OXFORD

*JNCI J Natl Cancer Inst* (2022) 114(5): djac011

https://doi.org/10.1093/jnci/djac011
First published online January 20, 2022
Article

# Associations Between Glycemic Traits and Colorectal Cancer: A Mendelian Randomization Analysis

Neil Murphy, PhD,[1,‡,*] Mingyang Song, MD, ScD,[2,3,4,5,‡] Nikos Papadimitriou, PhD,[1] Robert Carreras-Torres, PhD,[6] Claudia Langenberg, MD, PhD,[7,8,9] Richard M. Martin, PhD,[10,11,12] Konstantinos K. Tsilidis, PhD,[13,14] Inês Barroso, PhD,[15] Ji Chen, PhD,[15] Timothy M. Frayling, PhD,[15,16] Caroline J. Bull, PhD,[10,11,17] Emma E. Vincent, PhD,[10,11,17] Michelle Cotterchio, PhD,[18] Stephen B. Gruber, MD, PhD,[19,20] Rish K. Pai, MD, PhD,[21] Polly A. Newcomb, PhD,[22] Aurora Perez-Cornago, PhD,[23] Franzel J. B. van Duijnhoven, PhD,[24] Bethany Van Guelpen, MD, PhD,[25,26] Pavel Vodicka, PhD,[27,28,29] Alicja Wolk, PhD,[30] Anna H. Wu, PhD,[31] Ulrike Peters, PhD,[22,32] Andrew T. Chan, MD,[2,3,33,‡] Marc J. Gunter, PhD,[1,‡]

[1]Nutrition and Metabolism Branch, International Agency for Research on Cancer, Lyon, France; [2]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [3]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA; [5]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; [6]Colorectal Cancer Group, ONCOBELL Program, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; [7]MRC Epidemiology Unit, University of Cambridge, Cambridge, UK; [8]Computational Medicine, Berlin Institute of Health, Charité University Medicine, Berlin, Germany; [9]Health Data Research UK, Wellcome Genome Campus and University of Cambridge, Cambridge, UK; [10]MRC Integrative Epidemiology Unit (IEU), Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; [11]Bristol Medical School, Department of Population Health Sciences, University of Bristol, Bristol, UK; [12]National Institute for Health Research (NIHR) Bristol Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and the University of Bristol, Bristol, UK; [13]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece; [14]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK; [15]Exeter Centre of Excellence in Diabetes (ExCEeD), Exeter Medical School, University of Exeter, Exeter, UK; [16]Department of Human Genetics, University of Exeter, Research Innovation Learning & Development (RILD) Building, Royal Devon and Exeter Hospital, Exeter, UK; [17]School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK; [18]Prevention and Cancer Control, Clinical Institutes and Quality Programs, Ontario Health (Cancer Care Ontario), Ontario, Canada; [19]Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, CA, USA; [20]Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; [21]Department of Pathology and Laboratory Medicine, Mayo Clinic Arizona, Scottsdale, AZ, USA; [22]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [23]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; [24]Division of Human Nutrition and Health, Wageningen University and Research, Wageningen, the Netherlands; [25]Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; [26]Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden; [27]Department of Molecular Biology of Cancer, Institute of Experimental Medicine of the Czech Academy of Sciences, Prague, Czech Republic; [28]Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University, Prague, Czech Republic; [29]Faculty of Medicine and Biomedical Center in Pilsen, Charles University, Pilsen, Czech Republic; [30]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [31]University of Southern California, Preventative Medicine, Los Angeles, CA, USA; [32]Department of Epidemiology, University of Washington, Seattle, WA, USA; and [33]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

[‡]Authors contributed equally.

[*]**Correspondence to:** Neil Murphy, PhD, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France (e-mail: murphyn@iarc.fr).

ARTICLE

## Abstract

**Background:** Glycemic traits—such as hyperinsulinemia, hyperglycemia, and type 2 diabetes—have been associated with higher colorectal cancer risk in observational studies; however, causality of these associations is uncertain. We used Mendelian randomization (MR) to estimate the causal effects of fasting insulin, 2-hour glucose, fasting glucose, glycated hemoglobin (HbA1c), and type 2 diabetes with colorectal cancer. **Methods:** Genome-wide association study summary data were used to identify genetic variants associated with circulating levels of fasting insulin (n = 34), 2-hour glucose (n = 13), fasting glucose (n = 70), HbA1c (n = 221), and type 2 diabetes (n = 268). Using 2-sample MR, we examined these variants in relation to colorectal cancer risk (48 214 case patient and 64 159 control patients). **Results:** In inverse-variance models, higher fasting insulin levels increased colorectal cancer risk (odds ratio [OR] per 1-SD = 1.65, 95% confidence interval [CI] = 1.15 to 2.36). We found no evidence of any effect of 2-hour glucose (OR per 1-SD = 1.02, 95% CI = 0.86 to 1.21) or fasting glucose (OR per 1-SD = 1.04, 95% CI = 0.88 to 1.23) concentrations on colorectal cancer risk. Genetic liability to type 2 diabetes (OR per 1-

**Received:** June 15, 2021; **Revised:** September 29, 2021; **Accepted:** January 12, 2022

unit increase in log odds = 1.04, 95% CI = 1.01 to 1.07) and higher HbA1c levels (OR per 1-SD = 1.09, 95% CI = 1.00 to 1.19) increased colorectal cancer risk, although these findings may have been biased by pleiotropy. Higher HbA1c concentrations increased rectal cancer risk in men (OR per 1-SD = 1.21, 95% CI = 1.05 to 1.40), but not in women. **Conclusions:** Our results support a causal effect of higher fasting insulin, but not glucose traits or type 2 diabetes, on increased colorectal cancer risk. This suggests that pharmacological or lifestyle interventions that lower circulating insulin levels may be beneficial in preventing colorectal tumorigenesis.

Obesity is an established risk factor for colorectal cancer development (1–3) and is invariably characterized by dysregulated metabolism, such as insulin resistance, hyperinsulinemia, hyperglycemia, and type 2 diabetes (4). Extensive epidemiological research has shown that patients with type 2 diabetes are at higher colorectal cancer risk than those without diabetes (5,6). However, recent findings from 2 relatively small Mendelian randomization (MR) studies (both including fewer than 7000 colorectal cancer case patients) did not support a causal relationship between genetic liability to type 2 diabetes and colorectal cancer (7,8). Prior epidemiologic studies examining how prediagnostic concentrations of fasting glucose, glucose tolerance (the measurement of circulating glucose levels 2 hours after an oral glucose challenge), and glycated hemoglobin (HbA1c) relate to colorectal cancer risk have reported conflicting results (9–15). Numerous epidemiological studies have examined the associations between circulating levels of insulin and colorectal cancer risk, with positive associations generally found in studies that measured circulating levels of C-peptide (a marker of insulin secretion) (16–18), but inconsistent results reported in studies that directly measured insulin levels (19–24). Possible explanations for the conflicting results to date include the use of nonfasting blood samples in some studies, differences in laboratory assays used, and the vulnerability of prior investigations to the inherent biases of observational studies, such as residual confounding and reverse causality.

MR uses germline genetic variants as instrumental variables to allow causal effects of an exposure and outcome relationship to be estimated. Due to the random assortment of alleles during meiosis and germline genetic variants being fixed at conception, MR analyses are less susceptible to conventional confounding and reverse causality. To date, a large-scale MR study examining the associations between multiple glycemic traits and colorectal cancer has not been reported.

We used 2-sample MR to examine potential causal effects of glycemic traits on colorectal cancer risk. This involved combining genetic variants robustly associated with circulating concentrations of fasting insulin, 2-hour glucose, fasting glucose and HbA1c, and type 2 diabetes in genome-wide association studies (GWAS) and then assessing the association of these variants with colorectal cancer risk in a large consortium including up to 48 214 colorectal cancer case patients and 64 159 control patients (25).

## Methods

### Genetic Determinants of Glycemic Traits

Genetic instrumental variables comprised single nucleotide polymorphism (SNPs) identified as being robustly associated with each glycemic trait (at $P < 5 \times 10^{-8}$) from the largest GWAS of that trait to date (26–29). For circulating concentrations of 2-hour glucose, fasting glucose, and fasting insulin, the MeAnalyses of Glucose and Insulin-related traits Consortium (MAGIC) GWAS included 63 396, 200 622, and 151 013 participants, respectively (28). Each glycemic trait was regressed with body mass index (BMI), study-specific covariates, and principal components (28). For HbA1c, the GWAS conducted by the Neale laboratory included 361 194 UK Biobank participants (27) and used least-squares linear models with sex and the first 10 principal components from the UK Biobank sample quality control (QC) file as covariates. For type 2 diabetes, the GWAS included 74 124 type 2 diabetes cases and 824 006 controls without type 2 diabetes (26). Within each contributing study, all variants were tested for the association with type 2 diabetes using regression models, with and without adjustment for BMI, and additionally adjusted for study-specific covariates as well as principal components. Participants were of European ancestry, approximately 55% were women, and aged a mean of more than 50 years. From the genome-wide significant variants identified in these GWAS for each glycemic trait, we excluded correlated SNPs based on a linkage disequilibrium level of $R^2$ less than 0.01 using genotype data from European individuals from phase 3 (version 5) enrolled in the 1000 Genomes Project as a reference panel. The proportion of variance explained by the genetic instruments for the glycemic traits ranged from 0.6% to 5.7% (Table 1). We also estimated the F-statistic, a formal test of whether the proportion of variance explained is sufficiently high for a trait given the sample size used. In our study, the estimated F-statistic values were greater than 516 for all genetic instruments. Summary information on the genetic instruments, and the effect estimates for each individual SNP with concentrations of fasting insulin (n = 34 SNPs), 2-hour glucose (n = 13 SNPs), fasting glucose (n = 70 SNPs), HbA1c (n = 221 SNPs), and type 2 diabetes (n = 268 SNPs), are presented in Table 1 and Supplementary Tables 1 and 2 (available online).

### Data on Colorectal Cancer

Summary data for associations of the glycemic traits with colorectal cancer were obtained from a GWAS of 112 373 participants (48 214 colorectal cancer cases and 64 159 controls). For HbA1c, summary data were sourced from a smaller colorectal cancer GWAS of 85 638 participants (42 886 colorectal cancer cases and 42 752 controls) that excluded UK Biobank to avoid sample overlap. The GWAS data were from a meta-analysis that combined the ColoRectal Transdisciplinary Study (CORECT), the Colon Cancer Family Registry (CCFR), and studies within the Genetics and Epidemiology of Colorectal Cancer (GECCO) consortium (30). Imputation was performed using the Haplotype Reference Consortium r1.1 reference panel. Logistic regression models were adjusted for age, sex, and study or genotyping project to specific covariates, including principal components (of all genetic variants that surpassed quality control filtering) to adjust for population structure (25). Participants were of European ancestry, approximately 55% were women, and aged a mean of more than 50 years. All participants provided written informed consent, and each study was approved by the relevant

**Table 1.** Summary of the glycemic trait instrument variables used in this study[a]

| Glycemic trait | No. of SNPs | Variance explained, % |
|---|---|---|
| Fasting insulin (29) | 34 | 0.6 |
| 2-hour glucose (29) | 13 | 2.4 |
| Fasting glucose (29) | 70 | 1.4 |
| Glycated hemoglobin (HbA1c) (27) | 221 | 5.7 |
| Type 2 diabetes (26) | 268 | 2.0 |

[a]SNP = single nucleotide polymorphism.

research ethics committee or institutional review board. The effect estimates for associations of each individual glycemic trait related SNP with colorectal cancer from the GECCO, CORECT, and CCFR meta-analysis are presented in Supplementary Table 1 (available online). For sensitivity analyses, summary-level data for the associations for glycemic trait related variants with colorectal cancer were also obtained from a FinnGen consortium GWAS of 2435 colorectal cancer cases and 147 282 noncancer cases (31).

### Statistical Power

Post hoc statistical power was calculated using an online tool at https://shiny.cnsgenomics.com/mRnd/. We had sufficient statistical power (>80%) to detect relatively small causal effect estimates with minimum expected odds ratios (ORs) per 1 SD ranging from 1.09 to 1.24 for glycemic traits in relation to colorectal cancer risk (Supplementary Table 3, available online).

### Statistical Analysis

Two-sample random-effects inverse variance weighted methods were implemented. Odds ratios were scaled to a 1-SD increase in log of fasting insulin (mean approximately 57 pmol/mol; SD approximately 42 pmol/mol), 2-hour glucose (mean approximately 5 mmol/L; SD approximately 0.6 mmol/L), fasting glucose (mean approximately 6 mmol/L; SD approximately 1.6 mmol/L), and HbA1c (mean approximately 36 mmol/mol; SD approximately 6.7 mmol/mol) concentrations; and a 1-unit increase in log odds of type 2 diabetes. False discovery rate correction was computed (q-value; statistical significance level <.05) for the primary analyses—sexes combined inverse variance weighted models for colorectal cancer—using the Benjamini-Hochberg method (32). Heterogeneity by sex and anatomical subsite (colon, proximal colon, distal colon, and rectum) was assessed by calculating $\chi^2$ statistics. Cochran's Q statistics quantified heterogeneity across individual SNPs. Sensitivity analyses were conducted to assess and correct for the presence of horizontal pleiotropy (ie, genetic variants influencing colorectal cancer via an alternate biological pathway, independent of the glycemic exposure of interest). To evaluate the extent to which directional pleiotropy (nonbalanced horizontal pleiotropy in the MR risk estimates) may have affected the causal estimates, we used MR-Egger regression (33). We also computed odds ratios using the complementary weighted median method that can provide valid MR estimates under the presence of pleiotropy when up to 50% of the included instruments are invalid (34). The presence of pleiotropy was also assessed using the MR pleiotropy residual sum and outlier test (MR-PRESSO), in which outlying SNPs are excluded from the instruments and the effect estimates are reassessed (35).

The GWAS used for the fasting insulin genetic instrument adjusted for BMI, however, conditioning on BMI (a heritable covariable) may introduce bias if BMI is a collider in the pathway between the genetic instrument of fasting insulin and/or the genetic instrument to colorectal cancer relationships. Therefore, we conducted a sensitivity analysis excluding variants related to BMI at the *P* less than $5 \times 10^{-8}$ (n = 9) level (identified by searching http://www.phenoscanner.medschl.cam.ac.uk/; date checked May 2021). For type 2 diabetes, the genetic instrument included GWAS estimates unadjusted for BMI, but to assess the possible influence of collider bias on our MR estimates, we conducted a sensitivity analysis using BMI-adjusted GWAS summary estimates in the genetic instrument. Finally, in a sensitivity analysis, separate MR analyses were also conducted using data from the FinnGen consortium, and estimates were combined with those from our main analyses (GECCO, CORECT, and CCFR) using fixed-effects meta-analysis.

All statistical tests were 2-sided. Thresholds for nominal significance (for the secondary and sensitivity analyses) were set at *P* less than .05. All statistical analyses were performed using the *MendelianRandomization* R package (36).

## Results

### Effect of Fasting Insulin and Colorectal Cancer

Higher fasting insulin levels increased colorectal cancer risk (OR per 1-SD, 1.65, 95% confidence interval [CI] = 1.15 to 2.36, q-value = 0.035). Evidence of effect heterogeneity by SNP was found (Cochran's Q $P = 1.6 \times 10^{-7}$), but little evidence of directional pleiotropy was detected (MR-Egger intercept $P = .78$). Positive effect estimates were also found in the weighted median, MR-Egger, and MR-PRESSO models (Table 2). There was little evidence of heterogeneity by sex in the inverse variance weighted models ($P_{heterogeneity} = .9$), although evidence of pleiotropy was detected for women in the weighted median and MR-Egger models. Similar effect estimates were also found for all colorectal cancer subsites ($P_{heterogeneity}$ for colon vs rectal cancer = .98; $P_{heterogeneity}$ for proximal colon vs distal colon cancer = .98) (Table 2). In the sensitivity analysis that excluded genetic variants associated with BMI (n = 9 SNPs removed), similar strength positive effect estimates were found (Supplementary Table 4, available online). Scatter plots (with colored lines representing the slopes of the different regression analyses) for the fasting insulin, plus other glycemic traits, and colorectal cancer association are presented in Supplementary Figure 1 (available online). A similar association without evidence of heterogeneity ($I^2 = 0\%$) was found for fasting insulin with colorectal cancer when estimates using data from GECCO, CORECT, and CCFR and FinnGen were pooled (OR per 1-SD = 1.68, 95% CI = 1.12 to 2.23) (Supplementary Table 5, available online).

### Effects of 2-Hour Glucose, Fasting Glucose, and HbA1c on Colorectal Cancer

We found no evidence of any effects of 2-hour glucose (OR per 1-SD increase = 1.02, 95% CI = 0.86 to 1.21, q-value = 0.81) or fasting glucose (OR per 1-SD increase = 1.04, 95% CI = 0.88 to 1.23, q-value = 0.81) on colorectal cancer in the inverse variance weighted models. Similar null effect estimates were found for men and women ($P_{heterogeneity} > .2$), across anatomical subsites ($P_{heterogeneity}$ for colon vs rectal cancer >.2; $P_{heterogeneity}$ for

ARTICLE

**Table 2.** MR estimates for glycemic traits and risk of colorectal cancer

| Glycemic trait | IVW random effects OR (95% CI) | $P_{heterogeneity}$[a] | Weighted median OR (95% CI) | MR-Egger OR (95% CI) | MR-Egger intercept P[b] | MR-PRESSO | |
|---|---|---|---|---|---|---|---|
| | | | | | | OR (95% CI) | SNPs excluded |
| Fasting insulin[c] | | | | | | | |
| Colorectal cancer | | | | | | | |
| All | 1.65 (1.15 to 2.36) | $1.60 \times 10^{-7}$ | 1.48 (1.01 to 2.16) | 1.39 (0.43 to 4.57) | .78 | 1.52 (1.11 to 2.10) | rs11727676 |
| Men | 1.72 (1.05 to 2.80) | $5.70 \times 10^{-7}$ | 1.72 (1.05 to 2.80) | 2.32 (0.47 to 11.02) | .7 | 1.55 (1.00 to 2.39) | rs11727676 |
| Women | 1.65 (1.14 to 2.39) | .05 | 1.05 (0.66 to 1.70) | 0.68 (0.21 to 2.16) | .11 | No outliers | |
| Colon cancer | | | | | | | |
| All | 1.73 (1.16 to 2.59) | $8.70 \times 10^{-6}$ | 1.60 (1.04 to 2.46) | 1.63 (0.44 to 6.05) | .93 | 1.57 (1.12 to 2.23) | rs11727676 |
| Men | 1.57 (0.96 to 2.59) | .003 | 1.22 (0.69 to 2.16) | 1.80 (0.36 to 9.03) | .86 | 1.39 (0.91 to 2.14) | rs11727676 |
| Women | 1.92 (1.21 to 3.06) | .01 | 1.55 (0.88 to 2.75) | 1.35 (0.30 to 6.17) | .63 | No outliers | |
| Proximal colon cancer | | | | | | | |
| All | 1.77 (1.14 to 2.75) | .005 | 2.05 (1.22 to 3.46) | 1.55 (0.37 to 6.49) | .85 | 1.62 (1.08 to 2.41) | rs11727676 |
| Men | 1.43 (0.81 to 2.56) | .07 | 1.60 (0.78 to 3.29) | 1.34 (0.20 to 9.03) | .94 | No outliers | |
| Women | 2.23 (1.34 to 3.67) | .16 | 2.23 (1.15 to 4.35) | 1.77 (0.34 to 9.21) | .77 | No outliers | |
| Distal colon cancer | | | | | | | |
| All | 1.79 (1.08 to 2.94) | $1.50 \times 10^{-4}$ | 2.03 (1.16 to 3.56) | 2.10 (0.41 to 10.49) | .84 | 1.62 (1.02 to 2.53) | rs11727676 |
| Men | 1.79 (1.02 to 3.10) | .07 | 1.70 (0.83 to 3.42) | 2.66 (0.44 to 16.28) | .65 | No outliers | |
| Women | 1.79 (0.95 to 3.39) | .01 | 1.77 (0.79 to 3.90) | 1.46 (0.18 to 11.59) | .84 | No outliers | |
| Rectal cancer | | | | | | | |
| All | 1.72 (1.14 to 2.56) | .04 | 1.79 (1.07 to 3.00) | 1.19 (0.32 to 4.39) | .57 | No outliers | |
| Men | 2.08 (1.14 to 3.78) | .003 | 2.16 (1.09 to 4.31) | 2.66 (0.38 to 18.17) | .79 | 2.34 (1.34 to 4.06) | rs73013411 |
| Women | 1.39 (0.81 to 2.39) | .3 | 1.86 (0.87 to 3.94) | 0.46 (0.08 to 2.56) | .18 | No outliers | |
| 2-hour glucose[c] | | | | | | | |
| Colorectal cancer | | | | | | | |
| All | 1.02 (0.86 to 1.21) | $6.40 \times 10^{-7}$ | 1.05 (0.92 to 1.20) | 0.82 (0.52 to 1.28) | .3 | 1.12 (0.99 to 1.27) | rs1260326, rs117643180 |
| Men | 0.97 (0.81 to 1.17) | $9.90 \times 10^{-4}$ | 1.06 (0.90 to 1.25) | 0.75 (0.45 to 1.23) | .26 | 1.02 (0.87 to 1.20) | rs1260326 |
| Women | 1.06 (0.90 to 1.26) | .01 | 1.07 (0.90 to 1.26) | 0.90 (0.57 to 1.45) | .47 | No outliers | |
| Colon cancer | | | | | | | |
| All | 1.00 (0.84 to 1.17) | $3 \times 10^{-4}$ | 1.02 (0.88 to 1.19) | 0.79 (0.50 to 1.23) | .28 | 1.03 (0.89 to 1.20) | rs1260326 |
| Men | 0.98 (0.84 to 1.15) | .14 | 1.02 (0.84 to 1.25) | 0.78 (0.50 to 1.22) | .28 | No outliers | |
| Women | 1.02 (0.83 to 1.26) | .003 | 0.99 (0.81 to 1.21) | 0.81 (0.45 to 1.46) | .41 | No outliers | |
| Proximal colon cancer | | | | | | | |
| All | 0.98 (0.85 to 1.12) | .26 | 0.90 (0.75 to 1.06) | 0.77 (0.54 to 1.11) | .17 | No outliers | |
| Men | 0.95 (0.79 to 1.14) | .69 | 0.94 (0.73 to 1.21) | 0.90 (0.55 to 1.48) | .84 | No outliers | |
| Women | 1.01 (0.84 to 1.22) | .22 | 1.00 (0.79 to 1.27) | 0.70 (0.43 to 1.16) | .13 | No outliers | |
| Distal colon cancer | | | | | | | |
| All | 1.04 (0.84 to 1.30) | $5.00 \times 10^{-4}$ | 1.03 (0.85 to 1.25) | 0.87 (0.47 to 1.58) | .52 | 1.11 (0.93 to 1.31) | rs1260326 |
| Men | 1.04 (0.84 to 1.30) | .09 | 0.96 (0.75 to 1.23) | 0.79 (0.43 to 1.46) | .34 | No outliers | |
| Women | 1.05 (0.77 to 1.42) | $9.00 \times 10^{-4}$ | 0.97 (0.73 to 1.28) | 0.98 (0.40 to 2.36) | .86 | 1.12 (0.84 to 1.48) | rs1260326 |
| Rectal cancer | | | | | | | |
| All | 1.05 (0.89 to 1.26) | .02 | 1.06 (0.89 to 1.27) | 0.84 (0.52 to 1.34) | .29 | No outliers | |

(continued)

**Table 2.** (continued)

| Glycemic trait | IVW random effects OR (95% CI) | $P_{heterogeneity}$[a] | Weighted median OR (95% CI) | MR-Egger OR (95% CI) | MR-Egger intercept P[b] | MR-PRESSO | |
|---|---|---|---|---|---|---|---|
| | | | | | | OR (95% CI) | SNPs excluded |
| Men | 1.05 (0.84 to 1.32) | .03 | 1.03 (0.81 to 1.30) | 0.95 (0.50 to 1.82) | .74 | 1.12 (0.91 to 1.35) | rs1260326 |
| Women | 1.05 (0.86 to 1.30) | .3 | 0.93 (0.71 to 1.21) | 0.74 (0.43 to 1.27) | .17 | No outliers | |
| Fasting glucose[c] | | | | | | | |
| Colorectal cancer | | | | | | | |
| All | 1.04 (0.88 to 1.23) | $4.9 \times 10^{-10}$ | 1.05 (0.89 to 1.25) | 1.01 (0.75 to 1.36) | .84 | 0.97 (0.84 to 1.12) | rs1260326, rs174583 |
| Men | 0.90 (0.71 to 1.14) | $4.8 \times 10^{-4}$ | 0.96 (0.72 to 1.30) | 1.03 (0.68 to 1.57) | .47 | 0.90 (0.76 to 1.07) | rs1260326, rs174583 |
| Women | 1.11 (0.92 to 1.34) | .003 | 1.01 (0.80 to 1.28) | 1.02 (0.73 to 1.42) | .54 | 1.07 (0.90 to 1.27) | rs174583 |
| Colon cancer | | | | | | | |
| All | 0.96 (0.79 to 1.16) | $1.40 \times 10^{-7}$ | 0.90 (0.73 to 1.09) | 0.95 (0.68 to 1.34) | .96 | 0.93 (0.79 to 1.11) | rs174583 |
| Men | 0.90 (0.71 to 1.14) | $4.80 \times 10^{-4}$ | 0.97 (0.72 to 1.30) | 1.03 (0.68 to 1.57) | .47 | 0.90 (0.73 to 1.11) | rs1260326, rs174583 |
| Women | 1.22 (0.83 to 1.26) | .02 | 0.87 (0.66 to 1.14) | 0.89 (0.61 to 1.30) | .37 | 0.99 (0.81 to 1.21) | rs174583 |
| Proximal colon cancer | | | | | | | |
| All | 0.89 (0.73 to 1.06) | .04 | 0.82 (0.64 to 1.06) | 0.85 (0.61 to 1.19) | .78 | 0.87 (0.73 to 1.04) | rs174583 |
| Men | 0.89 (0.68 to 1.16) | .1 | 0.92 (0.63 to 1.36) | 1.03 (0.64 to 1.65) | .47 | No outliers | |
| Women | 0.88 (0.70 to 1.11) | .45 | 0.71 (0.51 to 1.00) | 0.72 (0.48 to 1.07) | .22 | No outliers | |
| Distal colon cancer | | | | | | | |
| All | 1.05 (0.83 to 1.34) | $6 \times 10^{-7}$ | 0.99 (0.75 to 1.30) | 0.97 (0.63 to 1.49) | .67 | 0.98 (0.80 to 1.20) | rs1260326, rs9348441, rs174583 |
| Men | 0.94 (0.71 to 1.25) | .01 | 0.99 (0.68 to 1.43) | 0.98 (0.59 to 1.60) | .86 | 0.90 (0.70 to 1.16) | rs174583 |
| Women | 1.19 (0.88 to 1.60) | .003 | 0.97 (0.66 to 1.42) | 0.94 (0.55 to 1.62) | .32 | 1.13 (0.85 to 1.51) | rs174583 |
| Rectal cancer | | | | | | | |
| All | 1.17 (0.96 to 1.43) | .01 | 1.12 (0.85 to 1.48) | 1.03 (0.73 to 1.46) | .38 | 1.14 (0.94 to 1.38) | rs174583 |
| Men | 1.11 (0.86 to 1.42) | .06 | 1.17 (0.83 to 1.65) | 1.05 (0.67 to 1.63) | .77 | No outliers | |
| Women | 1.23 (0.96 to 1.60) | .54 | 1.00 (0.67 to 1.49) | 0.98 (0.63 to 1.54) | .21 | No outliers | |
| Glycated hemoglobin (HbA1c)[c] | | | | | | | |
| Colorectal cancer | | | | | | | |
| All | 1.09 (1.00 to 1.19) | $2.80 \times 10^{-21}$ | 1.06 (0.95 to 1.17) | 0.93 (0.78 to 1.11) | .04 | 1.06 (0.99 to 1.14) | rs9273363, rs174549, rs76895963, rs61927768, rs10784889, rs11065979 |
| Men | 1.09 (0.98 to 1.21) | $4.80 \times 10^{-9}$ | 1.06 (0.92 to 1.23) | 0.95 (0.77 to 1.18) | .16 | 1.07 (0.97 to 1.17) | rs3104369, rs76895963 |
| Women | 1.09 (0.99 to 1.21) | $1.60 \times 10^{-6}$ | 1.03 (0.90 to 1.20) | 0.91 (0.74 to 1.11) | .04 | 1.07 (0.97 to 1.17) | rs11065979 |
| Colon cancer | | | | | | | |
| All | 1.06 (0.95 to 1.17) | $8.00 \times 10^{-17}$ | 1.05 (0.92 to 1.20) | 0.94 (0.77 to 1.15) | .2 | 1.03 (0.95 to 1.13) | rs174549, rs61927768, rs10784889, rs11065979 |
| Men | 1.08 (0.95 to 1.23) | $5.60 \times 10^{-9}$ | 1.03 (0.86 to 1.23) | 0.95 (0.72 to 1.24) | .28 | 1.08 (0.95 to 1.22) | rs3104369, rs76895963 |
| Women | 1.05 (0.94 to 1.17) | $9.80 \times 10^{-4}$ | 1.01 (0.84 to 1.20) | 0.94 (0.75 to 1.18) | .28 | 1.03 (0.93 to 1.15) | rs11065979 |
| Proximal colon cancer | | | | | | | |
| All | 1.06 (0.95 to 1.19) | $1.20 \times 10^{-9}$ | 1.00 (0.85 to 1.17) | 0.87 (0.69 to 1.10) | .06 | 1.06 (0.95 to 1.17) | rs10784889, rs11065979 |
| Men | 1.10 (0.94 to 1.28) | $2.40 \times 10^{-4}$ | 1.06 (0.85 to 1.33) | 0.94 (0.67 to 1.26) | .19 | 1.08 (0.94 to 1.26) | rs3104369 |
| Women | 1.03 (0.90 to 1.18) | .01 | 1.04 (0.84 to 1.30) | 0.83 (0.63 to 1.09) | .06 | No outliers | |
| Distal colon cancer | | | | | | | |

(continued)

Table 2. (continued)

| Glycemic trait | IVW random effects OR (95% CI) | $P_{heterogeneity}$[a] | Weighted median OR (95% CI) | MR-Egger OR (95% CI) | MR-Egger intercept P[b] | MR-PRESSO | |
|---|---|---|---|---|---|---|---|
| | | | | | | OR (95% CI) | SNPs excluded |
| All | 1.08 (0.96 to 1.22) | $1.90 \times 10^{-10}$ | 0.96 (0.82 to 1.14) | 1.07 (0.83 to 1.36) | .9 | 1.07 (0.96 to 1.19) | rs7766070, rs174549, rs61927768, rs11065979 |
| Men | 1.07 (0.92 to 1.26) | $3.80 \times 10^{-7}$ | 1.02 (0.81 to 1.29) | 0.99 (0.72 to 1.40) | .61 | 1.06 (0.90 to 1.24) | rs3104369 |
| Women | 1.09 (0.94 to 1.26) | .01 | 1.06 (0.84 to 1.32) | 1.13 (0.83 to 1.53) | .79 | 1.08 (0.94 to 1.25) | rs11065979 |
| Rectal cancer | | | | | | | |
| All | 1.19 (1.06 to 1.33) | $1.60 \times 10^{-6}$ | 1.07 (0.95 to 1.30) | 1.03 (0.82 to 1.30) | .16 | 1.14 (1.03 to 1.27) | rs9273363, rs61927768, rs11065979 |
| Men | 1.21 (1.05 to 1.40) | $5.90 \times 10^{-4}$ | 1.37 (1.11 to 1.70) | 1.26 (0.94 to 1.69) | .77 | No outliers | |
| Women | 1.16 (0.99 to 1.35) | .01 | 0.95 (0.75 to 1.22) | 0.78 (0.57 to 1.06) | .004 | 1.14 (0.98 to 1.32) | rs3130453 |
| Type 2 diabetes[d] | | | | | | | |
| Colorectal cancer | | | | | | | |
| All | 1.04 (1.01 to 1.07) | $1.90 \times 10^{-16}$ | 1.00 (0.96 to 1.04) | 0.97 (0.90 to 1.04) | .04 | 1.04 (1.01 to 1.07) | rs1260326, rs9379084, rs7756992, rs76895963 |
| Men | 1.02 (0.98 to 1.06) | $1.30 \times 10^{-6}$ | 1.00 (0.94 to 1.05) | 0.96 (0.88 to 1.05) | .15 | 1.02 (0.99 to 1.06) | rs76895963, rs2736177 |
| Women | 1.06 (1.02 to 1.09) | $4.00 \times 10^{-6}$ | 0.99 (0.94 to 1.05) | 0.98 (0.90 to 1.07) | .06 | 1.07 (1.03 to 1.11) | rs7756992 |
| Colon cancer | | | | | | | |
| All | 1.03 (1.00 to 1.07) | $3.30 \times 10^{-10}$ | 0.98 (0.94 to 1.03) | 0.97 (0.90 to 1.05) | .08 | 1.04 (1.01 to 1.08) | rs7756992, rs1561927 |
| Men | 1.01 (0.97 to 1.06) | .002 | 0.98 (0.91 to 1.05) | 0.93 (0.85 to 1.03) | .08 | 1.02 (0.98 to 1.07) | rs76895963 |
| Women | 1.05 (1.01 to 1.09) | $1.20 \times 10^{-4}$ | 1.01 (0.94 to 1.07) | 1.01 (0.91 to 1.12) | .34 | 1.06 (1.02 to 1.11) | rs7756992 |
| Proximal colon cancer | | | | | | | |
| All | 1.03 (0.99 to 1.07) | $4.20 \times 10^{-5}$ | 0.97 (0.92 to 1.03) | 0.96 (0.88 to 1.05) | .1 | 1.03 (0.99 to 1.06) | rs6518681 |
| Men | 1.01 (0.96 to 1.06) | .47 | 1.02 (0.94 to 1.11) | 0.93 (0.83 to 1.04) | .12 | No outliers | |
| Women | 1.05 (1.00 to 1.11) | .002 | 1.00 (0.91 to 1.08) | 1.00 (0.89 to 1.13) | .31 | No outliers | |
| Distal colon cancer | | | | | | | |
| All | 1.04 (1.00 to 1.08) | $1.25 \times 10^{-7}$ | 1.04 (0.98 to 1.11) | 0.98 (0.89 to 1.08) | .19 | 1.05 (1.01 to 1.09) | rs7756992, rs2736177, rs10811647 |
| Men | 1.02 (0.97 to 1.08) | .002 | 0.95 (0.88 to 1.04) | 0.95 (0.84 to 1.07) | .21 | No outliers | |
| Women | 1.06 (1.01 to 1.13) | $1.70 \times 10^{-4}$ | 1.02 (0.92 to 1.12) | 1.03 (0.90 to 1.17) | .56 | No outliers | |
| Rectal cancer | | | | | | | |
| All | 1.04 (1.00 to 1.08) | $2.90 \times 10^{-7}$ | 1.00 (0.93 to 1.07) | 0.97 (0.88 to 1.07) | .11 | 1.04 (1.00 to 1.08) | rs149717632 |
| Men | 1.03 (0.97 to 1.08) | .001 | 1.03 (0.94 to 1.13) | 0.98 (0.87 to 1.11) | .41 | 1.02 (0.97 to 1.08) | rs149717632 |
| Women | 1.06 (1.00 to 1.12) | .004 | 0.99 (0.90 to 1.08) | 0.96 (0.84 to 1.09) | .1 | No outliers | |

[a]Cochran's Q statistics (2-sided) quantified heterogeneity across individual SNPs. CI = confidence interval; IVW = inverse-variance-weighted; MR = Mendelian randomization; OR = odds ratio; PRESSO = pleiotropy residual sum and outlier test; SNP = single nucleotide polymorphism.
[b]MR-Egger intercept test (2-sided *P* value).
[c]Odds ratios scaled to 1-SD increase in log of genetically predicted 2-hour glucose, fasting glucose, glycated hemoglobin, and fasting insulin levels.
[d]Odds ratios scaled to 1-unit increase in log odds of genetic liability to type 2 diabetes.

proximal colon vs distal colon cancer >.3), and for the weighted median, MR-Egger, and MR-PRESSO models (Table 2).

In the inverse variance weighted model, a positive effect was found for HbA1c concentration with colorectal cancer risk (OR per 1-SD increase = 1.09, 95% CI = 1.00 to 1.19; q-value = 0.08), with similar effects in men and women ($P_{heterogeneity}$ = 1) (Table 2). However, evidence of effect heterogeneity (Cochran's Q $P = 2.8 \times 10^{-21}$) and directional pleiotropy was detected (MR-Egger intercept $P = .04$), with no evidence of causal effects found in the weighted median, MR-Egger, and MR-PRESSO models. Little evidence of heterogeneity was observed across anatomical subsites ($P_{heterogeneity}$ for colon vs rectal cancer = 0.14; $P_{heterogeneity}$ for proximal colon vs distal colon cancer = .83). A positive effect of HbA1c on rectal cancer was found (OR per 1-SD increase = 1.19, 95% CI = 1.06 to 1.33), but this effect was attenuated towards the null in the weighted median and MR-Egger models. For men, however, a positive effect was found for HbA1c concentration and rectal cancer (OR per 1-SD = 1.21, 95% CI = 1.05 to 1.40), with evidence of effect heterogeneity (Cochran's Q $P = 5.9 \times 10^{-4}$) but little evidence of directional pleiotropy (MR-Egger intercept $P = .77$). Similar effect estimates were observed for rectal cancer in men in the weighted median, MR-Egger, and MR-PRESSO models (Table 2).

### Effects of Type 2 Diabetes and Colorectal Cancer

In the inverse variance weighted model, a weak positive effect was found between genetic liability to type 2 diabetes and colorectal cancer (OR per 1-unit increase in log odds = 1.04, 95% CI = 1.01 to 1.07, q-value = 0.05), with similar magnitude of effects by sex ($P_{heterogeneity}$ = .14) and anatomical subsites ($P_{heterogeneity}$ for colon vs rectal cancer = .71; $P_{heterogeneity}$ for proximal colon cancer vs distal colon cancer = .73) (Table 2). However, no evidence of causal effects was detected in the weighted median (OR = 1.00, 95% CI = 0.96 to 1.04) or MR-Egger models (OR = 0.97, 95% CI = 0.90 to 1.04), with evidence of effect heterogeneity (Cochran's Q $P = 1.9 \times 10^{-16}$) and directional pleiotropy detected (MR-Egger intercept $P = .04$). A similar pattern of results to the inverse variance weighted model was found when the MR-PRESSO test detected outlier SNPs were excluded from the models (Table 2) and when type 2 diabetes GWAS summary estimates adjusted for BMI were used in the genetic instrument (Supplementary Table 6, available online).

## Discussion

We conducted the largest and most comprehensive study to date on the effects of multiple glycemic traits with colorectal cancer risk. We found that higher circulating fasting insulin levels increased colorectal cancer risk, with minimal evidence of heterogeneity by sex or anatomical subsite found. There was no evidence of effects of 2-hour glucose and fasting glucose on colorectal cancer risk. Genetic liability to type 2 diabetes and higher HbA1c concentration also appeared to increase colorectal cancer risk, but horizontal pleiotropy may have influenced these findings. Higher HbA1c concentrations increased rectal cancer risk in men.

Many experimental and observational epidemiological studies have examined the insulin and colorectal cancer relationship. Experimental studies have demonstrated that insulin, through binding to its cognate receptor or the insulin-like growth factor receptor, activates the phosphoinositide 3-kinase-protein kinase B -mammalian target of rapamycin (PI3K–AKT–mTOR) and Ras-mitogen-activated protein kinase (RAS to MAPK) pathways, which in turn can lead to downstream cellular proliferation and protein synthesis in tumor cells (37,38). Rat models have demonstrated that insulin can induce proliferation of colorectal epithelial cells and the development of aberrant crypt foci, the primary neoplastic lesions in colorectal development (39). In colonic tumor cells, the expression of the insulin receptor protein is elevated, particularly isoform A, which exerts mitogenic effects (40,41).

This experimental evidence is supported by results from epidemiological studies that have examined the association between prediagnostic C-peptide concentrations and colorectal cancer risk (17). Two US-based prospective studies from the early 2000s reported positive associations between circulating C-peptide levels and colorectal cancer risk (16–18). More recently, a meta-analysis of 8 prospective studies reported a pooled odds ratio of 1.39 (95% CI = 1.04 to 1.87) for the comparison of the highest vs lowest C-peptide–level groups (16). Prior prospective studies that assessed the association between circulating fasting insulin levels and colorectal cancer have yielded inconsistent results, with positive associations found in some studies that were attenuated after statistical adjustment for other colorectal cancer risk factors (19–21), and null results found in 2 studies that did not measure insulin levels in fasting blood samples (22,23). The use of nonfasting biospecimens, differences in laboratory assays, and the vulnerability of observational epidemiological studies to confounding or reverse causality limit causal inference of the fasting insulin and colorectal cancer association. In our MR analyses, we found a positive effect of fasting insulin on colorectal cancer, with consistent effect estimates in men and women, according to anatomical subsite, and for all the sensitivity analyses that assessed horizontal pleiotropy. This result, taken together with experimental data showing mitogenic and antiapoptotic effects of insulin (37,38), provides supportive evidence of a positive causal relationship between fasting insulin concentrations and colorectal cancer.

We found inconclusive evidence of causal effects of glucose on colorectal cancer. For 2-hour glucose and fasting glucose, our findings suggesting no evidence of an association are consistent with some (42,43) but not other (12,14,44) prior prospective observational studies. For HbA1c concentrations, we found a positive effect with colorectal cancer, but our sensitivity analyses indicated that alternate biological pathways (ie, horizontal pleiotropy) may have influenced this result. However, for rectal cancer, particularly for men, a positive effect was found that was robust to all the sensitivity analyses we used to assess the influence of horizontal pleiotropy. It is unclear why a robust positive causal effect was found for rectal cancer and for men only. Growing evidence indicates that the clinical features, genetic architecture, and risk factor profiles may differ for tumors across different anatomical locations in the colorectum (45–47). There are also emerging data that risk factors differ between men and women (45,47). However, we also cannot rule out the possibility that the HbA1c effect found for rectal cancer in men only is a chance finding. Additional well-powered studies are needed to examine the sex-specific relationship between different markers of metabolic dysregulation, including hyperglycemia, and risk of colorectal cancer at different anatomical regions.

Type 2 diabetes has been consistently associated with higher risk of developing colorectal cancer in prospective cohort studies, with a large umbrella review reporting a pooled relative risk of 1.27 (95% CI = 1.21 to 1.34) for the diabetes vs nondiabetes comparison (5,6). The results from this study, and those from 2 smaller MR studies (7,8), are generally unsupportive of a causal relationship between genetic liability to type 2 diabetes and colorectal cancer. Bias from reverse causality or residual confounding in the observational studies is a possible explanation for the divergent findings with the MR estimates. However, comparing results from these different study designs is challenging because we examined the genetic liability to type 2 diabetes, rather than the disease itself. In contrast, observational studies have included participants with or without an actual type 2 diabetes diagnosis. Collectively, our MR results suggest that elevated levels of insulin—a characteristic of prediabetes and uncontrolled diabetes—rather than glucose may be driving the positive association found between type 2 diabetes and colorectal cancer risk reported in observational studies. In support of this hypothesis, a recent Nurses' Health Study and Health Professionals Follow-up Study analysis found that the positive association between type 2 diabetes and colorectal cancer diminished over time as circulating insulin levels lowered (48). Additional studies are required to further examine which specific aspects of the pathophysiology of type 2 diabetes may promote colorectal cancer development.

Our study has several notable strengths. This was the largest MR study to date to estimate the causal effects of glycemic traits on colorectal cancer risk. We conducted multiple sensitivity analyses to examine the possible influence of pleiotropy in biasing our results. Crucially, the positive effects found for fasting insulin and colorectal cancer were generally robust according to these various sensitivity analyses. Several limitations of our study should be noted. First, our use of summary-level data precluded analyses according to subgroups of other colorectal cancer risk factors (eg, BMI, physical inactivity) and examination of possible nonlinear effects. In addition, the GWAS used to identify the fasting insulin genetic instruments was adjusted for BMI, which may have introduced collider bias into our MR estimates. However, we found similar results when we excluded variants associated with BMI from the fasting insulin genetic instrument. Further, similar MR estimates were found for the type 2 diabetes and colorectal cancer association using BMI unadjusted and adjusted GWAS estimates for type 2 diabetes, suggesting that collider bias had minimal influence on this relationship. In addition, results from a recent empirical study suggest that the use of covariate-adjusted GWAS summary estimates should not markedly influence downstream MR effect estimates (49). Finally, we acknowledge that the null effect estimates we observed in some of our analyses may have been a consequence of inadequate statistical power. However, our post hoc power calculation found that we had sufficient power (>80%) to detect relatively small causal effect estimates (minimum expected ORs per 1 SD ranging from 1.09 to 1.16 for 2-hour glucose, fasting glucose, HbA1c, and type 2 diabetes with colorectal cancer) (50).

In conclusion, our results support a causal effect of higher fasting insulin, but not glucose traits and genetic liability to type 2 diabetes, on colorectal cancer risk. These results suggest that high circulating insulin levels, rather than high glucose levels, may be the main driver of the positive associations found between type 2 diabetes and colorectal cancer in observational studies. The findings suggest that pharmacological or lifestyle interventions that lower circulating insulin levels may be beneficial in preventing colorectal tumorigenesis.

## Funding

This study was supported by Cancer Research UK (C18281/A29019).

RMM was supported by a Cancer Research UK (C18281/A29019) programme grant (the Integrative Cancer Epidemiology Programme) and the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol.

Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO): National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services (U01 CA137088, R01 CA059045, R01CA201407). This research was funded in part through the National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support Grant P30 CA015704. Scientific Computing Infrastructure at Fred Hutch funded by Office of Reseach Infrastructure Programs (ORIP) grant S10OD028685. Genotyping services were provided by the Center for Inherited Disease Research (CIDR) contract number HHSN2682012000081.

ASTERISK: a Hospital Clinical Research Program (PHRC-BRD09/C) from the University Hospital Center of Nantes (CHU de Nantes) and supported by the Regional Council of Pays de la Loire, the Groupement des Entreprises Françaises dans la Lutte contre le Cancer (GEFLUC), the Association Anne de Bretagne Génétique and the Ligue Régionale Contre le Cancer (LRCC).

The ATBC Study is supported by the Intramural Research Program of the U.S. National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

CLUE Cohort Study: Cancer data was PARTLY provided by the Maryland Cancer Registry, Center for Cancer Prevention and Control, Maryland Department of Health, with funding from the State of Maryland and the Maryland Cigarette Restitution Fund. The collection and availability of cancer registry data is also supported by the Cooperative Agreement NU58DP006333, funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services. CLUE funding was from the National Cancer Institute (U01 CA86308, Early Detection Research Network; P30 CA006973), National Institute on Aging (U01 AG18033), and the American Institute for Cancer Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

ColoCare: This work was supported by the National Institutes of Health (grant numbers R01 CA189184 [Li/Ulrich], U01 CA206110 [Ulrich/Li/Siegel/Figueiredo/Colditz], 2P30CA015704- 40 (Gilliland), R01 CA207371 [Ulrich/Li]), the Matthias Lackas-Foundation, the German Consortium for

Translational Cancer Research, and the EU TRANSCAN initiative.

The Colon Cancer Family Registry (CCFR, www.coloncfr.org) is supported in part by funding from the National Cancer Institute (NCI), National Institutes of Health (NIH) (award U01 CA167551). Support for case ascertainment was provided in part from the Surveillance, Epidemiology, and End Results (SEER) Program and the following U.S. state cancer registries: AZ, CO, MN, NC, NH; and by the Victoria Cancer Registry (Australia) and Ontario Cancer Registry (Canada). OFCCR ARCTIC: Additional funding for the OFCCR/ARCTIC was through award GL201-043 from the Ontario Research Fund (to BWZ), award 112746 from the Canadian Institutes of Health Research (to TJH), through a Cancer Risk Evaluation (CaRE) Program grant from the Canadian Cancer Society (to SG), and through generous support from the Ontario Ministry of Research and Innovation. The SFCCR Illumina HumanCytoSNP array was supported in part through NCI/NIH awards U01/U24 CA074794 and R01 CA076366 (to PAN). The CCFR Set-1 (Illumina 1M/1M-Duo) and Set-2 (Illumina Omni1-Quad) scans were supported by NIH awards U01 CA122839 and R01 CA143247 (to GC). The CCFR Set-3 (Affymetrix Axiom CORECT Set array) was supported by NIH award U19 CA148107 and R01 CA81488 (to SBG). The CCFR Set-4 (Illumina OncoArray 600K SNP array) was supported by NIH award U19 CA148107 (to SBG) and by the Center for Inherited Disease Research (CIDR), which is funded by the NIH to the Johns Hopkins University, contract number HHSN2682012000008I. The content of this manuscript does not necessarily reflect the views or policies of the NCI, NIH or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government, any cancer registry, or the CCFR.

COLON: The COLON study is sponsored by Wereld Kanker Onderzoek Fonds, including funds from grant 2014/1179 as part of the World Cancer Research Fund International Regular Grant Programme, by Alpe d'Huzes and the Dutch Cancer Society (UM 2012 to 5653, UW 2013 to 5927, UW2015-7946), and by TRANSCAN (JTC2012-MetaboCCC, JTC2013-FOCUS). The Nqplus study is sponsored by a ZonMW investment grant (98 to 10030); by PREVIEW, the project PREVention of diabetes through lifestyle intervention and population studies in Europe and around the World (PREVIEW) project which received funding from the European Union Seventh Framework Programme (FP7/2007 to 2013) under grant no. 312057; by funds from TI Food and Nutrition (cardiovascular health theme), a public to private partnership on precompetitive research in food and nutrition; and by FOODBALL, the Food Biomarker Alliance, a project from JPI Healthy Diet for a Healthy Life.

Colorectal Cancer Transdisciplinary (CORECT) Study: The CORECT Study was supported by the National Cancer Institute, National Institutes of Health (NCI/NIH), U.S. Department of Health and Human Services (grant numbers U19 CA148107, R01 CA81488, P30 CA014089, R01 CA197350; P01 CA196569; R01 CA201407) and National Institutes of Environmental Health Sciences, National Institutes of Health (grant number T32 ES013678).

CORSA: The CORSA study was funded by Austrian Research Funding Agency (FFG) BRIDGE (grant 829675, to Andrea Gsur), the "Herzfelder'sche Familienstiftung" (grant to Andrea Gsur) and was supported by COST Action BM1206.

CPS-II: The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort. This study was conducted with Institutional Review Board approval.

CRCGEN: Colorectal Cancer Genetics & Genomics, Spanish study was supported by Instituto de Salud Carlos III, co-funded by FEDER funds to a way to build Europe to (grants PI14-613 and PI09-1286), Agency for Management of University and Research Grants (AGAUR) of the Catalan Government (grant 2017SGR723), and Junta de Castilla y León (grant LE22A10-2). Sample collection of this work was supported by the Xarxa de Bancs de Tumors de Catalunya sponsored by Pla Director d'Oncología de Catalunya (XBTC), Plataforma Biobancos PT13/0010/0013 and ICOBIOBANC, sponsored by the Catalan Institute of Oncology.

Czech Republic CCS: This work was supported by the Grant Agency of the Czech Republic (18-09709S, 20-03997S), by the Grant Agency of the Ministry of Health of the Czech Republic (grants AZV NV18/03/00199 and AZV NV19-09 to 00237), and Charles University grants Unce/Med/006 and Progress Q28/LF1.

DACHS: This work was supported by the German Research Council (BR 1704/6 to 1, BR 1704/6 to 3, BR 1704/6 to 4, CH 117/1 to 1, HO 5117/2 to 1, HE 5998/2 to 1, KL 2354/3 to 1, RO 2270/8 to 1 and BR 1704/17 to 1), the Interdisciplinary Research Program of the National Center for Tumor Diseases (NCT), Germany, and the German Federal Ministry of Education and Research (01KH0404, 01ER0814, 01ER0815, 01ER1505A and 01ER1505B), the Interdisciplinary Research Program of the National Center for Tumor Diseases (NCT), Germany, and German Cancer Research Center.

DALS: National Institutes of Health (R01 CA48998 to M. L. Slattery).

EDRN: This work is funded and supported by the NCI, EDRN Grant (U01 CA 84968 to 06).

EPIC: The coordination of EPIC is financially supported by International Agency for Research on Cancer (IARC) and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). The national cohorts are supported by: Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy, Compagnia di SanPaolo and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS) - Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía,

ARTICLE

Asturias, Basque Country, Murcia and Navarra, and the Catalan Institute of Oncology—ICO (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C8221/A29017 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk; MR/M012190/1 to EPIC-Oxford). (United Kingdom).

EPICOLON: This work was supported by grants from Fondo de Investigación Sanitaria/FEDER (PI08/0024, PI08/1276, PS09/02368, P111/00219, PI11/00681, PI14/00173, PI14/00230, PI17/00509, 17/00878, PI20/00113, PI20/00226, Acción Transversal de Cáncer), Xunta de Galicia (PGIDIT07PXIB9101209PR), Ministerio de Economia y Competitividad (SAF07-64873, SAF 2010 to 19273, SAF2014-54453R), Fundación Científica de la Asociación Española contra el Cáncer (GCB13131592CAST), Beca Grupo de Trabajo "Oncología" AEG (Asociación Española de Gastroenterología), Fundación Privada Olga Torres, FP7 CHIBCHA Consortium, Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR, Generalitat de Catalunya, 2014SGR135, 2014SGR255, 2017SGR21, 2017SGR653), Catalan Tumour Bank Network (Pla Director d'Oncologia, Generalitat de Catalunya), PERIS (SLT002/16/00398, Generalitat de Catalunya), CERCA Programme (Generalitat de Catalunya) and COST Action BM1206 and CA17118. CIBERehd is funded by the Instituto de Salud Carlos III.

ESTHER/VERDI. This work was supported by grants from the Baden-Württemberg Ministry of Science, Research and Arts and the German Cancer Aid.

Harvard cohorts (HPFS, NHS, PHS): HPFS is supported by the National Institutes of Health (P01 CA055075, UM1 CA167552, U01 CA167552, R01 CA137178, R01 CA151993, and R35 CA197735), NHS by the National Institutes of Health (R01 CA137178, P01 CA087969, UM1 CA186107, R01 CA151993, and R35 CA197735) and PHS by the National Institutes of Health (R01 CA042182).

Hawaii Adenoma Study: NCI grants R01 CA72520.

HCES-CRC: the Hwasun Cancer Epidemiology Study to Colon and Rectum Cancer (HCES-CRC; grants from Chonnam National University Hwasun Hospital, HCRI15011-1).

Kentucky: This work was supported by the following grant support: Clinical Investigator Award from Damon Runyon Cancer Research Foundation (CI-8); NCI R01CA136726.

LCCS: The Leeds Colorectal Cancer Study was funded by the Food Standards Agency and Cancer Research UK Programme Award (C588/A19167).

MCCS cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further supported by Australian NHMRC grants 509348, 209057, 251553 and 504711 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry (VCR) and the Australian Institute of Health and Welfare (AIHW), including the National Death Index and the Australian Cancer Database.

MEC: National Institutes of Health (R37 CA54281, P01 CA033619, and R01 CA063464).

MECC: This work was supported by the National Institutes of Health, U.S. Department of Health and Human Services (R01 CA81488, R01 CA197350).

MSKCC: The work at Sloan Kettering in New York was supported by the Robert and Kate Niehaus Center for Inherited Cancer Genomics and the Romeo Milio Foundation. Moffitt: This work was supported by funding from the National Institutes of Health (grant numbers R01 CA189184, P30 CA076292), Florida Department of Health Bankhead-Coley Grant 09BN-13, and the University of South Florida Oehler Foundation. Moffitt contributions were supported in part by the Total Cancer Care Initiative, Collaborative Data Services Core, and Tissue Core at the H. Lee Moffitt Cancer Center & Research Institute, a National Cancer Institute-designated Comprehensive Cancer Center (grant number P30 CA076292).

NCCCS I & II: We acknowledge funding support for this project from the National Institutes of Health, R01 CA66635 and P30 DK034987.

NFCCR: This work was supported by an Interdisciplinary Health Research Team award from the Canadian Institutes of Health Research (CRT 43821); the National Institutes of Health, U.S. Department of Health and Human Serivces (U01 CA74783); and National Cancer Institute of Canada grants (18223 and 18226). The authors wish to acknowledge the contribution of Alexandre Belisle and the genotyping team of the McGill University and Génome Québec Innovation Centre, Montréal, Canada, for genotyping the Sequenom panel in the NFCCR samples. Funding was provided to Michael O. Woods by the Canadian Cancer Society Research Institute.

NSHDS: The research was supported by Biobank Sweden through funding from the Swedish Research Council (VR 2017 to 00650, VR 2017 to 01737), the Swedish Cancer Society (CAN 2017/581), Region Västerbotten (VLL-841671, VLL-833291), Knut and Alice Wallenberg Foundation (VLL-765961), and the Lion's Cancer Research Foundation (several grants) and Insamlingsstiftelsen, both at Umeå University.

OSUMC: OCCPI funding was provided by Pelotonia and HNPCC funding was provided by the NCI (CA16058 and CA67941).

PLCO: Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, NIH, DHHS. Funding was provided by National Institutes of Health (NIH), Genes, Environment and Health Initiative (GEI) Z01 CP 010200, NIH U01 HG004446, and NIH GEI U01 HG 004438.

SEARCH: The University of Cambridge has received salary support in respect of PDPP from the NHS in the East of England through the Clinical Academic Reserve. Cancer Research UK (C490/A16561); the UK National Institute for Health Research Biomedical Research Centres at the University of Cambridge.

SELECT: Research reported in this publication was supported in part by the National Cancer Institute of the National Institutes of Health under Award Numbers U10 CA37429 (CD Blanke), and UM1 CA182883 (CM Tangen/IM Thompson). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SMS and REACH: This work was supported by the National Cancer Institute (grant P01 CA074184 to J.D.P. and P.A.N., grants R01 CA097325, R03 CA153323, and K05

CA152715 to P.A.N., and the National Center for Advancing Translational Sciences at the National Institutes of Health [grant KL2 TR000421 to A.N.B.-H.])

The Swedish Low-risk Colorectal Cancer Study: The study was supported by grants from the Swedish research council; K2015-55X-22674 to 01-4, K2008-55X-20157 to 03-3, K2006-72X-20157 to 01-2 and the Stockholm County Council (ALF project).

Swedish Mammography Cohort and Cohort of Swedish Men: This work is supported by the Swedish Research Council/Infrastructure grant, the Swedish Cancer Foundation, and the Karolinska Institutés Distinguished Professor Award to Alicja Wolk.

UK Biobank: This research has been conducted using the UK Biobank Resource under Application Number 8614.

VITAL: National Institutes of Health (K05 CA154337).

WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

## Notes

**Role of the funders:** The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

**Disclosures:** The authors declare no potential conflicts of interest.

**Author contributions:** Conceptualization: NM, MS, ATC, MJG. Data Curation: NM, MS, ATC, MJG, UP Formal Analysis: NM, NP. Investigation: all authors. Methodology: NM, MS, ATC, MJG. Writing—original draft: NM, MS, ATC, and MJG. Writing—review & editing: all authors.

**Disclaimer:** Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

**Acknowledgements:** ASTERISK: We thank all those who agreed to participate in this study, including the patients and the healthy control persons, as well as all the physicians, technicians and students.

CCFR: The Colon CFR graciously thanks the generous contributions of their study participants, dedication of study staff, and the financial support from the U.S. National Cancer Institute, without which this important registry would not exist. The authors would like to thank the study participants and staff of the Seattle Colon Cancer Family Registry and the Hormones and Colon Cancer study (CORE Studies).

CLUE: We appreciate the continued efforts of the staff members at the Johns Hopkins George W. Comstock Center for Public Health Research and Prevention in the conduct of the CLUE II study. We thank the participants in CLUE. Cancer incidence data for CLUE were provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Maryland Department of Health, 201W. Preston Street, Room 400, Baltimore, MD 21201, 410 to 767-4055. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that support the collection and availability of the cancer registry data.

COLON and NQplus: the authors would like to thank the COLON and NQplus investigators at Wageningen University and Research and the involved clinicians in the participating hospitals.

CORSA: We kindly thank all individuals who agreed to participate in the CORSA study. Furthermore, we thank all cooperating physicians and students and the Biobank Graz of the Medical University of Graz.

CPS-II: The authors thank the CPS-II participants and Study Management Group for their invaluable contributions to this research. The authors would also like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program.

Czech Republic CCS: We are thankful to all clinicians in major hospitals in the Czech Republic, without whom the study would not be practicable. We are also sincerely grateful to all patients participating in this study.

DACHS: We thank all participants and cooperating clinicians, and everyone who provided excellent technical assistance.

EDRN: We acknowledge all contributors to the development of the resource at University of Pittsburgh School of Medicine, Department of Gastroenterology, Department of Pathology, Hepatology and Nutrition and Biomedical Informatics.

EPICOLON: We are sincerely grateful to all patients participating in this study who were recruited as part of the EPICOLON project. We acknowledge the Spanish National DNA Bank, Biobank of Hospital Clínic to IDIBAPS and Biobanco Vasco for the availability of the samples. The work was carried out (in part) at the Esther Koplowitz Centre, Barcelona.

Harvard cohorts (HPFS, NHS, PHS): The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We acknowledge Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital as home of the NHS. We would like to thank the participants and staff of the HPFS, NHS and PHS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

Kentucky: We would like to acknowledge the staff at the Kentucky Cancer Registry.

LCCS: We acknowledge the contributions of Jennifer Barrett, Robin Waxman, Gillian Smith and Emma Northwood in conducting this study.

NCCCS I & II: We would like to thank the study participants, and the NC Colorectal Cancer Study staff.

NSHDS investigators thank the Västerbotten Intervention Programme, the Northern Sweden MONICA study, the Biobank Research Unit at Umeå University and Biobanken Norr at Region Västerbotten for providing data and samples and acknowledge the contribution from Biobank Sweden, supported by the Swedish Research Council.

PLCO: The authors thank the PLCO Cancer Screening Trial screening center investigators and the staff from Information Management Services Inc and Westat Inc. Most importantly, we

ARTICLE

thank the study participants for their contributions that made this study possible. Cancer incidence data have been provided by the District of Columbia Cancer Registry, Georgia Cancer Registry, Hawaii Cancer Registry, Minnesota Cancer Surveillance System, Missouri Cancer Registry, Nevada Central Cancer Registry, Pennsylvania Cancer Registry, Texas Cancer Registry, Virginia Cancer Registry, and Wisconsin Cancer Reporting System. All are supported in part by funds from the Center for Disease Control and Prevention, National Program for Central Registries, local states or by the National Cancer Institute, Surveillance, Epidemiology, and End Results program. The results reported here and the conclusions derived are the sole responsibility of the authors.

SEARCH: We thank the SEARCH team.

SELECT: We thank the research and clinical staff at the sites that participated on SELECT study, without whom the trial would not have been successful. We are also grateful to the 35 533 dedicated men who participated in SELECT.

WHI: The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A full listing of WHI investigators can be found at: http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf

## Data Availability

Data supporting the findings of this study are available within the paper and its supplementary information files.

## References

1. WCRF-AICR. Diet, nutrition, physical activity and colorectal cancer. Continuous update project. https://www.wcrf.org/wp-content/uploads/2021/02/Colorectal-cancer-report.pdf (Accessed 20 September 2021).
2. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer — viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794–798.
3. Bull CJ, Bell JA, Murphy N, et al. Adiposity, metabolites, and colorectal cancer risk: Mendelian randomization study. *BMC Med*. 2020;18(1):396.
4. Murphy N, Jenab M, Gunter MJ. Adiposity and gastrointestinal cancers: epidemiology, mechanisms and future directions. *Nat Rev Gastroenterol Hepatol*. 2018;15(11):659–670.
5. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ*. 2015;350:g7607.
6. Pearson-Stuttard J, Papadimitriou N, Markozannes G, et al. Type 2 diabetes and cancer: an umbrella review of observational and Mendelian randomisation studies. *Cancer Epidemiol Biomarkers Prev*. 2021;30(6):1218–1228.
7. Goto A, Yamaji T, Sawada N, et al. Diabetes and cancer risk: a Mendelian randomization study. *Int J Cancer*. 2020;146(3):712–719.
8. Yuan S, Kar S, Carter P, et al. Is type 2 diabetes causally associated with cancer risk? Evidence from a two-sample mendelian randomization study. *Diabetes*. 2020;69(7):1588–1596.
9. Rinaldi S, Rohrmann S, Jenab M, et al. Glycosylated hemoglobin and risk of colorectal cancer in men and women, the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11):3108–3115.
10. Dashti SG, Viallon V, Simpson JA, et al. Explaining the link between adiposity and colorectal cancer risk in men and postmenopausal women in the UK Biobank: a sequential causal mediation analysis. *Int J Cancer*. 2020;147(7):1881–1894.
11. Peila R, Rohan TE. Diabetes, glycated hemoglobin, and risk of cancer in the UK Biobank study. *Cancer Epidemiol Biomarkers Prev*. 2020;29(6):1107–1119.
12. Xu J, Ye Y, Wu H, et al. Association between markers of glucose metabolism and risk of colorectal cancer. *BMJ Open*. 2016;6(6):e011430.
13. Lin J, Ridker PM, Pradhan A, et al. Hemoglobin $A_{1c}$ concentrations and risk of colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev*. 2005;14(12):3010–3012.
14. Pang Y, Kartsonaki C, Guo Y, et al. Diabetes, plasma glucose and incidence of colorectal cancer in Chinese adults: a prospective study of 0.5 million people. *J Epidemiol Community Health*. 2018;72(10):919–925.
15. Myte R, Gylling B, Häggström J, et al. Metabolic factors and the risk of colorectal cancer by KRAS and BRAF mutation status. *Int J Cancer*. 2019;145(2):327–337.
16. Chen L, Li L, Wang Y, et al. Circulating C-peptide level is a predictive factor for colorectal neoplasia: evidence from the meta-analysis of prospective studies. *Cancer Causes Control*. 2013;24(10):1837–1847.
17. Ma J, Giovannucci E, Pollak M, et al. A prospective study of plasma C-peptide and colorectal cancer risk in men. *J Natl Cancer Inst*. 2004;96(7):546–553.
18. Kaaks R, Toniolo P, Akhmedkhanov A, et al. Serum C-peptide, Insulin-Like Growth Factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst*. 2000;92(19):1592–1600.
19. Schoen RE, Tangen CM, Kuller LH, et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. *J Natl Cancer Inst*. 1999;91(13):1147–1154.
20. Limburg PJ, Stolzenberg-Solomon RZ, Vierkant RA, et al. Insulin, glucose, insulin resistance and incident colorectal cancer in male smokers. *Clin Gastroenterol Hepatol*. 2006;4(12):1514–1521.
21. Gunter MJ, Hoover DR, Yu H, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer Res*. 2008;68(1):329–337.
22. Palmqvist R, Stattin P, Rinaldi S, et al. Plasma insulin, IGF-binding proteins-1 and -2 and risk of colorectal cancer: a prospective study in Northern Sweden. *Int J Cancer*. 2003;107(1):89–93.
23. Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. cancer. *Epidemiol Biomarkers Prev*. 2003;12(5):412–418.
24. Myte R, Harlid S, Sundkvist A, et al. A longitudinal study of prediagnostic metabolic biomarkers and the risk of molecular subtypes of colorectal cancer. *Sci Rep*. 2020;10(1):5336.
25. Huyghe JR, Bien SA, Harrison TA, et al. Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet*. 2019;51(1):76–87.
26. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. *Nat Genet*. 2018;50(11):1505–1513.
27. NealeLab. *UK Biobank GWAS Results*. 2019; http://www.nealelab.is/uk-biobank. Accessed September 30, 2019.
28. Chen J, Spracklen CN, Marenne G, et al.; Meta-Analysis of Glucose and Insulin-related Traits Consortium (MAGIC). The trans-ancestral genomic architecture of glycemic traits. *Nat Genet*. 2021;53(6):840–860.
29. Chen J, Spracklen CN, Marenne G, et al. The trans-ancestral genomic architecture of glycaemic traits. *bioRxiv*. 2020;2020.07.23.217646. doi: 2020.2007.2023.217646.
30. Fred Hutchinson Cancer Research Center. 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. Accessed September 16, 2021.
31. FinnGen Consortium. FinnGen documentation of R4 Release. https://finngen.gitbook.io/documentation/. Accessed September 20, 2021.
32. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Sta Soc Ser B Methodol*. 1995;57(1):289–300.
33. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512–525.
34. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304–314.
35. Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50(5):693–698.
36. Yavorska OO, Burgess S. Mendelian randomization: an R package for performing Mendelian randomization analyses using summarized data. *Int J Epidemiol*. 2017;46(6):1734–1739.
37. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer*. 2008;8(12):915–928.
38. Gallagher EJ, LeRoith D. Hyperinsulinaemia in cancer. *Nat Rev Cancer*. 2020;20(11):629–644.
39. Tran TT, Naigamwalla D, Oprescu AI, et al. Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. *Endocrinology*. 2006;147(4):1830–1837.
40. Kiunga GA, Raju J, Sabljic N, Bajaj G, Good CK, Bird RP. Elevated insulin receptor protein expression in experimentally induced colonic tumors. *Cancer Letters*. 2004;211(2):145–153.
41. Santoro MA, Andres SF, Galanko JA, Sandler RS, Keku TO, Lund PK. Reduced insulin-like growth factor I receptor and altered insulin receptor isoform mRNAs in normal mucosa predict colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev*. 2014;23(10):2093–2100.
42. Rapp K, Schroeder J, Klenk J, et al. Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia*. 2006;49(5):945–952.
43. Stattin PR, BjöR O, Ferrari P, et al. Prospective study of hyperglycemia and cancer risk. *Diabetes Care*. 2007;30(3):561–567.

44. Kabat GC, Kim MY, Strickler HD, et al. A longitudinal study of serum insulin and glucose levels in relation to colorectal cancer risk among postmenopausal women. *Br J Cancer*. 2012;106(1):227–232.
45. Murphy N, Ward HA, Jenab M, et al. Heterogeneity of colorectal cancer risk factors by anatomical subsite in 10 European countries: a multinational cohort study. *Clin Gastroenterol Hepatol*. 2019;17(7):1323–1331.
46. Huyghe JR, Harrison TA, Bien SA, et al. Genetic architectures of proximal and distal colorectal cancer are partly distinct. *Gut*. 2021;70(7):1325–1334.
47. Wang L, Lo C-H, He X, et al. Risk factor profiles differ for cancers of different regions of the colorectum. *Gastroenterology*. 2020;159(1):241–256.e213.
48. Hu Y, Zhang X, Ma Y, et al. Incident type 2 diabetes duration and cancer risk: a prospective study in two US cohorts. *J Natl Cancer Inst*. 2021;113(4):381–389.
49. Walker VM, Harrison S, Carter AR, Gill D, Tzoulaki I, Davies NM. The consequences of adjustment, correction and selection in genome-wide association studies used for two-sample Mendelian randomization. *medRxiv*. 2021. doi: 2020.2007.2013.20152413.
50. Brion M-JA, Shakhbazov K, Visscher PM. Calculating statistical power in Mendelian randomization studies. *Int J Epidemiol*. 2013;42(5):1497–1501.