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Original article

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Investigating the association between anthropometry and colorectal cancer survival: a two-sample Mendelian randomization analysis

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Abstract

Background: Observational epidemiologic studies on the association of anthropometric traits and colorectal cancer (CRC) survival provide inconsistent results, and potential limitations prohibit the investigation of causality. We examined the associations between seven genetically predicted anthropometric traits [height, body mass index (BMI), waist circumference (WC), hip circumference (HC), waist–hip circumference ratio, birth weight and body fat percentage] and CRC-specific mortality among CRC cases using two-sample Mendelian randomization (MR).

Methods: Analyses were performed using 16 964 CRC cases, out of which 4010 died due to their disease, from the Genetics and Epidemiology of Colorectal Cancer Consortium and Colon Cancer Family Registry. We further conducted stratified analyses by anatomical site and stage. We applied the inverse variance weighted approach, and sensitivity analyses were conducted to assess the impact of potential violations of MR assumptions and adjust for collider bias.

Results: One standard deviation (SD 13.4 cm) higher genetically predicted levels of WC were associated with worse CRC survival [hazard ratio (HR); 1.22, 95% confidence interval (CI); 1.02–1.47]. Positive associations were further observed for a SD higher genetically predicted BMI (SD; 4.8 kg/m^2, HR; 1.5, 95% CI; 1.15–1.95) and HC (SD; 9.2 cm, HR; 1.32, 95% CI; 1.02–1.73) and CRC-specific mortality in cases of stages II/III. The latter associations were generally robust to sensitivity analyses. Positive but imprecisely estimated associations were found for most other anthropometric traits.

Conclusions: Despite the limitations of cancer survival research, our findings support that CRC cases should avoid obesity. Further research should inform the development of recommendations targeting overweight/obesity management during cancer surveillance.

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Keywords: height; body mass index; waist circumference; hip circumference; waist–hip circumference ratio; body fat percentage; birth weight; colorectal cancer; survival; Mendelian randomization.

Key Messages

- Using the Mendelian randomization framework, we investigated the association between genetically predicted height, body mass index, waist circumference, hip circumference, waist–hip circumference ratio, birth weight and body fat percentage and colorectal cancer (CRC) mortality among CRC cases.
- Positive associations were observed between genetically predicted levels of waist circumference and CRC-specific mortality overall, and hip circumference and body mass index with CRC-specific mortality in stages II/III, whereas positive but imprecisely estimated associations were found for most other anthropometric traits.
- Future research should focus on the development of targeted recommendations for overweight/obesity management in patients with CRC.

Introduction

Colorectal cancer (CRC) was the third most common and second deadliest malignant tumor among adults in 2022 [1]. Specifically, over 1.9 million individuals were diagnosed with the disease, and approximately 904 000 deaths occurred during the same year, accounting for almost 10% of all cancer cases and deaths globally [1]. Thanks to advancements in early detection and treatment, the number of CRC survivors is increasing [2]. Tumor and therapeutic characteristics are important in prognosis since survival depends significantly on disease stage and tumor location, as well as on patients' access and response to therapy [2].

Additional important drivers of CRC survival could be non-disease-related factors, such as body fatness and physical activity [3]. A substantive body of epidemiologic studies has indicated that elevated levels of anthropometric measures may be a causal risk factor for CRC incidence [4–10], but evidence regarding their association with survival after CRC diagnosis is inconsistent and potentially biased [11–16]. Differences in the timing of anthropometry assessment, reverse causation, collider bias, residual confounding, and survival bias are potential limitations of observational studies that tend to undermine the validity of their results. Furthermore, most studies focus on body mass index (BMI) and, hence, evidence on any other anthropometry-related trait is limited.

Mendelian randomization (MR) uses germline genetic variants as instruments of the risk factors of interest for testing hypotheses of causal inference. This method exploits the random allocation of genetic variants at meiosis and hence mimics the structure of a "natural" randomized controlled trial [17]. By using genetic variants as instrumental variables to evaluate the magnitude of association of lifetime exposure to a risk factor on disease outcomes, MR is less prone to residual confounding and reverse causation bias than traditional observational studies [18].

Following the MR approach, we aimed to investigate the associations between seven genetically predicted anthropometric traits, namely height, BMI, waist circumference (WC), hip circumference (HC), waist–hip circumference ratio (WHR), birth weight and body fat percentage, with CRC-specific mortality among CRC cases. Additionally, we conducted stratified analyses by anatomical site and tumor stage. We considered collider bias by CRC incidence, a selection bias structure that arises when conditioning on CRC incidence, which is the common effect of anthropometry and other measured or unmeasured factors (Fig. 1) [19]. For this purpose, we adjusted the CRC survival estimates using three recently proposed methods [20–22] and re-conducted the MR analyses.

Methods

This study is reported as per the guidelines for strengthening the reporting of Mendelian randomization studies (STROBE-MR) [23].

Data on CRC survival

The Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) comprise genetic, environmental and survival data from 15 studies of 16 964 individuals of European ancestry (50.3% males, median age at diagnosis; 67 years), diagnosed

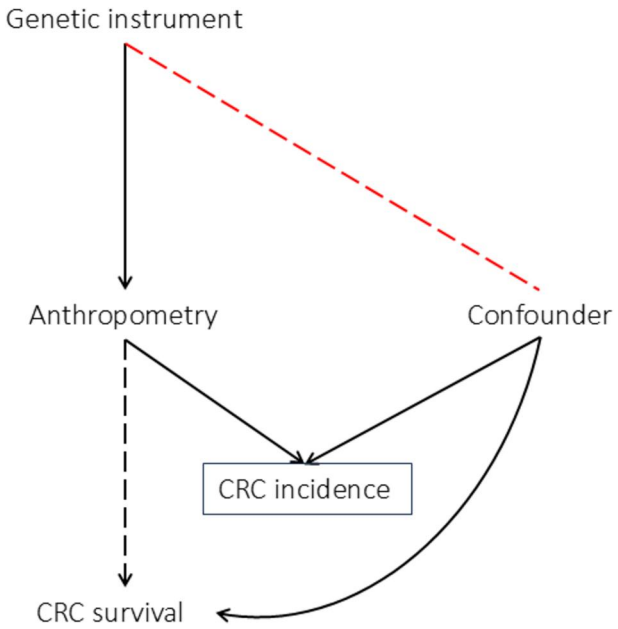

Figure 1. Directed acyclic graph demonstrating a typical example of collider bias in the anthropometry-colorectal cancer survival association in the two-sample Mendelian randomization setting. The genetic instrument is strongly associated with anthropometry, anthropometry is associated with risk of colorectal cancer incidence, and a measured or unmeasured confounder works as a common cause of both colorectal cancer incidence and survival (black solid lines). Conditioning on colorectal cancer incidence induces the association between the previously independent genetic instrument and the confounder (red dashed line). This would cause the violation of the second Mendelian randomization assumption, and hence threaten the validity of the survival estimate.

with incident, invasive CRC out of which 4010 died due to their disease during follow-up (Supplementary Table S1) [24]. Both consortia were accessed to obtain the genetic association estimates of single nucleotide polymorphisms (SNPs) with risk of CRC-specific mortality after diagnosis overall, by anatomical site [proximal colon (4881 cases, 978 deaths), distal colon (6214 cases, 1433 deaths), rectum (4749 cases, 1045 deaths)] and tumor stage at the time of diagnosis [stage I (3338 cases, 157 deaths), stages II/III as they are both considered regional (6420 cases, 1209 deaths), stage IV (1847 cases, 1448 deaths)]. Cox proportional hazards regression models were adjusted for age at diagnosis, sex, a joint variable encompassing genotyping platform and study, and the first five principal components to account for population stratification [24].

Instruments of anthropometric traits

Genetic association estimates for height reaching genome-wide significance ($P < 5 \times 10^{-8}$) were obtained from a meta-analysis of 173 studies of the Genetic Investigation of Anthropometric Traits (GIANT) consortium, including up to 4 080 687 individuals of European ancestry, and adjusted for age, sex, and the first 10 genetic principal components [25]. Similarly, SNPs associated with BMI and WHR at genome-wide significance ($P < 5 \times 10^{-8}$) were derived from a meta-analysis of genome-wide association studies (GWASs) by GIANT and the UK Biobank, comprising up to 806 834 individuals of European ancestry [26]. These estimates were adjusted for sex, age at assessment, age squared, and assessment center. Summary genetic association estimates for WC, HC, birth weight, and body fat percentage were also obtained from a separate GWAS of 349 376 UK Biobank participants [27]. Adjustments included sex, age at assessment, age squared, their interactions, and the first 20 genetic principal components. To ensure independence, SNPs in linkage disequilibrium (LD; $r^2 > 0.001$ within a 10 000-kb window, based on the 1000 Genome reference panel) were excluded, retaining only the SNP with the lowest *P*-value per locus.

Statistical analysis

MR analysis

We conducted a two-sample MR for CRC overall, by anatomical site and CRC stage using the random-effects inverse variance weighted (IVW) method. All associations were reported using hazard ratios (HRs) for CRC-specific mortality per standard deviation (SD) increment in the genetically predicted anthropometric traits (SD = 9.47 cm for height, 4.81 kg/m^2 for BMI, 0.09 for WHR, 9.27 cm for HC, 13.4 cm for WC, 0.67 kg for birth weight and 8.5% for body fat percentage).

Sensitivity analyses

As in any MR analysis, the selected SNPs must (i) be strongly associated with the anthropometric trait, (ii) be independent of any confounder of the anthropometry–CRC survival association, and (iii) affect CRC survival only through the anthropometry-related trait being instrumented and not via any other biological pathway (e.g. existence of horizontal pleiotropy) [28]. To measure the strength of the genetic instruments, we calculated the F-statistic and the proportion of the variance of the anthropometric traits explained by the corresponding genetic instrument (R^2). To examine for the potential violation of the second and third MR assumption, we computed Cochran's Q statistic, which expresses the degree to which differences in the measures of association among the selected SNPs are due to real variation rather than sampling error [29]. Horizontal pleiotropy was further investigated using MR-Egger regression, where the corresponding statistical test is based on its intercept term, when it is different from zero [30]. In the presence of horizontal pleiotropy, the slope of the MR-Egger regression and the weighted median approach may provide more valid MR estimates compared to IVW [30, 31]. The MR pleiotropy residual sum and outlier test (MR-PRESSO) was also applied to pinpoint and correct for potential outlying SNPs [32]. Analyses were implemented in the statistical software R 4.0.3 using the packages MendelianRandomization and MRPRESSO.

Adjustment for collider bias

In general, collider bias is a form of selection bias occurring when a study conditions on or adjusts for a collider. MR studies on CRC survival include only CRC cases and are prone to collider bias when the risk factor of interest, in this case, anthropometry, is also related to CRC incidence [33]. Conditioning on CRC incidence can induce an association between the genetic instrument and another measured or unmeasured cause for both CRC incidence and survival, violating the independence MR assumption (Fig. 1).

To detect whether our findings were influenced by collider bias, we applied the recently developed methods by Dudbridge and colleagues [20] [or Simulation Extrapolation (SIMEX) method], Mahmoud and colleagues [21] (or Slope-hunter method) and Cai and colleagues [or Corrected Weighted Least Squares (CWLS) method] [22].

Bias-correcting factors assessing the magnitude of bias were estimated using independent genetic incidence and survival estimates, and were calculated for overall CRC as well as by anatomical site and stage. Overall, site- and stage-specific CRC survival estimates were adjusted using the corresponding correcting factors, and IVW MR estimates and Cochran's Q statistic were re-calculated. We compared all bias-adjusted estimates to assess the robustness of SNP–survival effect estimates across methods. Additionally, we compared the initial IVW estimates with the bias-adjusted IVW estimates in terms of both direction and magnitude. A detailed description of the methods followed is presented in the Supplementary Material. Analyses were conducted using the R packages indexevent, SlopeHunter and ColliderBias.

Results

The final number of included SNPs was 987, 542, 353, 305, 267, 97, and 293 for height, BMI, WHR, HC, WC, birth weight, and body fat percentage, respectively. Controlling for collider bias required the identification of all common SNPs between CRC incidence and survival, thus, the final number of SNPs being instrumented was 982, 475, 354, 304, 263, 94, and 290 for height, BMI, WHR, HC, WC, birth weight, and body fat percentage, respectively.

The associations between the genetically predicted anthropometric traits and CRC survival overall and by anatomical site are shown in Table 1. An SD (13.4 cm) higher genetically predicted WC was associated with a 22% [95% confidence interval (CI); 2%–47%, $P = .03$] higher risk of CRC-specific mortality among CRC cases. The weighted median approach confirmed the aforementioned association (HR 1.43; 95% CI

Table 1. Results from the Mendelian Randomization study to evaluate associations between anthropometry-related traits and colorectal cancer survival overall and by anatomical site.[a]

		Overall	Proximal colon	Distal colon	Rectal
Height	IVW	0.98 (0.91–1.07)	0.89 (0.78–1.02)	1.07 (0.91–1.27)	1.15 (0.98–1.35)
	MR-Egger				
	Intercept *P*-value	.86	.83	.83	.94
	Slope	0.98 (0.83–1.14)	0.91 (0.7–1.19)	1.04 (0.76–1.43)	1.13 (0.83–1.54)
	WM	1.01 (0.89–1.15)	0.92 (0.74–1.15)	1.04 (0.79–1.35)	1.14 (0.88–1.47)
BMI	IVW	1.1 (0.96–1.27)	1.15 (0.91–1.45)	1.18 (0.9–1.54)	1.11 (0.85–1.46)
	MR-Egger				
	Intercept *P*-value	.77	.61	.83	.68
	Slope	1.16 (0.81–1.67)	1 (0.55–1.81)	1.1 (0.55–2.2)	0.97 (0.48–1.96)
	WM	1.16 (0.9–1.48)	1.08 (0.71–1.64)	1.18 (0.74–1.86)	1.24 (0.76–2.04)
WHR	IVW	1.1 (0.92–1.31)	1.06 (0.79–1.42)	0.88 (0.63–1.24)	1.17 (0.84–1.64)
	MR-Egger				
	Intercept *P*-value	.81	.51	.41	.93
	Slope	1.17 (0.71–1.92)	1.37 (0.6–3.15)	0.6 (0.23–1.58)	1.22 (0.47–3.18)
	WM	1.16 (0.89–1.52)	0.98 (0.62–1.55)	0.86 (0.49–1.5)	1.44 (0.86–2.41)
HC	IVW	1.07 (0.92–1.25)	1.19 (0.92–1.53)	1.1 (0.82–1.48)	1.01 (0.75–1.35)
	MR-Egger				
	Intercept *P*-value	.99	.66	.85	.9
	Slope	1.07 (0.68–1.68)	1.02 (0.48–2.13)	1.19 (0.5–2.83)	1.06 (0.45–2.5)
	WM	1.18 (0.94–1.5)	1.03 (0.69–1.52)	1.17 (0.75–1.85)	0.91 (0.57–1.43)
WC	IVW	*1.22 (1.02–1.47)*	1.13 (0.82–1.55)	1.3 (0.91–1.87)	1.24 (0.86–1.81)
	MR-Egger				
	Intercept *P*-value	.77	.65	.49	.68
	Slope	1.32 (0.75–2.31)	0.91 (0.35–2.41)	1.89 (0.62–5.77)	0.99 (0.32–3.12)
	WM	*1.43 (1.05–1.93)*	1 (0.59–1.7)	1.44 (0.81–2.56)	1.63 (0.87–3.06)
Birth weight	IVW	0.92 (0.73–1.15)	1.15 (0.81–1.64)	0.98 (0.63–1.51)	0.86 (0.58–1.28)
	MR-Egger				
	Intercept *P*-value	.59	.99	.89	.31
	Slope	1.11 (0.54–2.31)	1.16 (0.37–3.61)	1.07 (0.26–4.42)	1.62 (0.45–5.85)
	WM	1.03 (0.75–1.42)	1.14 (0.68–1.92)	0.99 (0.53–1.85)	1.06 (0.59–1.9)
% Body fat	IVW	1.05 (0.86–1.28)	0.93 (0.66–1.3)	1.25 (0.84–1.87)	0.98 (0.66–1.44)
	MR-Egger				
	Intercept *P*-value	.85	.81	.71	.44
	Slope	1.12 (0.55–2.29)	0.8 (0.25–2.64)	0.97 (0.23–4.02)	1.64 (0.42–6.48)
	WM	1.2 (0.88–1.64)	0.99 (0.59–1.68)	1.4 (0.76–2.58)	1.27 (0.7–2.33)

[a] Hazard ratios and 95% confidence intervals were calculated using the inverse variance weighted method and correspond to 1 SD increase in the anthropometry-related traits. Statistically significant estimates ($P < .05$) are shown in italics.

1.05–1.93; $P = .02$), with no evidence of horizontal pleiotropy (MR-Egger intercept $P = .77$). In general, positive but imprecisely estimated associations were found for most other anthropometric traits, except for height and birth weight, which yielded null and non-significant inverse results, respectively. Results did not differ by anatomical site.

Stratified analyses by CRC stage showed a positive association with CRC-specific mortality for HC (HR 1.32; 95% CI 1.02–1.73, $P = .04$) and BMI (HR 1.5; 95% CI 1.15–1.95; $P = .003$) among individuals with CRC of stages II/III (Table 2). These associations were consistent in the MR-Egger and weighted median analyses with no evidence of horizontal pleiotropy (MR-Egger intercept $P = .35$ and .54 for HC and BMI, respectively). Most of the genetically predicted anthropometric traits appeared to be associated with better survival among stage IV CRC cases, but with wide CIs, possibly due to the presence of selection bias when analyses are restricted to this subpopulation [34].

The F-statistic was >10 for all the included SNPs, implying the absence of weak instruments, and the R^2 ranged from 2.2% (birth weight) to 14.4% (height). The Cochran's Q statistic was not statistically significant in any of the associations mentioned above (Supplementary Table S3), and the MR-PRESSO analysis did not reveal any outlier SNPs (data not shown).

The estimated magnitude of bias obtained from all adjustment methods ranged from −1.404 to 0.568, with most estimates being positive. SIMEX and CWLS provided similar estimates, and the Slope-hunter method tended to yield either larger estimates or estimates with an opposite sign. (Supplementary Table S2). The associations between genetically predicted anthropometry-related traits and CRC mortality among CRC cases after controlling for collider bias are shown in Fig. 2 and Supplementary Table S3. The SIMEX and CWLS methods provided almost identical bias-adjusted estimates and concordant with the initial IVW estimates, with the magnitude of the associations between WC and CRC-specific mortality overall, and HC, BMI, and CRC-specific mortality in stages II/III ranging from 1.2 to 1.38 per SD. The Slope-hunter method led to the attenuation of all association estimates, except for HC (HR 1.31; 95% CI 1–1.71, $P = .05$), BMI (HR 1.32; 95% CI 1–1.75; $P = .05$) and CRC-specific mortality among individuals with stage II/III disease.

Discussion

In the current MR analysis of seven anthropometry-related measures with survival after CRC diagnosis, positive associations were observed between genetically predicted levels of WC and CRC-specific mortality overall, and HC and BMI with CRC-specific mortality in stages II/III. Positive but

Table 2. Results from the Mendelian randomization study to evaluate associations between anthropometry-related traits and colorectal cancer survival overall and by tumor stage.[a]

		Stage I	Stages II/III	Stage IV
Height	IVW	0.78 (0.51–1.21)	1.01 (0.87–1.18)	1.07 (0.93–1.24)
	MR-Egger			
	Intercept *P*-value	.56	.81	**.05**
	Slope	0.96 (0.43–2.17)	0.98 (0.73–1.32)	0.84 (0.64–1.11)
	WM	0.97 (0.48–1.95)	1.09 (0.85–1.4)	1.03 (0.82–1.3)
BMI	IVW	1.19 (0.58–2.4)	*1.5 (1.15–1.95)*	0.83 (0.66–1.05)
	MR-Egger			
	Intercept *P*-value	.61	0.54	.37
	Slope	0.77 (0.13–4.7)	1.23 (0.63–2.41)	1.08 (0.59–1.97)
	WM	0.87 (0.25–3.05)	*1.84 (1.19–2.85)*	0.8 (0.51–1.24)
WHR	IVW	0.82 (0.32–2.06)	1.19 (0.86–1.64)	1.11 (0.82–1.52)
	MR-Egger			
	Intercept *P*-value	.66	.56	.13
	Slope	0.46 (0.03–7)	0.93 (0.37–2.3)	2.11 (0.88–5.09)
	WM	0.37 (0.09–1.5)	1.26 (0.74–2.13)	0.81 (0.51–1.28)
HC	IVW	0.64 (0.29–1.41)	*1.33 (1.02–1.73)*	0.87 (0.67–1.13)
	MR-Egger			
	Intercept *P*-value	.9	.35	.87
	Slope	0.74 (0.07–7.28)	1.87 (0.87–4.04)	0.82 (0.38–1.76)
	WM	1.12 (0.34–3.72)	1.43 (0.94–2.16)	0.93 (0.62–1.39)
WC	IVW	1.16 (0.44–3.04)	1.38 (0.98–1.93)	0.88 (0.64-1.23)
	MR-Egger			
	Intercept *P*-value	.51	.36	.92
	Slope	0.46 (0.03–8.29)	2.15 (0.78–5.91)	0.93 (0.34–2.5)
	WM	0.76 (0.17–3.49)	*1.9 (1.12–3.22)*	0.76 (0.44–1.3)
Birth weight	IVW	1.3 (0.42–4)	0.89 (0.61–1.31)	0.87 (0.61–1.24)
	MR-Egger			
	Intercept *P*-value	.67	.53	.77
	Slope	2.66 (0.08–88.48)	0.62 (0.18–2.08)	1.02 (0.34–3.12)
	WM	0.73 (0.14–3.73)	0.82 (0.47–1.45)	0.93 (0.56–1.56)
% Body fat	IVW	1.48 (0.52–4.19)	1.18 (0.81–1.72)	0.89 (0.63–1.26)
	MR-Egger			
	Intercept *P*-value	.4	.15	.52
	Slope	0.35 (0.01–12)	2.92 (0.8–10.65)	1.29 (0.39–4.28)
	WM	1.63 (0.33–8.05)	1.43 (0.81–2.52)	0.82 (0.47–1.41)

[a] Hazard ratios and 95% confidence intervals were calculated using the inverse variance weighted method and correspond to 1 SD increase in the anthropometry-related traits. Statistically significant estimates ($P < .05$) are shown in italics.

imprecisely estimated associations were found for most other anthropometric traits.

Three different methods were applied to adjust for potential collider bias in our SNP–survival estimates. The SIMEX and CWLS methods yielded similar estimates of bias magnitude; therefore, the corresponding bias-adjusted estimates did not differ substantially and were highly similar to the initial IVW estimates. On the other hand, the Slope-hunter method provided slightly different bias-adjusted estimates with greater uncertainty. The differences across methods used to adjust for collider bias can potentially be explained by the underlying assumptions of each method. The SIMEX and CWLS methods may be more sensitive to the positive genetic correlation between CRC incidence and CRC-specific mortality [20, 22], which we reasonably believe exists. In contrast, the Slope-hunter method addresses this limitation but relies on the assumption that there are no common causes of CRC incidence and CRC-specific mortality that explain more of the variance in incidence than the SNPs that affect incidence only [21]. Although our results were generally robust across these bias-adjusted methods, they should be interpreted with caution, as the aforementioned assumptions cannot be verified using the available data.

Epidemiologic evidence on the association between anthropometry and survival among CRC patients comes primarily from observational studies, which have assessed anthropometric traits at various time points pre-, peri-, or post-CRC diagnosis. As part of the work for the Global Cancer Update Programme (CUP Global), a recent meta-analysis of 20 observational studies concluded that higher post-diagnosis BMI was associated with higher risk of overall and CRC-specific mortality, and the shape of the associations appeared reverse J-shaped with a nadir at 28 kg/m^2 [15]. While these findings highlighted the aggravating association of being high-overweight or obese with CRC outcomes, they also showed positive associations with low and low-normal BMI, and the CUP Global independent Expert Panel graded the totality of this evidence as limited due to methodological considerations of the included observational studies [15]. There is very little data available on WC and CRC outcomes. A relevant meta-analysis including five prospective cohort studies assessing WC before or at diagnosis of CRC, suggested that elevated WC was associated with increased mortality from CRC (HR 1.27; 95% CI 1.08–1.49) [35]. The literature on the association between HC and CRC survival is scarce as well. We identified only one cohort study involving 3924 CRC cases, where 1043 cases died due to CRC during a mean follow-up of 49 months, reporting that higher pre-diagnostic HC was associated with increased CRC-specific mortality (per 10 cm; HR 1.09; 95% CI 1.00–1.18) [13]. Finally, the association of anthropometry and CRC survival by tumor stage is poorly investigated in the literature. A

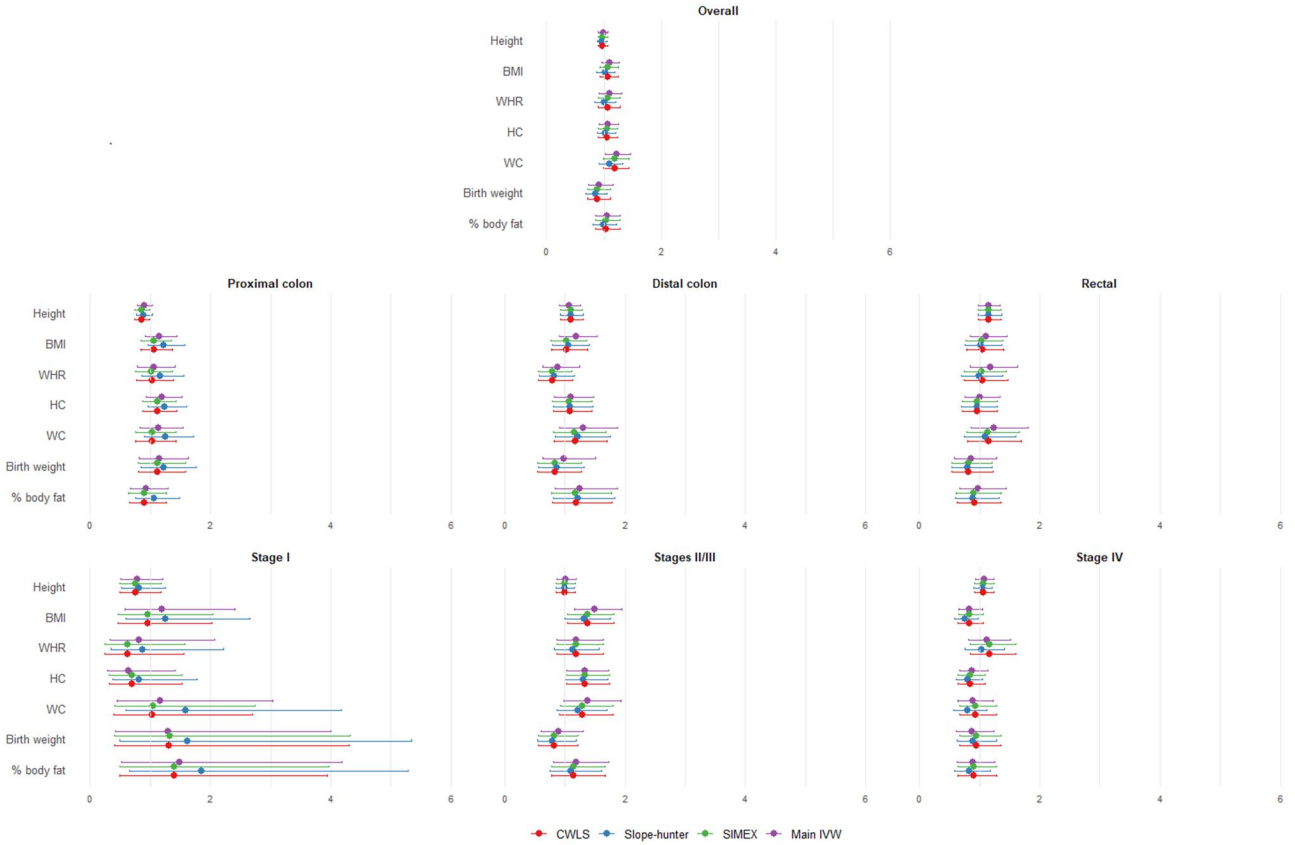

Figure 2. Mendelian randomization estimates for the association between genetically predicted anthropometric traits and colorectal cancer-specific mortality, overall and stratified by anatomical site and tumor stage. Hazard ratios and corresponding 95% confidence intervals are presented for each anthropometric trait using the main inverse variance weighted method and three approaches accounting for collider bias: Corrected Weighted Least Squares, Slope-hunter, and Simulation Extrapolation. Each dot represents the point estimate, and horizontal lines denote 95% confidence intervals.

meta-analysis of 13 prospective and retrospective studies assessing anthropometry either pre- or post-diagnosis reported that obesity (BMI $> 30\,kg/m^2$) was associated with worse overall survival (HR 1.10; 95% CI 1.05–1.15) in the subgroup of CRC patients of stages II/III [36]. Another systematic review concluded that there was insufficient evidence for a link between adiposity measures, such as BMI, and survival among stage IV CRC patients due to inherent biases in the included studies [37]. Although this evidence is generally concordant with our results, MR captures more effectively the effect of anthropometry across the lifespan and potentially helps overcome limitations arising from timing discrepancies in anthropometry assessment.

The exact biological pathways connecting anthropometry and CRC survival are not entirely understood and might be related to factors that are associated with CRC incidence. Evidence is mainly focused on BMI and suggests that its higher levels are associated with increased bioavailability of insulin growth factor (IGF) 1, decreased levels of IGF binding proteins, and increased production of adipokines and pro-inflammatory cytokines that may contribute to carcinogenesis and tumor progression [38]. Furthermore, WC is a proxy for visceral fat, which is metabolically more active in terms of secretion of the aforementioned adipokines and pro-inflammatory cytokines [39], and potentially related to serious implications in cancer prognosis.

Potential limitations should be considered in the interpretation of our findings. Some of our analyses were underpowered, mainly due to the small number of deaths. Larger GWASs on CRC patients are required to better investigate the link between genetically predicted anthropometry and CRC survival. MR analyses of summary-level data do not allow for stratified analyses by important covariates, such as sex and treatment status. Although several anthropometric traits exhibit sex-specific genetic architectures, we were unable to use sex-stratified summary statistics, as the genetic data for CRC-specific mortality were only available in a sex-combined format. An additional limitation would be that SNP-exposure estimates may differ in CRC cases compared to a generally healthy sample, as there may be effect modifications by factors relating to having the disease [33], though no GWASs have yet focused on SNPs of anthropometric traits in CRC cases alone. MR analyses on CRC survival can be susceptible to survival bias, which occurs when CRC cases must survive long enough to be included in the GWASs and contribute any person-time [33, 40]. IVW MR methods assume linear associations between the exposure and outcome, but nonlinear analysis was not performed, as the available methods do not work well with summary-level data, and statistical power would have been limited [41]. We also acknowledge that genetic correlations may exist among the studied anthropometric traits. Future research could select and prioritize strongly correlated traits and assess their influence on CRC-specific mortality. Finally, all included GWASs had a lack of ethnic diversity in the samples studied, limiting our capability to generalize our findings to populations of non-European ancestry.

Our study also has a number of strengths. To our knowledge, this is the first two-sample MR study on the association between anthropometry and CRC survival. All instrumental variables were robustly associated with anthropometry-related traits, included a large number of SNPs and scored an F-value >10. Using the two-sample MR design, we were able to attenuate the effect of significant biases on our results, including reverse causation, residual confounding, and collider bias.

In conclusion, we conducted the first two-sample MR study to investigate whether seven genetically predicted anthropometric traits were associated with CRC survival. Higher levels of WC, HC, and BMI were associated with higher mortality from CRC among CRC cases. Future studies are needed to replicate these findings and shed light on the underlying mechanisms across the CRC continuum.

Ethics approval

Not applicable.

Author contributions

AK contributed to methodology, data curation, statistical analysis, interpretation of results and original draft preparation. EB contributed to methodology, data curation, statistical analysis and interpretation of results. ATC, LLM, AW, AHW, MJG, KN, PH, SJL, RMM, VZ, AIP, UP and FJBvanD contributed to methodology, data curation and interpretation of results. KKT directed the study's implementation and contributed to conceptualization, methodology, data curation and interpretation of results. All authors have critically read and reviewed the manuscript. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the statistical analysis.

Supplementary data

Supplementary data are available at *IJE* online.

Conflict of interest

None declared.

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Data availability

The marginal associations are provided in the Supplementary material for replication purposes.

Use of artificial intelligence (AI) tools

No AI tools were used.

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