# Insulin resistance measured by the triglyceride-glucose index and risk of obesity-related cancers: An epidemiological investigation in more than 500,000 individuals.

**Metabolic Syndrome and Cancer Project**

http://me-can.se/

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## Background

Excess body weight is a major risk factor for many cancer forms [1]. Three biological candidate mechanisms mediating the association of excess body weight with cancer risk were proposed [2,3].

i. Increased bioavailability of steroid hormones and alterations in sex hormone metabolism.
ii. Adipokine pathophysiology and systemic (subclinical) inflammation.
iii. Insulin resistance and bioavailability of insulin-like growth factor I (IGF1) (**Figure 1**).

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. We aimed to determine to what extent insulin resistance, measured as the TyG index, mediates the effect of BMI on risk of obesity-related cancers, with a focus on gastrointestinal cancers and cancers of the female reproductive organs (gynecological cancers).

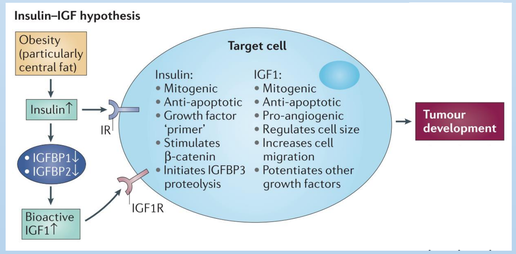


**Figure 1.** Biological mechanism of the insulin-IGF hypothesis. Adapted from [3].

## TyG index: A novel measure for insulin resistance

- ✓ The logarithmized product of fasting levels of triglycerides and glucose (denoted TyG index) has been suggested to be a simple measure of insulin resistance [4].
- ✓ Both lipotoxicity and glucotoxicity play crucial roles in insulin resistance modulation and are reflected in the TyG index.
- ✓ The TyG index is highly correlated with the euglycemic-hyperinsulinemic clamp test, and has validity similar to the frequently used homeostatic model assessment (HOMA) insulin resistance (IR) index [5].
- ✓ Due to its easy availability and cost-effectiveness, the TyG index is a promising surrogate measure for insulin resistance in large-scale epidemiological studies.

## Methods

A total of 510,471 individuals from six European cohorts (Me-Can project [6], http://me-can.se/, see graphic to the right) with a mean age of 43.1 years were included in the study. During a median follow-up of 17.2 years, 16,052 individuals developed obesity-related gastrointestinal and/or gynecologicial cancers.

We fitted Cox models, adjusted for relevant confounders, to investigate associations of TyG index with ten common obesity-related cancer sites, and quantified the proportion of the effect of BMI mediated through TyG index, using state-of-the-art mediation techniques according to VanderWeele [7].

**Table 1.** Baseline characteristics by quintiles of TyG index.

| | TyG index Quintile 1 (N=102,521) | Quintile 2 (N=102,020) | Quintile 3 (N=101,851) | Quintile 4 (N=101,954) | Quintile 5 (N=102,125) |
|---|---|---|---|---|---|
| **TyG index[1], mean (SD)** | 7.8 (0.2) | 8.3 (0.1) | 8.5 (0.1) | 8.9 (0.1) | 9.5 (0.4) |
| **TyG index[1], range** | <8.1 | 8.1 to 8.4 | 8.4 to 8.7 | 8.7 to 9.1 | >9.1 |
| **BMI categories** | | | | | |
| **<18.5 kg/m2** | 3,859 (3.8%) | 2,117 (2.1%) | 1,359 (1.3%) | 731 (0.7%) | 289 (0.3%) |
| **18.5 to 24.9 kg/m2** | 73,921 (72.1%) | 62,974 (61.7%) | 54,334 (53.3%) | 43,441 (42.6%) | 29,342 (28.7%) |
| **25 to 29.9 kg/m2** | 21,268 (20.7%) | 30,299 (29.7%) | 36,304 (35.6%) | 43,256 (42.4%) | 49,769 (48.7%) |
| **≥30.0 kg/m2** | 3,473 (3.4%) | 6,630 (6.5%) | 9,854 (9.7%) | 14,526 (14.2%) | 22,725 (22.3%) |
| **Sex, male** | 33,153 (32.3%) | 41,317 (40.5%) | 49,640 (48.7%) | 59,811 (58.7%) | 74,047 (72.5%) |
| **Age, yrs, mean (SD)** | 39.6 (11.0) | 42.8 (10.7) | 43.6 (10.7) | 44.4 (10.2) | 44.9 (9.4) |

[1]: TyG index calculated as ln[triglycerides (mg/dl) x blood glucose (mg/dl)/2].

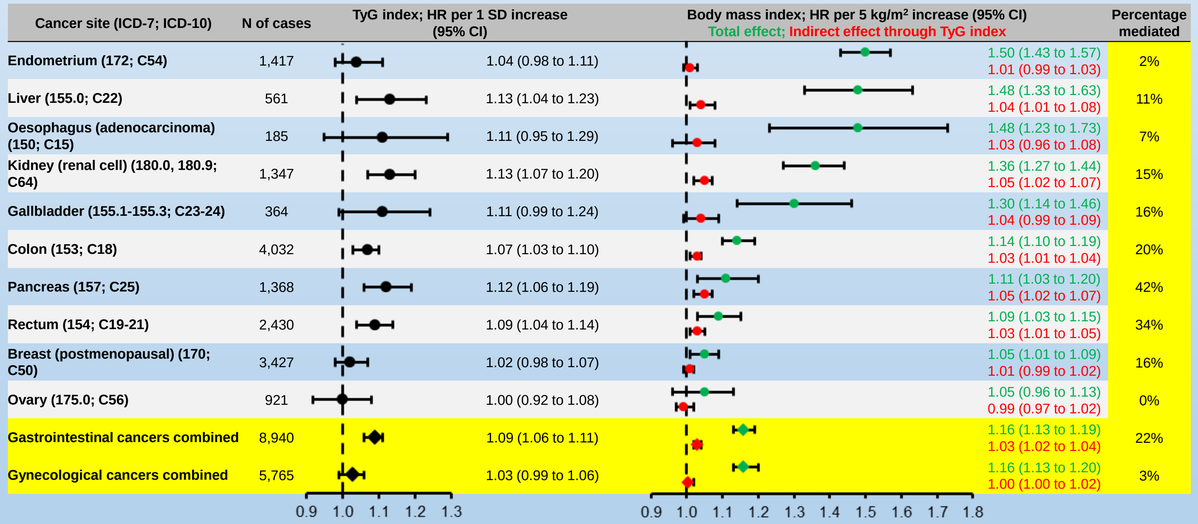


**Figure 2.** Effects of TyG index and BMI (total effect (in green) as well as indirect effect mediated through TyG index (in red)) on cancer risk, stratified by cancer site. All models adjusted for baseline age, sex, smoking status, fasting status, cohort, and decade of birth.

## Results

Distribution of baseline characteristics of our population across TyG index quintiles are shown in **Table 1**.

TyG index was markedly stronger associated with the risk of gastrointestinal cancers than gynecological cancers. As expected, BMI was associated with an increased risk of all investigated cancer sites. Substantial proportions of the effect of BMI were mediated by TyG index for cancers of the pancreas, rectum, and colon; smaller proportions for kidney and liver; none for endometrium, ovary and breast (postmenopausal). **Figure 2** summarizes our findings separately for all ten different cancer sites, as well as gastrointestinal and gynecological cancers combined.

**Further details will soon be published: Fritz J, Bjørge T, Nagel G, et al. The triglyceride-glucose index as a measure of insulin resistance and risk of obesity-related cancers. *Int J Epidemiol*. doi: 10.1093/ije/dyz053. [Epub ahead of print].**

## Conclusion and Key Messages

- ✓ In this pooled 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.

## References

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