The triglyceride-glucose index as a measure of insulin resistance and risk of obesity-related cancers

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KEY MESSAGES

- In this cohort study including more than 500 000 individuals, insulin resistance measured as the logarithmized triglyceride glucose product (TyG index) mediated part of the effect of overweight and obesity on risk of cancers of the pancreas, rectum, colon, kidney, and liver.
- In contrast, TyG index did not mediate the risk of cancers of the endometrium, ovary and breast.
- Our results confirm a promoting role of insulin resistance in the pathogenesis of gastrointestinal cancers.
- Although often claimed, our results provide limited evidence that insulin resistance connects excess body weight with risk of cancers of the female reproductive organs.

ABSTRACT

Background: The role of insulin resistance as a mediator in the association of body mass index (BMI) with site-specific cancer risk has, to our knowledge, never been systematically quantified.

Methods: Altogether 510 471 individuals from six European cohorts with a mean age of 43.1 years were included. We used the triglyceride glucose product (TyG index) as a surrogate measure for insulin resistance. We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with ten common obesity-related cancers, and quantified the proportion of the effect of BMI mediated through TyG index on the ln(HR) scale.

Results: During a median follow-up of 17.2 years, 16 052 individuals developed obesity-related cancers. TyG index was associated with the risk of cancers of the kidney (hazard ratio (HR) per one standard deviation increase 1.13, 95% confidence interval: 1.07-1.20), liver (1.13, 1.04-1.23), pancreas (1.12, 1.06-1.19), colon (1.07, 1.03-1.10), and rectum (1.09, 1.04-1.14). Substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas (42%), rectum (34%), and colon (20%); smaller proportions for kidney (15%) and liver (11%). Little or no mediation was observed for breast (postmenopausal), endometrial, and ovarian cancer. Results were similar for males and females, except for pancreatic cancer where the proportions mediated were 20% and 91%, respectively.

Conclusions: The TyG index was associated with increased risk of cancers of the digestive system and substantially mediated the effect of BMI, suggesting that insulin resistance plays a promoting role in the pathogenesis of gastrointestinal cancers.

Keywords: obesity, cancer, insulin resistance, mediation analysis, longitudinal study

INTRODUCTION

A large body of epidemiological evidence has established that excess body weight, both overweight (body mass index (BMI) of 25.0 to 29.9 kg/m²) and obesity (BMI ≥30.0 kg/m²), is a major risk factor for many cancer forms[1–8]. In 2004, Calle and Kaaks[9] proposed three biological candidate mechanisms potentially mediating the association of excess body weight with cancer risk: (i) increased bioavailability of steroid hormones and alterations in sex hormone metabolism; (ii) adipokine pathophysiology and systemic (subclinical) inflammation; and (iii) insulin resistance and bioavailability of insulin-like growth factor I (IGF1). The pathways triggering the effect of excess weight might differ between cancer sites. While in cancers of the female reproductive organs the effect of BMI might be largely mediated by increased oestrogen levels, there is mounting evidence for a substantial mediation through pathways connected to insulin resistance for some gastrointestinal cancers[9–11]. There are several mechanistic studies investigating these pathways (*i.e.* in vitro and animal models)[11]. In recent years, also epidemiological studies with prospective designs addressed this question of mediation for some selected cancer sites[12–15].

The logarithmized product of fasting levels of triglycerides and glucose (denoted TyG index) has been suggested to be a simple measure of insulin resistance[16]. Both lipotoxicity and glucotoxicity play crucial roles in insulin resistance modulation that are reflected in the TyG index[17,18]. The TyG index is highly correlated with the euglycemic-hyperinsulinemic clamp test, the gold standard for determining insulin resistance (Pearson correlation coefficient ρ=-0.68 between TyG index and total glucose metabolism rates as determined by the clamp procedure[19]), and thus has validity similar to the frequently used homeostatic model assessment (HOMA) insulin resistance (IR) index (ρ=-0.77 between HOMA-IR index and total glucose metabolism rates as determined by the clamp procedure[19]). Thus, due to its easy availability and cost-effectiveness, the TyG index is a promising surrogate measure for insulin resistance in large-scale epidemiological studies.

Given the well-established association of obesity with cancer risk of various sites and that one of the hypothesized links is insulin resistance, both an association of TyG index with the risk of obesity-related cancers as well as substantial mediation of the BMI effect through the parameter TyG index, seem biologically plausible. However, despite the TyG index' simplicity, neither its association with cancer risk nor its contribution to the effect of BMI on cancer risk has been previously investigated. The aim of this study was (i) to quantify the effect of TyG index on the risk of obesity-related cancers, and (ii) to estimate the proportion of the effect of BMI on cancer risk that is mediated through the TyG index, in a large, pooled European study.

METHODS

Data source and selection criteria

We used data from the Metabolic syndrome and Cancer project (Me-Can) 2.0, a pooling of six population-based cohorts; three Norwegian cohorts (Oslo study I, Norwegian Counties Study (NCS), the 40-year programme (40-y)), two Swedish cohorts (Västerbotten Intervention Programme (VIP), Malmö Preventive Project (MPP)), and one Austrian cohort (Vorarlberg Health Monitoring and Prevention Programme (VHM&PP)). Me-Can 2.0 is a follow-up project from Me-Can 1.0, which has been described in detail elsewhere[20], and includes additional individuals, more events and a longer follow-up as compared to Me-Can 1.0. The study was approved by research ethics committees in the respective countries.

Data on height, weight, smoking status and serum and plasma levels of glucose and triglycerides (including fasting time before sampling) have been collected at health examinations in all cohorts. Blood glucose values obtained from whole blood, as in the MPP cohort, were converted into the equivalent of serum/plasma levels by increasing the whole blood value by 11%[21]. BMI was calculated directly from weight and height records (weight (kg)/height $(m)^2$) measured by medical staff. The TyG index was calculated as ln[triglycerides

(mg/dl) x blood glucose (mg/dl)/2][16]. Diabetic status was further assessed in a questionnaire that was given to all participants, except for the VHM&PP cohort.

Out of overall 843 531 individuals, we excluded participants with missing or implausible information on BMI, triglycerides, glucose, smoking status and fasting time before measurement (n=321 464). The majority of these exclusions (93%) arose because glucose was not measured in the NCS and 40-year cohorts throughout all years. Glucose measurements were only available for 68% and 34% of participants in these cohorts, respectively. A total of 216 cases were excluded because information on the date of cancer diagnosis, death, or date of emigration was inconsistent. In addition, individuals with any record of cancer before (n=6045) or up to twelve months after study entry (n=1674) or a follow-up time less than twelve months (n=3661) were excluded, thereby reducing the possibility of reverse causation (*i.e.* parameters of interest affected by undiagnosed cancer). Thus, there were 510 471 individuals in our final analysis.

Follow-up and endpoint assessment

To obtain information on cancer diagnoses, date of death (for all cohorts) and date of migration (not available for the VHM&PP), each cohort was linked to their respective national Cancer Registry, Cause of Death Registry, and Population Registry. Cancer incidence, death and migration information was followed until December 31, 2012 for the Norwegian cohorts and until December 31, 2014 in all other cohorts. Incident cancers were grouped into relevant cancer types according to the International Classification of Diseases, seventh and tenth revision (ICD-7, ICD-10). We investigated those cancer sites where the evidence of association to BMI is strong or highly suggestive according to the current viewpoint of the IARC working group[6] and a recent umbrella review[7]: oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, pancreas, endometrium, ovary, breast (postmenopausal; defined as cancers diagnosed at the age of 60 years and older[22]), and kidney (renal cell carcinoma). Participants were followed from one year after study entry until the earliest of first cancer diagnosis (any site, including those not investigated here), death, emigration, or end of follow-up.

Statistical analysis

In our statistical analysis, we used baseline values measured at the first health examination as exposure and adjusting variables. We tabulated baseline characteristics both overall, and stratified by TyG index quintiles. In a linear model, we regressed TyG index on BMI, adjusting for baseline age, sex, smoking status, fasting status, cohort, and decade of birth. We estimated hazard ratios (HRs) for TyG index levels with risk of incident cancer using Cox proportional hazards regression models adjusted for baseline age, sex, smoking status, fasting status, cohort, decade of birth, and with and without adjustment for BMI category according to the WHO classification[23], using age as the underlying time variable, with entry time defined as the participant's age one year after baseline, and exit time as the earliest of first cancer diagnosis (any site, including those not investigated here), death, emigration, or end of follow-up. To calculate p-values for trend over quintiles (with cut-off levels determined separately for each sex, cohort, and fasting time category), the Wald test of a linear association of a value's quintile (1-5) with cancer risk was used. Interaction effects between sex and TyG index were evaluated by including the respective multiplicative term in the Cox models.

To assess mediation and to estimate total, direct, and indirect effects between BMI, TyG index levels and cancer risk, we used the 2-stage regression method proposed by VanderWeele[24]. First, we fitted a linear regression model for the mediator TyG index, conditional on the exposure BMI and covariates baseline age, sex, smoking status, fasting status, cohort, and decade of birth. Secondly, we fitted a Cox proportional hazards regression model for cancer risk on BMI, TyG index, and the same covariates as in the model above. Finally, we estimated the desired effects combining the coefficients of these two regression models as described by VanderWeele[24].

This method is developed in the counterfactual framework and gives estimates of the natural direct and natural indirect effects which allow for decomposition of the total effect into natural direct and indirect effects. In the context of our main analysis estimating risk changes per 5 kg/m^2 increase in BMI, the natural direct effect hazard ratio compares the cancer risk in

individuals showing a certain reference BMI with individuals whose BMI is 5 kg/m^2 higher, if, also in the group with the higher BMI, the TyG index had been set to the level that would have been observed if the individuals had the reference BMI. The natural indirect effect hazard ratio quantifies the change in cancer risk in individuals if the TyG index would have been changed from the level which was actually observed to the level which would have been observed if the individuals had a 5 kg/m^2 lower BMI. Detailed definitions of these effects can be found elsewhere[25,26].

Since we found no interaction between BMI and TyG index (**Table S1**, column 2), we did not include exposure-mediator interaction terms in our final models. The contribution of the natural indirect effect to the total effect of BMI was calculated on the ln(HR) scale since HRs are additive on this scale. Ninety-five percent confidence intervals (CIs) were computed by stratified bootstrap using 2000 replications with strata for sex, smoking status, fasting status, cohort, and decade of birth. We assessed mediation by treating BMI both as a continuous and a categorical variable (according to the WHO classification underweight (BMI<18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), and obesity (BMI≥30.0)). We repeated this analysis restricted to individuals with a fasting status of 8h or more, and to individuals free of diabetes at baseline (*i.e.* self-report to be non-diabetic and glucose value in the normal range). For female VHM&PP participants, data on hysterectomies were available. As sensitivity analysis, we repeated the analysis for endometrial cancer in the VHM&PP cohort, excluding women undergoing a hysterectomy before baseline or within 12 months after baseline, and treating hysterectomy as a censoring event. In models including BMI as a linear term, we restricted analyses to participants with a BMI≥18.5 (*i.e.* no underweight) since the assumption of a log-linear association of BMI with cancer risk was violated in the underweight range for some cancer sites.

We checked if the proportional hazards assumption was fulfilled for the Cox regression models, by calculating the Pearson correlation coefficient between transformed survival time and the scaled Schoenfeld residuals. Only for cancers of the colon and rectum we detected deviations of proportional hazards for the variable sex. **Table S2** shows analyses for males

and females separately. Although total effects of BMI were larger for men than for women (a finding already reported by Bhaskaran et al.[5]), the proportion mediated was similar to the results of our main analysis.

To provide valid estimates of the natural direct and indirect effects, the method we used requires as a first assumption that the outcome is relatively rare (*i.e.* cumulative incidence ≤15%). In our study, the cumulative incidence of all cancers investigated combined was about 12%, and much less for single cancer sites. Secondly, it relies on four non-confounding assumptions; we have to assume that there is no unmeasured confounding of (i) the exposure-mediator, (ii) the exposure-outcome, and (iii) the mediator-outcome association; finally, for effects to be identifiable, we have to assume that (iv) there is no exposure-induced mediator-outcome confounding at all (even if known and measured, natural effects cannot be identified)[26–28].

In particular, the "cross-world counterfactual independence" assumption, which denies exposure-induced mediator-outcome confounding, has to be met[26,28,29]. In contrast to the natural direct effect, this assumption is not required for estimation of the controlled direct effect[28]. Therefore, we also calculated controlled direct effects to verify the robustness of our results. This was done by fixing the mediator (TyG index) at certain values (specifically the first quartile, the median, and the third quartile) and estimating controlled direct effects for these values of the mediator in models allowing for exposure-mediator interaction[26,30]. HRs of controlled direct effects were comparable to natural direct effects for all cancer sites investigated (**Table S1**).

Finally, we compared associations of BMI with cancer risk (conditioning on the same covariates as listed above), both adjusted and unadjusted for TyG index, also known as the difference method for mediation analysis[31].

All analyses were conducted in R, version 3.4.0[32].

RESULTS

Study population

Out of a total of 510 471 study participants, 213 372 (41.8%) individuals originated from the Norwegian cohorts, 173 538 (34.0%) from the Austrian cohort, and 123 561 (24.2%) from the Swedish cohorts. The mean age at baseline was 43.1 (SD = 10.6) years, and 257 968 (50.5%) individuals were males. Mean (SD) values of BMI [kg/m^2], glucose [mmol/l], triglycerides [mmol/l], and the TyG index [ln(mg^2/(2*dl^2))] were 25.2 (4.0), 5.3 (1.2), 1.6 (1.1), and 8.6 (0.6), respectively (**Table 1**).

Over a median follow-up time of 17.2 years (*i.e.* a total of 9 735 122 person-years), 16 052 obesity-related cancers were recorded.

TyG index and baseline characteristics

Table 2 shows the distribution of BMI, sex, baseline age, smoking status, and fasting status, stratified by quintiles of TyG index. TyG index and BMI showed a positive linear association. An increase in BMI of 5 kg/m^2 was associated with a 0.24 unit increase in TyG index (R^2=0.26) after adjustment for relevant covariates.

TyG index and risk of cancer

When TyG index was treated as a linear term in the statistical model (**Table 3**, columns 3 to 4), TyG index was associated with the risk of incident cancer of the kidney (renal cell) (hazard ratio (HR) per one standard deviation increase 1.13, 95% CI: 1.07 to 1.20), liver (1.13, 1.04 to 1.23), pancreas (1.12, 1.06 to 1.19), colon (1.07, 1.03 to 1.10), and rectum (1.09, 1.04 to 1.14), adjusting for relevant confounders including BMI (Model 2). The corresponding HR for the combination of cancers of all digestive organs (oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, and pancreas) was 1.09 (1.06 to 1.11). Sex did not modify the association of TyG index with risk of cancer for any site. However, there was a trend towards an interaction (p=0.064) for pancreatic cancer (HR in males: 1.08 (1.00 to 1.16), HR in females: 1.19 (1.09 to 1.31)). For cancers of the female reproductive organs, *i.e.* endometrium, ovary, and breast (postmenopausal; *i.e.* age at cancer diagnosis ≥60 years), no linear associations

of TyG index with risk could be observed, neither individually, nor combined (1.03, 0.99 to 1.06). The quintile analyses of the association between TyG index and cancer risk (**Table 3**, columns 5 to 10) provided similar results, with small discrepancies for cancers of the liver and endometrium.

BMI and risk of cancer mediated by TyG index

As expected, BMI was associated with an increased risk of all investigated cancer sites (**Table 4**). For cancers of the colon, breast (postmenopausal), endometrium, and kidney (renal cell), the increase in risk with rising BMI was monotonic over all BMI categories, while the other cancer forms revealed a J-shaped association with BMI, with normal weight being associated with the lowest risk (**Table 5**).

When including BMI as a linear term (per 5 kg/m² increase) in mediation analyses adjusted for relevant confounders and restricted to individuals with BMI values ≥18.5 (**Table 4**), substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas (42% of a total effect (HR, per 5 kg/m² increase) of 1.11 (1.03 to 1.20)), rectum (34% of a total effect of 1.09 (1.03 to 1.15)), colon (20% of a total effect of 1.14 (1.10 to 1.19)), and cancers of all digestive organs combined (22% of a total effect of 1.16 (1.13 to 1.19)). Smaller proportions where mediated for cancers of the kidney (renal cell) (15% of a total effect of 1.36 (1.27 to 1.44)) and the liver (11% of a total effect of 1.48 (1.33 to 1.63)). For adenocarcinomas of the oesophagus and cancers of the gallbladder – the two cancer types with the lowest number of cases - the proportions mediated were 7% of a total effect of 1.48 (1.23 to 1.73) and 16% of a total of 1.30 (1.14 to 1.46), respectively, with the null effect contained in the 95% CIs for proportions mediated, however. Results were similar for men and women with the exception of pancreatic cancer (proportion mediated in males: 20% of a total effect of 1.17 (1.05 to 1.31), proportion mediated in females: 91% of a total effect of 1.07 (0.97 to 1.17)). The effect of BMI on cancer risk was mediated by TyG index to a much lesser degree (specifically, natural indirect effects ≤1.01) for cancers of the female reproductive organs (*i.e.* breast

(postmenopausal), endometrium, ovary,). **Figure 1** illustrates the different mediation patterns for gastrointestinal cancers vs. cancers of the female reproductive organs.

When including BMI as a categorical term according to the WHO classification in the mediation analyses (**Table 5**), increased cancer risk of overweight and obese individuals was mediated by TyG index for cancers of the rectum, pancreas, colon, kidney (renal cell), and liver. The increased risk of underweight (BMI<18.5) was not mediated by TyG index.

Additionally, we restricted our analyses to individuals with a fasting status of 8h or more, and to participants who reported to be free of diabetes at baseline. The results were similar to our findings in the full study population (**Tables S3** and **S4**). Incorporating data on hysterectomies in the analysis for endometrial cancer in the VHM&PP cohort, left the results virtually unchanged (HRs of 1.50 (1.36 to 1.66), 1.03 (1.00 to 1.07), and 1.46 (1.31 to 1.61) for total, natural indirect, and direct effects when ignoring information on hysterectomies vs. HRs of 1.51 (1.36 to 1.65), 1.03 (1.00 to 1.07), and 1.46 (1.31 to 1.62) when treating hysterectomy as censoring event).

The findings of the mediation analysis were confirmed in separate analyses using the traditional difference method for mediation analysis. **Table S5** shows that additionally adjusting for TyG index noticeably attenuated the association of BMI with cancers of the oesophagus, colon, rectum, liver, gallbladder, pancreas, and kidney, while this was not the case for the association of BMI with cancers of the endometrium, ovary, and breast (postmenopausal).

DISCUSSION

In this large prospective cohort study, TyG index was associated with cancers of the digestive organs (colon, rectum, liver, and pancreas) and the kidney (renal cell), and a substantial fraction of the effect of BMI on cancer risk was mediated by the TyG index. In contrast, such mediation was not observed for cancers of the female reproductive organs (endometrium, ovary, and breast (postmenopausal)). While for both triglycerides and glucose, associations with cancer risk have been demonstrated[33–36], attempts to relate the TyG index,

a surrogate measure for insulin resistance, to cancer risk, have to our knowledge never been undertaken before.

Which biological mechanisms link excess body weight with cancer risk is debated[9–11]. Obesity results in alterations in sex hormone metabolism, chronic (subclinical) inflammation, and increased circulating insulin levels, the latter of which results in increased levels of free or bioactive IGF1. All these three consequences of obesity are known to induce mechanisms that promote carcinogenesis. According to the sex hormone hypothesis, the insulin-IGF hypothesis, and the inflammation and adipokine hypothesis, these pathways are mediators in the association of increased BMI with cancer risk[11]. However, the exact contributions of these three pathways to the positive association of BMI and cancer risk among different cancer sites are still incompletely understood.

Considering that TyG index has been shown to be a valid surrogate measure of insulin resistance with a validity comparable to the frequently used HOMA insulin resistance index[19], treating the TyG index as a mediator in the association of BMI with cancer risk seems biologically plausible. Our results support the insulin-IGF hypothesis for cancers of the digestive organs and the kidney; in particular when considering that (i) reducing complex conditions to single measures (as introduced by capturing insulin resistance by the TyG index) and (ii) using only one measurement at a single time-point in life, thereby ignoring whole lifetime trajectories (and thus cumulative effects), in general lead to an underestimation of indirect effects[26,37], which would mean that the true contribution of the insulin-IGF pathway to the BMI effect on cancer risk is likely even higher. On the other hand, the near absence of any mediation through TyG index for cancers of the female reproductive organs provides an indirect support of the sex hormone hypothesis for these cancers.

Most of our results are in line with existing literature[9–12]. However, for breast and endometrial cancer, associations of fasting insulin levels and HOMA-IR score with cancer risk have been reported[13,14,38,39], in contrast to our results utilizing the TyG index as a measure of insulin resistance. Reasons for these discrepancies might be that the TyG index captures different aspects of insulin resistance than insulin or HOMA-IR, and, particularly, that there are

marked differences in the age distribution of the study cohorts at baseline. In the studies of Hvidtfeldt et al.[13] and Gunter et al.[14] on postmenopausal breast cancer and Gunter at al. on endometrial cancer[38], using data of the Women's Health Initiative, the median age at measurement of insulin and HOMA-IR was beyond 65 years, whereas in our study the median age at measurement of TyG index was 41.5 years. This huge age difference combined with differently selected populations makes a comparison between these studies very difficult. In addition, regarding postmenopausal breast cancer, the age cut-off (we defined cancer occurring at 60 years and later as postmenopausal) is crucial for the strength of the association of breast cancer risk with obesity.

Strengths of this study include the large sample size from six European population-based cohorts, long follow-up and use of national cancer registries ensuring a virtually complete capture of cancer cases. Furthermore, in our study we applied a new analytic tool for estimating mediating effects originating from the counterfactual framework. Traditional approaches to mediation analysis typically involve the comparison of Cox models with and without adjustment for the mediator. Such an approach is limited, most importantly because the estimates do not have a causal interpretation and are not mathematically consistent[26,40]. Although the new counterfactual approaches are greatly preferably to the traditional ones, for the purpose of comparison, we also performed such a traditional analysis and obtained very similar results.

Limitations of our study include the lack or limited availability of complete data on covariates other than the ones included in the analyses that potentially may have influenced the results, like information on lipid-lowering and/or antidiabetic medication, alcohol consumption, physical activity, and female reproductive factors such as parity, age at first birth, or postmenopausal hormone therapy. Furthermore, we did not have measurements of parameters of inflammation. Since evidence suggests that obesity-induced inflammation might be one of the underlying mechanisms of insulin resistance in obese individuals[41,42], not having taken the confounding effect of inflammation into account might have led to an overestimation of the estimated indirect effect through the insulin resistance pathway.

Other limitations are the different protocols for measurement of triglycerides and glucose applied in the single cohorts, the lack of information on abdominal obesity, body shape, or body fat proportion, and insufficiently detailed data to investigate potentially important differences between cancer subtypes (e.g. breast cancer by receptor status[43], microsatellite stable vs. instable colorectal cancer[44]). Different composition of subtypes could explain slightly different effect estimates of BMI for these cancers in our study compared to other literature[5,6]. For liver cancer, the lower prevalence of hepatitis in our study region, a strong risk factor for liver cirrhosis and liver cancer, may explain why we observed quite a strong association of obesity with risk of liver cancer compared to other sources[5,8].

We did not include further obesity-related cancer sites, such as lymphoma or leukemia[5,8], into our analyses because insulin resistance as a biological mechanism has been predominately discussed for gastrointestinal cancers and cancers of the female reproductive organs[11].

In conclusion, we showed that a higher TyG index is associated with increased risk of cancers of the digestive organs (colon, rectum, liver, and pancreas) and the kidney (renal cell), and that a substantial fraction of the effect of increased BMI on the risk of these cancers can be explained via the TyG index pathway. In contrast, this does not hold true for obesity-related cancers of the female reproductive organs (endometrium, ovary, and breast (postmenopausal)). As TyG index is indicative of insulin resistance, our findings support the insulin-IGF hypothesis for cancers of the digestive organs and the kidney; *i.e.* insulin and potentially IGFs may be important pathways through which obesity affects cancer risk.

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CONFLICT OF INTEREST DISCLOSURES

No conflicts of interest to declare.

REFERENCES

1. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington DC: AICR, 2007.

2. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;335:1134.

3. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569-578.

4. Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol* 2015;16:36-46.

5. Bhaskaran K, Douglas I, Forbes H, Dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5 24 million UK adults. *Lancet* 2014;384:755-765.

6. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer — Viewpoint of the IARC Working Group. *N Engl J Med* 2016;375:794-798.

7. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ* 2017;356:j477.

8. Fang X, Wei J, He X, et al. Quantitative association between body mass index and the risk of cancer: A global Meta-analysis of prospective cohort studies. *Int J Cancer* 2018;143:1595-1603.

9. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4:579-591.

10. Renehan AG, Roberts DL, Dive C. Obesity and cancer: Pathophysiological and biological mechanisms. *Arch Physiol Biochem* 2008;114:71-83.

11. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. *Nat Rev Cancer* 2015;15:484-498.

12. 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;68:329-337.

13. Hvidtfeldt UA, Gunter MJ, Lange T, et al. Quantifying Mediating Effects of Endogenous Estrogen and Insulin in the Relation between Obesity, Alcohol Consumption, and Breast Cancer. *Cancer Epidemiol Biomarkers Prev* 2012;21:1203-1212.

14. Gunter MJ, Xie X, Xue X, et al. Breast Cancer Risk in Metabolically Healthy but Overweight Postmenopausal Women. *Cancer Res* 2015;75:270-274.

15. Schairer C, Fuhrman BJ, Boyd-Morin J, et al. Quantifying the Role of Circulating Unconjugated Estradiol in Mediating the Body Mass Index-Breast Cancer Association. *Cancer Epidemiol Biomarkers Prev* 2016;25:105-113.

16. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The Product of Fasting Glucose and Triglycerides As Surrogate for Identifying Insulin Resistance in Apparently Healthy Subjects. *Metab Syndr Relat Disord* 2008;6:299-304.

17. Abbasi F, Reaven GM. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides × glucose versus triglyceride/high-density lipoprotein cholesterol. *Metabolism* 2011;60:1673-1676.

18. Er LK, Wu S, Chou HH, et al. Triglyceride Glucose-Body Mass Index Is a Simple and Clinically Useful Surrogate Marker for Insulin Resistance in Nondiabetic Individuals. *PLoS One* 2016;11:e0149731.

19. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, et al. The Product of Triglycerides and Glucose, a Simple Measure of Insulin Sensitivity. Comparison with the Euglycemic-Hyperinsulinemic Clamp. *J Clin Endocrinol Metab* 2010;95:3347-3351.

20. Stocks T, Borena W, Strohmaier S, et al. Cohort Profile: The Metabolic syndrome and Cancer project (Me-Can). *Int J Epidemiol* 2009;39:660-667.

21. D'Orazio P, Burnett RW, Fogh-Andersen N, et al. Approved IFCC recommendation on reporting results for blood glucose. *Clin Chem Lab Med* 2006;44:1486-1490.

22. Bjorge T, Lukanova A, Jonsson H, et al. Metabolic Syndrome and Breast Cancer in the Me-Can (Metabolic Syndrome and Cancer) Project. *Cancer Epidemiol Biomarkers Prev* 2010;19:1737-1745.

23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157-163.

24. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology* 2012;22:582-585.

25. Pearl J. Direct and Indirect Effects. In: Proceedings of the Seventeenth Conference on Uncertainty and Artificial Intelligence, MIRA Digital Publishing, Brentwood, MO, 2005, pp. 1572e1581 (Technical report R-273).

26. VanderWeele TJ. *Explanation in Causal Inference: Methods for Mediation and Interaction*. 1st ed. New York: Oxford University Press; 2015.

27. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. *Annu Rev Public Health* 2016;37:17-32.

28. Vansteelandt S, Daniel RM. Interventional Effects for Mediation Analysis with Multiple Mediators. *Epidemiology* 2017;28:258-265.

29. VanderWeele TJ. A unification of mediation and interaction: a 4-way decomposition. *Epidemiology* 2014;25:749-761.

30. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol* 2010;172:1339-1348.

31. Judd CM, Kenny DA. Process Analysis: Estimating Mediation in Treatment Evaluations. *Eval Rev* 1981;5:602-619.

32. R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria; 2013.

33. Stocks T, Rapp K, Bjørge T, et al. Blood Glucose and Risk of Incident and Fatal Cancer in the Metabolic Syndrome and Cancer Project (Me-Can): Analysis of Six Prospective Cohorts. *PLoS Med* 2009;6:e1000201.

34. Crawley DJ, Holmberg L, Melvin JC, et al. Serum glucose and risk of cancer: a meta-analysis. *BMC Cancer* 2014;14:985..

35. Borena W, Stocks T, Jonsson H, et al. Serum triglycerides and cancer risk in the metabolic syndrome and cancer (Me-Can) collaborative study. *Cancer Causes Control* 2011;22:291-299.

36. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic Syndrome and Risk of Cancer: A systematic review and meta-analysis. *Diabetes Care* 2012;35:2402-2411.

37. VanderWeele TJ, Valeri L, Ogburn EL. The role of measurement error and misclassification in mediation analysis. *Epidemiology* 2012;23:561-564.

38. Gunter MJ, Hoover DR, Yu H, et al. A Prospective Evaluation of Insulin and Insulin-like Growth Factor-I as Risk Factors for Endometrial Cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:921-929.

39. Hernandez AV, Pasupuleti V, Benites-Zapata VA, Thota P, Deshpande A, Perez-Lopez FR. Insulin resistance and endometrial cancer risk: A systematic review and meta-analysis. *Eur J Cancer* 2015;51:2747-2758.

40. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Int J Epidemiol* 2002;31:163-165.

41. Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? *Curr Opin Endocrinol Diabetes Obes* 2012;19:81-87.

42. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell* 2011;144:646-674.

43. Ritte R, Lukanova A, Berrino F, et al. Adiposity, hormone replacement therapy use and breast cancer risk by age and hormone receptor status: a large prospective cohort study. *Breast Cancer Res* 2012;14:R76.

44. Campbell PT, Jacobs ET, Ulrich CM, et al. Case-Control Study of Overweight, Obesity, and Colorectal Cancer Risk, Overall and by Tumor Microsatellite Instability Status. *J Natl Cancer Inst* 2010;102:391-400.

FIGURE LEGEND

Figure 1. Total, natural indirect (TyG mediated), and direct effects of continuous BMI on cancer risk of digestive organs (oesophagus, colon, rectum, liver, gallbladder, and pancreas) vs. female reproductive organs (endometrium, ovary, and breast (postmenopausal))

HR = hazard ratio; BMI = body mass index.

Supplementary Material

The triglyceride-glucose index as a measure of insulin resistance and risk of obesity-related cancers

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Table S1. Comparison of natural direct and controlled direct effects of continuous BMI on cancer risk, stratified by cancer site

Site (ICD-7; ICD-10)	Interaction term BMI*TyG index HR (95% CI)*	Total effect† HR (95% CI)	Natural direct effect† HR (95% CI)	Controlled direct effect with TyG index fixed at Q1 HR (95% CI)*	Controlled direct effect with TyG index fixed at median value HR (95% CI)*	Controlled direct effect with TyG index fixed at Q3 HR (95% CI)*
Oesophagus (adenocarcinoma‡) (150; C15)	1.07 (0.91 to 1.26)	1.48 (1.23 to 1.73)	1.44 (1.20 to 1.70)	1.33 (1.04 to 1.68)	1.38 (1.13 to 1.67)	1.45 (1.20 to 1.70)
Colon (153; C18)	1.01 (0.97 to 1.05)	1.14 (1.10 to 1.19)	1.11 (1.07 to 1.16)	1.10 (1.04 to 1.17)	1.11 (1.06 to 1.16)	1.11 (1.07 to 1.16)
Rectum (154; C19-21)	1.00 (0.95 to 1.05)	1.09 (1.03 to 1.15)	1.06 (1.00 to 1.12)	1.06 (0.98 to 1.14)	1.06 (0.99 to 1.12)	1.06 (0.99 to 1.12)
Liver (155.0; C22)	1.05 (0.97 to 1.15)	1.48 (1.33 to 1.63)	1.42 (1.27 to 1.57)	1.33 (1.17 to 1.52)	1.38 (1.23 to 1.52)	1.43 (1.28 to 1.57)
Gallbladder (155.1-155.3; C23-24)	0.92 (0.81 to 1.05)	1.30 (1.14 to 1.46)	1.25 (1.09 to 1.42)	1.35 (1.12 to 1.60)	1.28 (1.11 to 1.46)	1.21 (1.05 to 1.37)
Pancreas (157; C25)	1.00 (0.94 to 1.07)	1.11 (1.03 to 1.20)	1.06 (0.99 to 1.15)	1.06 (0.96 to 1.17)	1. 06 (0.97 to 1.15)	1. 06 (0.98 to 1.15)
Pancreas - males	0.97 (0.87 to 1.07)	1.17 (1.05 to 1.31)	1.14 (1.01 to 1.29)	1.19 (1.00 to 1.39)	1.16 (1.01 to 1.33)	1.13 (0.99 to 1.27)
Pancreas - females	1.02 (0.93 to 1.12)	1.07 (0.97 to 1.17)	1.01 (0.90 to 1.11)	0.99 (0.87 to 1.13)	1.00 (0.90 to 1.10)	1.01 (0.91 to 1.12)
Breast (postmenopausal) (170; C50)	0.98 (0.94 to 1.02)	1.05 (1.01 to 1.09)	1.04 (1.00 to 1.09)	1.06 (1.01 to 1.12)	1.05 (1.00 to 1.09)	1.03 (0.98 to 1.08)
Endometrium (172; C54)	1.03 (0.98 to 1.08)	1.50 (1.43 to 1.57)	1.49 (1.41 to 1.57)	1.45 (1.36 to 1.56)	1.48 (1.40 to 1.56)	1.51 (1.42 to 1.59)
Ovary (175.0; C56)	1.02 (0.94 to 1.10)	1.05 (0.96 to 1.13)	1.06 (0.97 to 1.15)	1.04 (0.94 to 1.15)	1.05 (0.96 to 1.14)	1.07 (0.96 to 1.16)
Kidney (renal cell) (180.0, 180.9; C64)	0.99 (0.93 to 1.05)0.	1.36 (1.27 to 1.44)	1.30 (1.21 to 1.38)	1.32 (1.19 to 1.1.44)	1.30 (1.21 to 1.40)	1.29 (1.21 to 1.39)
Digestive organs combined§	1.01 (0.98 to 1.04)	1.16 (1.13 to 1.19)	1.12 (1.09 to 1.16)	1.11 (1.07 to 1.15)	1.12 (1.08 to 1.15)	1.12 (1.09 to 1.16)
Endometrium, ovary and breast (postmenopausal) combined	1.01 (0.98 to 1.04)	1.16 (1.13 to 1.20)	1.16 (1.12 to 1.19)	1.15 (1.11 to 1.20)	1.16 (1.12 to 1.19)	1.16 (1.12 to 1.20)

* HRs (per 5 kg/m² increase for BMI; per 5 kg/m^2 * 1 SD of TyG index for the interaction term BMI*TyG index) from Cox models regressing cancer risk on BMI, TyG index, the multiplicative interaction term BMI* TyG index, baseline age, sex, smoking status, cohort, and decade of birth, with attained age as the underlying time scale. Analyses were restricted to participants with a BMI≥18.5 (i.e. no underweight). TyG index Q1 was at 8.18 ln(mg²/(2*dl²)). TyG index median was at 8.55 ln(mg²/(2*dl²)). TyG index Q3 was at 8.98 ln(mg²/(2*dl²)).

†HRs (per 5 kg/m² increase) were estimated according to the 2-stage regression method proposed by VanderWeele, adjusted for baseline age, sex, smoking status, cohort, and decade of birth, with attained age as the underlying time scale. Analyses were restricted to participants with a BMI≥18.5 (i.e. no underweight).

‡Adenocarcinomas were identified via information on morphology (ICD-O-3 morphologic key).

§Digestive organs combined include the following sites: oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, and pancreas.

HR = hazard ratio; BMI = body mass index; CI = confidence interval; ICD = International Classification of Diseases; SD – standard deviation; Q1 – first quartile; Q3 – third quartile.

Table S2: Decomposition of the total effect of continuous BMI on cancer risk into natural direct and indirect effect mediated by the TyG index for cancers of the colon, cancers of the rectum, and cancers of the digestive organs combined, separately for males and females

Site (ICD-7; ICD-10)	Total effect† HR (95% CI)	Natural indirect effect† HR (95% CI)	Natural direct effect† HR (95% CI)	Proportion mediated (95% CI)
Colon (153; C18) - males	1.23 (1.15 to 1.30)	1.04 (1.02 to 1.06)	1.18 (1.10 to 1.26)	19.3% (8.2% to 34.8%)
Colon (153; C18) - females	1.09 (1.03 to 1.14)	1.02 (1.00 to 1.03)	1.07 (1.02 to 1.13)	17.5% (-7.0% to 58.4%)
Rectum (154; C19-21) - males	1.12 (1.03 to 1.20)	1.03 (1.00 to 1.06)	1.08 (0.99 to 1.17)	28.5% (2.3% to 100%)
Rectum (154; C19-21) - females	1.09 (1.01 to 1.18)	1.04 (1.01 to 1.07)	1.05 (0.96 to 1.14)	46.6% (7.5% to 100%)
Digestive organs combined‡ - males	1.23 (1.18 to 1.28)	1.04 (1.02 to 1.05)	1.19 (1.14 to 1.23)	17.4% (10.0% to 26.5%)
Digestive organs combined‡ - females	1.11 (1.07 to 1.15)	1.03 (1.02 to 1.05)	1.08 (1.03 to 1.12)	30.4% (17.5% to 53.0%)

†HRs (per 5 kg/m² increase) were estimated according to the 2-stage regression method proposed by VanderWeele, adjusted for baseline age, smoking status, fasting status, cohort, and decade of birth, with attained age as the underlying time scale. Analyses were restricted to participants with a BMI≥18.5 (i.e. no underweight).

‡Digestive organs combined include the following sites: oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, and pancreas.

HR = hazard ratio; BMI = body mass index; CI = confidence interval; ICD = International Classification of Diseases.

Table S3. Risk of cancer by TyG index and decomposition of the total effect of continuous BMI on cancer risk into natural direct and indirect effect mediated by the TyG index, stratified by cancer site, restricted to individuals with a fasting status of 8h or more (N=300 121)

Site (ICD-7; ICD-10)	HR of TyG index (per 1 SD increase) (95% CI)*	Total effect of BMI† HR (95% CI)	Natural indirect effect of BMI† HR (95% CI)	Natural direct effect of BMI† HR (95% CI)	Proportion mediated (95% CI)‡
Oesophagus (adenocarcinoma§) (150; C15)	1.03 (0.85 to 1.26)	1.23 (0.98 to 1.52)	1.00 (0.94 to 1.08)	1.23 (0.96 to 1.51)	-
Colon (153; C18)	1.08 (1.03 to 1.13)	1.11 (1.05 to 1.16)	1.03 (1.01 to 1.05)	1.07 (1.02 to 1.13)	30.5% (12.9% to 67.3%)
Rectum (154; C19-21)	1.12 (1.06 to 1.19)	1.11 (1.03 to 1.18)	1.04 (1.02 to 1.06)	1.06 (0.99 to 1.14)	38.9% (15.0% to 100%)
Liver (155.0; C22)	1.12 (1.02 to 1.24)	1.49 (1.33 to 1.64)	1.04 (1.00 to 1.08)	1.44 (1.28 to 1.59)	9.7% (-0.3% to 20.5%)
Gallbladder (155.1-155.3; C23-24)	1.11 (0.97 to 1.27)	1.26 (1.09 to 1.43)	1.04 (0.99 to 1.10)	1.21 (1.04 to 1.38)	18.1% (-5.6% to 62.9%)
Pancreas (157; C25)	1.12 (1.04 to 1.21)	1.13 (1.03 to 1.24)	1.04 (1.01 to 1.07)	1.09 (0.99 to 1.20)	29.3% (6.2% to 100%)
Pancreas - males	1.08 (0.98 to 1.19)	1.16 (1.00 to 1.34)	1.03 (0.97 to 1.08)	1.13 (0.97 to 1.31)	17.0% (-38.3% to 100%)
Pancreas - females	1.18 (1.06 to 1.32)	1.12 (0.99 to 1.23)	1.05 (1.01 to 1.09)	1.06 (0.94 to 1.19)	-
Breast (postmenopausal) (170; C50)	1.03 (0.99 to 1.08)	1.06 (1.02 to 1.10)	1.01 (1.00 to 1.02)	1.05 (1.01 to 1.10)	15.8% (-8.5% to 70.8%)
Endometrium (172; C54)	1.08 (1.00 to 1.17)	1.46 (1.38 to 1.55)	1.02 (0.99 to 1.04)	1.44 (1.35 to 1.53)	4.6% (-2.0% to 11.0%)
Ovary (175.0; C56)	0.99 (0.89 to 1.10)	1.03 (0.94 to 1.14)	0.99 (0.96 to 1.02)	1.05 (0.94 to 1.15)	-
Kidney (renal cell) (180.0, 180.9; C64)	1.08 (1.01 to 1.16)	1.38 (1.27 to 1.48)	1.03 (1.00 to 1.06)	1.34 (1.24 to 1.45)	8.2% (-0.6% to 17.6%)
Digestive organs combined¶	1.10 (1.07 to 1.13)	1.15 (1.11 to 1.19)	1.04 (1.02 to 1.05)	1.11 (1.07 to 1.15)	24.8% (15.7% to 36.6%)
Endometrium, ovary and postmenopausal breast combined	1.04 (1.00 to 1.08)	1.14 (1.11 to 1.18)	1.01 (1.00 to 1.02)	1.13 (1.10 to 1.17)	6.2% (-2.4% to 15.4%)

*HRs were estimated in Cox proportional hazards models adjusted for BMI category, baseline age, sex, smoking status, cohort, and decade of birth, with attained age as the underlying time scale.

†HRs (per 5 kg/m² increase) were estimated according to the 2-stage regression method proposed by VanderWeele[15], adjusted for baseline age, sex, smoking status, cohort, and decade of birth, with attained age as the underlying time scale. Analyses were restricted to participants with a BMI≥18.5 (i.e. no underweight).

‡Proportion mediated not given in cases where the null-effect (*i.e.* 1) is contained in the 95% CI of the HR of the total effect.

§Adenocarcinomas were identified via information on morphology (ICD-O-3 morphologic key).

¶Digestive organs combined include the following sites: oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, and pancreas.

HR = hazard ratio; BMI = body mass index; CI = confidence interval; ICD = International Classification of Diseases.

Table S4. Risk of cancer by TyG index and decomposition of the total effect of continuous BMI on cancer risk into natural direct and indirect effect mediated by the TyG index, stratified by cancer site, restricted to individuals free of diabetes at baseline (N=323 911; participants of the VHM&PP cohort not included since information on diabetic status was not captured in the VHM&PP cohort)

Site (ICD-7; ICD-10)	HR of TyG index (per 1 SD increase) (95% CI)*	Total effect of BMI† HR (95% CI)	Natural indirect effect of BMI† HR (95% CI)	Natural direct effect of BMI† HR (95% CI)	Proportion mediated (95% CI)‡
Oesophagus (adenocarcinoma§) (150; C15)	1.18 (0.96 to 1.45)	1.59 (1.23 to 1.95)	1.05 (0.96 to 1.14)	1.51 (1.17 to 1.88)	10.1% (-10.1% to 35.7%)
Colon (153; C18)	1.09 (1.04 to 1.15)	1.16 (1.10 to 1.23)	1.04 (1.02 to 1.06)	1.12 (1.06 to 1.19)	23.1% (10.1% to 42.5%)
Rectum (154; C19-21)	1.06 (1.00 to 1.13)	1.09 (1.01 to 1.17)	1.02 (1.00 to 1.05)	1.06 (0.98 to 1.15)	27.6% (-8.6% to 100%)
Liver (155.0; C22)	1.15 (0.99 to 1.35)	1.42 (1.18 to 1.68)	1.04 (0.98 to 1.10)	1.36 (1.13 to 1.61)	12.0% (-6.6% to 35.2%)
Gallbladder (155.1-155.3; C23-24)	1.08 (0.91 to 1.28)	1.37 (1.14 to 1.61)	1.02 (0.96 to 1.10)	1.33 (1.10 to 1.59)	7.8% (-16.5% to 40.6%)
Pancreas (157; C25)	1.09 (1.01 to 1.19)	1.06 (0.95 to 1.16)	1.04 (1.01 to 1.07)	1.02 (0.91 to 1.12)	-
Pancreas – males	1.06 (0.96 to 1.17)	1.11 (0.94 to 1.28)	1.03 (0.98 to 1.07)	1.11 (0.94 to 1.28)	-
Pancreas - females	1.17 (1.01 to 1.35)	1.00 (0.86 to 1.14)	1.06 (1.01 to 1.12)	0.94 (0.81 to 1.07)	-
Breast (postmenopausal) (170; C50)	1.02 (0.95 to 1.08)	1.06 (1.00 to 1.11)	1.01 (0.98 to 1.03)	1.05 (0.99 to 1.11)	13.2% (-60.0% to 100%)
Endometrium (172; C54)	1.00 (0.92 to 1.09)	1.55 (1.45 to 1.65)	0.99 (0.96 to 1.02)	1.56 (1.45 to 1.67)	-2.3% (-9.3% to 3.5%)
Ovary (175.0; C56)	1.03 (0.93 to 1.14)	1.10 (0.99 to 1.21)	1.00 (0.97 to 1.04)	1.09 (0.98 to 1.21)	-
Kidney (renal cell) (180.0, 180.9; C64)	1.17 (1.08 to 1.28)	1.36 (1.23 to 1.49)	1.06 (1.02 to 1.10)	1.28 (1.16 to 1.41)	18.5% (7.6% to 34.1%)
Digestive organs combined¶	1.09 (1.05 to 1.12)	1.15 (1.11 to 1.19)	1.03 (1.02 to 1.05)	1.11 (1.07 to 1.16)	22.8% (13.1% to 36.6%)
Endometrium, ovary and postmenopausal breast combined	1.01 (0.97 to 1.06)	1.20 (1.16 to 1.25)	1.00 (0.99 to 1.02)	1.20 (1.15 to 1.25)	0.7% (-8.0% to 9.2%)

*HRs were estimated in Cox proportional hazards models adjusted for BMI category, baseline age, sex, smoking status, fasting status, cohort, and decade of birth, with attained age as the underlying time scale.

†HRs (per 5 kg/m² increase) were estimated according to the 2-stage regression method proposed by VanderWeele[15], adjusted for baseline age, sex, smoking status, fasting status, cohort, and decade of

1 birth, with attained age as the underlying time scale. Analyses were restricted to participants with a
2 BMI≥18.5 (i.e. no underweight).
3 ‡Proportion mediated not given in cases where the null-effect (*i.e.* 1) is contained in the 95% CI of the
4 HR of the total effect.
5 §Adenocarcinomas were identified via information on morphology (ICD-O-3 morphologic key).
6 ¶Digestive organs combined include the following sites: oesophagus (adenocarcinoma), colon, rectum,
7 liver, gallbladder, and pancreas.
8 HR = hazard ratio; BMI = body mass index; CI = confidence interval; ICD = International Classification
9 of Diseases.
10

Table S5: Associations of BMI with cancer risk, with and without adjusting for TyG index, stratified by cancer site

Site (ICD-7; ICD-10)	Adjusted HR (95% CI)† Model 1	Adjusted HR (95% CI)† Model 2 (with TyG index)
Oesophagus (adenocarcinoma‡) (150; C15)	1.48 (1.22 to 1.78)	1.44 (1.18 to 1.76)
Colon (153; C18)	1.14 (1.09 to 1.19)	1.11 (1.06 to 1.16)
Rectum (154; C19-21)	1.09 (1.04 to 1.15)	1.06 (1.00 to 1.12)
Liver (155.0; C22)	1.47 (1.34 to 1.62)	1.42 (1.28 to 1.57)
Gallbladder (155.1-155.3; C23-24)	1.29 (1.15 to 1.46)	1.25 (1.09 to 1.42)
Pancreas (157; C25)	1.11(1.04 to 1.19)	1.06 (0.99 to 1.15)
Pancreas - males	1.17 (1.05 to 1.31)	1.14 (1.01 to 1.28)
Pancreas - females	1.07 (0.97 to 1.17)	1.01(0.91 to 1.11)
Breast (postmenopausal) (170; C50)	1.05 (1.01 to 1.09)	1.04 (1.00 to 1.09)
Endometrium (172; C54)	1.50 (1.43 to 1.57)	1.49 (1.41 to 1.57)
Ovary (175.0; C56)	1.05 (0.97 to 1.13)	1.06 (0.97 to 1.15)
Kidney (renal cell) (180.0, 180.9; C64)	1.35 (1.27 to 1.44)	1.30 (1.21 to 1.39)
Digestive organs combined§	1.16 (1.12 to 1.19)	1.12 (1.09 to 1.15)
Endometrium, ovary and breast (postmenopausal) combined	1.16 (1.13 to 1.20)	1.16 (1.12 to 1.19)

Model 1: adjusted for baseline age, sex, smoking status, fasting status, cohort, and decade of birth.

Model 2: adjusted for the same variables as in Model 1, plus additionally for TyG index.

Analyses were restricted to participants with a BMI≥18.5 (i.e. no underweight).

†HRs for BMI were estimated in Cox proportional hazards models with attained age as the underlying time scale and are given per 5 kg/m² increase.

‡Adenocarcinomas were identified via information on morphology (ICD-O-3 morphologic key).

§Digestive organs combined include the following sites: oesophagus (adenocarcinoma), colon, rectum, liver, gallbladder, and pancreas.

HR = hazard ratio; BMI = body mass index; CI = confidence interval; ICD = International Classification of Diseases.