Is Type 2 Diabetes Mellitus Causally Associated with Cancer Risk? Evidence from a Two-Sample Mendelian Randomisation Study

Running head: Type 2 diabetes and cancer risk

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Abstract

We conducted a two-sample Mendelian randomisation study to investigate the causal associations of type 2 diabetes mellitus (T2DM) with risk of overall cancer and 22 site-specific cancers. Summary-level data for cancer were extracted from the Breast Cancer Association Consortium and UK Biobank. Genetic predisposition to T2DM was associated with higher odds of pancreatic, kidney, uterine and cervical cancer, lower odds of oesophageal cancer and melanoma, but not associated with 16 other site-specific cancers or overall cancer. The odds ratios (95% confidence interval) were 1.13 (1.04, 1.22), 1.08 (1.00, 1.17), 1.08 (1.01, 1.15), 1.07 (1.01, 1.15), 0.89 (0.81, 0.98), and 0.93 (0.89, 0.97) for pancreatic, kidney, uterine, cervical, and oesophageal cancer and melanoma, respectively. The association between T2DM and pancreatic cancer was also observed in a meta-analysis of this and a previous Mendelian randomisation study (odds ratio 1.08; 1.02, 1.14; p=0.009). There was limited evidence supporting causal associations between fasting glucose and cancer. Genetically predicted fasting insulin levels were positively associated with cancers of the uterus, kidney, pancreas and lung. The present study found causal detrimental effects of T2DM on several cancers. We suggested to reinforce the cancers screening in T2DM patients to enable the early detection of cancer.

Keywords: cancer; fasting glucose; fasting insulin; Mendelian randomisation study; single-nucleotide polymorphisms; type 2 diabetes

Introduction

Type 2 diabetes mellitus (T2DM) and cancer are two major global health issues, causing around 5.0 and 8.7 million death and 143.0 and 208.3 million disability-adjusted life years in 2015 worldwide, respectively (1, 2). Evidence from epidemiological studies indicates that T2DM is as a risk factor for overall cancer (3) and several site-specific cancers, such as colorectal (4, 5), liver (6), kidney (7, 8), uterine (9), and breast cancer (10). A bidirectional relationship has been suggested for T2DM and pancreatic cancer (11-15), whereas an inverse association has been observed between T2DM and risk of prostate cancer (16, 17). Findings for other site-specific cancers are conflicting (3) and the causality of the observed associations remains unclear due to possible residual confounding and reverse causality in observational studies.

Exploiting genetic variants as proxies for a risk factor, Mendelian randomisation (MR) is a method that can strengthen the exposure-outcome association inference by diminishing the likelihood of confounding and eliminating reverse causality in conventional observational studies (18). This method minimizes confounding since genetic variants are randomly assorted at conception, thereby being irrelevant with self-adapted lifestyle and environmental factors. In addition, it overcomes reverse causality as allelic randomisation antedates the disease's onset.

Given the inconsistent results and potential methodological limitations of previous observational studies of T2DM and cancer risk, we conducted a two-sample MR study to assess the causal associations of liability to T2DM with the risk of overall cancer and 22 site-specific cancers. For pancreatic cancer, a bidirectional MR study was conducted. We additionally explored the causal associations of genetically predicted fasting glucose (FG) and fasting insulin (FI) levels with the same cancer outcomes in secondary analyses. Moreover, we

performed meta-analyses of available MR studies of the associations of T2DM, FG or FI levels with cancer risk.

Methods

Data sources

This two-sample MR study utilised summary-level genetic data from the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium (19), the Meta-Analyses of Glucose and Insulin-related traits (MAGIC) Consortium (20), Pancreatic Cancer Cohort Consortium (PanScan) and the Pancreatic Cancer Case-Control Consortium (PanC4) (21), Breast Cancer Association Consortium (BCAC) (22), and UK Biobank (23) (**Supplementary Table 1**). Data for breast cancer came from BCAC and UK Biobank and were based on 228 951 European-descent participants (122 977 breast cancer cases and 105 974 controls) and 367 643 European-descent participants (13 666 breast cancer cases and 353 977 controls), respectively. The GWAS in BCAC used Phase 3 of 1000 Genomes Project as reference panel in imputation stage and adjusted for genetic principal components and country. From UK Biobank, we additionally derived genetic associations data, adjusted for age, sex and ten genetic principal components, for overall cancer and 21 other site-specific cancers among 367 643 unrelated participants. We identified a total of 75 037 cancer cases and information on incident cancer cases was obtained until March 31, 2017 in UK Biobank. Cancer diagnosis source of included studies is shown in **Supplementary Table 2**. Most studies defined the cancer cases based on cancer registry or hospital/clinics data. The original genome-wide association studies (GWASs) had been approved by corresponding ethical committee and the present study was approved by the Swedish Ethical Review Authority.

Instrumental variable selection

Instrumental variables selection for T2DM, and FG and FI levels was based on a meta-analysis of 32 GWASs with 74 124 type 2 diabetes cases and 824 006 controls of European ancestry (known as DIAGRAM consortium) (19) and a genome-wide association meta-analysis of up to 133 010 individuals of European ancestry without diabetes (known as MAGIC) (20), respectively. Instrumental variables for pancreatic cancer were obtained from a GWAS of 9040 cancer cases and 12 496 controls of European ancestry from PanScan and PanC4 (21). Single nucleotide polymorphisms (SNPs) that met the locus-wide significance level ($p<10^{-5}$) and the genome-wide statistical significance threshold ($p<5\times10^{-8}$) were proposed as instrumental variables for T2DM (n=403), FG (n=35), FI (n=18) and pancreatic cancer (n=22). Selected SNPs explained around 17.4%, 4.8% and 1.2% variance associated with T2DM, FG and FI, respectively. Used instrumental variables for T2DM and glycaemic traits were validated in previous studies (24-26). Previous studies reported that the effects of T2DM and FI-related genetic variants in *FTO* gene were entirely driven by body mass index-mediation effects (20, 27). Thus, we excluded SNPs in or near *FTO* gene region, leaving 399 SNPs as instrumental variables for T2DM, 35 for FG, and 17 for FI. With regard to T2DM, 295 SNPs (variants in *FTO* excluded) reaching the genome-wide significance level were used in the sensitivity analysis. Detailed information for instrumental variables of T2DM, FG, FI and pancreatic cancer is presented in **Supplementary Table 3 and Supplementary Table 4.**

Meta-analysis of MR studies

The procedure of systematic review and literature selection is shown in **Supplementary Figure 1.** A systematic literature search was conducted in two datasets of PubMed and Embase. We identified 165 papers published before October 17th, 2019, by use of the following medical subject heading terms and/or text words: “diabetes”, “glucose”, “insulin”, “glycemic”, “cancer”, “carcinoma”, “Mendelian randomization”, “Mendelian randomisation”,

"instrumental variable causal inference", "causal inference using instrumental variable" and "causal inference using genetic variants". After title, abstract and full text screening, seven studies were included in this meta-analysis (28-34). Details of exclusion criteria is presented in **Supplementary Figure 1**. We extracted data of publication data (the first author's name and year of publication), T2DM and related traits (FG and FI), cancer site, number of cancer cases and controls, number of SNPs used as instrumental variables, variance explained by used SNPs and risk estimates with their corresponding confidence intervals. Information of included studies is shown in **Supplementary Table 5**.

Statistical analysis

The random effects inverse-variance weighted method was used to assess the associations of genetically predicted T2DM, FG FI with overall cancer and 22 site-specific cancers. Cochrane I^2 was used to measure heterogeneity among instrumental variables. For T2DM, three sensitivity analyses, including the weighted median, MR-Egger and MR-PRESSO methods, were performed for the associations that showed suggestive evidence of associations in the inverse-variance weighted analysis. The weighted median approach provides accurate estimates with the prerequisite that at least half of the instrumental variables are valid (35). The MR-Egger regression detects and adjusts for pleiotropy; however, the derived estimates are imprecise (36). The MR-PRESSO method is able to detect and correct for possible outliers, thereby removing horizontal pleiotropy via outlier removal (37). To minimize the influence from body mass index, a multivariable MR method was used with the adjustment of body mass index. In the meta-analysis, effect sizes from different MR studies were combined using fixed-effects meta-analysis. Odds ratios (ORs) and confidence intervals (CIs) of cancer were scaled to one-unit increase in log odds of liability to T2DM and one standard deviation (SD) increase in log of genetically predicted FG and FI levels. The SD of FG and FI corresponds to 0.65

mmol/L and 0.60 pmol/L, respectively, based on the Fenland or Ely studies (38, 39). For pancreatic cancer, we additionally performed a bidirectional MR analysis. Power calculation for the analyses of T2DM was based on a web-tool (40) and results are displayed in **Supplementary Table 6**. All statistical tests were two-sided and performed in Stata/SE 15.0 and R 3.6.0 software. We did not use *p* values strictly to define statistical significance but interpreted the results based on the strengths of the associations (41) as well as the consistency across sensitivity analyses.

Data availability

Data for T2DM-associated SNPs can be obtained from the DIAGRAM consortium (https://diagram-consortium.org/index.html). Data for fasting glucose and insulin-associated SNPs can be obtained from MAGIC (https://www.magicinvestigators.org/). Summary-level data from BCAC are publicly available (http://bcac.ccge.medschl.cam.ac.uk/). The PanScan and PanC4 genome-wide association data are available through dbGAP (accession numbers phs000206.v5.p3 and phs000648.v1.p1, respectively). UK Biobank data are available through application (https://www.ukbiobank.ac.uk/). Summary-level data for the used SNPs in the present study are available upon a reasonable request to the corresponding author.

Results

We found no MR evidence of association between genetic liability to T2DM and overall cancer in the primary analysis or the sensitivity analyses (**Figure 1**). However, there was some evidence of associations of genetic liability to T2DM with higher odds of liver, pancreatic, kidney, uterine, and cervical cancer and lower odds of melanoma and oesophageal cancer (**Figure 2**). The ORs per one-unit increase in genetically predicted log odds of T2DM were 1.16 (95% CI, 0.99, 1.36; p=0.059) for liver cancer, 1.13 (95% CI, 1.04, 1.22; p=0.002) for

pancreatic cancer, 1.08 (95% CI, 1.00, 1.17; *p*=0.039) for kidney cancer, 1.08 (95% CI, 1.01, 1.15; *p*=0.031) for uterine cancer, 1.07 (95% CI, 1.01, 1.15; *p*=0.031) for cervical cancer, 0.93 (95% CI, 0.89, 0.97; *p*=0.001) for melanoma and 0.89 (95% CI, 0.81, 0.98; *p*=0.018) for oesophageal cancer (**Figure 2**). Estimates of similar magnitude were observed between genetic liability to T2DM and thyroid cancer (OR=1.08; 95% CI, 0.94, 1.24; *p*=0.281) and brain cancer (OR=0.92; 95% CI, 0.84, 1.02; *p*=0.104) (**Figure 2**). The findings were consistent between analyses using 399 SNPs and 295 SNPs for T2DM (**Supplementary Figure 2**). Results of sensitivity analyses showed same patterns in the analysis of oesophageal and pancreatic cancer and melanoma (**Figure 3**). We detected significant heterogeneity in the analysis of uterine and liver cancer and melanoma, and pleiotropy in the MR-Egger analysis of cervical cancer. After outlier removal, all significant associations obtained from inverse-variance weighted model remained in the MR-PRESSO analysis. In addition, a suggestive positive association between genetically predicted risk of pancreatic cancer and T2DM was observed in the reverse MR analysis (**Supplementary Figure 3**). After adjusting for body mass index, the patterns of the associations between genetically predicted log odds of T2DM and cancers remained albeit with wider CIs (**Supplementary Figure 4)**.

In the meta-analysis combining the present MR findings with those of previous MR studies (**Supplementary Table 5)**, an association was observed between genetically predicted log odds of T2DM and pancreatic cancer (OR=1.08; 95% CI, 1.02, 1.14; *p*=0.009) among a total of 8374 pancreatic cancer cases. The results of meta-analysis showed no associations of genetically predicted log odds of T2DM with kidney, uterine, or ovarian cancer (**Figure 4**).

There was limited evidence of associations of genetically predicted FG and FI levels with overall cancer and the 22 site-specific cancers (**Supplementary Figure 5, Supplementary Figure 6, and Supplementary Figure 7**). However, the precision was low in most analyses and the magnitude of the estimates was relatively strong for some cancer sites.

For example, the OR was above 1.5 for genetically predicted high_FG levels in relation to biliary tract cancer (**Supplementary Figure 6)**. In addition, for FI levels, the ORs were above 1.5 for kidney, uterine, cervical, and stomach cancer and below 0.5 for liver cancer (**Supplementary Figure 7)**.

In the meta-analysis, there was no evidence of association between genetically predicted FG levels and five site-specific cancers (**Supplementary Figure 8**). Genetically predicted FI levels showed evidence of positive associations with cancers of the pancreas, kidney, uterus, and lung by combining the findings from this MR study and previous MR studies (**Supplementary Figure 9**).

Discussion

The present study is the first MR study that systematically investigated the causal associations of genetic liability to T2DM and related traits with overall cancer and 22 site-specific cancers. We found evidence that genetic liability to T2DM was associated with increased risks of pancreatic, kidney, uterine and cervical cancer and with lower risks of melanoma and oesophageal cancer. The positive association between genetic liability to T2DM and pancreatic cancer was further verified in a supplementary meta-analysis of MR studies. There was limited MR evidence supporting causal associations between genetically predicted FG and any cancer but genetically predicted high FI levels increased the risks of pancreatic, kidney, uterine, and lung cancer.

The present MR findings do not support observational studies suggesting an elevated risk of overall cancer among T2DM patients (3). An umbrella meta-analysis of 27 studies found that having T2DM was associated with a 10% higher risk of developing cancer (38 010 cancer cases) and a 16% higher cancer mortality rate (11 386 cancer-caused deaths) (3). In a national register-based cohort study in Australia, the standardized incidence and mortality ratios for all

cancers combined were significantly higher (ORs ranging from 1.03 to 1.22) among both men and women with T2DM than in non-diabetic individuals (16). However, our findings were in line with a recent individual-level MR study with 10 536 Japanese adults (3541 cancer cases). Using 29 SNPs as instrumental variables for T2DM, that study found no strong evidence supporting an association between T2DM and overall cancer (42). The discrepancy with our overall cancer findings may be explained by the driver effects of the T2DM-unrelated cancers that contributed a large proportion of cancer cases, including breast cancer (18%), prostate cancer (10%), and colorectal cancer (7%), in the present MR study, or from residual confounding or reverse causation bias in the observational studies.

Findings of the present MR study and the meta-analysis of MR studies showed a consistent causal positive association between T2DM and pancreatic cancer, supporting observational studies. An umbrella meta-analysis of 27 studies obtained a pooled OR of 1.95 when compared T2DM patients with controls based on 52 445 pancreatic cancer cases (3). It has been demonstrated that both new-onset and longstanding T2DM facilitate the development of pancreatic cancer (11, 12). Pathophysiologically, this may relate to carcinogenic or cancer-promoting effects of glucose and glycation end products in reactive oxygen species generation, DNA damage and cell proliferation (15, 43, 44). It could also be due to the role of diabetes in the metabolic syndrome which is associated with increased risk of pancreatic cancer (15, 45), or due to increased insulin levels (15). Pre-diabetes is characterised by a long-standing increase in insulin secretion by the beta cells of the pancreas to compensate for insulin-resistance which occurs in the early stages of diabetes development. Such an increase in insulin in the pancreatic portal circulation could be carcinogenic or cancer-promoting, as insulin has proliferative effects (15). It is therefore notable that we also report a positive association between fasting insulin levels our findings in combination suggest that the insulin resistance of early diabetes, in combination with hyperglycaemia may increase risk of pancreatic cancer and importantly

this could be targeted with insulin-sensitizing agents such as metformin which reduce such risk (46). Nevertheless, a recent MR study did not observe a positive association between diabetes and pancreatic cancer among Japanese adults. This null finding might be caused by inadequate power since the study only had 129 pancreatic cancer cases (42).

A bidirectional relationship between T2DM and pancreatic cancer has been found in recent years (11, 15). Pancreatic cancer can increase diabetes risk through enhanced insulin secretion with consequent insulin resistance, or, due to destruction of pancreatic tissue with loss of insulin-producing beta cells. Even though several pathological features, such as insulin levels and glucose-dependent insulinotropic polypeptide levels, were different between new-onset T2DM and pancreatic cancer-caused T2DM, inaccurate classification of diabetes was common in clinical practice (15). Thus, the established observational association between T2DM and pancreatic cancer could be the result of reverse causality. The present study using MR design confirmed a causal pathway from T2DM to pancreatic cancer but also found suggestive evidence of an inverse causal pathway from pancreatic cancer to T2DM risk. This could be important clinically, and with further research the development of diabetes or pre-diabetes could be useful in monitoring cancer progression.

The present study also detected possible positive associations of liability to T2DM with some other site-specific cancers, with the strongest evidence for kidney, uterine, and cervical cancer. A systematic review including nine cohort studies stated that patients with diabetes had a significant increased risk of kidney cancer after adjusting for body mass index and cigarette smoking (8). It could relate to increased exposure to carcinogenic or cancer-promoting growth factors or insulin-like products due to reduced excretion, or, as a consequence of urinary tract infections which are common due to the relative immunosuppression seen in diabetes (47, 48). Similarly, the association of T2DM with uterine cancer is supported by the findings of a meta-analysis of 16 observational studies with multivariate adjustment (49). However, studies

concerning the association of T2DM with cervical cancer are limited and conflicting. A retrospective cohort study with 328 994 diabetic patients and 327 572 non-diabetic participants found that newly diagnosed T2DM cases (within 3 month) had significantly increased risk of cervical cancer. However, the risk was not higher among T2DM patients after the initial 3-month period compared with those without T2DM (50). In another study including 397 783 adults, the prevalence of cervical cancer was 30% higher in diabetic group compared with non-diabetic counterparts with adjustment of age, body mass index, ethnicity, lifestyle and physical activity (51). A nation-wide Australian study showed that long-term T2DM was associated with the age-standardized incidence ratio of cervical cancer but was not with mortality from cervical cancer (16). Further studies are warranted to verify the causal positive association between T2DM and cervical cancer.

Our finding of an inverse association between T2DM and melanoma is in line with most but not all observational studies. A nationwide hospital-based study showed that the risk of melanoma for familial T2D patients was lower among 26 641 patients (including 125 126 T2DM patients) who had an T2DM affected family member compared with all patients in Sweden (52). Another nationwide study in Australia also found a decreased risk of melanoma among 953 382 T2DM cases compared with the general Australian population (16). Nonetheless, a study with 4501 578 veterans admitted to Veterans Affairs hospitals reported that men with diabetes had a higher risk of melanoma (53). With regard to oesophageal cancer, previous findings were inconsistent. Three meta-analyses documented a positive association between T2DM and oesophageal cancer; however, the results might be less robust due to substantial heterogeneity and potential confounding factors within the included studies (3, 54, 55). A large-scale cohort study of 4501 578 black and white U.S. veterans found that T2DM male patients had a decreased risk of oesophageal cancer (53). Findings of two studies focusing on T2DM and risk of oesophageal cancer in Australian and Asian population showed no

association between diabetes diagnosis and risk of oesophageal cancer (16, 56). Thus, the role of T2DM in oesophageal cancer development and mortality needs more investigation.

Even though most observational studies observed a strong inverse association between T2DM and risk of prostate cancer (17), the present study provided limited evidence supporting such a causal association, which is supported by a previous MR study (25). The possible reason explaining the discrepancy is anticancer effect of several drugs used for the management of T2DM, such as metformin and thiazolidinediones (57) in previous observational studies. There was suggestive evidence of a positive association of T2DM with liver cancer in the present MR study, confirming previous observational findings (3) and is likely to occur through driving non-alcoholic fatty liver disease which can progress to hepatocellular carcinoma.

The detrimental effects of T2DM on certain site-specific cancers may be driven by high insulin levels in response to insulin resistance which occurs in the development of pre-diabetes. It is therefore notable that we found positive associations of both T2DM and FI with pancreatic, kidney and uterine cancer, which suggests a possible pathophysiologic mechanism. Meta-analysis of FI was also positively associated with lung cancer risk. Observational studies have proposed that hyperinsulinemia increases the risk of several cancers, such as pancreatic (58), uterine (59), ~~and~~ gastric (60) and kidney (61) cancer, but not lung cancer (62) and insulin has multiple potential carcinogenic or cancer-promoting effects (63). Although limited evidence of an association between FG and cancer was found in the present study, except for a possible positive association with biliary tract cancer (64), hyperglycaemia might play a role in the onset of certain cancers, especially liver (65) and bladder (64, 65) cancer. Inflammation (66), elevated Haemoglobin A1c levels (67), and drugs used for the management of T2DM (68) may also mediate the pathway from T2DM to cancer. Detailed mechanisms need further investigations. Further validating our findings or hypothesis, several T2DM medications have been revealed to lower the risk of common cancers, such as lung, colorectal and breast cancer,

in pre-clinical and/or clinical settings among diabetes patients (69, 70). Review articles suggested that even though metformin and thiazolidinedione appeared to inhibit the proliferation and growth of certain cancer types in preclinical data, a vast majority of clinical trials have been conducted to assess the usefulness of these medications in cancer prevention and treatment (69, 70). Those results will facilitate the assessment of the place of metformin in cancer prevention and therapy and define the target populations.

A major strength of this study is the MR study design, which diminishes confounding and reverse causality potentially biasing the results in observational studies. In addition, we comprehensively assessed the causal associations of T2DM and related-traits with overall cancer and 22 site-specific cancers using summary-level data from large genetic consortia. We conducted our study merely among European populations. Thus, the results were less likely to be biased by population stratification, but this confined the transferability of our findings to other populations. A major limitation is that the number of cases was few for several site-specific cancers, causing low precision of the estimates. Thus, it is likely that we have missed weak associations. However, we have performed a systematic review and meta-analysis to combine the data from the previous and present MR studies, thereby expanding the sample size and increasing the accuracy of the estimation as possible. Furthermore, we interpreted results relying on the consistency across three sensitivity analyses and the strengths of the associations, but not the significance level (41). Even though there was heterogeneity among instrumental variables in a few analyses, no pleiotropy in the MR-Egger suggested balanced pleiotropy, which is less likely to bias the results (36). We still cannot exclude that there is any direct causal pathway from the T2DM-predisposing genetic variants to cancer. A further limitation is that we examined the liability to T2DM rather than the disease itself. Our results are therefore not fully comparable with those of observational studies where study participants have or do not have a T2DM diagnosis. Even though most of the included studies defined cancer cases

based on a reliable source, such as registry and hospital/clinics data, a possible detection bias in T2DM patients may overestimate the association between T2DM and cancer. Nonetheless, considering that we examined the association of T2DM with over 20 site-specific cancers, it is less likely that an increased or decreased chance of being diagnosed with a site-specific cancer is caused by the diagnosis of diabetes assuming no causal association between them.

Conclusions

This MR study strengthened the evidence in favour of causal associations of T2DM with increased risks of pancreatic, kidney, uterine and cervical cancer, and decreased risks of oesophageal cancer and melanoma. Additionally, there was evidence of a positive association of FI levels with some overlapping cancers, which may suggest that insulin resistance in early diabetes may contribute to this risk. This study lent limited support to causal associations of T2DM, FG, and FI with overall cancer risk. We suggest a higher index of suspicion for cancer and reinforcement of cancer screening recommendations among patients with T2DM to enable the early detection of cancer in this group of patients.

Additional information

Acknowledgments

Summary-level data for SNPs associated with T2DM-related traits were extracted from DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium and Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). Summary-level data for genetic associations with the cancers were contributed by the Breast Cancer Association Consortium, PanScan and PanC4, and UK Biobank. The analyses of UK Biobank data were conducted under application 29202. The authors thank all investigators for sharing these data.

Authors' contributions

S.Y. analysed and interpreted data and wrote and reviewed the manuscript. S.K., M.V. and P.C. reviewed the manuscript. A.M.M. and S.B. prepared the data and reviewed the manuscript. S.C.L. designed the research, analysed and interpreted the data and reviewed the manuscript. All authors read and approved the final manuscript.

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Transparency statement

S.C.L. as the manuscript's guarantor confirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

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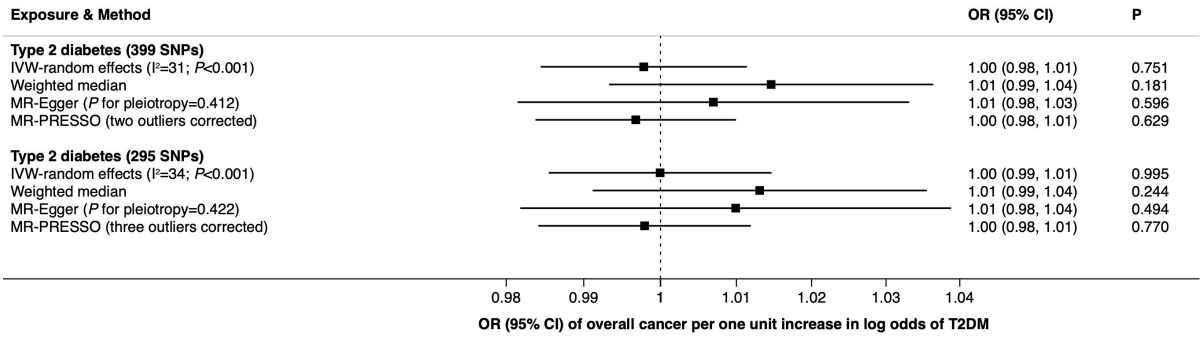

Figure 1. Association between type 2 diabetes mellitus and overall cancer in UK Biobank with 75 037 cancer cases and 292 606 non-cancer participants

CI indicates confidence interval; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier; IVW, inverse-variance weighted; OR, odds ratio. Heterogeneity was observed in both analyses. There was no detected pleiotropy in MR-Egger analyses. Two and three outliers were detected and corrected in the MR-PRESSO analysis using 399 SNPs and 295 SNPs for T2DM, respectively.

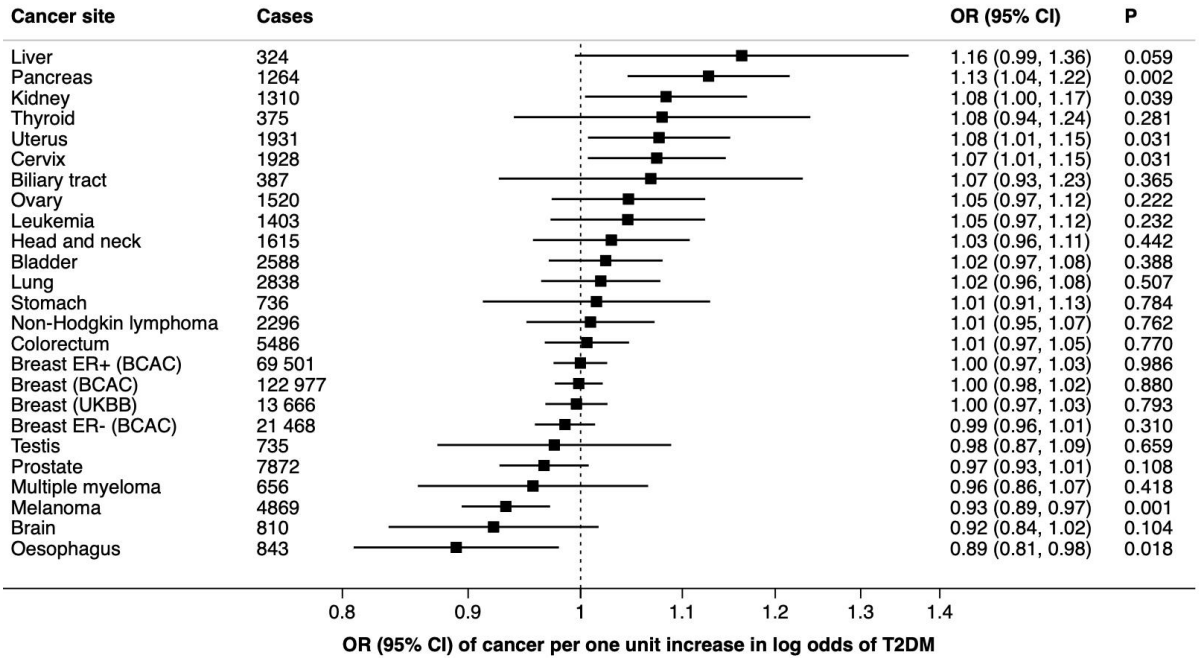

Figure 2. Associations between type 2 diabetes mellitus (399 SNPs) and 22 site-specific cancers in UK Biobank

BCAC indicates breast cancer association consortium; CI; confidence interval; ER, oestrogen receptor; OR, odds ratio; UKBB, UK Biobank.

All estimations were based on the inverse-variance weighted method.

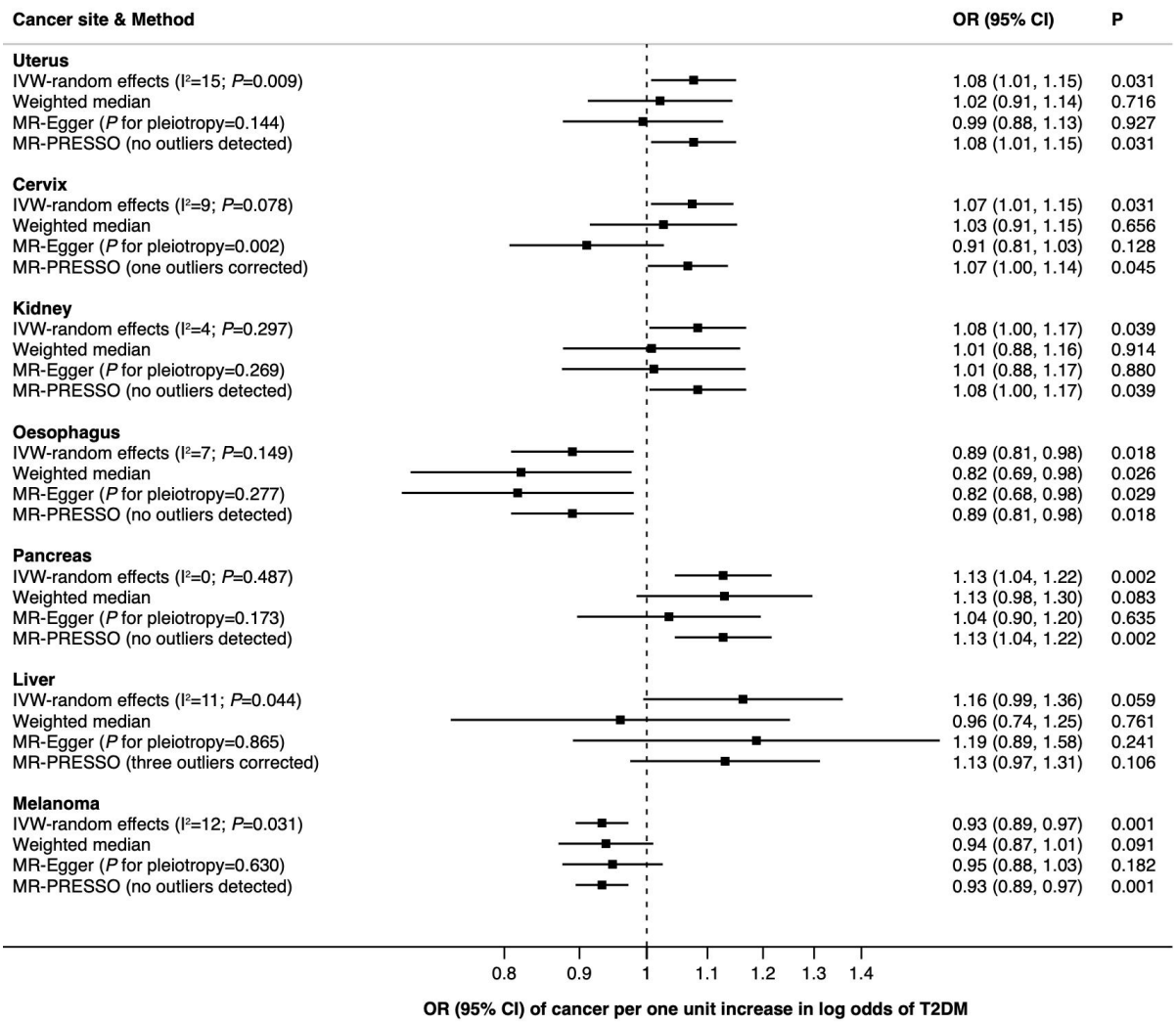

Figure 3. Sensitivity analyses of the associations between type 2 diabetes mellitus and certain site-specific cancers in UK Biobank

CI indicates confidence interval; MR-PRESSO, Mendelian randomization-pleiotropy residual sum and outlier; IVW, inverse-variance weighted; OR, odds ratio. Heterogeneity was observed in the analysis of uterine, liver and melanoma cancer. There was detected pleiotropy in MR-Egger analysis of cervix cancer. One and three outliers were detected and corrected in the MR-PRESSO analysis of cervix and liver cancer, respectively.

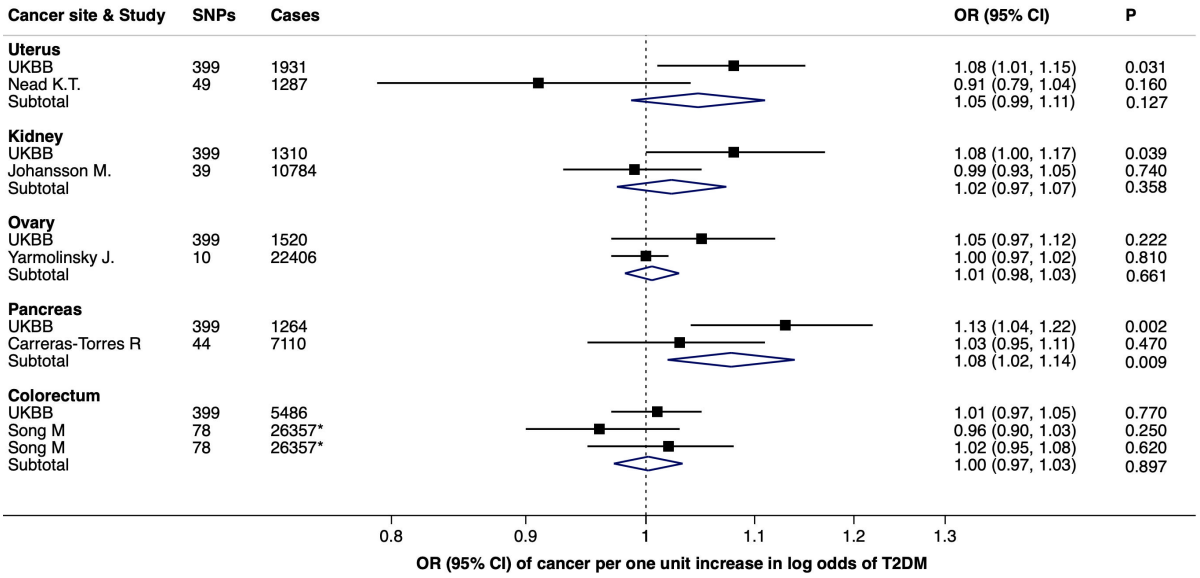

Figure 4. Meta-analysis of the association of type 2 diabetes mellitus with certain site-specific cancers

CI indicates confidence interval; OR, odds ratio; SD, standard deviation; UKBB, UK Biobank. *Effect size in Song M study was estimated in men and women separately.