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Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study

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Abstract

Background: Higher adiposity increases the risk of colorectal cancer (CRC), but whether this relationship varies by anatomical sub-site or by sex is unclear. Further, the metabolic alterations mediating the effects of adiposity on CRC are not fully understood.

(Continued on next page)

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Methods: We examined sex- and site-specific associations of adiposity with CRC risk and whether adiposity-associated metabolites explain the associations of adiposity with CRC. Genetic variants from genome-wide association studies of body mass index (BMI) and waist-to-hip ratio (WHR, unadjusted for BMI; $N = 806{,}810$), and 123 metabolites from targeted nuclear magnetic resonance metabolomics ($N = 24{,}925$), were used as instruments. Sex-combined and sex-specific Mendelian randomization (MR) was conducted for BMI and WHR with CRC risk (58,221 cases and 67,694 controls in the Genetics and Epidemiology of Colorectal Cancer Consortium, Colorectal Cancer Transdisciplinary Study, and Colon Cancer Family Registry). Sex-combined MR was conducted for BMI and WHR with metabolites, for metabolites with CRC, and for BMI and WHR with CRC adjusted for metabolite classes in multivariable models.

Results: In sex-specific MR analyses, higher BMI (per 4.2 kg/m^2) was associated with 1.23 (95% confidence interval (CI) = 1.08, 1.38) times higher CRC odds among men (inverse-variance-weighted (IVW) model); among women, higher BMI (per 5.2 kg/m^2) was associated with 1.09 (95% CI = 0.97, 1.22) times higher CRC odds. WHR (per 0.07 higher) was more strongly associated with CRC risk among women (IVW OR = 1.25, 95% CI = 1.08, 1.43) than men (IVW OR = 1.05, 95% CI = 0.81, 1.36). BMI or WHR was associated with 104/123 metabolites at false discovery rate-corrected $P \leq 0.05$; several metabolites were associated with CRC, but not in directions that were consistent with the mediation of positive adiposity-CRC relations. In multivariable MR analyses, associations of BMI and WHR with CRC were not attenuated following adjustment for representative metabolite classes, e.g., the univariable IVW OR for BMI with CRC was 1.12 (95% CI = 1.00, 1.26), and this became 1.11 (95% CI = 0.99, 1.26) when adjusting for cholesterol in low-density lipoprotein particles.

Conclusions: Our results suggest that higher BMI more greatly raises CRC risk among men, whereas higher WHR more greatly raises CRC risk among women. Adiposity was associated with numerous metabolic alterations, but none of these explained associations between adiposity and CRC. More detailed metabolomic measures are likely needed to clarify the mechanistic pathways.

Keywords: Body mass index, Waist-to-hip ratio, Colorectal cancer, Mendelian randomization, Metabolism, NMR, Epidemiology, GECCO, CORECT, CCFR

Background

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers among adults globally [1–3]. Obesity is viewed as a likely cause of CRC by the International Agency for Research on Cancer (IARC), the American Institute for Cancer Research (AICR), and the World Cancer Research Fund (WCRF) [3, 4], based largely on positive associations between adiposity and CRC risk from observational epidemiology. Further, the limited data available from observational studies suggest that intentional weight loss lowers the risk of CRC in post-menopausal women [5]. Mendelian randomization (MR) studies, which use genetic variants as instruments (proxies) for adiposity given their randomly allocated and fixed nature [6], further support causality [7–9]. Despite this growing consensus, it remains unclear whether the effect of adiposity on CRC risk differs among men and women, whether the relationship varies by CRC sub-site, and what the underlying biological mechanisms are. These are important to clarify given the ongoing obesity epidemic and difficulties in reducing adiposity itself [10, 11].

Observationally, body mass index (BMI) relates more strongly to CRC risk among men and waist-to-hip ratio (WHR) relates similarly to CRC risk among men and women [12]. However, recent MR studies suggest that higher BMI more greatly raises CRC risk among women, while higher WHR more greatly raises CRC risk among men [7, 8]. Whether these MR estimates are robust is unclear because they were based on relatively small sample sizes, genetic instruments that were not sex-specific, and genetic instruments for WHR that were conditioned on BMI—all potential sources of bias [13–17].

Adiposity alters the systemic metabolism [18–20], but evidence for the effects of adiposity-altered metabolites on CRC is scarce. One MR study suggested that total cholesterol raises CRC risk [21], while others suggested no effect of blood glucose [22] and mixed support for fatty acids [23]. Overall, the scope of metabolic traits examined has also been narrow. Targeted metabolomics allows deeper phenotyping at a large scale [24], and its recent integration with genotype data [25] enables us to examine the associations of metabolites with CRC using MR. Expanded genotype data for CRC is also available [26], affording a sample size six times larger than used in previous MR studies (58,221 cases, 67,694 controls).

This study has two aims. First, we aimed to better estimate sex-specific effects of adiposity on CRC risk using two-sample MR. We examined associations of BMI and WHR with CRC risk using expanded GWAS data and

genetic instruments for exposures that were sex-specific and were not mutually conditioned, to reduce bias [13–17]. Second, we aimed to identify potential metabolic mediators of effects of adiposity on CRC risk using two-step MR (by examining associations of BMI and WHR with metabolites, and of BMI- or WHR-related metabolites with CRC risk) and multivariable MR (by adjusting associations of BMI and WHR with CRC for representative metabolites).

Methods

Study design

We used two-sample MR to examine the associations (pertaining to estimates of the effect predicted from genetic variants used as instruments) of adiposity with CRC risk, of adiposity with metabolites, of adiposity-associated metabolites with CRC risk, and finally of adiposity with CRC risk adjusted for representative metabolites. In two-sample MR, SNP-exposure and SNP-outcome associations are obtained from different study sources and combined as a ratio to estimate the effects of exposures on outcomes [13, 27]. Our study aims and assumptions are shown in Fig. 1.

Adiposity instruments

We identified SNPs that were independently associated (low linkage disequilibrium (LD), $R^2 < 0.001$) with BMI and WHR (unadjusted for BMI) at $P < 5 \times 10^{-8}$ from a recent large-scale genome-wide association study (GWAS) meta-analysis of 221,863 to 806,810 male and female adults of European ancestry from the Genetic Investigation of ANthropometric Traits (GIANT) consortium and the UK Biobank [33] (Additional file 1: Table S1). BMI and WHR are expressed in standard deviation (SD) units. For sex-combined analyses of BMI and WHR, 312 and 209 SNPs were used, respectively. For sex-specific analyses of BMI, 185 and 152 SNPs were used for women and men, respectively. For sex-specific analyses of WHR, 153 and 64 SNPs were used for women and men, respectively. The proportion of variance explained in adiposity traits by instruments ranged from 0.3 to 5.04% (these were based on approximations for BMI using the equation described by Shim et al. [34]), and *F*-statistics (a formal test of whether variance explained is sufficiently high to avoid weak instrument bias) for adiposity instruments ranged from 75.81 to 124.49 (Additional file 1: Table S2) which indicated

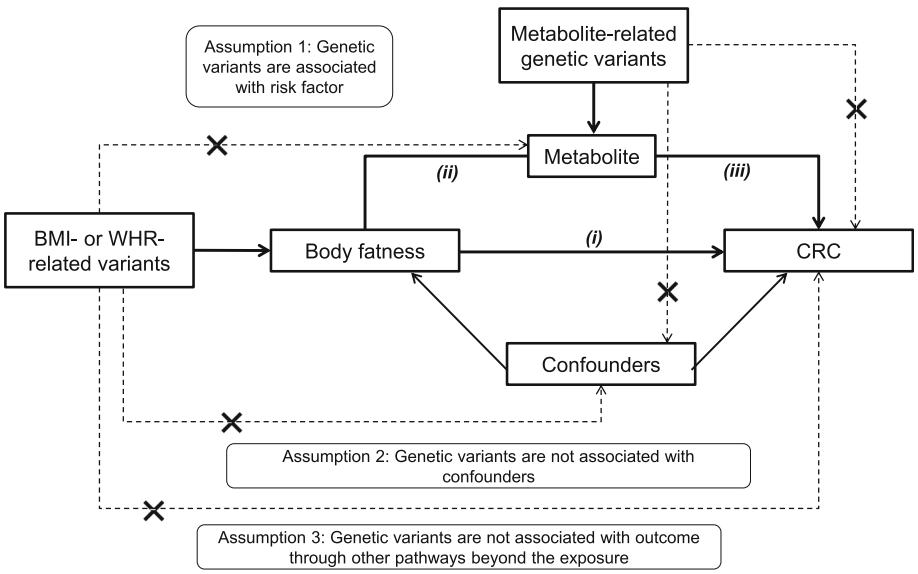


Fig. 1 Study aims and assumptions. Study aims are to (1) estimate the total effect of adiposity on CRC risk using genetic instruments for BMI and WHR ((i) unadjusted for BMI) and (2) estimate the mediated effect of adiposity on CRC risk by metabolites from targeted NMR metabolomics. Aim 2 is addressed using two approaches: (1) two-step MR wherein effects are examined of adiposity on metabolites (ii) and of adiposity-related metabolites on CRC risk (iii) and (2) multivariable MR wherein effects of adiposity on CRC (i) are examined with adjustment for the effect of representative metabolite classes on CRC (iii). Sex-specific analyses were performed when sex-specific GWAS estimates for exposure and outcome were both available. When ≥ 2 SNP instruments were available, up to 4 MR models were applied: the inverse-variance-weighted (IVW) model which assumes that none of the SNPs are pleiotropic [28], the weighted median (WM) model which allows up to half of the included SNPs to be pleiotropic and is less influenced by outliers [28], the weighted mode model which assumes that the most common effect is consistent with the true causal effect [29], and the MR-Egger model which provides an estimate of association magnitude allowing all SNPs to be pleiotropic [30]. Analyses with metabolites as outcomes were conducted within discovery aims wherein *P* value thresholds are applied to prioritize traits with the strongest evidence of association to be taken forward into further stages of analysis (with CRC risk). Analyses with CRC as outcomes were conducted within estimation aims wherein *P* values are interpreted as continuous indicators of evidence strength and focus is on effect size and precision [31, 32]

instrument strength above the recommended minimum levels [35].

Metabolite instruments

We identified SNPs that were independently associated ($R^2 < 0.001$ and $P < 5 \times 10^{-8}$) with metabolites from a GWAS of 123 traits from targeted nuclear magnetic resonance (NMR) metabolomics (Additional file 1: Table S1); these included lipoprotein subclass-specific lipids, amino acids, fatty acids, inflammatory glycoproteins, and others [25]. Between 13,476 and 24,925 adults (men and women combined) of European ancestry were included. Metabolic traits are expressed in SD units. The proportion of variance explained in metabolites by instruments ranged from 0.44 to 12.49%, and *F*-statistics for metabolite instruments ranged from 30.2 to 220.8 (Additional file 1: Table S2) which indicated sufficient instrument strength for univariable analyses.

Colorectal cancer GWAS data

We obtained SNP estimates from the most comprehensive GWAS of CRC to date [26], including 58,221 cases and 67,694 controls (sexes combined) from 45 studies within 3 consortia: Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), Colorectal Cancer Transdisciplinary Study (CORECT), and Colon Cancer Family Registry (CCFR). Across these studies, there were 28,207 CRC cases and 22,204 controls among men, and 24,568 CRC cases and 23,736 controls among women. Cases were diagnosed by a physician and recorded overall and by site (colon, proximal colon, distal colon, rectum). Approximately 92% of the participants were White-European (~ 8% were East Asian). Case distributions are outlined in Additional file 1: Table S3; other study characteristics are detailed elsewhere [26]. Ethics were approved by respective institutional review boards.

Statistical approach

First, we examined the associations of BMI and WHR with overall and site-specific CRC using SNP estimates from sex-combined GWAS of exposures as well as outcomes. We then examined the associations of BMI and WHR with overall CRC based on SNP estimates from sex-specific GWAS of exposure as well as outcome (sex-specific GWAS were not available and thus not used for site-specific CRC). Summary statistics were harmonized using the harmonise_data function within the TwoSampleMR R package [36]. All GWAS were assumed to be coded on the forward strand, and harmonization was confirmed as consistent using option 2 of the "action" argument. As sensitivity analyses, up to four MR methods were used to generate effect estimates using the TwoSampleMR R package [36] which make differing pleiotropy assumptions (detailed in Fig. 1 legend) [29, 36, 37]. When only a single SNP was available, the Wald ratio was used [38]. When ≥ 2 SNPs were available, random-effects inverse-variance-weighted (IVW) [36], MR-Egger [30], weighted median (WM) [28], and weighted mode [29] models were used. Cochrane's *Q*-statistic was used to assess the heterogeneity of SNP effects (smaller *P* values indicating higher heterogeneity and higher potential for directional pleiotropy [39]). Scatter plots were used to compare MR models, and "leave-one-SNP-out" analyses were used to detect SNP outliers [40].

Second, we examined associations of BMI and WHR with metabolites using results from sex-combined GWAS for exposures as well as outcomes (sex-specific GWAS were not available for metabolites, and so sex-specific analyses were not conducted) and the MR models described above. Each metabolite (analyzed as an outcome) that was associated with either BMI or WHR based on an IVW model *P* value ≤ 0.05 following a false discovery rate (FDR) correction (Benjamini-Hochberg method [41]) was taken forward and examined for association with CRC risk using the IVW model (if ≥ 2 SNPs) or the Wald ratio (if 1 SNP). Multivariable MR [42] was also used to examine the associations of BMI and WHR with CRC risk, adjusting for single metabolites that were representative of various metabolite classes based on previous network analyses [43] and that had the highest instrument strength based on the *F*-statistic (Additional file 1: Table S2). As a positive control, we adjusted BMI for WHR as a covariate (which is expected to attenuate the association of BMI with CRC risk), and likewise, we adjusted WHR for BMI as a covariate with the same expectation. A smaller set of SNPs for BMI and WHR based on earlier GWAS [44, 45] was used for these multivariable models to avoid a relative dilution of metabolite instrument strength given that the number of SNPs for BMI and WHR from expanded GWAS far outnumbered those for metabolites. Conditional *F*-statistics were calculated for exposures in multivariable models [46].

In each instance, MR estimates are interpreted as the change in outcome per SD unit change in the exposure. Estimates for metabolite outcomes reflect SD unit change, and estimates for CRC outcomes reflect odds ratios (OR). Statistical analyses were performed using R (version 3.5.2).

Results

Associations of BMI and WHR with CRC risk

In sex-combined analyses (Fig. 2; Additional file 1: Table S4), higher BMI (per 4.8 kg/m^2) was associated with a higher risk of overall CRC (IVW OR = 1.16, 95% CI = 1.07, 1.26). The WM estimate was similar, but the MR-Egger and weighted mode estimates were both reduced

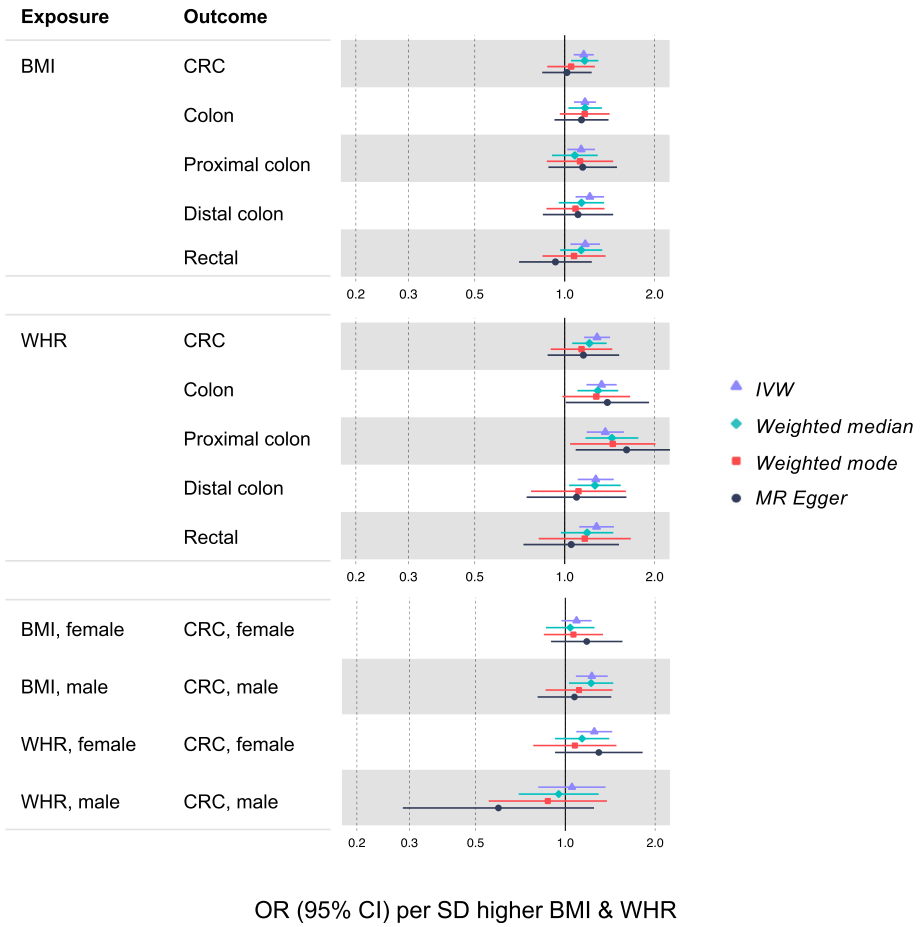


Fig. 2 Associations of BMI and WHR with CRC risk based on two-sample MR. Sex-combined estimates are based on GWAS done among women and men together (for both exposure and outcome). Sex-specific estimates are based on GWAS done separately among women and men (for exposure as well as outcome)

(e.g., MR-Egger OR = 1.02, 95% CI = 0.84, 1.25). BMI associations were consistent across CRC sites. Associations were directionally consistent for WHR as for BMI but were marginally stronger—e.g., higher WHR (per 0.09 ratio) was associated with 1.28 (95% CI = 1.16, 1.42) times higher odds of CRC in an IVW model (MR-Egger and weighted mode estimates were each positive but of a smaller magnitude with wide intervals spanning the null). WHR associations were more consistent for colon rather than rectal sub-sites. SNP heterogeneity was similarly high for BMI and WHR (P value range across models = 9.54×10^{-10} to 1.97×10^{-8}).

In sex-specific IVW models (Fig. 2; Additional file 1: Table S4), higher BMI (per 4.2 kg/m^2) was associated with 1.23 (95% CI = 1.08, 1.38) times higher odds of CRC among men and 1.09 (95% CI = 0.97, 1.22) times higher odds of CRC (per 5.2 kg/m^2) among women. In a WM model, this BMI estimate was robust among men (OR = 1.22, 95% CI = 1.02, 1.46) but reduced among women (OR = 1.04, 95% CI = 0.86, 1.26). MR-Egger and weighted mode estimates were similarly imprecise among men and women, and SNP heterogeneity was similar for both. In IVW models, higher WHR (per 0.07 ratio) was associated with 1.25 (95% CI = 1.08, 1.43) times higher odds of CRC among women; this estimate was 1.05 (95% CI = 0.81, 1.36) among men (per 0.07 ratio). This pattern was also supported by WM estimates (OR = 1.14, 95% CI = 0.91, 1.42 among women and OR = 0.95, 95% CI = 0.90, 1.29 among men), and by MR-Egger and weighted mode estimates. SNP heterogeneity was similarly high among men and women.

Scatter plots comparing different MR models and results of the "leave-one-SNP-out" analyses are presented in Additional file 2: Figures S1-42.

Associations of BMI and WHR with metabolites

In sex-combined analyses, higher BMI (per 4.8 kg/m^2) or WHR (per 0.09 ratio) was associated with 104 metabolites based on FDR-corrected P value ≤ 0.05 in IVW

models (Additional file 2: Figures S43-47; Additional file 1: Table S5). Evidence was strong in relation to lipids including total cholesterol and triglycerides in very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL)—e.g., 0.23 SD (95% CI = 0.15, 0.31) higher triglycerides in large VLDL from higher BMI. Associations of higher BMI were also strong with lactate, pyruvate, and branched-chain amino acids—e.g., 0.19 SD (95% CI = 0.13, 0.25) higher isoleucine—and with inflammatory glycoproteins (0.28 SD, 95% CI = 0.20, 0.36 higher). Similar patterns were seen for WHR.

Associations of BMI- or WHR-related metabolites with CRC

Of 104 metabolites associated (as outcomes) with BMI or WHR in sex-combined analyses, 100 had SNPs for use in Wald or IVW models. As shown in Additional file 1: Table S1, 321 unique SNPs were used to instrument 100 metabolites (3 metabolites had 1 SNP, 13 metabolites had < 5 SNPs, and 51 metabolites had < 10 SNPs; SNP counts across metabolites ranged from 1 to 26). Lipid traits showed generally weak associations with CRC which were also in directions inconsistent with the mediation of the adiposity-CRC relationship—e.g., lipids in medium HDL were positively associated with CRC, but these had been negatively associated with BMI or WHR (Fig. 3; Additional file 1: Table S6). In contrast, there was more consistent evidence of a positive association of lipids in intermediate-density lipoprotein (IDL), VLDL, and LDL with a risk of distal colon cancer, and these lipids had been positively associated with higher BMI or WHR. For example, higher total lipids in IDL (per SD) were associated with 1.09 (95% CI = 1.02, 1.15) times higher odds of distal colon cancer. Lipids were unassociated with the risk of proximal colon cancer. Fatty acids were unassociated with CRC risk except for higher monounsaturated fatty acid levels which were associated with a lower risk of rectal cancer (IVW OR = 0.85, 95% CI = 0.75, 0.95; Fig. 4). Lactate and pyruvate were inversely associated with CRC at 0.66 (95% CI = 0.42, 1.03) times lower odds and 0.64 (95% CI = 0.52, 0.80) times lower odds, respectively. However, these metabolites were positively associated with BMI, and so directions were inconsistent with the mediation of the adiposity-CRC relationship. Amino acids and glycoprotein acetyls were unassociated with CRC risk.

Associations of BMI and WHR with CRC risk independent of metabolites

The association of BMI with overall CRC was not attenuated following adjustment for various metabolite classes (Fig. 5; Additional file 1: Table S7). The univariable IVW OR for BMI (per 4.77 kg/m^2 higher, based on 67 SNPs) in relation to CRC was 1.12 (95% CI = 1.00, 1.26), whereas this IVW OR was 1.14 (95% CI = 1.01, 1.29) adjusting for VLDL lipids and 1.11 (95% CI = 0.99, 1.26) adjusting for IDL and LDL lipids. Attenuation was greater when adjusting the BMI-CRC association for WHR (positive control), at IVW OR = 0.93 (95% CI = 0.78, 1.11). Results for WHR in relation to CRC were directionally consistent as seen for BMI, with a lack of attenuation upon adjustment for metabolite classes.

Discussion

We aimed to better estimate sex-specific effects of adiposity on CRC risk and to identify potential metabolic mediators of the effects of adiposity on CRC, using two-sample MR methods and expanded sample sizes. Our results, based on genetic instruments for adiposity that were sex-specific and were not mutually conditioned, suggest that higher BMI more greatly raises CRC risk among men, whereas higher WHR more greatly raises CRC risk among women. In sex-combined mediation analyses, adiposity was associated with numerous metabolic alterations, but none of these alterations explained the associations between adiposity and CRC. More detailed metabolomic measures are likely needed to clarify the mechanistic pathways.

Observational [3, 47] and MR [7–9] studies have suggested adverse effects of adiposity on CRC risk, but causal evidence has been lacking regarding sex specificity. Previous MR studies suggested stronger effects of BMI on CRC risk among women [7–9], which contradicts observational suggestions of stronger effects among men [12]. The genetic regulation of BMI and WHR shows strong sexual dimorphism, thought attributable to the influence of sex hormones, namely estrogen, and it is important to capture these differences in MR estimates [48, 49]. Our new results are based on instruments for BMI and WHR that were sex-specific and a sample size for CRC that was six times larger than used previously which enabled higher power relative to two previous MR studies of BMI, WHR, and CRC risk [7, 8] (Additional file 2: Figure S48). These new results suggest that BMI more greatly raises CRC risk among men—a reversal of previous MR estimates. This new pattern for BMI and CRC (22% higher risk among men per 4.2 kg/m^2 and 9% higher risk among women per 5.2 kg/m^2) is highly consistent with observational estimates reviewed by IARC (22% higher risk in men and 9% higher risk in women per 5 kg/m^2 [4]). Our results also support a reversal of previous MR estimates for WHR, with risk now appearing higher among women than among men. This is unexpected since BMI and abdominal fat measures correlate highly [50, 51]; however, given that fat storage is more peripheral in women [18, 19], WHR (unadjusted for BMI) may be a better proxy for the extremeness of

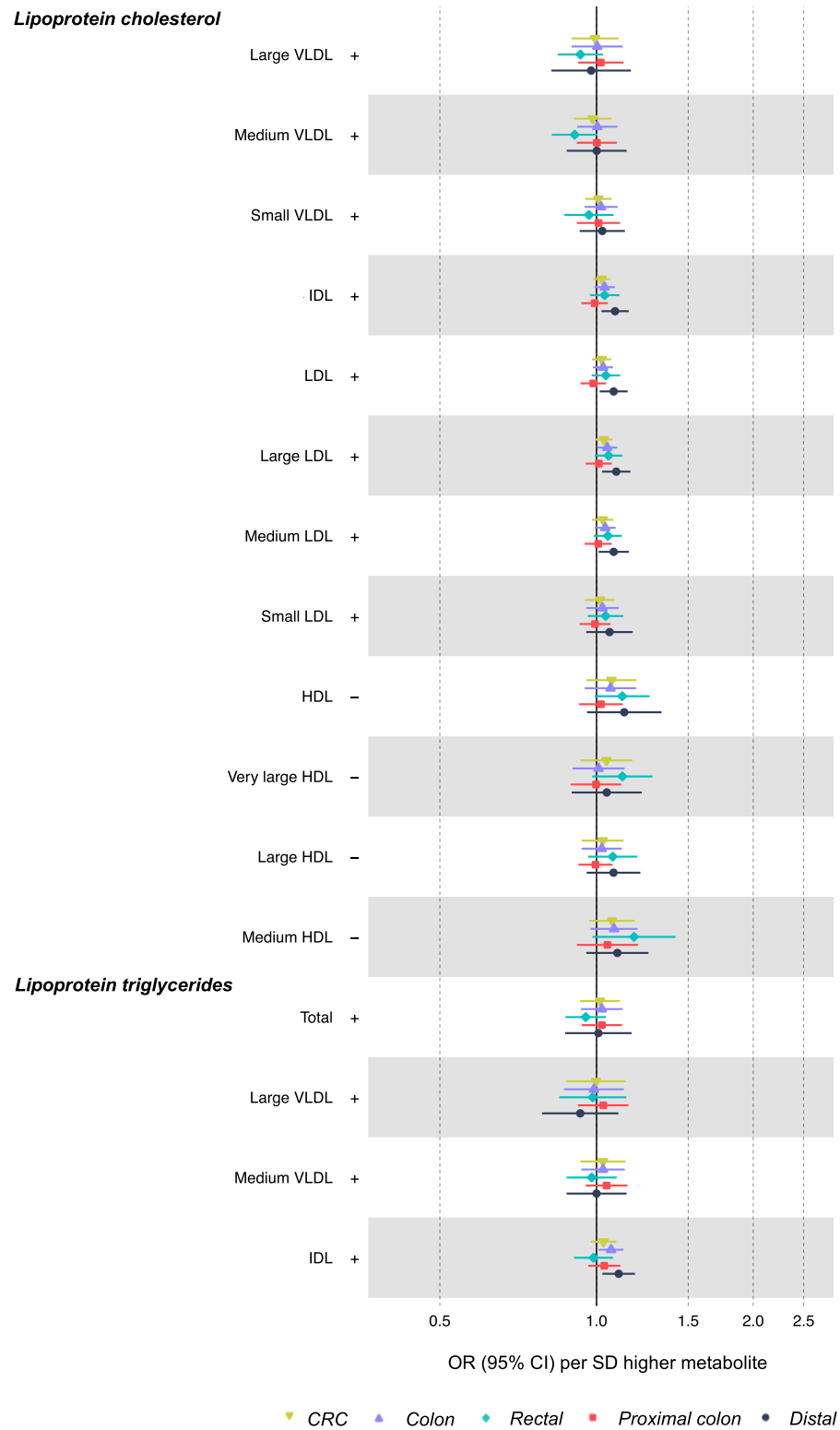


Fig. 3 Associations of BMI- or WHR-related lipid metabolites with CRC risk based on two-sample MR (IVW method). Estimates reflect the OR (95% CI) for CRC per SD higher metabolite that is associated (as an outcome) with BMI or WHR. +/– symbols indicate the direction of association of BMI or WHR with that metabolite

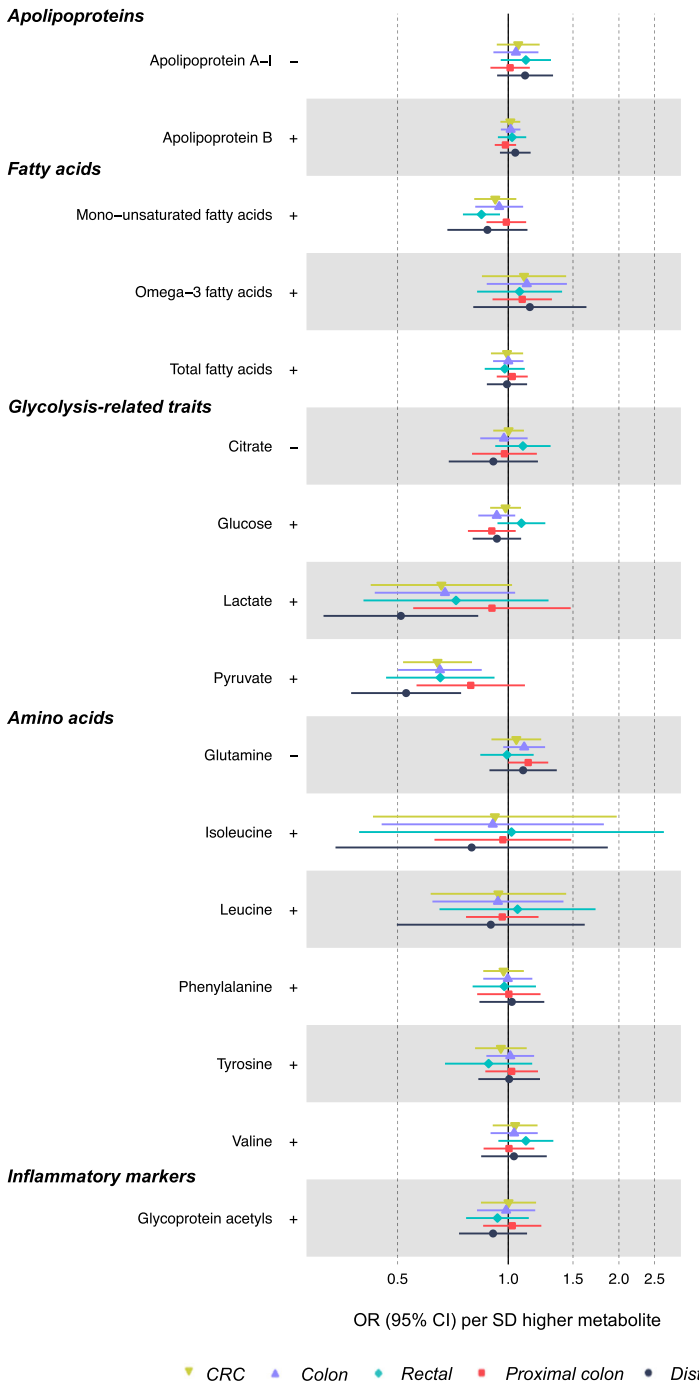


Fig. 4 Associations of BMI- or WHR-related non-lipid metabolites with CRC risk based on two-sample MR (IVW method). Estimates reflect the OR (95% CI) for CRC per SD higher metabolite that is associated (as an outcome) with BMI or WHR. +/− symbols indicate the direction of association of BMI or WHR with that metabolite

fat volume among women since fat may be stored more abdominally only when peripheral fat stores are overwhelmed. As a post hoc comparison, we repeated analyses of the main effects of adiposity on CRC using the sex-combined adiposity instruments in relation to split samples of men and women (Additional file 1: Table S8, A) to examine the potential for biased results. These suggest that use of sex-combined instruments for BMI and WHR would lead to the conclusion that both are associated with higher CRC risk in males as well as females, but with still higher risk with BMI among males and with WHR among females, in contrast to previous

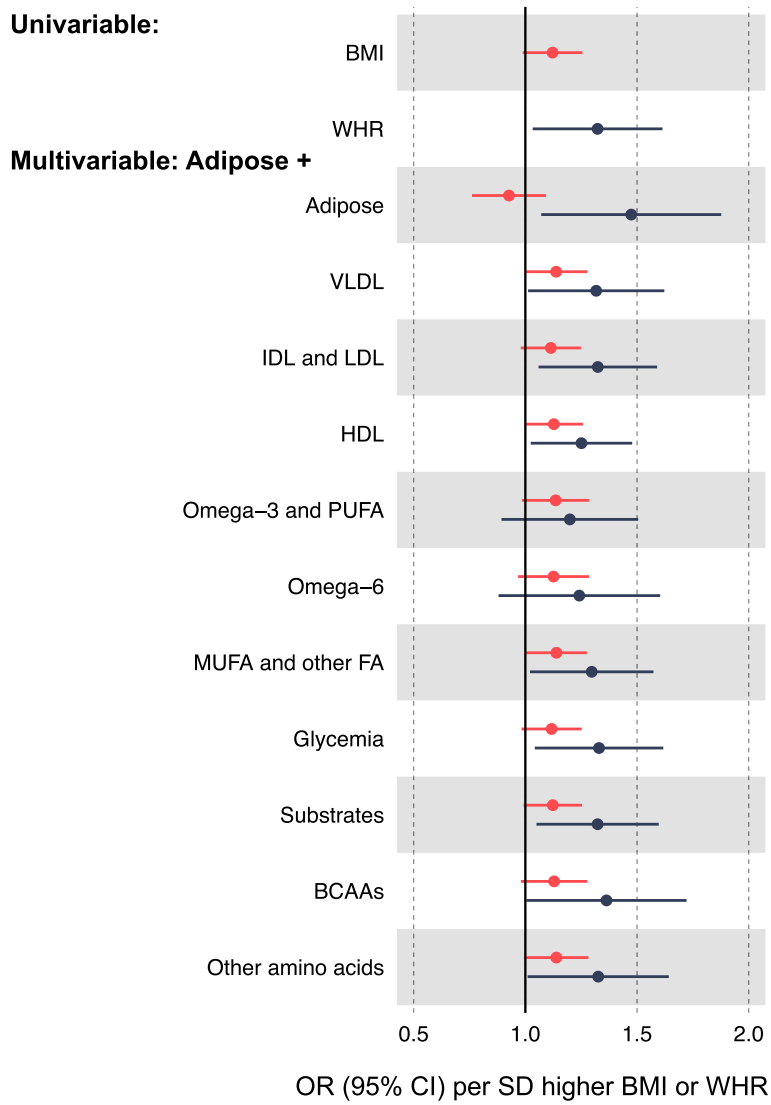


Fig. 5 Associations of BMI and WHR with CRC risk independent of various metabolite classes based on multivariable MR. Metabolite classes are based on a single representative metabolite from a previous network analysis [43], as follows: VLDL (triglycerides in small VLDL); IDL and LDL (total cholesterol in medium LDL), HDL (triglycerides in very large HDL), Omega-3 and PUFA (other polyunsaturated fatty acids than 18:2), Omega-6 (18:2, linoleic acid), MUFA and other fatty acids (Omega-9 and saturated fatty acids), glycemia (glucose), substrates (citrate), branched-chain amino acids (leucine), and other amino acids (glutamine). Adipose adjustments include the alternative adiposity trait (WHR or BMI) as a positive control

MR studies [7, 8]. This suggests that discrepancies in the result patterns are most likely due to the differences in the power of the main adiposity-CRC relationship (Additional file 2: Figure S48).

SNP heterogeneity was high for BMI and WHR with CRC, although this was similar between sexes and directions of effect from sensitivity models were consistent, suggesting balanced SNP heterogeneity. One cause of heterogeneity may be pleiotropy in violation of the exclusion restriction criteria (assumption 3, Fig. 1). This is not unexpected due to the large number of SNPs included in the adipose trait instruments and the many underlying biological pathways that explain variation in adiposity. A future approach to minimizing heterogeneity in instrument selection could be to analyze the association between subsets of genetic variants related to specific pathways of BMI and WHR in relation to CRC; this requires more biological knowledge of these genetic variants than currently exists.

Given the difficulty of weight loss [11] and the ongoing obesity epidemic, it is increasingly important to identify the biological pathways which explain the effect of adiposity on the risk of chronic diseases including CRC [10]. Adipose tissue is highly metabolically active and

secretes pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha which may promote tumor initiation [52]. Adipose tissue-derived inflammation also promotes insulin resistance in glucose storage tissues that can lead to hyperinsulinemia [53], and insulin and insulin-like growth factors (IGF) such as IGF-1 have pro-mitogenic and anti-apoptotic effects that are cancer promotive [47, 54–58]. Our current results suggest effects of BMI or WHR on numerous lipids and pre-glycemic traits; however, few of these traits had any strong association with CRC risk, and the few that did were in a direction that was inconsistent with a mediating role in the adiposity-CRC relationship. Results of a series of multivariable MR models, which adjusted for various metabolites considered representative of broader metabolite classes [42], suggested that associations of BMI and WHR with CRC risk were highly independent of these metabolites. However, this analysis may be limited by weak instrument bias [59] given that *F*-statistics for metabolite instruments included in each multivariable MR model were relatively low. Nevertheless, the results of two complementary approaches to mediation (two-step MR and multivariable MR) provide little evidence that the effects of adiposity on CRC risk are mediated by adiposity-related metabolites that are detectable by NMR metabolomics. Future studies could examine metabolites, proteins, hormones, and inflammatory factors that are detectable by other metabolomic and proteomic platforms.

The few traits that did show consistent directions of effect included total lipids in IDL, LDL, and VLDL particles which were raised by BMI and which in turn raised the risk of distal colon cancer specifically (not proximal colon or rectal cancer). If robust, this pattern may reflect differential sensitivity of colon regions to lipid exposure owing to divergent functions (the distal colon functions primarily in the storage of resultant fecal matter whereas the proximal colon functions primarily in water absorption and fecal solidification [60]), or it may reflect differential detectability through screening (proximal colon tumors tend to be detected in older ages and at more advanced stages [60]). Colorectal anatomical regions may also have distinct molecular features [61], e.g., the distal colon may be more susceptible to p53 mutations and chromosomal instability [62], whereas the proximal colon may be more mucinous and susceptible to microsatellite instability and B-Raf proto-oncogene expression [63, 64]. Several meta-analyses of long-term follow-ups of randomized controlled trials of LDL cholesterol-lowering statin use suggested no strong evidence of a protective effect of statin used on CRC risk [65–67]; CRC sub-sites were largely unexamined. One previous MR study suggested an adverse effect of higher LDL cholesterol, and a protective effect of genetically proxied statin use, on overall CRC risk [21]; again, CRC sub-sites were not examined. Prospective observational evidence for LDL cholesterol and CRC risk is less consistent than for total cholesterol or triglycerides; heterogeneity in meta-analyzed effect estimates is much higher for LDL cholesterol (82.7% based on an I^2 statistic) compared with total cholesterol and triglycerides (46.7% and 47.8%, respectively) [68]. Prospective estimates of lipoprotein subclass measures from metabolomic platforms are lacking as these are only recently available at scale.

The limitations of this study include the non-specificity of genetic variants used as instruments for some metabolites which stems from their expectedly correlated nature (e.g., rs1260326, a SNP in *GCKR*, was included in genetic instruments for 54 metabolites). A total of 321 unique SNPs was used to instrument 100 metabolites, but the number of instruments available for a given metabolite was typically small. This limits causal inference for individual traits but should not prevent the identification of relevant classes of traits (e.g., lipid, amino acid). It should also be stressed that genetic variants used for metabolites may alter the enzyme expression and so serve as instruments for the metabolizing enzyme itself, not factors influenced downstream of that enzyme. Since inference in MR applies to the most proximal trait that the genetic variant relates to [15], directing inference to specific glycolytic traits as distinct from their downstream consequences like insulin resistance [69] (a key result of higher fatness and trigger of tumorigenesis [61]) is difficult and requires stronger genetic instruments alongside mechanistic insights from preclinical studies [70]. Adiposity was measured indirectly using BMI and WHR because these correlate highly with more objectively measured fat indexes [50, 51] and allow much larger GWAS sample sizes than otherwise possible (comparably strong GWAS were unavailable for waist circumference). UK Biobank data are included within GWAS for both the exposure and outcome used for MR estimates of adiposity for CRC risk. Sample overlap in a two-sample MR setting is reported to contribute to weak instrument bias and inflated type one error rates, resulting in MR estimates that are biased towards confounding-prone observational estimates [71]. However, given that the proportion of sample overlap is presently low (< 5%) and estimated *F*-statistics are relatively high (each > 70 for adiposity traits), we do not expect considerable bias here. As a post hoc comparison, we obtained CRC summary GWAS statistics with UK Biobank excluded and repeated MR analyses of adiposity for CRC risk. Estimates were largely consistent with or without the inclusion of UK Biobank data (Additional file 1: Table S8, B). Our sex-specific MR investigations were confined to effects of adiposity on overall CRC because sex-specific GWAS were unavailable for site-specific CRC and metabolite outcomes. Sex-stratified GWAS of such outcomes would enable these in the future.

Conclusions

Our results based on sex-specific MR instruments and expanded sample sizes suggest that higher BMI more greatly raises CRC risk among men, whereas higher WHR more greatly raises CRC risk among women. In sex-combined mediation analyses, adiposity was associated with numerous metabolic alterations, but none of these alterations explained the associations between adiposity and CRC. More detailed metabolomic measures are likely needed to clarify the mechanistic pathways.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-020-01855-9.

Additional file 1: Table S1. Genetic variants used to instrument BMI, WHR and metabolites. **Table S2.** Assesment of instrument strength. **Table S3.** Colorectal cancer case distributions by study, sex and site. **Table S4.** LogOR colorectal cancer per SD higher BMI or WHR. **Table S5.** Beta change in NMR-detected metabolite per SD higher BMI or WHR. **Table S6.** LogOR colorectal cancer per SD higher BMI or WHR-driven NMR-detected metabolite. **Table S7.** Risk of overall colorectal cancer per SD higher adipose or metabolite trait, estimated using multivariable Mendelian randomization. **Table S8.** Posthoc investigations.

Additional file 2: Figure S1. Scatter plot of SNP-BMI and SNP-CRC associations. **Figure S2.** Scatter plot of SNP-BMI and SNP-CRC associations (female specific). **Figure S3.** Scatter plot of SNP-BMI and SNP-CRC associations (male specific). **Figure S4.** Scatter plot of SNP-BMI and SNP-colon cancer associations. **Figure S5.** Scatter plot of SNP-BMI and SNP-proximal colon cancer associations. **Figure S6.** Scatter plot of SNP-BMI and SNP-distal colon cancer associations. **Figure S7.** Scatter plot of SNP-BMI and SNP-rectal cancer associations. **Figure S8.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on CRC. **Figure S9.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on CRC (female specific). **Figure S10.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on CRC (male specific). **Figure S11.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on colon cancer. **Figure S12.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on proximal colon cancer. **Figure S13.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on distal colon cancer. **Figure S14.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of BMI on rectal cancer. **Figure S15.** Leave-one-out plot showing the association between BMI and CRC, following SNP-by-SNP removal from the model. **Figure S16.** Leave-one-out plot showing the association between BMI and CRC (femalespecific), following SNP-by-SNP removal from the model. **Figure S17.** Leave-one-out plot showing the association between BMI and CRC (malespecific), following SNP-by-SNP removal from the model. **Figure S18.** Leave-one-out plot showing the association between BMI and colon cancer, following SNP-by-SNP removal from the model. **Figure S19.** Leave-one-out plot showing the association between BMI and proximal colon cancer, following SNP-by-SNP removal from the model. **Figure S20.** Leave-one-out plot showing the association between BMI and distal colon cancer, following SNP-by-SNP removal from the model. **Figure S21.** Leave-one-out plot showing the association between BMI and rectal cancer, following SNP-by-SNP removal from the model. **Figure S22.** Scatter plot of SNP-WHR and SNP-CRC associations. **Figure S23.** Scatter plot of SNP-WHR and SNP-CRC associations (female specific). **Figure S24.** Scatter plot of SNP-WHR and SNP-CRC associations (male specific). **Figure S25.** Scatter plot of SNP-WHR and SNP-colon cancer associations. **Figure S26.** Scatter plot of SNP-WHR and SNP-proximal colon cancer associations. **Figure S27.** Scatter plot of SNP-WHR and SNP-distal colon cancer associations. **Figure S28.** Scatter plot of SNP-WHR and SNP-rectal cancer associations. **Figure S29.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on CRC. **Figure S30.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on CRC (female specific). **Figure S31.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on CRC (male specific). **Figure S32.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on colon cancer. **Figure S33.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on proximal colon cancer. **Figure S34.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on distal colon cancer. **Figure S35.** Forest plot showing individual SNP (black) and combined MR estimates (red; Egger and IVW) for the effect of WHR on rectal cancer. **Figure S36.** Leave-one-out plot showing the association between WHR and CRC, following SNP-by-SNP removal from the model. **Figure S37.** Leave-one-out plot showing the association between WHR and CRC, following SNP-by-SNP removal from the model (female specific). **Figure S38.** Leave-one-out plot showing the association between WHR and CRC, following SNP-by-SNP removal from the model (male specific). **Figure S39.** Leave-one-out plot showing the association between WHR and colon cancer, following SNP-by-SNP removal from the model. **Figure S40.** Leave-one-out plot showing the association between WHR and proximal colon cancer, following SNP-by-SNP removal from the model. **Figure S41.** Leave-one-out plot showing the association between WHR and distal colon cancer, following SNP-by-SNP removal from the model. **Figure S42.** Leave-one-out plot showing the association between WHR and rectal cancer, following SNP-by-SNP removal from the model. **Figure S43.** Effects of BMI and WHR on circulating metabolite levels (NMR-detected metabolites, 1 of 5), based on two-sample MR (IVW models) in summary GWAS consortia data. **Figure S44.** Effects of BMI and WHR on circulating metabolite levels (NMR-detected metabolites, 2 of 5), based on two-sample MR (IVW models) in summary GWAS consortia data. **Figure S45.** Effects of BMI and WHR on circulating metabolite levels (NMR-detected metabolites, 3 of 5), based on two-sample MR (IVW models) in summary GWAS consortia data. **Figure S46.** Effects of BMI and WHR on circulating metabolite levels (NMR-detected metabolites, 4 of 5), based on two-sample MR (IVW models) in summary GWAS consortia data. **Figure S47.** Effects of BMI and WHR on circulating metabolite levels (NMR-detected metabolites, 5 of 5), based on two-sample MR (IVW models) in summary GWAS consortia data. **Figure S48.** Power curves for MR analyses, based on samples sizes for colorectal cancer in the present study (black), Thrift et al., 2015 (blue) and Jarvis et al., 2016 (purple). Upper and lower power curves describe genetic instruments explaining 5% and 0.3% of variance respectively for each study.

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Authors' contributions

CJB, JAB, NM, ES, GDS, EEV, and MJG planned the study. CJB had access to the data and conducted the analyses. JAB, CJB, and EEV wrote the first draft. All authors read and approved the final manuscript.

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Availability of data and materials

The summary-level GWAS data on outcomes used in this study are available following an application to the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO): https://www.fredhutch.org/en/research/divisions/public-health-sciences-division/research/cancer-prevention/genetics-epidemiology-colorectal-cancer-consortium-gecco.html.
A copy of the code used in this analysis is available at https://github.com/cb12104/adiposity_metabolites_crc.

Ethics approval and consent to participate

All participants provided written informed consent, and each study was approved by the relevant research ethics committee or institutional review board.

Consent for publication

Not applicable

Competing interests

None to declare.

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