



Pubertal-onset overweight and COPD in men: a cohort study

To the Editor:

A global obesity epidemic has occurred among both adults and children during the last three decades [1]. Among patients with chronic obstructive pulmonary disease (COPD), low body mass index (BMI) is associated with poor prognosis and excess mortality [2], while obesity appears protective [3], a phenomenon known as the obesity paradox. Still, in milder forms of COPD, obesity is associated with increased risk of mortality, possibly mediated *via* the strong association with diabetes and hypertension [4]. Furthermore, abdominal fat accumulation is the strongest predictor of lung function impairment [5], and abdominal circumference is almost twice as high in COPD patients as in sex- and age-matched controls [6]. Thus, previous studies on the relationship between BMI and COPD have evaluated the associations for adult BMI, while it is unknown if BMI during childhood or adolescence, *i.e.* many years before onset of COPD, predicts the development of COPD later in life.

The aim of the present study was therefore to determine if overweight established during childhood or puberty, many years before the COPD diagnosis, affects the risk of developing COPD.

In BEST (BMI Epidemiology Study) Gothenburg, we collected birth weight as well as measurements of height and weight from centrally archived School Health Care records and from military conscription tests for all men born between 1945 and 1961 in Gothenburg, Sweden, as previously described [7]. The main exposures were childhood BMI at 8 years of age and young adult BMI at 20 years of age [7], and childhood and young adult overweight (BMI ≥17.9 [8] or ≥25 kg·m⁻², respectively). Pubertal BMI change was calculated (BMI at 20 - BMI at 8 years of age). We retrieved the study subjects' highest achieved education level during the years 1990-2012, categorised as low, medium or high, from registers held by Statistics Sweden. Through linkage to the National Patient Register held by the National Board of Health and Welfare, Sweden, we obtained information on COPD diagnosis coded according to the International Classification of Diseases (ICD) system and defined as J44 in ICD10 or 496 in ICD9 as the main or auxiliary diagnosis. The 37670 men included in the study were followed from 20 years of age until censoring due to a COPD diagnosis (n=672), migration (n=2745), death (n=3929) or until 31 December 2016, whichever came first. Hazard ratios (HRs) and 95% confidence intervals were estimated by Cox regressions including birth year and country of birth (categorised as Sweden if the subject and both parents were born in Sweden, or other) as covariates. The statistical analyses were performed in SPSS (version 24; IBM, Armonk, NY, USA).

The ethics committee of the University of Gothenburg, Sweden, approved the study.

In this population-based study, 37670 men with information on both childhood BMI at age 8 years (mean \pm sD 15.7 \pm 1.4 kg·m⁻²) and BMI change during puberty (BMI at age 20 – BMI at age 8 years; 5.6 \pm 2.0 kg·m⁻²) were included and followed until 31 December 2016. Mean follow-up starting from 20 years of age was 40.2 years (1512923 person-years of follow-up). There were 672 cases of COPD before the end of follow-up and the mean age at diagnosis was 58.9 \pm 6.1 years.

Cox regression analyses did not reveal a significant association between childhood BMI at 8 years of age and risk of a COPD diagnosis. However, BMI change during puberty displayed a significant nonlinear association with risk of COPD (p-value for quadratic term <0.05).

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Men who develop overweight specifically during puberty (*i.e.* normal weight at age 8, overweight at age 20 years) have 70% increased risk of COPD as adults compared to men without overweight http://bit.ly/2TradZA

Cite this article as: Tengvall S, Ohlsson C, Bygdell M, *et al.* Pubertal-onset overweight and COPD in men: a cohort study. *ERJ Open Res* 2020; 6: 00326-2019 [https://doi.org/10.1183/23120541.00326-2019].

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Whereas childhood overweight (n=2357) was not associated with the risk of COPD later in life (HR 1.00, 95% CI 0.73-1.37), young adult overweight (n=2788) demonstrated a significant association with the risk of COPD (HR 1.49, 95% CI 1.15-1.93). To determine the importance of timing of onset of overweight, we analysed the risk of COPD for four combinations of normal weight/overweight status at childhood and young adult age. These analyses demonstrated that men who developed overweight during puberty (i.e. normal weight at 8, overweight at 20 years) had a substantially increased risk of COPD (HR 1.72, 95% CI 1.28-2.32) compared with men who were never overweight (table 1). In contrast, men with childhood-onset overweight that resolved during puberty (i.e. overweight at 8, normal weight at 20 years), and men with childhood-onset overweight who were persistently overweight throughout childhood and puberty (i.e. overweight at 8 and 20 years of age) did not have a significantly increased risk of adult COPD compared with men who were never overweight (table 1). Unfortunately, the analyses could not be adjusted for smoking as information on smoking was not available in this retrospective study. When we adjusted the association between overweight status and risk of COPD for the individuals' maximal education level, we found unaltered results compared to before adjustment (table 1). Similar results were also seen after adjustment for birthweight, and in the subgroup of subjects with Sweden as country of birth for the subject and both parents (table 1).

Thus, our findings suggest that pubertal-onset overweight is associated with >70% increased risk of developing COPD compared with men who were never overweight.

We have previously observed that BMI increase specifically during puberty is associated with the amount of visceral adipose tissue [9] in men. COPD patients have excessive visceral fat mass that is retained in patients with more advanced stages of COPD despite normal or underweight status [10]. A potential mechanistic link between visceral adipose tissue and COPD probably includes proinflammatory adipokines such as leptin released by adipocytes in response to tissue hypoxia [10]. Based on the findings in the present study, we speculate that visceral fat is involved in the mediation of the association between pubertal-onset overweight and the observed risk of COPD.

Childhood/young adult overweight status	Cases of COPD	HR (95% CI)
Base model		
Normal weight/normal weight (n=33514)	585	Ref.
Overweight/normal weight (n=1368)	23	1.00 (0.66–1.51)
Normal weight/overweight (n=1799)	47	1.72 (1.28–2.32)
Overweight/overweight (n=989)	17	1.08 (0.67–1.75)
Model adjusted for education level		
Normal weight/normal weight (n=32523)	585	Ref.
Overweight/normal weight (n=1334)	23	1.13 (0.75–1.72)
Normal weight/overweight (n=1753)	47	1.52 (1.12–2.04)
Overweight/overweight (n=961)	17	1.02 (0.63–1.65)
Model adjusted for birthweight		
Normal weight/normal weight (n=31714)	542	Ref.
Overweight/normal weight (n=1292)	21	1.05 (0.68–1.63)
Normal weight/overweight (n=1713)	42	1.67 (1.22–2.29)
Overweight/overweight (n=941)	16	1.12 (0.68–1.84)
Subcohort with Sweden as country of birth		
Normal weight/normal weight (n=27979)	496	Ref.
Overweight/normal weight (n=1138)	20	1.03 (0.66–1.61)
Normal weight/overweight (n=1469)	40	1.72 (1.25–2.37)
Overweight/overweight (n=821)	12	0.92 (0.52–1.63)

TABLE 1 Risk of COPD in relation to overweight status at childhood and at young adult age

Hazard Ratios (HRs) for COPD were calculated using Cox proportional hazards regression. All models were adjusted for birth year and country of birth. Base model: entire cohort, n=37670). Model adjusted for maximal education level: n=36571; categorised as low (n=6647, 17.6%), medium (n=16213, 43.0%) or high (n=13711, 36.4%). Model adjusted for birthweight: n=35660. Subcohort of subjects born in Sweden and with parents born in Sweden: n=31407. Normal weight/normal weight: not overweight at 8 or 20 years of age; overweight/normal weight: overweight at 8 but not at 20 years of age; normal weight/overweight: overweight at 8 un at 20 years of age; coverweight at 8 un at 20 years of age; coverweight at 8 un at 20 years of age. Childhood overweight at 8 years of age was defined as body mass index (BMI) \ge 17.9 kg·m⁻² while young adult overweight at 20 years of age was defined as BMI \ge 25 kg·m⁻².

The strengths of the present study include the well-powered cohort, and the long and nearly complete follow-up in Swedish registers. A COPD diagnosis in the National Patient Register in Sweden has good validity as compared with medical records [11]. The limitations include that COPD diagnoses were captured through hospital-based registers, thus overlooking patients who were never treated at a hospital but only in primary care, resulting in a lower prevalence of COPD than expected. Furthermore, we do not have information on tobacco smoking or measurement of visceral fat. Given the fact that tobacco smoking is the major contributor to development of COPD in adults in industrialised countries, the lack of information on smoking is a clear limitation. It has been highlighted that never-smokers comprise a substantial proportion of individuals with COPD [12, 13], and there is a strong relationship between prevalence of COPD and obesity among adult never-smokers [14]. These findings indicate that obesity may be a risk factor for COPD in nonsmokers.

The observational nature of our study precludes making conclusive statements about the observed associations and the lack of adjustment for smoking makes the results more uncertain. Our findings could, however, be useful for hypothesis generation.

In conclusion, we demonstrate that pubertal-onset overweight is associated with >70% higher risk of developing COPD later in life in Swedish men. Future studies are needed to elucidate the mechanisms behind this finding, and the possible link between visceral fat and the risk of developing COPD.

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Received: 7 Aug 2019 | Accepted after revision: 27 Dec 2019

Conflict of interest: S. Tengvall has nothing to disclose. C. Ohlsson has nothing to disclose. M. Bygdell has nothing to disclose. J. Martikainen has nothing to disclose. A. Andersson reports lectures in pulmonary medicine outside this work for AstraZeneca and Novartis. J.M. Kindblom has nothing to disclose.

Support statement: This study was supported by the Swedish Research Council and the Heart–Lung Foundation, and by grants from the Swedish state under the agreement between the Swedish government and the county councils (the ALF-agreement; 723791, 238261), the Lundberg Foundation, the Torsten Söderberg Foundation, the Novo Nordisk Foundation, and the Knut and Alice Wallenberg Foundation. Funding information for this article has been deposited with the Crossref Funder Registry.

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