0.703 [0.376–1.315]	0.515 [0.182–1.458]	0.813 [0.245–2.693]
Overweight	1.247 [1.028–1.513] ⁺	2.024 [1.393–2.942] ^f	1.585 [1.066–2.356] ^{¶¶}
Obese	1.363 [1.059–1.755] [§]	2.096 [1.228–3.580] ^{##}	1.537 [0.866–2.730]

FEV₁: forced expiratory volume in 1 s; PD₂₀: provocative dose of methacholine producing a fall in FEV₁ of 20%. [#]: for FEV₁, sex, age and seasons; [¶]: composite logistic model that included an interaction term for smoking status per weight status (reference: normal weight/nonsmoking condition); ⁺: $p=0.025$; [§]: $p=0.016$; ^f: $p<0.0001$; ^{##}: $p=0.007$; ^{¶¶}: $p=0.023$.

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.



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

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Received: June 20 2013 | Accepted after revision: June 26 2013

Conflict of interest: None declared.

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Eur Respir J 2014; 43: 651–653 | DOI: 10.1183/09031936.00099513 | Copyright ©ERS 2014

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