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Brief Communications

Body Size at Different Ages and Risk of 6 Cancers: A Mendelian Randomization and Prospective Cohort Study

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Abstract

It is unclear if body weight in early life affects cancer risk independently of adult body weight. To investigate this question for 6 obesity-related cancers, we performed univariable and multivariable analyses using 1) Mendelian randomization (MR) analysis and 2) longitudinal analyses in prospective cohorts. Both the MR and longitudinal analyses indicated that larger early life body size was associated with higher risk of endometrial (odds ratio$_{MR}$ = 1.61, 95% confidence interval = 1.23 to 2.11) and kidney (odds ratio$_{MR}$ = 1.40, 95% confidence interval = 1.09 to 1.80) cancer. These associations were attenuated after accounting for adult body size in both the MR and cohort analyses. Early life body mass index (BMI) was not consistently associated with

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the other investigated cancers. The lack of clear independent risk associations suggests that early life BMI influences endometrial and kidney cancer risk mainly through pathways that are common with adult BMI.

Adult obesity is associated with increased risk of several common cancers (1,2). Body mass index (BMI) in children and young adults is also associated with cancer risk (3-12), but the extent to which body weight in early life affects cancer risk independently of body weight later in life is poorly understood. Mendelian randomization (MR) studies using genetic proxies for BMI have generally confirmed previously reported associations for BMI from large, longitudinal cohort studies (13-19). A recent MR study found that elevated childhood BMI was associated with a decreased risk of breast cancer, whereas adult BMI had no additional effect on risk after accounting for childhood BMI (20). Whether other cancers present a similar pattern is largely unknown.

We sought to investigate body size at different ages in relation to risk of 6 common obesity-related cancers by carrying out 2 complementary lines of analyses using 1) genetic proxies for body size in an MR framework and 2) BMI measurements in large, prospective cohort studies, respectively.

We identified genetic instruments for body size at age 10 years and at ages 40-69 years in 453 169 UK Biobank participants. The instruments were subsequently evaluated in relation to risk of cancer of the colorectum, kidney, pancreas, lung, ovary, and endometrium using summary statistics from genome-wide association studies of between 10 000 and 100 000 samples (Supplementary Methods, available online)(21-28). There was no clear violation of the NO Measurement Error assumption and instruments explained between 2% and 5% of the body size variance (Supplementary Table 1, available online). We estimated odds ratios (ORs) of cancer for genetically predicted body size at age 10 years and adult body size, initially using univariable MR to estimate their main effects and subsequently using multivariable MR to evaluate their independence (29).

In parallel with the MR analysis, we conducted a longitudinal cohort analysis for the association of BMI at ages 18-20 years and 40-69 years with cancer risk in 185 361 participants of the European Prospective Investigation into Cancer and Nutrition study (Supplementary Methods, available online). We estimated hazard ratios of cancer for BMI at age 18-20 years and 40-69 years using Cox proportional hazards regression models and subsequently fitted mutually adjusted models to evaluate their independence (Supplementary Methods, available online). All statistical tests were 2-sided and a P less than .05 was considered statistically significant.

We found concordant risk association results in both MR and cohort analyses for kidney and endometrial cancer (Figure 1). Larger body size at age 10 years (OR = 1.40, 95% confidence interval [CI] = 1.09 to 1.80) and adult body size (OR = 1.74, 95% CI = 1.43 to 2.11) were clearly associated with higher kidney cancer risk in univariable MR. Similarly, higher BMI at ages 18-20 years and 40-69 years was associated with higher risk in the corresponding cohort analysis. The risk associations for adult body size remained in mutually adjusted multivariable analyses, whereas the associations for early life body size were attenuated (Figure 1). We found a similar pattern of risk associations for

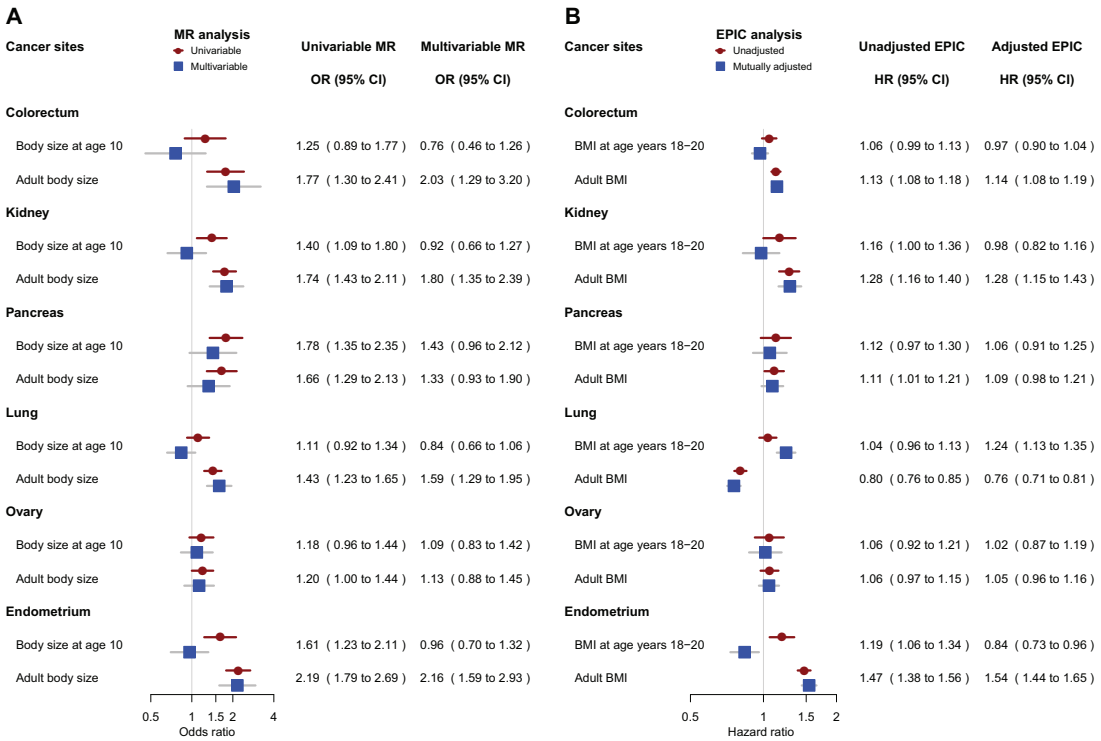

Figure 1. Mendelian randomization (MR) results and EPIC cohort results for different cancer sites. **A)** Odds ratios (ORs) and 95% confidence intervals (CIs) for category increase (ie, thinner than average, average, larger than average) in body size at age 10 years and adult body size before (univariable) and after (multivariable) mutual adjustment. **B)** Hazard ratios (HRs) for a 5-unit increase in BMI expressed in kg/m^2 at age 18-20 years and in adulthood before (unadjusted) and after (adjusted) mutual adjustment. BMI = body mass index; EPIC = European Prospective Investigation into Cancer and Nutrition.

endometrial cancer, with early life (OR = 1.61, 95% CI = 1.23 to 2.11) and adult (OR = 2.19, 95% CI = 1.79 to 2.69) body size clearly associated with risk in univariable MR. The risk association for early life body size was attenuated in multivariable MR but became inverse in the cohort analysis adjusted for adult BMI.

The associations of body size at different ages with risk of colorectal, pancreatic, lung, and ovarian cancer were less clear (Figure 1). For colorectal cancer, early life body size was not clearly associated with risk neither in MR nor in cohort analyses. For pancreatic cancer, the MR and cohort analyses showed similar risk associations for early life (univariable MR OR = 1.78, 95% CI = 1.35 to 2.35) and adult BMI (univariable MR OR = 1.66, 95% CI = 1.29 to 2.13), but mutually adjusted analyses slightly attenuated the risk association estimates for both exposures. The associations for lung cancer varied by histology (Figure 2). In MR, adult body size was associated with higher lung cancer risk to a various extent for different subtypes, whereas body size at age 10 years was not associated with risk after accounting for adult body size (Figure 2, A). In contrast, adult BMI was inversely associated with risk of lung squamous cell and adenocarcinoma in the cohort analysis, and BMI at age 18-20 years was positively associated with lung cancer risk after mutual adjustment but not after additional adjustment for smoking (Figure 2, B and C). The relationship between BMI and lung cancer risk is complex because obesity and smoking affect each other (30), but the 2 approaches taken together suggest that early life BMI may increase lung cancer risk through its effect on smoking behavior. For ovarian cancer overall, MR and the longitudinal analysis showed weak associations of early life or adult body size with risk (31) (Supplementary Table 2, available online).

Because studying correlated exposures may introduce the issues of pleiotropy and collinearity, we carried out a series of

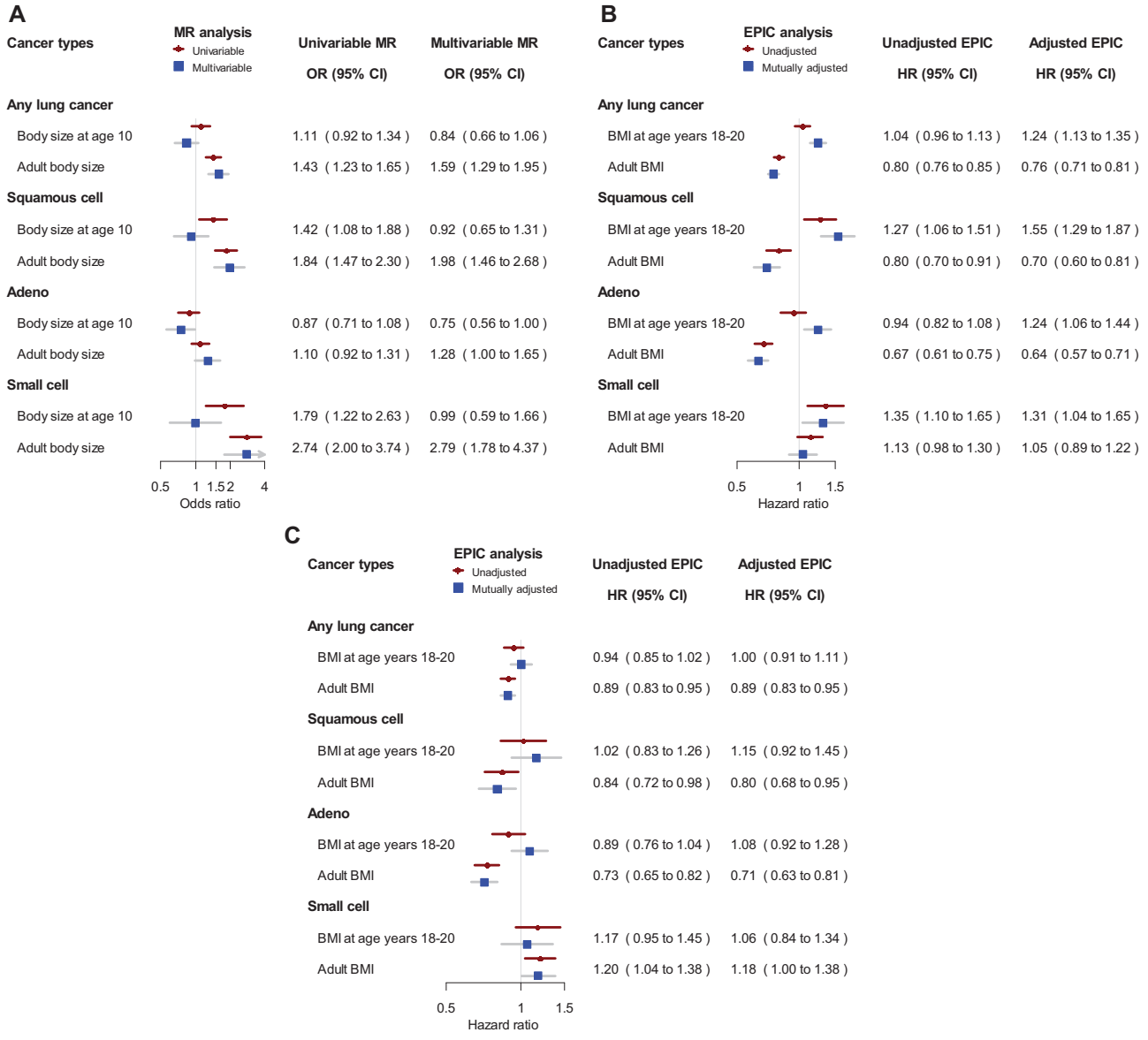

Figure 2. Mendelian randomization (MR) results and EPIC cohort results for lung cancer by histological subtypes. **A)** Odds ratios (ORs) and 95% confidence intervals (CIs) for category increase (ie, thinner than average, average, larger than average) in body size at age 10 years and adult body size before (univariable) and after (multivariable) mutual adjustment. **B)** Hazard ratios (HRs) for a 5-unit increase in BMI expressed in kg/m^2 before (unadjusted) and after (adjusted) mutual adjustment. **C)** Hazard ratios for a 5-unit increase in BMI expressed in kg/m^2 after adjustment for smoking before recruitment. BMI = body mass index; EPIC = European Prospective Investigation into Cancer and Nutrition.

sensitivity analyses but found the observed risk associations robust (Supplementary Table 2 and Supplementary Figures 1-3, available online). The main cohort analysis deliberately did not account for other risk factors because most are likely to lie on the same causal pathway as obesity (Supplementary Table 3, available online), but we note that additional adjustments for smoking, alcohol, physical activity, and education at recruitment (Supplementary Table 4, available online) did not materially influence the associations estimates.

Owing to limitations in available data, we assessed body size at age 10 years for MR but BMI at age 18-20 years for the cohort analysis. BMI during childhood and early adulthood could have different importance in cancer etiology, which may explain some of the differences between MR and cohort results. Considering this caveat, we chose to limit our research question to whether the risk associations of early life and adult body size are independent and conservatively focused our interpretation on those cancers where consistent results are observed between the MR and cohort analyses.

In conclusion, early life BMI may be a risk factor for renal and endometrial cancer, but our findings indicate that the risk associations of early life BMI are not independent to that of adult BMI. This suggests that early life obesity contributes to risk of these 2 cancers through mechanistic pathways common to adult BMI.

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Notes

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Data Availability

The data presented in this study are available on request from the corresponding author johanssonm@iarc.fr. This research was conducted accessing the UK Biobank data under application number 15825. Requests for the cancer data require formal approval by the principal investigators of each genetic consortium. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

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