Body size at different ages and risk of six 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 six obesity-related cancers, we performed univariable and multivariable analyses using *i)* Mendelian randomization (MR) analysis and *ii)* longitudinal analyses in prospective cohorts. Both the MR and longitudinal analyses indicated that larger body size at age 10 was associated with higher risk of endometrial (OR_{MR}=1.61, 95%CI=1.23-2.11) and kidney cancer (OR_{MR}=1.40, 95%CI=1.09-1.80). These associations were attenuated after accounting for adult body size in both the MR and cohort analyses. Early life BMI was not consistently associated with 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 [13-18]. A recent MR study found that elevated childhood BMI was associated with a decreased risk of breast cancer while adult BMI had no additional effect on risk after accounting for childhood BMI [19]. Whether other cancers present a similar pattern is largely unknown.

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

We identified genetic instruments for body size at age 10 and at age 40-69 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) [20-27]. There was no clear violation of the NO Measurement Error (NOME) assumption and instruments explained between 2% and 5% of the body size variance (Supplementary Table 1). We estimated odds ratios of cancer (ORs) for genetically predicted body size at age 10 and adult body size, initially using univariable MR to estimate their main effects, and subsequently using multivariable MR to evaluate their independence [28].

In parallel with the MR analysis, we conducted a longitudinal cohort analysis for the association of BMI at age 18-20 years and 40-69 years with cancer risk in 185,361 participants of the European Prospective Investigation into Cancer and Nutrition study (EPIC) cohort (Supplementary Methods). We estimated hazard ratios of cancer (HRs) 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). All statistical tests were two-sided.

We found concordant risk association results in both MR and cohort analyses for kidney and endometrial cancer (Figure 1). Higher body size at age 10 (OR=1.40, 95%CI=1.09-1.80) and adult body size (OR=1.74, 95% CI=1.43-2.11) were clearly associated with higher kidney cancer risk in univariable MR (UVMR). Similarly, higher BMI at age 18-20 and age 40-69 adult BMI were 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 endometrial cancer, with early life (OR=1.61, 95%CI=1.23-2.11) and adult (OR=2.19, 95%CI=1.79-2.69) body size clearly associated with risk in UVMR. The risk association for early life body size was attenuated in MVMR, 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 (UMVR OR=1.78, 95%CI=1.35-2.35) and adult BMI (UMVR OR=1.66, 95%CI=1.29-2.13), 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 was not associated with risk after accounting for adult body size (Figure 2A). 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 was positively associated with lung cancer risk after mutual adjustment but not after additional adjustment for smoking (Figure 2B-2C). The relationship between BMI and lung cancer risk is complex because obesity and smoking affect each other [38], but the two approaches taken together suggest that early life BMI may increase lung cancer risk through its effect on smoking behaviour. For ovarian cancer overall, both MR and the longitudinal analysis showed weak associations of early life or adult body size with risk [29] (Supplementary Table 2).

Because studying correlated exposures may introduce the issues of pleiotropy and collinearity, we carried out a series of sensitivity analyses but found the observed risk associations robust (Supplementary Table 2, Supplementary Figures 1-3). 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), but we note that additional adjustments for smoking, alcohol, physical activity and education at recruitment (Supplementary Table 4) did not materially influence the associations estimates.

Owing to limitations in available data, we assessed body size at age 10 for MR but BMI at age 18-20 for the cohort analysis. BMI during childhood and early adulthood could have different importance in cancer aetiology 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 suggest that early life obesity contributes to risk of these two 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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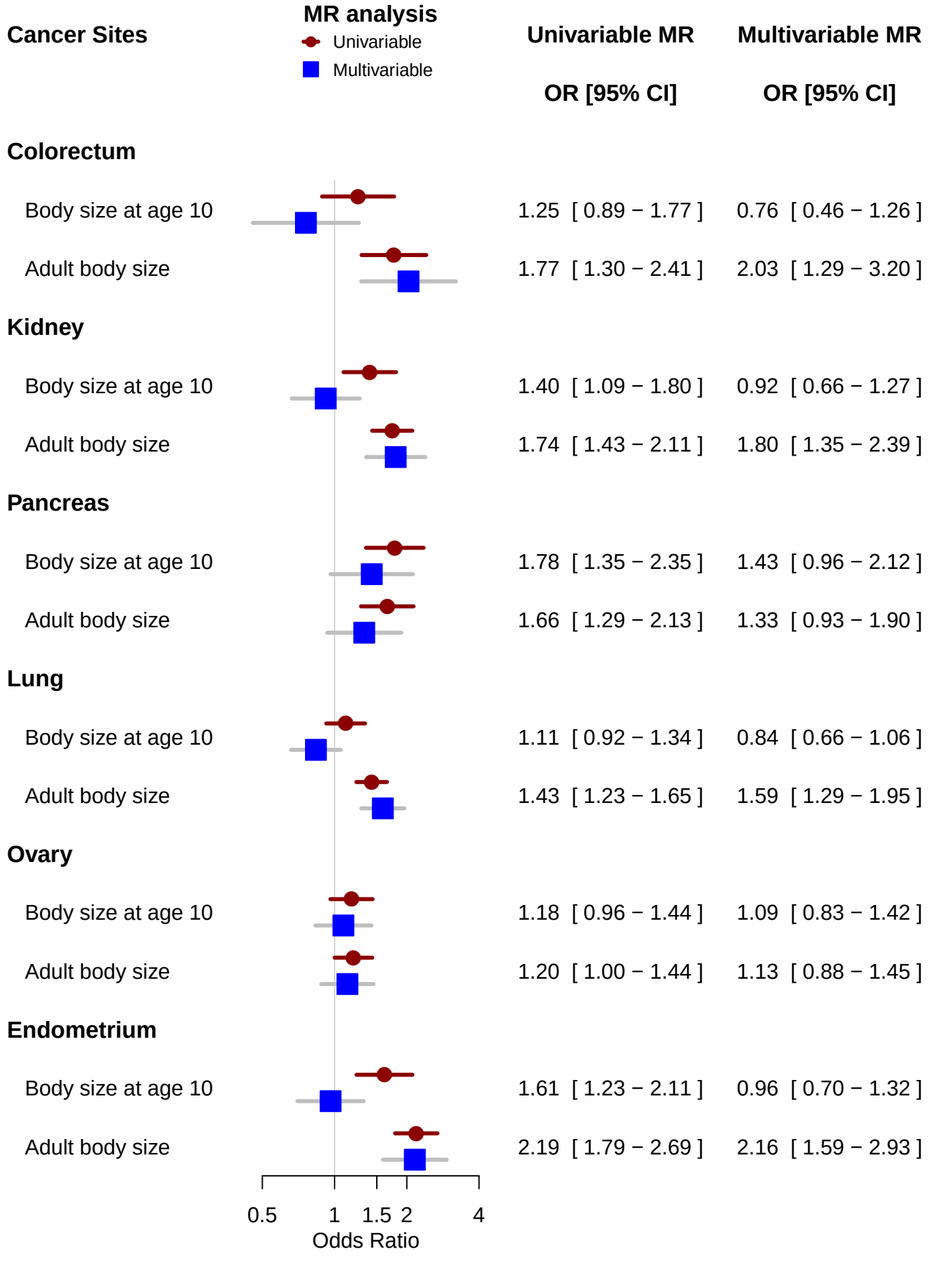
Figure Legends

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 (i.e. thinner than average, average, larger than average) in body size at age 10 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 and in adulthood before (unadjusted) and after (adjusted) mutual adjustment.

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 (i.e. thinner than average, average, larger than average) in body size at age 10 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.

A



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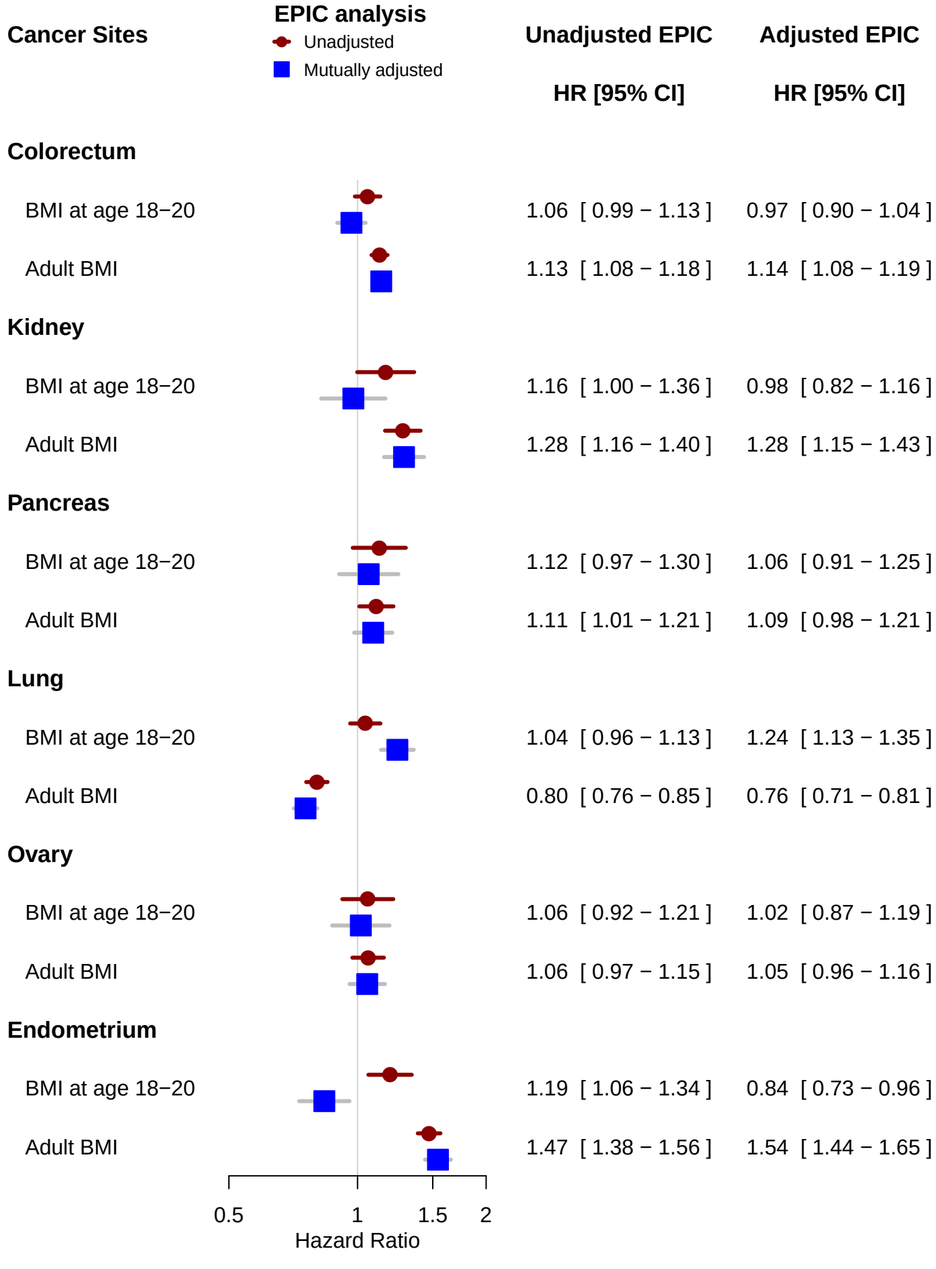

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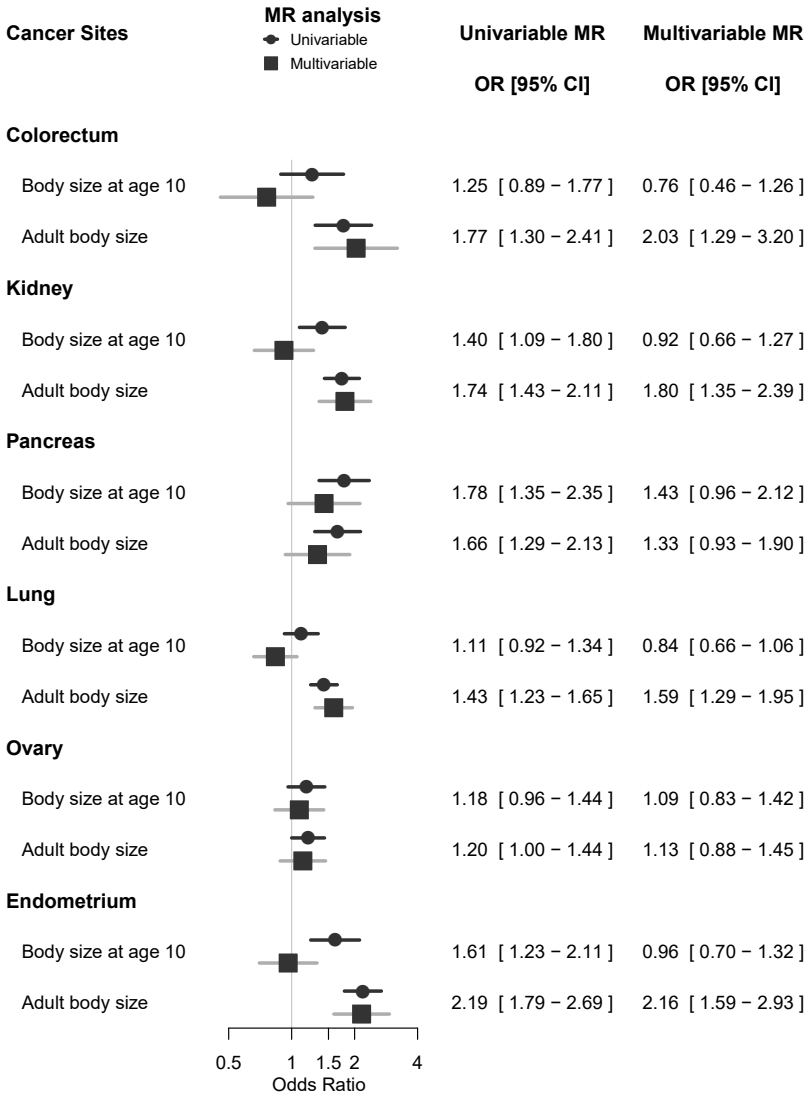

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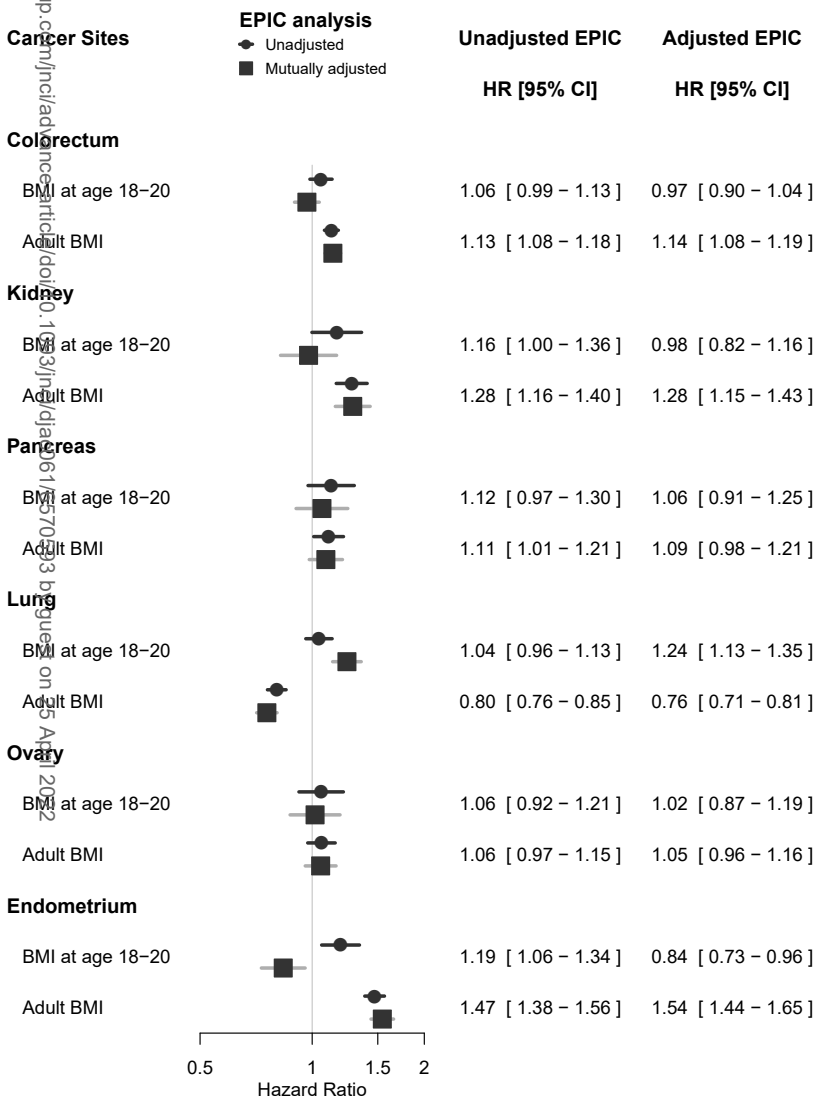
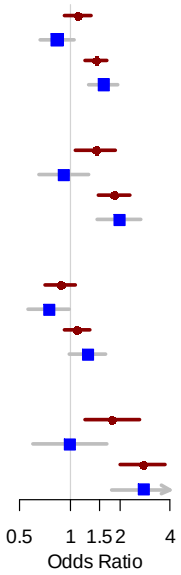


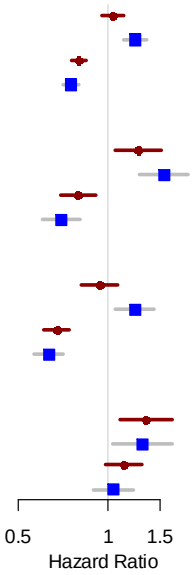
A

Cancer Types	Univariable MR OR [95% CI]	Multivariable MR OR [95% CI]
Any lung cancer		
Body size at age 10	1.11 [0.92 - 1.34]	0.84 [0.66 - 1.06]
Adult body size	1.43 [1.23 - 1.65]	1.59 [1.29 - 1.95]
Squamous cell		
Body size at age 10	1.42 [1.08 - 1.88]	0.92 [0.65 - 1.31]
Adult body size	1.84 [1.47 - 2.30]	1.98 [1.46 - 2.68]
Adeno		
Body size at age 10	0.87 [0.71 - 1.08]	0.75 [0.56 - 1.00]
Adult body size	1.10 [0.92 - 1.31]	1.28 [1.00 - 1.65]
Small cell		
Body size at age 10	1.79 [1.22 - 2.63]	0.99 [0.59 - 1.66]
Adult body size	2.74 [2.00 - 3.74]	2.79 [1.78 - 4.37]



B

Cancer Types	Unadjusted EPIC HR [95% CI]	Adjusted EPIC HR [95% CI]
Any lung cancer		
BMI at age 18-20	1.04 [0.96 - 1.13]	1.24 [1.13 - 1.35]
Adult BMI	0.80 [0.76 - 0.85]	0.76 [0.71 - 0.81]
Squamous cell		
BMI at age 18-20	1.27 [1.06 - 1.51]	1.55 [1.29 - 1.87]
Adult BMI	0.80 [0.70 - 0.91]	0.70 [0.60 - 0.81]
Adeno		
BMI at age 18-20	0.94 [0.82 - 1.08]	1.24 [1.06 - 1.44]
Adult BMI	0.67 [0.61 - 0.75]	0.64 [0.57 - 0.71]
Small cell		
BMI at age 18-20	1.35 [1.10 - 1.65]	1.31 [1.04 - 1.65]
Adult BMI	1.13 [0.98 - 1.30]	1.05 [0.89 - 1.22]



C

Cancer Types	Unadjusted EPIC HR [95% CI]	Adjusted EPIC HR [95% CI]
Any lung cancer		
BMI at age 18-20	0.94 [0.85 - 1.02]	1.00 [0.91 - 1.11]
Adult BMI	0.89 [0.83 - 0.95]	0.89 [0.83 - 0.95]
Squamous cell		
BMI at age 18-20	1.02 [0.83 - 1.26]	1.15 [0.92 - 1.45]
Adult BMI	0.84 [0.72 - 0.98]	0.80 [0.68 - 0.95]
Adeno		
BMI at age 18-20	0.89 [0.76 - 1.04]	1.08 [0.92 - 1.28]
Adult BMI	0.73 [0.65 - 0.82]	0.71 [0.63 - 0.81]
Small cell		
BMI at age 18-20	1.17 [0.95 - 1.45]	1.06 [0.84 - 1.34]
Adult BMI	1.20 [1.04 - 1.38]	1.18 [1.00 - 1.38]

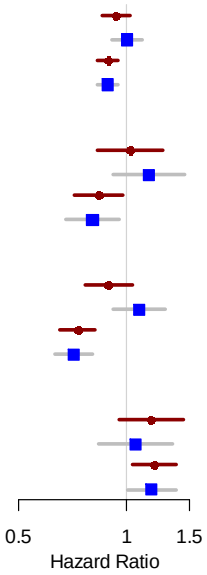


Figure 2 Black and White--FINAL

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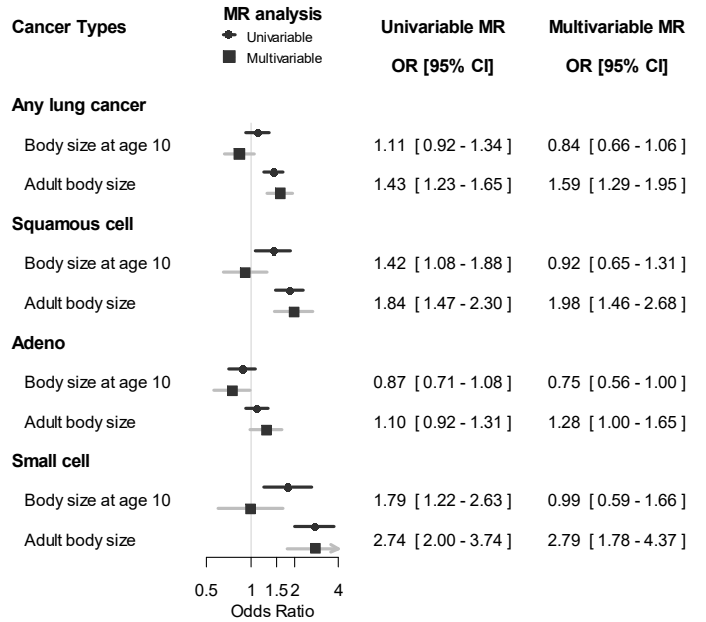
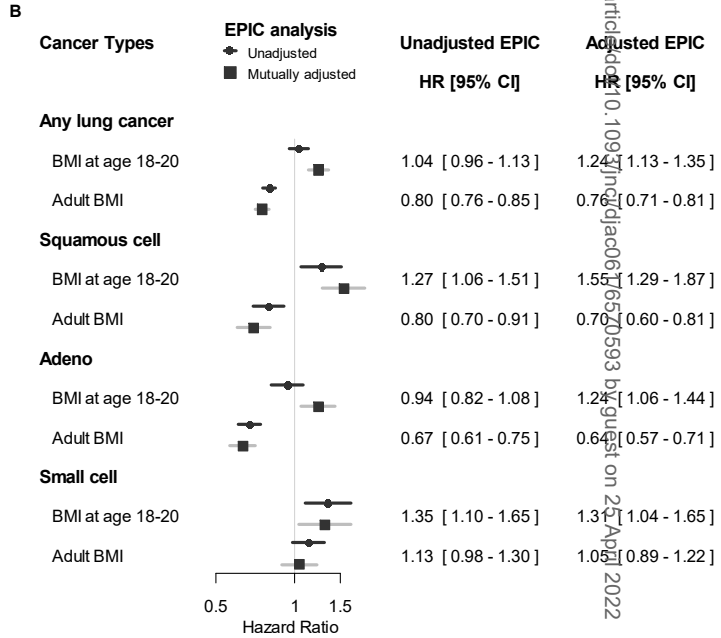
A



B



C