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Associations between blood glucose and early- and late-onset colorectal cancer: evidence from two prospective cohorts and Mendelian randomization analyses

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ABSTRACT

Background: The incidence of early-onset colorectal cancer (EOCRC), which exhibits differential clinical, pathological, and molecular features compared to late-onset CRC (LOCRC), is rising globally. The potential differential effects of blood glucose on EOCRC compared to LOCRC have not been investigated.

Methods: This study analyzed 374,568 participants from the UK Biobank cohort and 172,809 participants from the Kailuan cohort. The linear associations between blood glucose and EOCRC/LOCRC were estimated using Cox regression models. Restricted cubic spline (RCS) analysis and non-linear Mendelian randomization (MR) analysis using a 70-SNPs genetic instrument for fasting glucose were used to explore the potential non-linear associations.

Results: Participants in the highest quintile of blood glucose had higher overall CRC risk compared to the lowest quintile (HR = 1.10 in the UK Biobank cohort, 95% CI: 1.01–1.21, *P*-trend = 0.012; HR = 1.23 in the Kailuan cohort, 95% CI: 1.01–1.51, *P*-trend = 0.036). Elevated glucose (>7.0 mmol/L) was more strongly associated with increased risk of EOCRC (HR = 1.61, 95% CI: 1.07–2.44) than with LOCRC (HR = 1.14, 95% CI: 1.02–1.27) in the UK Biobank cohort (*P*-heterogeneity = 0.014). Elevated glucose (>7.0 mmol/L) was associated with increased risk of LOCRC (HR = 1.25, 95% CI: 1.04–1.65) in the Kailuan cohort as well. There was no evidence for non-linear associations between blood glucose and risks of EOCRC/LOCRC.

Conclusions: This study showed a positive association between blood glucose and CRC risk in a dose-response manner, particularly for EOCRC, suggesting that tighter glucose control should be a priority for younger age groups.

1. Introduction

Colorectal cancer (CRC) remains one of the most prevalent malignancies worldwide, with more than 1.9 million new CRC cases and 935,000 deaths in 2020.[1] Despite the fact that overall CRC incidence has remained stable or decreased in recent decades in large part attributable to enhanced screening and colonoscopic polypectomy,[2] the incidence of early-onset CRC (EOCRC), i.e., CRC diagnosed in patients under the age of 50 years, has steadily risen.[3] EOCRC exhibits differential epidemiological, clinical, pathological, and molecular features compared to late-onset CRC (LOCRC).[4] Identifying the specific role of key risk factors to EOCRC is critical to curb this worrying trend.

Several prospective studies have reported varying blood glucose levels and their corresponding risk for CRC. However, the exact relationships between blood glucose concentrations and CRC susceptibility remain controversial across these investigations.[5–8] Previous observational studies with small sample sizes, case-control designs, and the use of linear models have inherent limitations (potential residual confounders, reverse causality, selection bias, etc.) in deducing causality and capturing non-linear associations. The non-linear causal effects of glucose on CRC risk remained to be examined. Furthermore, the poten-

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tial differential effects of glucose on EOCRC compared to LOCRC have not been elucidated.

Mendelian randomization (MR) utilizes germline genetic variants as instrumental variables to perform causal inferences between exposures and outcomes, which is less susceptible to reverse causation and confounding bias than observational studies.[9] Non-linear MR is a novel method that conditions on quantiles of the instrumental variable to estimate localized average causal effects (LACE) and identify non-linear associations.[10] Applying these cutting-edge statistical methods can confer novel and comprehensive insights into the association between blood glucose and CRC.

In this study, we conducted analyses using two large-scale prospective cohorts (the United Kingdom [UK] Biobank cohort and the Kailuan cohort in China) to assess the associations between glucose and EOCRC/LOCRC risk. We also performed restricted cubic spline (RCS) and non-linear MR analyses to explore the non-linear associations between glucose and EOCRC/LOCRC risk simultaneously.

2. Methods

2.1. Study population

The present study was conducted using the UK Biobank cohort and the Kailuan cohort. Briefly, the UK Biobank recruited more than 500,000 individuals aged from 40 to 69 years between 2006 and 2010 at 22 assessment centers in the UK. Details of the UK Biobank cohort study have been reported elsewhere.[11,12] The UK Biobank cohort study was approved by the North West Multi-Center Research Ethics Committee, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. All participants provided written informed consent.

We excluded participants diagnosed with any invasive cancer (excluding non-melanoma skin cancer) at recruitment, without blood glucose data, without genetic data, or withdrew consent over the study period. Data analysis was performed from April 2023 to April 2024.

The Kailuan cohort, a prospective dynamic cohort study conducted in Tangshan city of China, was designed to investigate the risk factors for common non-communicable chronic diseases including cancer. Even if the cohort size is smaller than its UK counterpart, among the existing prospective cohort studies in China, the Kailuan cohort still has the advantages of a large sample size, long follow-up time, high follow-up rate, high participant compliance, and standardized control of the follow-up process, effectively filling the gap of the relative lack of large prospective cohorts and open data access in China. Furthermore, differed CRC disease patterns and incidences between China and western countries have been reported by previous studies. Therefore, the study on the Kailuan cohort is of significance.

The Kailuan cohort study was performed according to the guidelines of the Helsinki declaration and was approved by the Medical Ethics Committee of Kailuan General Hospital. Informed consent was obtained from all participants included in the study. The details of the study design and procedures were published previously.[13,14] Briefly, employees, including retired individuals, of the Kailuan Group who were older than 18 years were invited to participate in health examinations biennially since 2006, which included questionnaire assessments, clinical examinations, and laboratory tests. We included participants in the Kailuan cohort who met the following criteria: 1) older than 18 years; 2) had signed informed consent; 3) baseline blood glucose measurements were obtained at recruitment; and 4) were not diagnosed with any prevalent cancer before cohort entry.

2.2. Assessment of blood glucose

As part of the UK Biobank Biomarker Project, the blood glucose was measured by hexokinase analysis on Beckman Coulter AU5800 analytical platform (Beckman Coulter, California, USA) at baseline, with a manufacturer's analytical range from 0.6 to 45 mmol/L. A special detail of collection and processing of blood samples has been described elsewhere.[15] Given the considerable difficulties obtaining fasting blood samples from over 500,000 participants at multiple assessment centers and their future applicability to a wide range of diseases, blood samples were obtained randomly with no regard to fasting status.[15]

As for the Kailuan cohort, venous blood samples were obtained from participants in the morning after overnight fasting, and fasting blood glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. All tests were conducted in the central laboratory of the Kailuan General Hospital using a standard operating procedure, and all blood samples were measured using an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan).[16]

2.3. Ascertainment of CRC

The outcomes for this study were incident CRC, EOCRC and LOCRC. While the delineation between EOCRC and LOCRC lacks a clearly defined age threshold, the majority of studies defined 50 years as the demarcation, consistent with the minimum recommended CRC screening age in most guidelines.[17] To ensure adequate cases for the younger population in our analyses, we adopted an extended age threshold of 55 years.

In the UK Biobank cohort, incident cancer cases and deaths were identified through linkage to national cancer and national death registries. Complete follow-up was available through November 30, 2022.[18] In the Kailuan cohort, incident cancer cases were identified by linkage with the Kailuan Social Security System, Tangshan Medical Insurance System, and provincial vital statistics data annually until December 31, 2019. CRC was coded using the 10th Revision of the International Classification of Diseases (ICD-10): C18-C20.

2.4. Assessment of covariates

Information on the UK Biobank participants' sociodemographic characteristics, health, medical history, medication use, and lifestyle was collected using a self-administered touchscreen questionnaire and nurse-led interviews at enrollment. During the interviews, the participants' body weight, waist circumference (WC), and height were measured by trained staff using standardized procedures.[11] In the Kailuan cohort, face-to-face interviews were performed by trained physicians or nurses for all participants using standardized questionnaires at baseline entry. Body weight, WC, and height were measured while participants were wearing light clothes without shoes.[16]

Since several lifestyle-related factors have been positively associated with increased CRC risk and tend to co-exist, we used a modified healthy lifestyle index (HLI) based on the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) Cancer Prevention Recommendations in both cohorts.[19,20] Specifically, HLI included diet, alcohol consumption, smoking, physical activity, body mass index (BMI), and WC. Specific items definition and corresponding score allocations are detailed in the Supplementary Tables 1 and 2.

Besides, we also included age, sex, ethnicity, education, Townsend deprivation index, assessment center, CRC screening history, family CRC history of parents and siblings, standard polygenic risk score (PRS) for CRC, and diabetes medication uses as covariates in the UK Biobank cohort, and age, sex, education, income status, diabetes medication uses as covariates in the Kailuan cohort. The Townsend deprivation index is a measure of socioeconomic deprivation that incorporates four variables: unemployment, non-car ownership, non-home ownership, and household overcrowding. Lower index scores indicate higher socioeconomic status.[21] CRC screening history was defined based on the answer of question "Have you ever had a screening test for bowel (colorectal) cancer? (Please include tests for blood in the stool/feces or a colonoscopy or a sigmoidoscopy)". Standard PRS for CRC has been recently released

by the UK Biobank, as described in Thompson et al.[22] The missing values on continued covariates were replaced with the sex-specific mean value, and missing values on categorical covariates were considered as the "unknown" category.

2.5. Genotyping and genetic instrument for blood glucose in the UK Biobank cohort

Detailed information on the genotyping process, quality control, and arrays used in UK Biobank has been described in a previous study.[23] Briefly, genome-wide genotyping was performed using the Applied Biosystems UK BiLEVE Axiom Array or the Applied Biosystems UK Biobank Axiom Array (Waltham, MA, USA). The two arrays share 95% of marker content. Genotype data were phased and imputed based on merged UK10K and 1000 Genomes phase 3 panels using SHAPEIT3 and IMPUTE3.

To assess the non-linear causal effect of blood glucose on CRC risk, we performed non-linear MR analysis using PRS as an instrumental variable. The PRS for fasting glucose was constructed using 70 single nucleotide polymorphisms (SNPs) (Supplementary Table 3) previously identified in genome-wide association studies (GWAS) in individuals without diabetes,[24] following a standard pruning and thresholding procedure.[25] The PRS was calculated as the weighted sum of the SNP effect size estimates (β) from the GWAS and the genotype (G) in each selected SNP: $PRS = \sum_i^m \beta_i G_{i,\ j}$, where i represents the SNP, m represents the total number of SNP loci, β represents the effect size of the SNP, $G_{i,\ j}$ represents the genotype of the SNP, denoted by 0, 1, and 2 for no mutation, heterozygous mutation, and homozygous mutation, respectively. The F statistic was calculated to test the statistical significance of the correlation between the instrument variable and glucose: $F = \frac{R^2(n-k-1)}{(1-R^2)\times k}$, where R^2 represents the variability explained by instrumental variable, n indexes the number of individuals, and k refers to the number of SNPs.

2.6. Statistical analysis

2.6.1. Linear association evaluation

Baseline characteristics were presented as n (%) if categorical and mean (standard deviation) if normally distributed. Chi-square tests and Student t-test were used to compare the distribution of baseline characteristics across categories of CRC status, respectively. Since Schoenfeld residuals showed that the proportional hazards assumption was not violated, Cox proportional hazards models were applied to examine the associations of blood glucose and CRC risk. Person-time was measured from the date of recruitment until the date of CRC diagnosis, death, lost to follow-up, or the end of the study period, whichever came first. For EOCRC, participants were followed from the date of recruitment until the date of CRC diagnosis, death, 55th birthday, loss to follow-up, or the end of the study period, whichever came first. The results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Two multivariable-adjusted models were constructed to account for potential confounders: Model 1, adjusted for age, sex, race (white, Asian, African, mixed background, unknown) in UK Biobank, and adjusted for age, sex in Kailuan; Model 2, further adjusted for Townsend deprivation index, region of the recruitment assessment center, educational level (college/university degree, non-college/university degree, unknown), CRC screening history, family history of CRC, standard PRS for CRC, diabetes medication uses and HLI in UK Biobank, and adjusted for education level (illiterate or primary school, junior high school, senior high school, and college and above), income status (<500, 500–1000, 1001–3000, 3001–5000, >5000 yuan per month), diabetes medication uses and HLI in the Kailuan cohort based on Model 1.

To mitigate the influence of extreme outliers, blood glucose measurements were winsorized by setting observations above the 99th percentile to the 99th percentile value and those below the 1st percentile to the 1st percentile value. In the primary analysis, we classified blood glucose into quintiles and calculated the HRs using the lowest quintile as the reference. We also calculated the HRs per 1 mmol/L increment and tested for a linear trend. Furthermore, following the American Diabetes Association's classification guidelines,[26] we categorized blood glucose levels into two groups using 7.0 mmol/L as the cutoff value. We performed subgroup analyses according to age at CRC diagnosis (≤55 or >55 years), sex (female, male) and anatomical subsite (colon, rectal cancer). P-heterogeneity was calculated assuming a linear association between glucose vs EOCRC or LOCRC using a likelihood ratio test.

Sensitivity analyses were performed after (1) excluding CRC within the first 2 years of follow-up; (2) excluding participants with abnormally low or high biomarker levels; (3) using multiple imputation by chained equations (R package "MICE"[27]) with predictive mean matching to impute missing blood glucose values; and (4) excluding participants diagnosed with diabetes.

2.6.2. Non-linear association evaluation

We applied RCS analysis to explore the potential non-linear association and tested spline models with 3 to 5 knots and selected the model with the lowest Akaike Information Criterion (AIC) value.

We also performed non-linear MR analyses using the fractional polynomial method.[10] The key assumptions of MR are that the genetic variants: (1) are robustly associated with the exposure (no horizontal pleiotropy); (2) are not associated with any confounders of the exposure-outcome association; and (3) affect the outcome only through the exposure.[28] Specifically, We first stratified the UK Biobank population into 10 strata using the doubly-ranked stratification method, where the stratification were performed by firstly ranking participants into the preliminary strata based on the instrument level and then stratifying them into the final strata on the basis of the glucose level. Within each stratum, we computed stratum-specific glucose and CRC effect estimates and then applied the ratio-of-coefficients method to calculate the LACE estimate.[10] A fractional polynomial test was conducted to examine whether a nonlinear model fit the exposure-outcome association better than a linear model. Covariates, including age, sex, and the top 10 genetic principal components, were adjusted to account for residual population stratification. We also performed subgroup analyses according to age, sex and anatomical subsite. In addition, we re-estimated the causal associations 1) using a previous GWAS by Lagou, which provides estimates unadjusted for BMI (Supplementary Table 4)[29]; 2) further adjusting for other covariates as described in cox Model 2.

All analyses were performed using PLINK version 2.0 and R version 4.1. Cox proportional hazard model analysis was performed using the "survival" and "survminer" R package.[30] RCS analysis was performed using the "rms" R package.[31] Non-linear MR analysis was performed using the "DRMR" R package.[32] A two-sided P value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Finally, a total of 374,568 participants in the UK Biobank study and 172,809 participants in the Kailuan study were included in our study (See the flowchart in Fig. 1). The distribution of the baseline characteristics of the participants by incident CRC status were showed in Supplementary Tables 5–6, and the baseline characteristics of CRC cases by age at CRC diagnosis (≤55 or >55 years) were detailed in Supplementary Tables 7–8. During a total of 4,363,899 person-years (median follow-up 11.8 years), 4,656 CRC cases (357 EOCRC and 4,299 LOCRC cases) were documented in the UK Biobank cohort. In the Kailuan cohort, during a total of 2,089,346 person-years (median follow-up 12.1 years), 936 CRC cases (112 EOCRC and 824 LOCRC cases) were documented. In both cohorts, incident CRC cases were more likely to be older, male, have lower socioeconomic status, higher BMI, lower healthy lifestyle index, and higher blood glucose levels compared to controls.

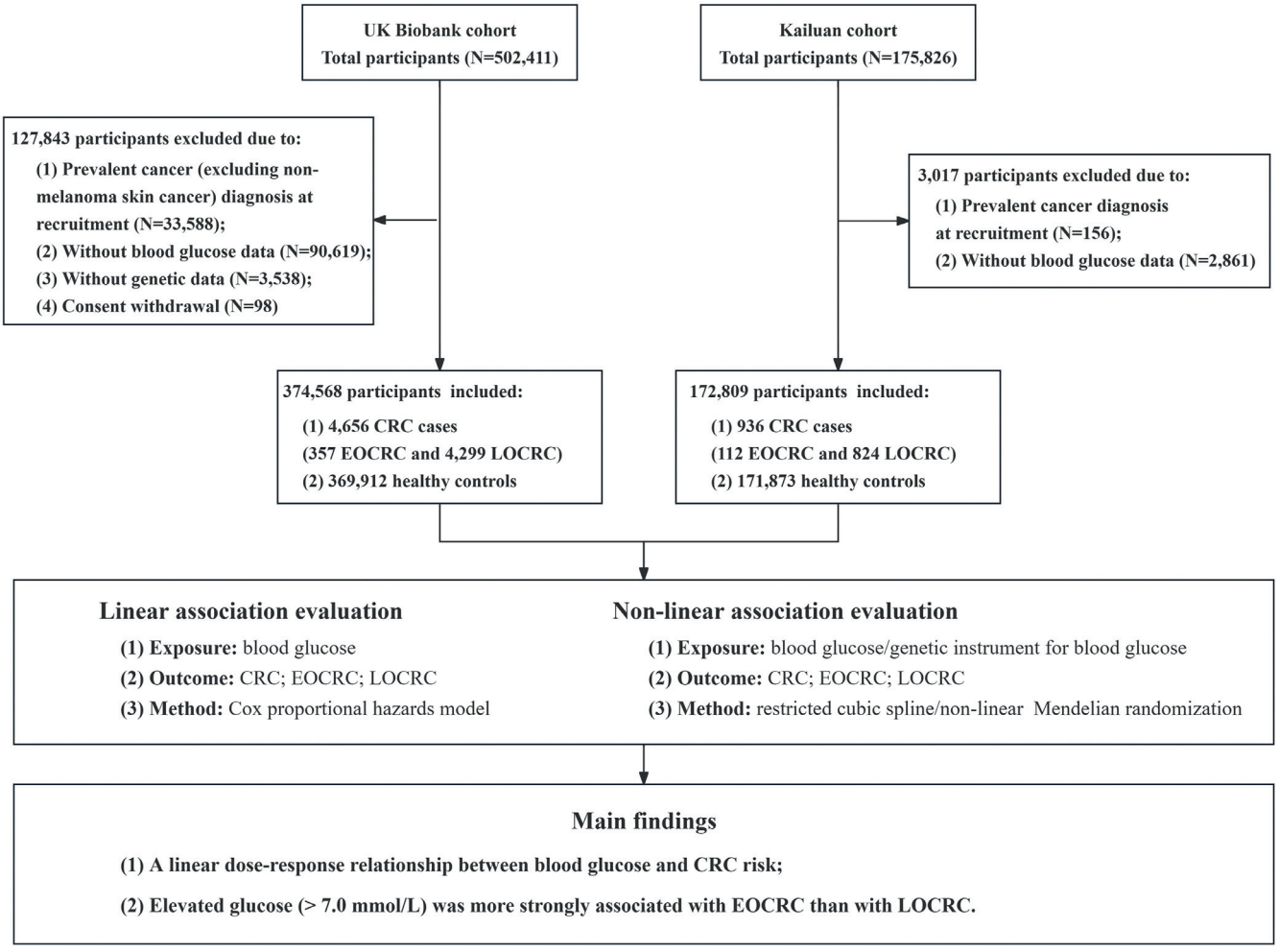

Fig. 1. Flowchart of the study design. CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; UK, United Kingdom.

Table 1
Hazard ratios for the associations between glucose levels and colorectal cancer risk in UK Biobank and Kailuan cohorts.

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	HR (95% CI) per 1 mmol/L increase	*P*-trend
UK Biobank cohort							
Glucose, median (IQR), mmol/L	4.29 (0.35)	4.67 (0.14)	4.93 (0.13)	5.21 (0.18)	5.87 (0.97)		
No. of cases	825	822	903	958	1148		
No. of person years	892,012	878,809	872,149	862,505	858,421		
Model 1, HR (95% CI)	Ref	0.96 (0.87–1.05)	1.00 (0.91–1.10)	1.00 (0.91–1.10)	1.12 (1.02–1.23)	1.06 (1.03–1.09)	0.006
Model 2, HR (95% CI)	Ref	0.96 (0.87–1.06)	1.01 (0.92–1.11)	1.01 (0.92–1.11)	1.10 (1.01–1.21)	1.05 (1.02–1.07)	0.012
Kailuan cohort							
Glucose, median (IQR), mmol/L	4.33 (0.40)	4.80 (0.19)	5.15 (0.17)	5.59 (0.26)	6.62 (1.83)		
No. of cases	184	161	172	185	234		
No. of person years	446,840	406,051	418,897	413,960	403,596		
Model 1, HR (95% CI)	Ref	1.06 (0.86–1.31)	1.08 (0.88–1.33)	1.10 (0.90–1.36)	1.23 (1.02–1.50)	1.03 (1.01–1.07)	0.022
Model 2, HR (95% CI)	Ref	1.08 (0.88–1.34)	1.09 (0.88–1.34)	1.12 (0.91–1.37)	1.23 (1.01–1.51)	1.04 (1.00–1.06)	0.036

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range Ref, reference.

3.2. Linear association evaluation

Overall, after adjusting for potential confounders (Model 2), a positive dose-response association was observed in the UK Biobank cohort (HR = 1.05 per 1 mmol/L increase, 95% CI: 1.02–1.07, *P*-trend = 0.012). Compared with participants in the first quintile of blood glucose (median glucose 4.29 mmol/L), those in the fifth quintile (median glucose 5.87 mmol/L) had a 10% higher risk of CRC (HR = 1.10; 95% CI: 1.01–1.21) in the UK Biobank cohort (Table 1). Similar associations were observed in the Kailuan cohort (Table 1): Higher blood glucose levels were associated with an increased risk of CRC (HR = 1.04 per 1 mmol/L increase, 95% CI: 1.00–1.06 *P*-trend = 0.036), and those in the highest quintile of glucose (median 6.62 mmol/L) had a 23% increased risk of CRC compared to the lowest quintile (HR = 1.23; 95% CI: 1.01–1.51).

When stratified by early- versus late-onset CRC and risk of hyperglycemia by the American Diabetes Association,[26] diabetic blood glucose (>7.0 mmol/L) was associated with a 61% higher risk of EOCRC compared to glucose levels ≤7.0 mmol/L (HR = 1.61; 95% CI: 1.07–2.44; *P* = 0.023) in the UK Biobank cohort. For LOCRC, diabetic glucose was associated with a 14% higher risk (HR = 1.14; 95% CI: 1.02–1.27; *P* = 0.022). The test for heterogeneity of the HR estimates between

Table 2
Hazard ratios for the associations between binary blood glucose level and early-onset and late-onset colorectal cancer risk in UK Biobank and Kailuan cohorts.

	Glucose category	No. of cases	No. of person years	HR (95% CI) [a]	*P*	*P*-heterogeneity
UK Biobank cohort						
<55 years	≤7.0 mmol/L	342	1,701,553	Ref		0.014
	>7.0 mmol/L	15	42,582	1.61 (1.07–2.44)	0.023	
≥55 years	≤7.0 mmol/L	4,056	2,505,599	Ref		
	>7.0 mmol/L	243	114,162	1.14 (1.02–1.27)	0.022	
Kailuan cohort						
<55 years	≤7.0 mmol/L	102	1,290,890	Ref		0.046
	>7.0 mmol/L	10	75,696	1.65 (0.80–3.42)	0.174	
≥55 years	≤7.0 mmol/L	726	644,475	Ref		
	>7.0 mmol/L	98	78,283	1.25 (1.04–1.65)	0.038	

[a] Estimated using the Cox regression Model 2.
Abbreviations: CI, confidence interval; HR, hazard ratio; Ref, reference.

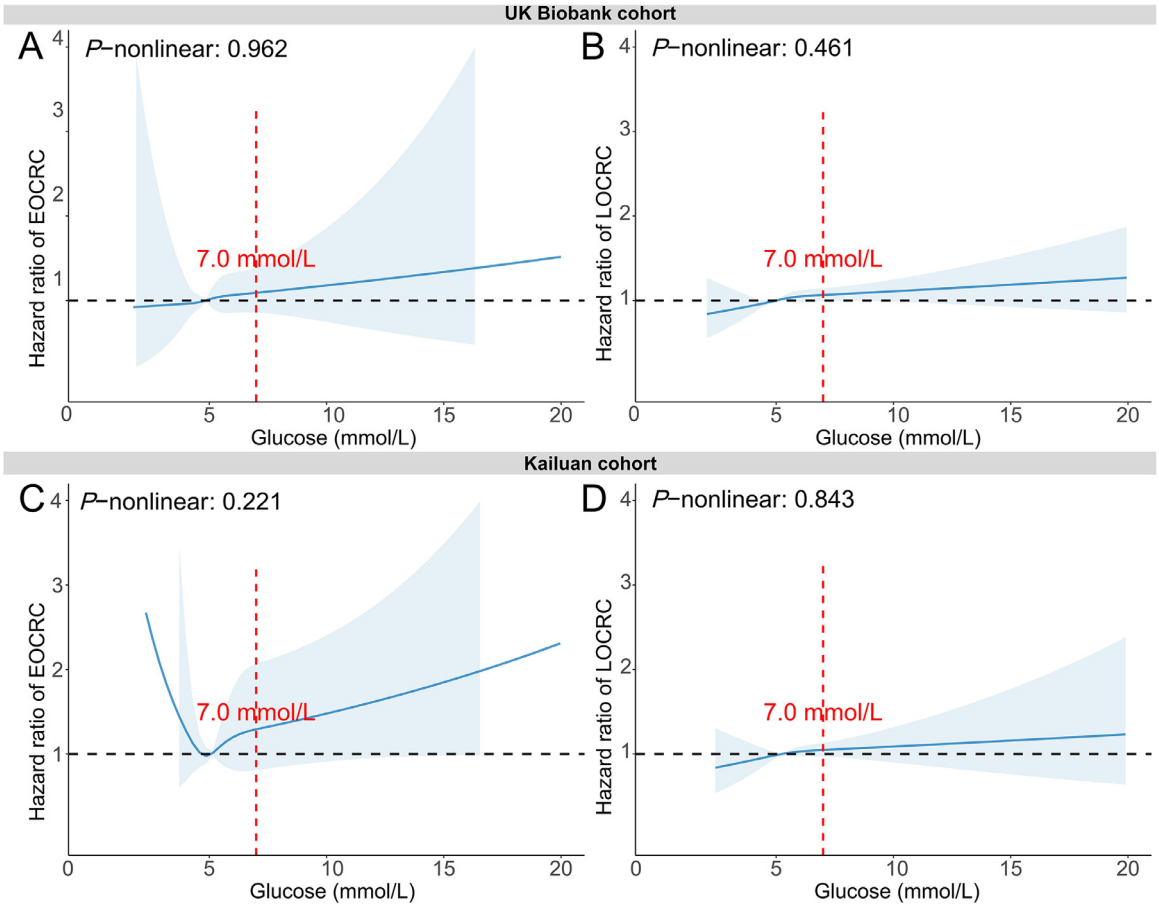

Fig. 2. Analyses of the relationship between blood glucose and EOCRC/LOCRC using RCS regression. A and B for the UK Biobank cohort ; C and D for the Kailuan cohort. EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; UK, United Kingdom.

the two subgroups demonstrated a statistically significant disparity (*P*-heterogeneity = 0.014) (Table 2).

In the Kailuan cohort, diabetic glucose (>7.0 mmol/L) was associated with a 65% higher EOCRC risk compared to normal glucose levels (HR = 1.65; 95% CI: 0.80–3.42; *P* = 0.174). This association was not statistically significant, likely due to the smaller number of EOCRC cases in this cohort. For LOCRC, elevated glucose was associated with a 25% higher risk (HR = 1.25; 95% CI: 1.04–1.65; *P* = 0.038). The test for heterogeneity demonstrated a statistically significant disparity (*P*-heterogeneity = 0.046). (Table 2).

As for subgroup analyses, diabetic glucose (>7.0 mmol/L) was associated with higher risk of CRC in male (HR = 1.15, 95% CI: 1.03–1.29), and colon cancer (HR = 1.20, 95% CI: 1.06–1.36) in the UK Biobank cohort. Similarly, in the Kailuan cohort, diabetic glucose was associated with higher risk of CRC in male and both colon and rectal cancer (Supplementary Table 9). However, the association was not statistically significant in female in both cohorts. Similar results were consistently observed when blood glucose levels were categorized into quintiles (Supplementary Table 10–11).

Sensitivity analyses showed robust associations between blood glucose and CRC after excluding CRC cases within the first 2 years of follow-up, using multiple imputation by chained equations (MICE) for blood glucose missing value, excluding participants with abnormally low or high biomarker levels, and excluding participants with diabetes (Supplementary Tables 12–15).

3.3. Non-linear association evaluation

The RCS models didn't show non-linear associations between blood glucose and EOCRC and LOCRC risk in both the UK Biobank and Kailuan

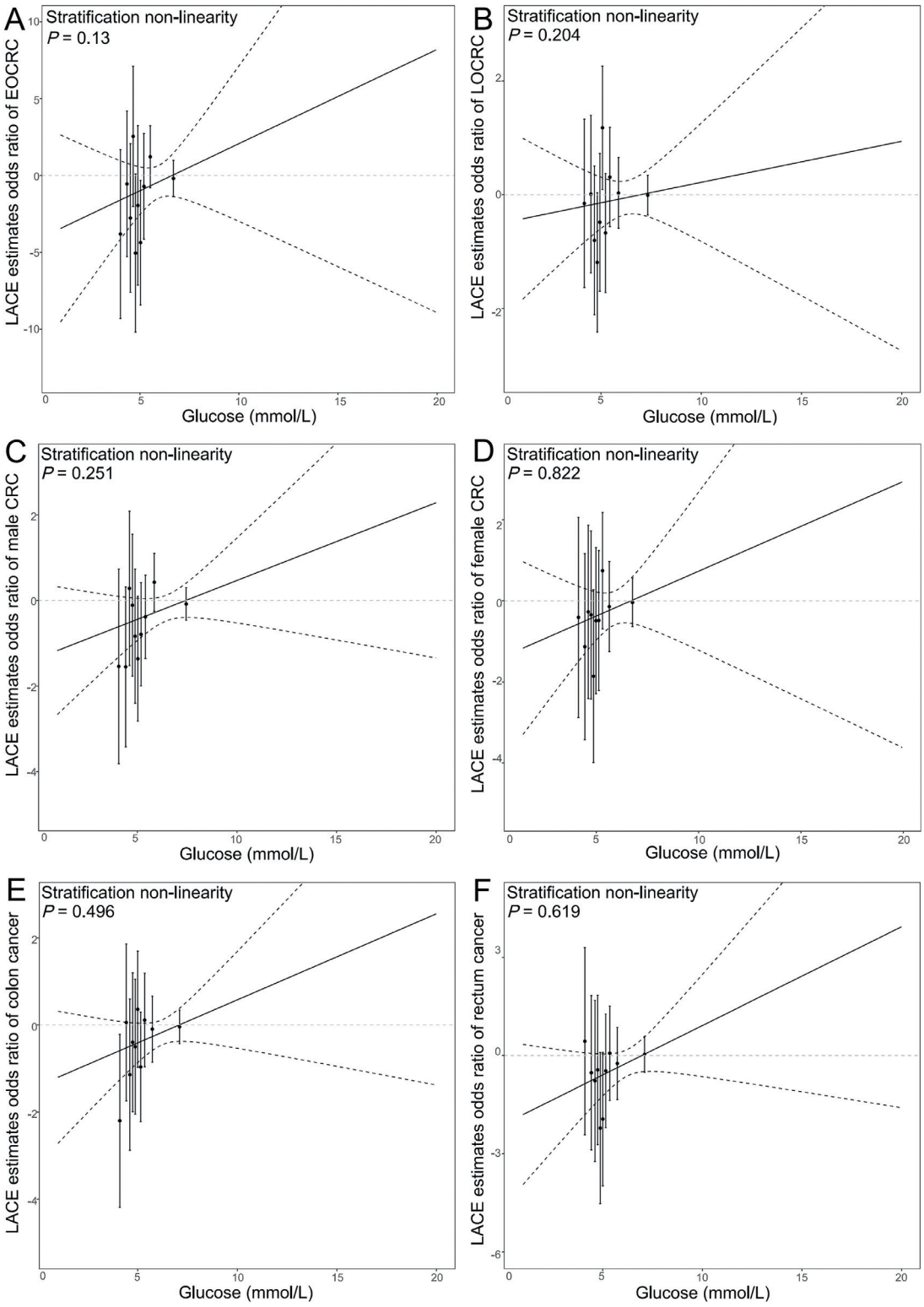

Fig. 3. (A-F) Analyses of the casual relationship between blood glucose and CRC using the non-linear Mendelian randomization method across the age (A and B), sex (C and D), site (E and F) subgroups. CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LACE, localized average causal effects; LOCRC, late-onset colorectal cancer.

cohorts (Fig. 2). The *F* statistic was calculated using the formula as follows: $F = \frac{R^2(n-k-1)}{(1-R^2)\times k}$, where $R^2 = 0.021$, $n = 374{,}568$, and $k = 70$. Cumulatively, the genetic instrument displayed relatively strong association with glucose, with an *F* statistic of 116 and could explain 2.1% of the variance of glucose. According to the non-linear MR analysis, there was also no evidence of non-linear causal effects between genetically predicted fasting blood glucose and CRC risk across the subgroups stratified by age at CRC diagnosis, sex, and anatomical subsite (Fig. 3). Subgroup RCS analyses according to sex and anatomical subsite didn't show non-linear associations between glucose and CRC risk in both the

UK Biobank and Kailuan cohorts (Supplementary Fig. 1–2). Sensitivity analyses showed no evidence of non-linear causal effects between genetically predicted fasting blood glucose and CRC risk. (Supplementary Fig. 3–4).

4. Discussion

In the present study, analyses of two large-scale prospective cohorts demonstrated elevated blood glucose levels are associated with an increased risk of CRC in a linear, dose-response manner. Importantly, elevated glucose (>7.0 mmol/L) was more strongly associated with EOCRC than with LOCRC. Neither the use of RCS nor non-linear MR analysis revealed any non-linear association between blood glucose and the risk of CRC. Our result showed that the incidence risk of CRC did increase with the elevation of blood glucose concentration, implying that blood glucose was a dose-dependent risk factor for the incidence of CRC, which is consistent with a previous meta-analysis conducted by Shi et al.[5]

The mechanisms underlying the relationship between hyperglycemia and increased CRC risk involve direct effects of high glucose, metabolic advantages for cancer cells, insulin/IGF signaling dysregulation, and associated factors like oxidative stress, inflammation, and adipokine imbalance. First, high glucose concentrations can directly induce DNA damage independent of insulin in human endothelial cells,[33] promote cell proliferation, enhance cancer-related signaling pathways like the Wnt/β-catenin pathway,[34] and facilitate migration and invasion of CRC cells.[35] Second, sustained hyperglycemia provides a metabolic advantage for cancer cells, which preferentially utilize glucose and divert glycolytic intermediates into biosynthetic pathways (the Warburg effect).[36]

A third crucial factor is the dysregulation of the insulin/insulin-like growth factor (IGF) signaling pathway. Hyperglycemia and insulin resistance lead to increased levels of insulin and IGFs, which can bind to their respective receptors and activate the PI3K/Akt and MAPK signaling cascades,[37,38] thereby stimulating cellular proliferation, survival, motility, angiogenesis, and suppressing apoptosis. Finally, hyperglycemia has been associated with increased oxidative stress, chronic inflammation, and adipokine dysregulation, which are potential contributors to carcinogenesis.[39]

A novel and clinically significant finding was the stronger association between hyperglycemia and EOCRC compared to LOCRC, implicating hyperglycemia as a potentially important modifiable risk factor preferentially impacting EOCRC. In recent decades, EOCRC incidence has been increasing in both men and women across the world, which represents a significant cancer burden among younger adults.[4] In Europe, the average annual percent changes in EOCRC incidence were 7.9% in individuals aged 20–29, 4.9% in those aged 30–39, and 1.6% in those aged 40–49 during 2004–2016.[40]

The drivers of this disturbing trend are not well understood, but plausible hypotheses include greater exposure to potential risk factors including genetic, environmental, lifestyle, and metabolic factors, especially during the early prenatal to adolescent periods of life.[3]

There are several plausible explanations for the age-related differences in the association between hyperglycemia and CRC risk. First, elevated glucose may have a greater carcinogenic effect when exposure occurs during adolescence, a period accompanied by accelerated cell proliferation and genetic instability. Individuals with chronic hyperglycemia beginning in childhood or early adulthood would experience decades of excessive metabolic derangements, oxidative stress, inflammatory signaling, etc., which provides a robust tumor-promoting milieu over an extended period.[42] Findings from Joh et al.[41] also indicate that high intake of simple sugars and sugar-sweetened beverages during adolescence was significantly associated with increased risk of colorectal adenoma (CRC precancerous lesions), highlighting adolescence as a potentially crucial period when individuals may be more susceptible to the adverse effects of high glucose.

Second, younger individuals may be more susceptible to the growth-promoting effects of physiological (obesity-unrelated) hyperinsulinemia compared to older adults. The number of insulin receptors has been shown to decrease with age (up to 4-fold lower than in adolescence), potentially attenuating insulin/IGF-1 signaling in later life.[43] The insulin/IGF1 system can promote carcinogenesis by activating intracellular signaling pathways associated with altered gene expression, inhibiting apoptosis and stimulating cell proliferation, differentiation and angiogenesis.[38,44] Third, younger individuals tend to have relatively decreased insulin sensitivity.[43] The combination of more pronounced hyperinsulinemia and decreased insulin sensitivity could create an environment that is particularly permissive for malignant transformation in younger populations. Finally, hormonal and reproductive factors may modify the effects of hyperglycemia in a manner that varies by age. The potential interactions between hyperglycemia, obesity, insulin resistance, and sex hormones represent an important area for future research.

A major strength of this study is the comprehensive examination of the associations between glucose levels and CRC risk, encompassing two large-scale prospective cohorts, with linear and non-linear analyses performed for overall CRC as well as EOCRC and LOCRC, respectively. To our knowledge, this is the first study to compare the effects of glucose levels on EOCRC and LOCRC in large prospective cohorts. However, we also acknowledge several limitations of this study. First, blood samples were obtained randomly without regard to fasting status and glucose was assessed on a single measure at baseline in the UK Biobank cohort, and changes during the follow-up may have an effect on risk evaluation. Second, although there was a relatively strong association between genetic instrumental variable and blood glucose, these variants only explain a small proportion of variance in blood glucose concentration. Third, despite the overall large sample size, the number of EOCRC cases was still quite limited, which limited the power and precision of analyses of EOCRC-specific associations.

5. Conclusions

In these two large-scale prospective cohorts, we demonstrated a positive association between blood glucose and CRC risk in a dose-response manner, particularly for EOCRC. No non-linear associations were observed in the RCS analysis and non-linear MR analysis. While the precise mechanisms remain to be fully elucidated, our findings underscore the need for greater public health efforts targeting obesity, metabolic dysfunction, and hyperglycemia as part of a multi-pronged approach to mitigate the growing burden of CRC, especially across younger age groups.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics statement

UK Biobank data use (Project Application Number 90170) was approved by the UK Biobank according to their established access procedures. Ethical approval for the UK Biobank was obtained from the North West-Haydock Research Ethics Committee (REC reference: 16/NW/0274). Further details can be found at https://www.UKBiobankiobank.ac.uk.

The Kailuan cohort study was conducted according to the principles of the Declaration of Helsinki and its revised version and was approved by the Ethics Committee of Kailuan General Hospital (approval number: 2006-05).

We confirm that all necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived, and that any patient/participant/sample identifiers included were not

known to anyone (e.g., hospital staff, patients or participants themselves) outside the research group so cannot be used to identify individuals.

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Author contributions

C.L. conducted the conceptualization. C.L. and J.L performed the data curation, methodology and formal analysis. C.L. wrote the original draft. Y.Z., B.L., N.L., Y.Z., S.C., S.W., Q.Z., M.D. and H.C. conducted review and editing. M.D. and H.C. acquired funding. M.D., H.C. and Q.Z. provided technical, or material support and conducted the project administration and supervision.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.04.006.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on colorectal cancer. *Gastroenterology*. 2017;153(1):307–323. doi:10.1053/j.gastro.2017.05.013.
3. Akimoto N, Ugai T, Zhong R, et al. Rising incidence of early-onset colorectal cancer - a call to action. *Nat Rev Clin Oncol*. 2021;18(4):230–243. doi:10.1038/s41571-020-00445-1.
4. Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol*. 2022;7(3):262–274. doi:10.1016/S2468-1253(21)00426-X.
5. Shi J, Xiong L, Li J, et al. A linear dose-response relationship between fasting plasma glucose and colorectal cancer risk: systematic review and meta-analysis. *Sci Rep*. 2015;5:17591. doi:10.1038/srep17591.
6. 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. doi:10.1136/jech-2018-210651.
7. 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. doi:10.1136/bmjopen-2016-011430.
8. Wang SY, Zhang WS, Jiang CQ, et al. Association of measures of glucose metabolism with colorectal cancer risk in older Chinese: a 13-year follow-up of the Guangzhou Biobank Cohort Study-cardiovascular disease substudy and meta-analysis. *Diabetes Metab J*. 2024;48(1):134–145. doi:10.4093/dmj.2022.0383.
9. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA*. 2017;318(19):1925–1926. doi:10.1001/jama.2017.17219.
10. Tian H, Mason AM, Liu C, Burgess S. Relaxing parametric assumptions for non-linear Mendelian randomization using a doubly-ranked stratification method. *PLoS Genet*. 2023;19(6):e1010823. doi:10.1371/journal.pgen.1010823.
11. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779. doi:10.1371/journal.pmed.1001779.
12. Allen N, Sudlow C, Downey P, et al. UK Biobank: current status and what it means for epidemiology. *Health Policy Technol*. 2012;1(3):123–126. doi:10.1016/j.hlpt.2012.07.003.
13. Feng X, Wang G, Li N, et al. The association between fasting blood glucose and the risk of primary liver cancer in Chinese males: a population-based prospective study. *Br J Cancer*. 2017;117(9):1405–1411. doi:10.1038/bjc.2017.296.
14. Lyu Z, Li N, Wang G, et al. Independent and joint associations of blood lipids and lipoproteins with lung cancer risk in Chinese males: a prospective cohort study. *Int J Cancer*. 2019;144(12):2972–2984. doi:10.1002/ijc.32051.
15. Elliott P, Peakman TC, Biobank UK. The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol*. 2008;37(2):234–244. doi:10.1093/ije/dym276.
16. Li X, Chen H, Wang G, et al. Metabolic syndrome components and the risk of colorectal cancer: a population-based prospective study in Chinese men. *Front Oncol*. 2019;9:1047. doi:10.3389/fonc.2019.01047.
17. Li N, Lu B, Luo C, et al. Incidence, mortality, survival, risk factor and screening of colorectal cancer: a comparison among China, Europe, and northern America. *Cancer Lett*. 2021;522:255–268. doi:10.1016/j.canlet.2021.09.034.
18. External info : data_providers_and_dates. Accessed August 16, 2023. https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=Data_providers_and_dates.
19. Shams-White MM, Brockton NT, Mitrou P, et al. Operationalizing the 2018 World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) cancer prevention recommendations: a standardized scoring system. *Nutrients*. 2019;11(7):1572. doi:10.3390/nu11071572.
20. Arthur RS, Wang T, Xue X, Kamensky V, Rohan TE. Genetic factors, adherence to healthy lifestyle behavior, and risk of invasive breast cancer among women in the UK Biobank. *J Natl Cancer Inst*. 2020;112(9):893–901. doi:10.1093/jnci/djz241.
21. Townsend P. Deprivation. *J Soc Policy*. 1987;16(2):125–146. doi:10.1017/S0047279400020341.
22. Thompson D., Wells D., Selzam S., et al. UK Biobank release and systematic evaluation of optimised polygenic risk scores for 53 diseases and quantitative traits. Published online June 16, 2022. doi:10.5281/zenodo.6631952.
23. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature*. 2018;562(7726):203–209. doi:10.1038/s41586-018-0579-z.
24. Chen J, Spracklen CN, Marenne G, et al. The trans-ancestral genomic architecture of glycemic traits. *Nat Genet*. 2021;53(6):840–860. doi:10.1038/s41588-021-00852-9.
25. Murphy N, Song M, Papadimitriou N, et al. Associations between glycemic traits and colorectal cancer: a Mendelian randomization analysis. *J Natl Cancer Inst*. 2022;114(5):740–752. doi:10.1093/jnci/djac011.
26. Genuth S, Alberti KGMM, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*. 2003;26(11):3160–3167. doi:10.2337/diacare.26.11.3160.
27. Buuren S van, Groothuis-Oudshoorn K., Vink G., et al. mice: multivariate imputation by chained equations. Published online June 5, 2023. Accessed October 23, 2023. https://cran.r-project.org/web/packages/mice/index.html.
28. Sekula P, Del Greco M F, Pattaro C, Köttgen A. Mendelian randomization as an approach to assess causality using observational data. *J Am Soc Nephrol*. 2016;27(11):3253–3265. doi:10.1681/ASN.2016010098.
29. Lagou V, Jiang L, Ulrich A, et al. GWAS of random glucose in 476,326 individuals provide insights into diabetes pathophysiology, complications and treatment stratification. *Nat Genet*. 2023;55(9):1448–1461. doi:10.1038/s41588-023-01462-3.
30. Therneau T.M., Lumley T., Elizabeth A., Cynthia C. Survival: survival analysis. Published online August 14, 2023. Accessed October 23, 2023. https://cran.r-project.org/web/packages/survival/index.html.
31. Harrell F.E. Jr. rms: regression modeling strategies. Published online September 12, 2023. Accessed October 23, 2023. https://cran.r-project.org/web/packages/rms/index.html.
32. HDTian. HDTian/DRMR. Published online March 8, 2024. Accessed April 6, 2024. https://github.com/HDTian/DRMR.
33. Lorenzi M, Montisano DF, Toledo S, Barrieux A. High glucose induces DNA damage in cultured human endothelial cells. *J Clin Invest*. 1986;77(1):322–325. doi:10.1172/JCI112295.
34. Chocarro-Calvo A, García-Martínez JM, Ardila-González S, De la Vieja A, García-Jiménez C. Glucose-induced β-catenin acetylation enhances Wnt signaling in cancer. *Mol Cell*. 2013;49(3):474–486. doi:10.1016/j.molcel.2012.11.022.
35. Lin CY, Lee CH, Huang CC, Lee ST, Guo HR, Su SB. Impact of high glucose on metastasis of colon cancer cells. *World J Gastroenterol*. 2015;21(7):2047–2057. doi:10.3748/wjg.v21.i7.2047.
36. Tekade RK, Sun X. The Warburg effect and glucose-derived cancer theranostics. *Drug Discov Today*. 2017;22(11):1637–1653. doi:10.1016/j.drudis.2017.08.003.
37. Stefani C, Miricescu D, Stanescu-Spinu II, et al. Growth factors, PI3K/AKT/mTOR and MAPK signaling pathways in colorectal cancer pathogenesis: where are we now? *Int J Mol Sci*. 2021;22(19). doi:10.3390/ijms221910260.
38. Kasprzak A. Insulin-like growth factor 1 (IGF-1) signaling in glucose metabolism in colorectal cancer. *Int J Mol Sci*. 2021;22(12):6434. doi:10.3390/ijms22126434.
39. Chen YC, Ou MC, Fang CW, Lee TH, Tzeng SL. High glucose concentrations negatively regulate the IGF1R/Src/ERK axis through the MicroRNA-9 in colorectal cancer. *Cells*. 2019;8(4):326. doi:10.3390/cells8040326.
40. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut*. 2019;68(10):1820–1826. doi:10.1136/gutjnl-2018-317592.
41. Joh HK, Lee DH, Hur J, et al. Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors. *Gastroenterology*. 2021;161(1):128–142.e20. doi:10.1053/j.gastro.2021.03.028.
42. Li W, Zhang X, Sang H, et al. Effects of hyperglycemia on the progression of tumor diseases. *J Exp Clin Cancer Res*. 2019;38(1):327. doi:10.1186/s13046-019-1309-6.
43. Hannon TS, Janosky J, Arslanian SA. Longitudinal study of physiologic insulin resistance and metabolic changes of puberty. *Pediatr Res*. 2006;60(6):759–763. doi:10.1203/01.pdr.0000246097.73031.27.
44. Vigneri PG, Tirrò E, Pennisi MS, et al. The insulin/IGF system in colorectal cancer development and resistance to therapy. *Front Oncol*. 2015;5:230. doi:10.3389/fonc.2015.00230.