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CANCER EPIDEMIOLOGY

SHORT REPORT

Causal association of childhood obesity with cancer risk in adulthood: A Mendelian randomization study

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Abstract

In observational studies of children and adolescents, higher body weight has been associated with distinct disease outcomes, including cancer, in adulthood. Therefore, we performed a two-sample Mendelian randomization (MR) study to evaluate the causal effect of childhood obesity on long-term cancer risk. Single-nucleotide polymorphisms associated with higher childhood body mass index (BMI) from large-scale genome-wide association studies were used as genetic instruments. Summary-level data for 24 site-specific cancers were obtained from UK Biobank. We found that a 1-SD increase in childhood BMI (kg/m^2) was significantly associated with a 60% increase in risk of pancreatic cancer (odds ratio [OR]: 1.60; 95% confidence interval [CI]: 1.12-2.28; $P < 0.01$) and a 47% increase in risk of esophageal cancer (OR: 1.47; 95% CI: 1.09-1.97; $P < 0.01$) in adults. In contrast, there was an inverse association of genetic predisposition to childhood obesity with throat (OR: 0.46; 95% CI: 0.27-0.79; $P < 0.01$) and breast cancer (OR: 0.77; 95% CI: 0.64-0.94; $P < 0.01$) in adult life. For the other 20 cancers studied, no statistically significant association was observed. Our MR analyses found causal effects of childhood obesity on several cancers. Maintaining a healthy weight should be emphasized during childhood and adolescence to prevent cancer risk later in life.

KEYWORDS
cancer, childhood obesity, gene, Mendelian randomization

What's new?

Higher body weight during childhood has been associated with various diseases later in life, but it's not known whether being overweight as a kid is the cause. Here, the authors used

Abbreviations: BMI, body mass index; CI, confidence interval; EGG, early growth genetics; GWAS, genome-wide association studies; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio; SD, standard deviation; SNP, single-nucleotide polymorphism.

Mendelian randomization analysis to look at the relationship between genetic predisposition to childhood obesity and adult cancer risk loci. For 20 cancers, they found no association. They determined that higher childhood BMI was associated with higher risk of pancreatic and esophageal cancer, and lower risk of throat and breast cancer. However, childhood BMI is also associated with adult BMI, so it's not entirely clear when the cancer-promoting effect happens.

1 | INTRODUCTION

Obesity has emerged to a global epidemic and accounts for the increasing burden of major chronic diseases, such as cardiovascular disease, diabetes and cancer.[1,2] It is more worrisome that children and adolescents are becoming overweight at progressively younger ages.[3] According to the estimation based on the Global Burden of Disease study, 107.7 million children were obese worldwide and the overall prevalence of obesity was 5.0% among children in 2015.[4]

Observational studies have suggested that higher body weight during childhood is associated with increased morbidity and mortality in adult life due to metabolic disorders.[5] One important consequence of these disorders is the high cancer risk.[6] However, observational studies are unable to fully account for residual confounding, thus the causality of the association remains poorly understood.

By using genetic variants as instruments, Mendelian randomization (MR) analysis is a method to assess the potential causality between exposure and outcome.[7] Previously, MR analysis has investigated the causal association between childhood BMI with breast cancer.[8,9] Here, we conducted a two-sample MR study to systematically examine the causal effects of childhood obesity on risk of 24 site-specific cancers.

2 | METHODS

For unbiased detection of causal effects, the genetic variants used as genetic variants in this MR analysis must satisfy three key assumptions: (a) the used genetic variants should be robustly associated with childhood BMI, (b) the used should not be associated with any confounders and (c) the genetic variants should influence the outcome (cancer risk in adulthood) only through childhood BMI, rather than alternative pathways. The second and third assumptions are collectively known as independence from pleiotropy.[10]

In the present MR study, childhood obesity was evaluated for body mass index (BMI) using genome-wide significant single-nucleotide polymorphisms (SNPs) from previous genome-wide association studies (GWAS) by the early growth genetics (EGG) consortium.[11] The large GWAS included 47 541 children from 33 individual studies, and identified 15 loci associated with childhood obesity ($P < 5 \times 10^{-8}$).

Types of cancer	Case/Control *n*	MR estimates OR (95% CI)	*P*	$P_{heterogeneity}$	$P_{pleiotropy}$
Pancreatic cancer	1060/400294	1.60 (1.12, 2.28)	<0.01	0.85	0.82
Gallbladder/bile duct cancer	323/400294	1.55 (0.74, 3.22)	0.24	0.64	0.79
Multiple myeloma	1005/414840	1.50 (0.97, 2.30)	0.07	0.58	0.36
Esophageal cancer	1068/400294	1.47 (1.09, 1.97)	0.01	0.96	0.43
Testicular cancer	332/400294	1.42 (0.53, 3.75)	0.49	0.09	0.24
Endometrial cancer	1765/198791	1.34 (0.94, 1.91)	0.11	0.40	0.87
Leukemia	2555/414840	1.17 (0.87, 1.58)	0.29	0.40	0.23
Thyroid cancer	518/418625	1.17 (0.64, 2.15)	0.60	0.64	0.56
Malignant melanomas	3658/402691	1.17 (0.91, 1.49)	0.22	0.41	0.49
Colorectal cancer	6375/401350	1.11 (0.93, 1.32)	0.25	0.55	0.18
Bone cancer	200/419977	1.09 (0.36, 3.27)	0.89	0.33	0.91
Lung cancer	3755/416654	1.05 (0.84, 1.33)	0.65	0.55	0.44
Kidney cancer	1468/415431	1.05 (0.74, 1.50)	0.77	0.57	0.75
Mouth cancer	875/418011	1.04 (0.71, 1.52)	0.84	0.87	0.45
Ovarian cancer	1301/207089	1.02 (0.66, 1.59)	0.92	0.28	0.41
Prostate cancer	8639/176489	1.00 (0.80, 1.25)	0.98	0.02	0.67
Non-Hodgkin's lymphoma	2552/414840	0.99 (0.78, 1.25)	0.92	0.82	0.51
Stomach cancer	852/400294	0.92 (0.51, 1.65)	0.77	0.13	0.98
Brain cancer	748/418389	0.91 (0.52, 1.59)	0.75	0.35	0.08
Liver cancer	271/400294	0.80 (0.35, 1.84)	0.60	0.64	0.42
Bladder cancer	3269/415431	0.80 (0.62, 1.03)	0.09	0.46	0.39
Breast cancer	15249/416252	0.77 (0.64, 0.94)	<0.01	<0.01	0.40
Cervical cancer	345/198725	0.68 (0.37, 1.22)	0.19	0.89	0.97
Throat cancer	871/418011	0.46 (0.27, 0.79)	<0.01	0.26	0.85

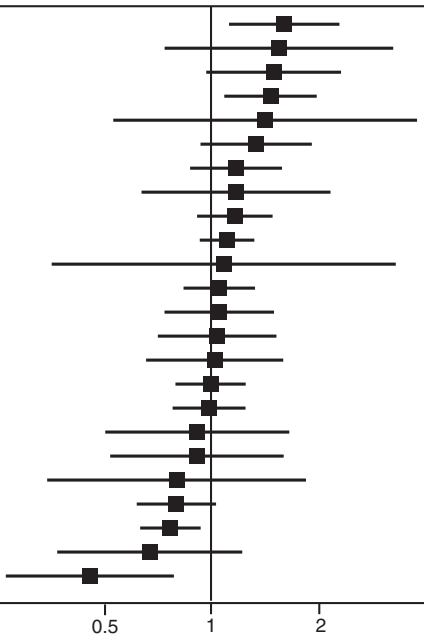

FIGURE 1 Associations between childhood body mass index (BMI) and 24 site-specific cancers. All estimations were based on the random-effects inverse variance weighted method and were standardized to a 1-SD decrease in childhood BMI due to genetic variants

TABLE 1 Sensitivity analyses of the associations between childhood BMI and site-specific cancers

	OR (95% CI)		
Types of cancer	**Weighted median**	**Simple median**	**MR-Egger**
Mouth cancer	1.09 (0.59-2.02)	1.07 (0.53-2.14)	2.16 (0.33-14.17)
Throat cancer	0.47 (0.22-0.99)	0.46 (0.21-0.99)	0.57 (0.07-4.88)
Esophageal cancer	1.23 (0.70-2.16)	1.40 (0.80-2.44)	2.89 (0.53-15.68)
Stomach cancer	0.62 (0.31-1.24)	0.93 (0.45-1.90)	0.94 (0.09-9.98)
Colorectal cancer	1.11 (0.86-1.42)	1.13 (0.86-1.49)	1.82 (0.89-3.69)
Liver cancer	0.91 (0.26-3.20)	0.73 (0.21-2.59)	3.34 (0.10-112.09)
Pancreatic cancer	1.53 (0.83-2.83)	1.75 (0.92-3.34)	1.95 (0.35-10.95)
Gallbladder/bile duct cancer	1.44 (0.45-4.62)	1.20 (0.35-4.12)	1.02 (0.05-22.74)
Lung cancer	1.02 (0.74-1.41)	1.03 (0.73-1.43)	0.74 (0.29-1.86)
Bone cancer	0.95 (0.20-4.49)	0.72 (0.16-3.34)	0.84 (0.01-68.64)
Malignant melanomas	1.11 (0.80-1.53)	1.14 (0.81-1.59)	0.84 (0.33-2.17)
Breast cancer	0.86 (0.71-1.03)	0.83 (0.68-0.99)	0.94 (0.44-1.99)
Cervical cancer	0.63 (0.21-1.90)	0.63 (0.21-1.90)	0.71 (0.03-14.80)
Endometrial cancer	1.41 (0.89-2.23)	1.51 (0.93-2.46)	1.50 (0.36-6.23)
Ovarian cancer	1.25 (0.68-2.29)	1.26 (0.68-2.36)	1.99 (0.36-11.03)
Prostate cancer	0.95 (0.73-1.22)	0.95 (0.72-1.25)	1.21 (0.49-2.96)
Testicular cancer	1.83 (0.55-6.12)	1.45 (0.42-5.03)	1.82 (0.05-72.77)
Kidney cancer	1.06 (0.64-1.75)	1.12 (0.66-1.91)	0.84 (0.20-3.54)
Bladder cancer	0.79 (0.56-1.12)	0.82 (0.57-1.19)	0.52 (0.19-1.39)
Brain cancer	0.74 (0.37-1.49)	0.79 (0.36-1.72)	0.14 (0.02-1.07)
Thyroid cancer	1.42 (0.58-3.47)	1.19 (0.46-3.07)	1.82 (0.14-23.70)
Non-Hodgkin's lymphoma	1.05 (0.71-1.57)	1.11 (0.74-1.67)	0.68 (0.22-2.07)
Multiple myoloma	1.90 (1.01-3.56)	1.62 (0.82-3.20)	0.66 (0.11-3.88)
Leukemia	1.17 (0.78-1.75)	1.13 (0.73-1.75)	0.59 (0.19-1.78)

Note: Results were standardized to a 1-SD decrease in childhood BMI due to genetic variants.
Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

The first-stage F statistic was used to evaluate the strength of each instrument. The following equation was used: $F = (R^2/k)/([1 - R^2]/[n - k - 1])$, where R^2 is the proportion of the variability accounted for by the SNP, k is the number of instruments used in the model and n is the sample size.[12] To minimize weak instrument bias, only SNPs with an F statistic >10 were included in subsequent analyses.

Summary-level data for 24 site-specific cancers were obtained from the Pan-ancestry genetic analysis of the UK Biobank.[13] The UK-based prospective cohort study was approved by the North West Multicentre Research Ethics Committee, and recruited 488 377 genotyped adults aged 40 to 69 years. In the current analyses, we confided the study samples to European-descent participants, in order to control the bias introduced by population stratification. Cases were obtained until 31 March 2017 and cancer diagnoses were based on the national registries (International Classification of Diseases, 10th revision code).

For MR estimation, we used the inverse variance weighted (IVW) method to assess the combined causal associations. Due to heterogeneity among the causal estimates of different variants, a random-effects model would be more appropriate than a fixed-effects model.[14] Because a simple instrumental variable analysis alone may not be relied on to give a causal conclusion, we used simple median, weighted median and MR-Egger methods as sensitivity analyses to explore the robustness of our findings.[15] Briefly, the median-based methods give a consistent estimate of the causal effect when over 50% of the genetic variants are valid instruments, while MR-Egger regression can detect violations of standard instrumental variable assumptions.

To explore the direct effect of adult BMI, we performed a multivariable MR analysis.[16] Publicly available summarized data regarding the genetic association of instruments with adult BMI were acquired from the Genetic Investigation of Anthropometric Traits.[17]

We considered the associations significant if the directions of the estimates by three methods were consistent and the main IVW MR reached a threshold of $P < 0.05$. Odds ratios (ORs) with 95% confidence intervals (CIs) of cancers are per one standard deviation (SD) increase in genetically predicted childhood BMI in all analyses. The SD of childhood BMI corresponds to 2.45 kg/m^2 based on the EGG study. Power calculations were based on a method designed by Burgess (https://sb452.shinyapps.io/power),[18] and results from these analyses were displayed in Supplementary Table 1. To assess the heterogeneity and pleiotropy, we used P-values from Cochran's Q test

and MR-Egger regression, respectively. All analyses were performed using Stata 15.0 and R 4.0.2 software.

3 | RESULTS

Characteristics of the 15 childhood BMI-associated SNPs used as instruments were presented in Supplementary Table 2.[19] *F* statistics for these SNPs ranged from 37 to 109, which making significant bias from the use of weak instruments is unlikely. There was also no evidence of pleiotropy observed by MR-Egger regression in all analyses (Figure 1).

Pooled MR estimates for the effect of childhood obesity on risk of different cancers were shown in Figure 1. And 1-SD unit increase in genetically predicted childhood BMI was associated with a 60.0% increase in pancreatic cancer risk (OR: 1.60; 95% CI: 1.12-2.28; $P < 0.01$), as well as a 46.5% increase in esophageal cancer risk (OR: 1.47; 95% CI: 1.09-1.97; $P < 0.01$). MR analysis also showed significant inverse associations between higher childhood BMI and risk of throat cancer (OR: 0.46; 95% CI: 0.27-0.79; $P < 0.01$) and breast cancer (OR: 0.77; 95% CI: 0.64-0.94; $P < 0.01$). No association was found in the other 20 cancers (Figure 1). We detected significant heterogeneity only in the analyses of prostate cancer ($P = 0.02$) and breast cancer ($P < 0.01$). Sensitivity analyses using simple median- or weighted median-based methods showed similar patterns of the effect for childhood obesity on cancer risk, supporting the consistency and robustness of our findings (Table 1).

In addition, we also showed that a 1-SD increase in childhood BMI was associated with a 0.62-SD increase in adult BMI (OR: 1.87; 95% CI: 1.60-2.18; $P = 1.17 \times 10^{-15}$) (Supplementary Table 3). When considering adult BMI using multivariable MR method, although the directions of the causal links were consistent with univariable MR results, no significant associations between childhood BMI and those cancers were found (Supplementary Table 4). These results suggested that the effect of childhood BMI on cancer is not independent of adult BMI and long-term weight loss intervention might alleviate the unfavorable influence of childhood obesity on cancer risk.

4 | DISCUSSION

In this MR study, we systematically evaluated the causality between childhood obesity and cancer risk in adult life, and found that higher childhood BMI was associated with higher risk of pancreatic and esophageal cancer, and lower risk of throat and breast cancer. Compared to two previously published MR studies only involving cancers of breast, colorectum, lung, ovary and prostate,[8,9] the similar inverse association was found between childhood obesity and breast cancer risk in later life. However, the associations between childhood obesity and lower risks of throat and breast cancer remain poorly understood, but sex hormones such as estrogen may play a role.[20]

Our findings were consistent with results from the cohort studies that have demonstrated a pathogenetic impact of higher childhood BMI on pancreatic and esophageal cancer risk.[21,22] Mechanically, the detrimental effects of childhood obesity in relation to certain site-specific cancers might be driven by increased secretion of pro-inflammatory cytokines.[23] Using mice carrying a pancreas-specific oncogenic Kras mutation, Chang et al suggested that dysregulated autophagy, in addition to inflammation, may contribute to obesity-induced pancreatic cancer development.[24] Additionally, previous studies have demonstrated that obese individuals are more likely to have gastroesophageal reflux disease (GERD), a well-established risk factor for esophageal cancer.[25] Thus, interaction between childhood obesity and GERD may increase the risk of developing esophageal cancer.

Since the relationship between obesity and cancer is increasingly recognized, the benefit of weight loss on cancer risk also has got attention.[26] For instance, Parker and Folsom found an 11% lower incidence of any cancer in women who experienced intentional weight loss (more than 20 pounds) since age 18 years.[27] However, most of these studies are limited to adult populations, and the impact of weight loss in children and adolescents is less well defined. Thus, there is a need for further investigation evaluating the anti-cancer effect of intentional weight loss in overweight and obese children.

Key strengths of the study are primarily attributed to the MR design, which overcomes the limitations of observational studies. In addition, inclusion of multiple instrumental variables allows us to examine and adjust pleiotropy. Another strength is that the consistency between different MR approaches suggests the robustness of our findings.

However, our study also has several limitations. First, the statistical power was low in several analyses due to limited case number. Second, potential pleiotropy could not be completely ruled out, although no evidence was found by the MR-Egger method. Third, our analyses only included individuals of European origin, thus we may not be unable to generalize these estimates to other populations.

Finally, childhood obesity is significantly associated with increased adult levels of BMI, hip circumference-adjusted BMI and waist circumference-adjusted BMI.[19] Observation from cohort studies also suggested that adult BMI is positively associated with esophageal adenocarcinoma and pancreas cancer.[20] Therefore, it is difficult to specify when the cancer-promoting effect happens. Although other anthropometric measures, such as waist circumference, were reported to be associated with cancer risk,[28] we cannot assess the causal effect because of unavailability of genetic data.

In summary, our current results provide important evidence supporting an effect of childhood obesity on cancer and imply a substantial public health impact of childhood BMI modification. Normalization of body weight should be emphasized during childhood and adolescence to prevent cancer risk later in life.

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analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

ETHICS STATEMENT

Studies included in the consortia were approved by the institutional review board of Hangzhou Normal University and all participants provided written informed consent.

DATA AVAILABILITY STATEMENT

The UK Biobank data are available through the Pan-UKB team (https://pan.ukbb.broadinstitute.org). EGG data are available through online application (http://www.egg-consortium.org). Summary-level data used for the study will be made available upon reasonable request to authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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