

## LETTER TO THE EDITOR

# Childhood overweight and risk of obesity-related adult cancer in men

Dear Editor,

The global burden of cancer is significant. The list of malignancies regarded as obesity-related continues to expand as evidence accumulates [1, 2]. Fueled by the ongoing obesity epidemic, obesity has emerged as one of the most important preventable causes of cancer worldwide [1, 3]. Given the long latency periods of many obesity-related adult cancers, risk factors with onset during early age and accumulation of risks during one's life course are likely to be of importance [4].

Early age overweight is a proposed risk factor for obesity-related cancer as isolated measurements of high body mass index (BMI) in both childhood and late adolescence have been reported to associate with certain obesity-related cancers [2, 5, 6]. However, obesity-related cancer as a composite group has so far only been studied in relation to adult BMI [7]. Studies of the relative contribution of overweight or obesity in childhood and young adulthood for the risk of adult cancer have been scarce [4]. In this present study, we tested our hypothesis that childhood overweight is associated with the risk of obesity-related adult cancer (Supplementary Table S1), independent of overweight status in young adulthood, using the BMI Epidemiology Study Gothenburg [8]. This population-based cohort was initiated with the overall objective to study the associations between developmental BMI and the risk of adult disease. A total of 36,566 men born in 1945-1961 with height and weight measurements from school health care records were investigated. Childhood body mass index (BMI) at age 8 years and young adult BMI at 20 years of age were calculated using the raw data of all paired height and weight measurements in the age period of 6.5-9.5 years for childhood BMI, and in the age period of 17.5-22.0 years for young adults. During the 1.5 million person-years of follow-up after 20 years of age (median follow-up 41.3 years, interquartile range 37.7-45.6 years), 1,562 (32% of all cancer diagnoses) obesity-related cancer diagnoses and 570

deaths (55% of all cancer deaths) due to cancer classified as obesity-related occurred. The cohort is detailed in Supplementary Table S2 and the inclusion process in Supplementary Figure S1.

We found that boys with childhood overweight (BMI > 17.9 kg/m<sup>2</sup>; Supplementary Methods 1.2) had a markedly increased risk of obesity-related adult cancer and death due to obesity-related cancer, compared with their normal-weight peers (Table 1, Panel A). Overweight in young adulthood (BMI ≥ 25 kg/m<sup>2</sup>) was moderately associated with increased risk of obesity-related adult cancer, but not with obesity-related cancer death. In the model including both overweight status in childhood and young adulthood in the same analysis (Table 1, Panel A), the associations between childhood overweight and obesity-related cancer incidence and mortality were robust. The association between overweight in young adulthood and obesity-related cancer incidence did not reach statistical significance after adjustment for childhood overweight.

Next, we evaluated the impact of change in overweight status from childhood to young adulthood on the risk of obesity-related adult cancer. Interestingly, men with childhood overweight that normalized during puberty had a 38% increased risk of obesity-related adult cancer, compared with men who had normal weight both in childhood and young adulthood (Table 1). In contrast, men with pubertal onset overweight did not have an increased risk of obesity-related adult cancer compared with men who had normal weight both in childhood and young adulthood (Table 1). The results were robust even after adjustments (Supplementary Table S3). Results from sensitivity analyses were coherent with our main analyses (Supplementary Results 2.1 and 2.2), including analyses where the first 10 years of follow-up were excluded to rule out undiagnosed disease-related weight loss (Supplementary Table S4), and using the less inclusive definition of obesity-related cancer by the International Agency for Research on Cancer (IARC) from 2016 (Supplementary Table S5). Further assessments did not indicate that mortality from causes other than obesity-related cancer had

**Abbreviations:** BMI, Body Mass Index; IARC, International Agency for Research on Cancer; IGF-1, Insulin-Like Growth Factor 1

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**TABLE 1** Risk of obesity-related adult cancer in relation to overweight status at childhood and young adulthood. Hazard ratios (HR) for obesity-related adult cancer were calculated using Cox proportional hazards regression models adjusted for birth year, country of birth and educational level. **Panel A:** HRs for obesity-related adult cancer incidence (1562 cases) and mortality (570 deaths) in relation to overweight in childhood and young adulthood, compared to normal weight, i.e., either overweight at 8 years ( $n = 2204$ , 136 cases, 45 deaths) together with the covariates birth year, country of birth and education level, or overweight at 20 years ( $n = 2714$ , 135 cases, 43 deaths) together with covariates. In the combined model, both childhood overweight and young adult overweight were included, in addition to birth year, country of birth and educational level. Total cohort ( $n = 36,566$ ) included in analyses. \*  $p < 0.05$ . **Panel B:** HRs for obesity-related adult cancer incidence ( $n = 1562$ ) for combinations of overweight status at childhood and young adult ages were calculated using Cox proportional hazards regression adjusted for birth year, country of birth and educational level. 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 20 but not at 8 years of age, Overweight – Overweight = Overweight both at 8 and 20 years of age

Panel A: Association of childhood and young adult overweight with adult obesity-related cancer		
Separate and combined analyses of overweight status at different ages	Incidence HR (95% CI) compared to normal weight	Mortality HR (95% CI) compared to normal weight
Childhood overweight ( <i>separate analysis</i> )	1.51 (1.26-1.80)	1.38 (1.02-1.87)
Young adult overweight ( <i>separate analysis</i> )	1.25 (1.05-1.49)	1.15 (0.83-1.59)
Childhood overweight ( <i>both in the same analysis</i> )	1.46 (1.20-1.76)	1.39 (1.00-1.93)*
Young adult overweight ( <i>both in the same analysis</i> )	1.09 (0.90-1.33)	0.98 (0.70-1.37)
Panel B: Association of change in childhood and young adult overweight with adult obesity-related cancer incidence		
BMI status at 8 and 20 years	Incidence	
	HR (95% CI)	Total number of persons (number of cancer cases)
Normal weight – Normal weight	Reference	32,519 (1355)
Overweight – Normal weight	1.38 (1.09-1.75)	1333 (72)
Normal weight – Overweight	1.04 (0.81-1.31)	1753 (71)
Overweight – Overweight	1.69 (1.31-2.17)	961 (64)

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index;

**Note:** Total cohort  $n = 36,566$ . Childhood refers to 8 years of age; young adulthood refers to 20 years of age. According to the Centers for Disease Control and Prevention, childhood overweight was defined as BMI  $\geq 17.9$  kg/m<sup>2</sup> at 8 years of age, and young adulthood overweight as BMI  $\geq 25$  kg/m<sup>2</sup> at 20 years of age, including both overweight and obese subjects.

biased the observed increased risk of obesity-related cancer for boys with childhood overweight (Supplementary Figure S2). The absolute event rates of obesity-related cancer per 100,000 person-years were significantly higher for boys with childhood overweight than normal-weight boys (Supplementary Results 2.3). Thus, overweight in childhood was associated with an increased risk of obesity-related adult cancer, and this risk was not reversed if the childhood overweight status normalized before young adulthood.

These findings establish childhood overweight as an independent risk factor for obesity-related adult cancer in men. Studies using BMI from the conscription examination in Israel and Sweden have reported that BMI in late adolescence was associated with the risk of some cancer diagnoses in men [2, 6]. However, these previous studies [2, 6, 9] had only one BMI measurement available and were therefore unable to evaluate the relative importance of childhood overweight and overweight in young adulthood for the risk of obesity-related adult can-

cer diagnosis. The results of this present study from analyses of overweight in young adulthood alone are in agreement with these studies. However, when childhood overweight was included in the same model, childhood overweight, but not overweight in young adulthood, was associated with the risk of adult obesity-related cancer. The present results suggest that being overweight, specifically during the childhood period, may initiate biological processes that eventually lead to an increased risk of cancer and that this effect initiated during childhood was not reversed by normalization of BMI during puberty. It is plausible that being overweight at sensitive developmental stages could stimulate long-term changes that promote cancer genesis. We propose that childhood might be a developmental period especially sensitive to the deleterious effects of overweight on cancer genesis. Possible mechanisms include epigenetic, endocrine, or metabolic programming through hyperinsulinemia, systemic inflammation, adipokine aberration, or excess stimulation by growth hormone/insulin-like growth factor-1 (IGF-1) [10].

For our main analyses, obesity-related cancer was defined according to the IARC report [1], with the addition of the cancer types (oral cancer, malignant melanoma, male breast cancer, lymphoma, and leukemia) where accumulated evidence, including the findings from the recent well-powered Israeli military study in adolescents [2], support a link with obesity in men. However, the main findings of this present study were unaltered when using the less inclusive, conservative IARC-definition of obesity-related cancer. The strengths of the present study include the large size of the cohort and the long and near-complete follow-up in high-quality national disease registers. The population-based nature of the cohort with BMI available both in childhood and young adulthood provides a unique possibility to study the relative contribution of the onset of overweight during childhood and puberty to adult disease. The limitations include that we were not able to include women. Further, adjustment for potential residual confounders such as overweight later in the adult period or for lifestyle habits such as smoking, diet, alcohol intake, or physical exercise was not possible. Prevalence of childhood obesity at the time of the present cohort was low, and hence, analyses of childhood obesity included too few cases.

In conclusion, we identified childhood overweight as a risk factor for obesity-related adult cancer in men, which was independent of overweight status in young adulthood. Our findings suggest that weight control during childhood could prevent obesity-related adult cancer in men. Key issues for the future include finding effective strategies for the prevention and treatment of childhood overweight and obesity, and to define the associations between childhood overweight, adult overweight status and obesity-related cancer in women.

## DECLARATIONS

### AUTHORSHIP

Conceptualization: CO, JC, JMK. Data curation: JM, JMK, JC, MB. Formal analysis: JC, JM, JMK. Funding acquisition: CO, JC, JMK. Investigation: JC, JM. Methodology: CO, JK, JC. Project administration: JC, JMK. Resources: CO, JMK, MB. Software: JM. Supervision: JMK. Validation: CO, JC, JMK. Analyzed data: CO, JC, JMK. Writing - original draft: JC. Writing, review and editing: CO, JC, JM, MB, JMK.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethics Committee of the University of Gothenburg, Sweden, approved the study (protocol code DNR 013-10, 28-01-2010) and waived the need for informed consent due to the register-based nature of the study.

## CONSENT FOR PUBLICATION

The Ethics Committee waived consent for publication.

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## COMPETING INTERESTS

None of the authors have any competing interests to declare.

## DATA AVAILABILITY STATEMENT

Research data is not publicly available due to privacy and ethical restrictions. However, anonymized data that are minimally required to reproduce results can be made available from the corresponding author upon reasonable request, upon approval from the University of Gothenburg, if the data can be made available according to mandatory national law.

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