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Review

Triglyceride-glucose index predicts independently type 2 diabetes mellitus risk: A systematic review and meta-analysis of cohort studies

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ABSTRACT

Objective: Our objective was to perform a systematic review and meta-analysis of cohort studies evaluating the triglyceride-glucose (TyG) index as a tool for type 2 diabetes (T2D) prediction in adults and older adults.
Methods: Studies were identified in PubMed, Cochrane, Scopus, and Lilacs. Studies with cohort design, which evaluated the T2D incidence through the hazard ratio (HR) or relative risk (RR) or odds ratio values were included. Were included both studies that evaluated the incidence of T2D from tertiles, quartiles, quintiles, or single TyG index values. First, a meta-analysis only for studies that reported data in HR values was performed. Additionally, given the different association measurements used, the number of T2D cases, non-T2D cases, and the total number of participants were extracted from exposed and non-exposed groups when available. Then the risk ratio was calculated. A meta-analysis using the inverse variance method and the random-effects model was performed. Heterogeneity was assessed by I^2 statistics and by inspecting funnel plots.
Results: Thirteen cohort studies with a total of 70,380 subjects, both sexes, adults, and older adults were included in the meta-analysis. Ten studies showed a significant association of the TyG index with T2D risk through HR estimative (overall HR: 2.44, 95% CI: 2.17–2.76). After estimating RR for nine studies, we also observed a significant association of the TyG index with T2D risk (RR: 3.12, 95 CI: 2.31–4.21). For all analyses, high heterogeneity was verified by I^2 and visual inspection of funnel plots.
Conclusions: TyG index has a positive and significant association with T2D risk, suggesting that the TyG index may become an applicable tool to identify subjects with T2D risk. However, due to the high heterogeneity observed in overall HR and RR analysis, more studies could be necessary to confirm these results.

Contents

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1. Introduction

Type 2 diabetes (T2D) is a non-communicable chronic disease with a high incidence in the world, which can lead to premature morbidity and mortality [1]. Currently, 422 million adults have diabetes [1] and the projections indicate an increase in the number for the year 2045, corresponding to 963 million people [2]. Due to the socio-economic impacts attributed to T2D with severe consequences for subjects, families, communities, and overloading health systems, developing measures to prevent and control T2D is one of the main challenges of the 21st century [3,4].

Insulin resistance (IR), a condition in which cells have reduced insulin responsiveness, is the origin of the metabolic alterations that lead to the development of T2D, cardiovascular diseases, metabolic syndrome, and other comorbidities [5,6]. Thus, the early diagnosis of IR is fundamental, since it allows the implementation of therapeutic strategies to prevent health complications [7]. However, the current IR assessment method like the *euglycemic-hyperinsulinemic clamp* (the gold standard method to IR diagnosis) is poorly applicable in the clinical practice and epidemiological studies because it requires a lot of time to execute and is quite expensive [8,9].

Given the role of the IR as a risk factor for T2D, efforts have been directed to understand the mechanisms to early detection of subjects with this condition as well as new methods for prediction and diagnostic of IR [5]. In this sense, the triglyceride-glucose index (TyG index), published in 2008, emerged as a tool to identify IR in apparently healthy subjects. The TyG index highlights for its low-cost because it uses accessible and routine biomarkers of clinical practice: fasting triglyceride (mg/dl) and fasting glucose (mg/dl) concentrations. Furthermore, the TyG index has a good especifity in relation to the *euglycemic-hyperinsulinemic clamp* [9].

Cohort studies have recently shown that the TyG index is associated with T2D risk [10,11,20–22,12–190]. However, no review has summarized and critically evaluated the relationship between the TyG index and the incidence of T2D, as far as we know at the moment. Therefore, we aimed to carry out a systematic review and meta-analysis of cohort studies to evaluate the TyG index as a tool for T2D prediction in adults or older adult subjects.

2. Methods

2.1. Protocol and registration

The current systematic review and meta-analysis followed the guideline for conducting and reporting Meta-analysis of Observational Studies in Epidemiology (MOOSE) [23], and was registered at PROSPERO (www.crd.york.ac.uk/prospero/): registration number CRD42018114496.

2.2. Eligibility criteria

Cohort studies that evaluated the TyG index in the T2D prediction in subjects ≥18 years were required. Besides, we included both studies that evaluated the incidence of T2D from tertiles, quartiles, quintiles, or single TyG index values. The formula used to calculate the TyG index in the articles was: Ln [fasting triglycerides (mg/dL)/fasting glucose (mg/dL)/2] [8,9]. Studies with children and adolescents were excluded, as well as case–control, clinical trials, cross-sectional studies, case/series reports, comments, reviews, letters, unpublished articles, and expert opinions. The T2D incidence was the outcome evaluated according to the hazard ratio (HR) or relative risk (RR) or odds ratio (OR) values.

2.3. Search strategy

Two investigators (AS and APSC) independently performed the search of original prospective studies that evaluate the predictive capacity of the TyG index in T2D incidence in subjects ≥18 years. The following electronic bibliographic databases were used: PubMed/MEDLINE (www.pubmed.com), Cochrane (www.cochrane.org), Scopus (www.scopus.com), and Lilacs (www.lilacs.bvsalud.org). We made an exhaustive literature review with the following search terms: “TyG index” OR “triglyceride-glucose index” OR “triglyceride glucose index” to identify all studies with the TyG index and type 2 diabetes risk. These search terms were keywords from previously read articles.

No date restriction was applied, but the English language was required and was limited to human studies. The literature search was conducted on November 22, 2018, but an updated search was performed on October 01, 2019. Additionally, we perform a backward reference search to identify possible relevant cohort articles cited in the papers selected. Duplicates manuscripts were manually identified.

2.4. Study selection and data extraction

The selection of the studies was performed according to the analysis of titles, abstracts, and full texts by two authors (AS and APSC) independently and the divergent decisions were settled by consensus, or if necessary, by a third author (DMUPR). When the article was not available or to obtain additional information to the analyses, an e-mail was sent to the author requesting the article or information.

From the eligible studies, two review authors (AS and APSC) independently extracted relevant information, and the divergent decisions were settled by a third author (DMUPR): (i) name of the first author, year of publication; (ii) country of origin, study name; (iii) total years or mean or median of years of follow-up period; (iv) subjects characteristics at baseline (sample size, age, and body

mass index – BMI); (v) number and percent of T2D incidence; (vi) variables used in adjustment models; (vii) TyG index value associated with the T2D incidence; (viii) HR or RR or OR adjusted values with 95% CI values.

2.5. Risk of bias

Two investigators (AS and APSC) performed the risk of bias independently. Disagreements were resolved through consensus or by a third reviewer (DMUPR). To the risk of bias evaluation, the Newcastle–Ottawa Scale (NOS) was utilized [24]. The scale has a rating from 0 to 9 points, allocated according to three domains: population selection (maximum of four points), comparability of the groups (maximum of two points), and outcome assessment (maximum of three points). A score ≥7 points was used to classified studies with high quality [24].

2.6. Statistical analysis

We extracted the reported risk measure – HR or RR or OR values – and 95% confidence interval (95% CI) for T2D from multiple-adjusted outcome data. In addition, the number of T2D cases, non-T2D cases, and the total number of participants were extracted from exposed and non-exposed groups when available. In this case, the reference group used in multiple regression models were considered as a non-exposed group. On the other hand, was considered as an exposed group the other categories evaluated in regression models. For example, in studies that reported data in quartiles of the TyG index, quartiles 2, 3, and 4 were grouped as exposed groups while the quartile 1 was defined as a non-exposed group.

First, we performed a meta-analysis only for studies that reported data in HR values. For this studies, the HR was log-transformed, and we calculated the standard error for each study. Subgroup analyses were conducted according to the data presented in each article. A first subgroup meta-analysis was conducted for studies that reported the data in a single general HR. After, we performed a subgroup meta-analysis for papers that reported this association according to sex, or according to TyG index quartiles, and according to TyG index quartiles but stratified by sex. Then, the overall effect estimate was calculated.

Although the most of studies evaluated in this systematic review have reported the HR values as association measure, some studies presented their data in OR or RR. Given the different association measurements used, the number of T2D cases, non-T2D cases, and the total number of participants were extracted from exposed and non-exposed groups when available. Then the risk ratio could be calculated and enabled us to better investigate the estimative effect of the TyG index in the T2D risk.

The statistical analyses were performed by using the software Review Manager® (RevMan) software, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The inverse variance method and the random-effects model were used for all meta-analyses. We assessed heterogeneity by Q-test, I^2 statistics, and by visual inspection of funnel plots. For the Cochrane Q test, if p-value was below 0.1, the analysis was considered significant heterogeneous; and for I^2, heterogeneity was classified into low, moderate, and high according to the following cut-off values of 25%, 50% and 75% [25,26].

3. Results

3.1. Literature search

We identified 383 studies after searched in all four databases. We removed a total of 121 duplicates resulting in 252 articles. Based on the titles and abstracts, we excluded 229 studies according to the inclusion/exclusion criteria. Therefore, we assessed 23 studies for eligibility through full-text reading. From these, a total of 13 studies met all the inclusion criteria for the systematic review and meta-analysis. Three studies were not entered in a meta-analysis with HR, because they no reported data in HR values. Then, were collected data for RR calculation from studies when this information was available. For four studies, we did not get to extract sufficient data for RR calculation [17,18,20,21] Despite this, they entered in a meta-analysis using HR values (Fig. 1).

3.2. Study characteristics

A total of 13 cohort studies comprised the systematic review and meta-analysis, which 11 studies were with Asians and two with Caucasians ethnicities. The sample size ranged from 617 to 11,113 and in total 70,380 subjects, both sexes, adults, and older adults were studied. Although we do not have the T2D incidence rate for 1000 person-years, we have the total number of T2D incidence. Thus, considering the total of individuals analyzed, the total T2D incidence was 6540 (9.3%) among the studies selected, and the minimum mean of follow-up was 1.4 years (Table 1). Furthermore, the TyG index value of at least 8.31 was associated with a risk of T2D, considering the studies that reported the TyG index data in quartiles in both sexes. The diagnostic criteria of T2D used in the articles were according to the American Diabetes Association and updates [27–31], China guideline for T2D [32], or World Health Organization guideline [33]. The more common variables used in the adjustment model were socio-demographics, clinical, and anthropometrics.

From the 13 studies included in the systematic review, 11 presented high quality (NOS ≥ 7 points) (Supplementary Table 1).

3.3. Meta-analysis for T2D risk reported as HR values

For the meta-analysis on the association between TyG index and T2D risk reported as HR values, 10 studies were eligible [12–21] (Fig. 1). Subgroups analysis was performed due to different ways that authors presented their results. Four studies reported T2D risk according to general TyG index values (HR: 2.10; 95% CI: 1.58–2.80), three showed results according to general TyG index values by female sex (HR: 2.11; 95% CI: 1.61–2.76), and male sex (HR: 1.60; 95% CI: 1.35–1.88). Additionally, five studies reported T2D risk through quartiles of TyG index or metabolic health status based on TyG index values (**Quartile 2:** HR: 1.62; 95% CI: 1.29–2.03, **Quartile 3:** HR: 2.56; 95% CI: 2.03–3.24, and **Quartile 4:** HR: 4.32; 95% CI: 3.41–5.46). Besides, two studies presented data through quartiles of TyG index by female sex (**Quartile 2:** HR: 2.12; 95% CI: 1.20–3.73, **Quartile 3:** HR: 3.02; 95% CI: 1.81–5.04, and **Quartile 4:** HR: 6.09; 95% CI: 3.73–9.93), and male sex (**Quartile 2:** HR: 1.42; 95% CI: 0.96–2.19, **Quartile 3:** HR: 2.48; 95% CI: 1.69–3.63, and **Quartile 4:** HR: 4.41; 95% CI: 2.91–6.68). Finally, the overall analysis was obtained and showed the presence of a positive and significant association of the TyG index with the T2D risk (HR: 2.44; 95% CI: 2.17–2.76). A high percentage of heterogeneity was verified in the overall analysis (I^2 = 80%, p < 0.00001) (Fig. 2). Besides, visual inspection of funnel plots revealed significant publication bias.

3.4. Meta-analysis for T2D risk reported as RR values

From 13 eligible studies, one study reported data in RR values and eight studies present sufficient information for RR estimation [10–12,14–16,19,22]. We observed a positive and significant risk of T2D in the exposed group (those classified in TyG index risk values) versus the comparator group (RR = 3.12, 95% CI, 2.31–4.21). However, high heterogeneity could be observed in the analysis (I^2 = 87%,

Table 1
Characteristics of selected studies for systematic review and meta-analysis.

Author (year)	Study name, country	Follow-up (years)	Sample characteristics	T2D incidence n (%)[a]	Diagnostic criteria of T2D	Adjustment	TyG index value associated with T2D incidence	Multivariate relative risk/odds ratio (OR)/hazard ratio (HR) (95% CI)
Lee et al. (2014) [10]	CMC study, South Korea	Median: 4.6 (4–8.8)	*N*: 5354F/M: 3335/2019Age: 61.6 ± 9.3 yBMI: 24.2 ± 3.2 kg/m^2	420 (7.8)	ADA criteria published in 1997 [27] or 2003 [30]	Sex, age, BMI, WC, SBP, HDL-C, family history of DM, smoking, alcohol intake, and education level	8.40 (for Q2) 8.80 (for Q3) 9.40 (for Q4)	Relative risk: Q1: 1 (reference) Q2: 2.28 (1.50–3.47)Q3: 2.02 (1.31–3.10) Q4: 4.09 (2.70–6.20)
Janghorbani et al. (2015) [11]	IDPS, Iran	Mean: 6.9(3–10)	*N*: 1488 F/M: 1127/361 Age: 30–70 anosBMI: 28. 9 kg/m^2	195 (13.0)	ADA criteria published in 2010 [28]	Sex, age, BMI, WC, SBP, SBP, HbA1c, HDL-C, LDL-C, and TC	8.50 (for Q2) 8.84 (for Q3) 9.17 (for Q4)	OR: Q1: 1 (reference) Q2: 1.72 (0.90–3.27)Q3: 2.21 (1.19–4.11) Q4: 3.36 (1.83–6.19)
Lee et al. (2016) [12]	South Korea	Median: 4	*N*: 2900 F/M: 822/2078 Age: 44.3 ± 6.5 yBMI: 19.5 –27.9 kg/m^2	101 (3.5)	ADA criteria published in 2014 [29]	Sex, age, smoking, alcohol intake, PA, SBP, HDL-C, LDL-C, HOMA-IR, and ultrasensitive C reactive protein	8.21 (for Q2) 8.57 (for Q3) 8.97 (for Q4)	HR: Q1: 1 (reference) Q2: 2.61 (0.86–7.96)Q3: 4.06 (1.39 –11.88) Q4: 5.65 (1.91–16.73)
Navarro-González et al. (2016a) [13]	VMCUN cohort, Spain	Median: 10	*N*: 4939F/M: 1923/3016Age: 39.6–69.3 yBMI: 22 –36.1 kg/m^2	406 (8.2)	ADA criteria published in 1997 [27], 2010 [28]	Sex, age, BMI, smoking, alcohol intake, PA, SAH, CVD, antiaggregation therapy, HDL-C, LDL-C, and triglycerides	8.10 (for MHNO) 8.30 (for MHO) 9.10 (for MUNO) 9.20 (for MUO)	HR: MHNO: 1 (reference) MHO: 2.26 (1.25–4.07) MUNO: 3.04 (1.69–5.47) MUO: 4.68 (2.19–10.01)

Table 1 (*Continued*)

Author (year)	Study name, country	Follow-up (years)	Sample characteristics	T2D incidence n (%)[a]	Diagnostic criteria of T2D	Adjustment	TyG index value associated with T2D incidence	Multivariate relative risk/odds ratio (OR)/hazard ratio (HR) (95% CI)
Navarro-González et al. (2016b) [14]	VMCUN cohort, Spain	Median: 10	*N*: 4820 F/M: 1889/2931 Age: 39.6–69.3 yBMI: 20.9 –32.7 kg/m^2	332 (6.9)	ADA criteria published in 1997 [27], 2010 [28]	Sex, age, BMI, smoking, alcohol intake, PA, SAH, CVD, HDL-C, and LDL-C	7.95 (for Q2) 8.31 (for Q3) 8.67 (for Q4)	HR: Q1: 1 (reference) Q2: 1.23 (0.71–2.11)Q3: 3.01 (1.87–4.85)Q4: 5.59 (3.51 –8.91) F: Q1: 1 (reference) Q2: 1.28 (0.42–3.94)Q3: 2.77 (1.02–7.54)Q4: 5.91 (2.26 –15.43) M: Q1: 1 (reference) Q2: 1.33 (0.75–2.36)Q3: 2.73 (1.61–4.63) Q4: 5.41 (3.26–8.97)
Zhang et al. (2017) [15]	The Rural Chinese Cohort Study, China	Median: 6	*N*: 5706F/M: 3195/2511Age: 36–62 yBMI: 18.5 –23.9 kg/m^2	96 (1.7)	China guideline for T2D published in 2016 [32]	Sex, age, family history of DM, WC, education level, marital status, smoking, alcohol intake, PA, SBP, DBP, TC, HDL-C, and LDL-C	8.09 (for Q2) 8.40 (for Q3) 8.69 (for Q4)	HR: 3.12 (2.31–4.22) Q1: 1 (reference) Q2: 1.34 (0.48–3.76)Q3: 4.29 (1.72 –10.67) Q4: 5.88 (2.06–16.76)F: 4.04 (2.76–5.92) M: 2.05 (1.23–3.41)
Low et al. (2018) [16]	Singapore	Mean: 1.4	*N*: 4109F/M: 2584/1525Age: 46–66 yBMI: 18.3–28. 6 kg/m^2	117 (2.8)		Sex, age, ethnicity, BMI, WC, HDL-C, SBP, and coping with stress	8.30 (for Q2) 8.60 (for Q3) 9.10 (for Q4)	HR: Q1: 1 (reference) Q2: 1.79 (0.80–3.99)Q3: 2.54 (1.18–5.49) Q4: 4.68 (2.19–10.01)
Kim et al. (2018) [17]	Ansung-Ansan cohort study, South Korea	10	*N*: 7643F/M: 4040/3603Age: 42–60 yBMI: 21.3–27.5 kg/m^2	1306 (17.1)	ADA criteria published in 1997 [27]	Sex, age, BMI, smoking, hypertension, physical activity, and energy intake	4.69[b]	HR: 2.17 (1.92–2.45)
Tohidi et al. (2018) [18]	Tehran Lipid and Glucose Study, Iran	Median: 12	*N*: 4419F/M: 2561/1858Age: 27–53 yBMI: 22.1–31. 1 kg/m^2	503 (11.4)	ADA criteria published in 1997 [27], 2010 [28]	Sex, age, BMI, WC, SBP, HDL-C, education level, anti-hypertensive medications, and family history of diabetes	Not valued	HR: 1.53 (1.38–1.69)F: 1.75 (1.60–1.90) M: 1.71 (1.47–1.98)

Lee et al. (2018) [22]	Korean Genome and Epidemiology Study (KoGES), South Korea	10	*N*: 7708F/M: 4072/3636Age:M: 51.4 ± 8.6 yF: 52.0 ± 8.9 y BMI: M: 24.1 ± 2.9 kg/m^2 F: 24.7 ± 3.2 kg/m^2	1563 (20.3) F: 797 (19.6) M: 766 (21.1)	ADA criteria published in 2010 [28]	Age, BMI, status of hypertension, family history of diabetes, smoking status, alcohol intake, and physical activity	M: 8.4–8.6 (for Q2)8.7–9.0 (for Q3)≥9.1 (for Q4)F:8.2–8.4 (for Q2)8.5–8.7 (for Q3)≥ 8.8 (for Q4)	OR: F: Q1: 1 (reference) Q2: 1.19 (0.91–1.55)Q3: 1.97 (1.53–2.53)Q4: 2.85 (2.22 –3.66) M: Q1: 1 (reference) Q2: 1.26 (0.97–1.64)Q3: 1.82 (1.41–2.36) Q4: 2.79 (2.16–3.60)
Wang et al. (2018) [21]	China	Median: 6	*N*: 11,113F/M [c]: 6844/4269 Age: 50.00 (41.00, 59.00) y BMI[c]: 23.91 (21.62, 26.37) kg/m^2	439 (3.95) M: 188 (4.4) F: 251 (3.7)	ADA criteria published in 2005 [31]	Age, family history of diabetes, family history of hypertension, education level, marital status, smoking, alcohol consumption, physical activity, and SBP	M: 8.25–8.57 (for Q2)8.58–8.95 (for Q3)≥ 8.96 (for Q4) F: 8.27–8.62 (for Q2)8.63–9.00 (for Q3)≥ 9.01 (for Q4)	HR: F: Q1: 1(reference) Q2: 2.50 (1.36–4.60)Q3: 3.12 (1.72–5.67)Q4: 6.15 (3.48 –10.85) M: Q1: 1(reference) Q2: 1.59 (0.88–2.88)Q3: 2.22 (1.27–3.88) Q4: 3.54 (2.08–6.03)
Chamroonkiadtikun et al. (2019) [19]	Thailand	Median: 9.2	*N*: 617 F/M: 411/206 Age: 66.88 ± 10.18 BMI: 25.65 (23.76–27.95)	163 (26.4)	–	Age, BMI, history of hypertension and dyslipidemia, TC, LDL-C, and DBP	Not valued	HR: 2.03 (1.38–3.00) Q1: 1 (reference) Q2: 1.55 (1.13–2.12)Q3: 1.95 (1.4–2.71) Q4: 3.38 (2.38–4.8)
Brahimaj et al. (2019) [20]	Rotterdam Study, Netherlands	Median: 6.5	*N*: 9564 F/M: 5576/3988 Age: F: 65.1 ± 10.3M: 64.3 ± 9.5BMI: F: 27.1 ± 4.5M: 26.7 ± 3.4	899 (9.4)	WHO guideline published in 2006 [33]	Age, cohort; BMI; SBP, treatment for hypertension, smoking, prevalent CVD, HDL-C, triglycerides, and serum lipid-reducing agents	F: 2.8 ± 0.5M: 2.9 ± 0.5	HR: F: 1.73 (1.52–1.98)M: 1.43 (1.26 –1.62)

Legend: ADA, American Diabetes Association; BMI, body mass index; CMC, Chungju metabolic disease cohort; CVD, cardiovascular disease; DBP, diastolic blood pressure; F, female; HDLc, cholesterol high density lipoprotein; HOMA-IR, homeostatic assessment insulin resistance; IDPS, Isfahan diabetes prevention study; LDL-C, cholesterol low density lipoprotein; M, male; MHO, metabolically healthy obese; MHNO, metabolically healthy non obese; MUNO, metabolically unhealthy non obese; MUO, metabolically unhealthy obese; PA, physical activity; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SAH, systemic arterial hypertension; SBP, systolic blood pressure; TC, total cholesterol; T2D, type 2 diabetes; VMCUN, vascular-metabolic CUN cohort; WC, waist circumference.

[a] values of total T2D in the study population.

[b] Cut-off TyG index value.

[c] Median (interquartile range).

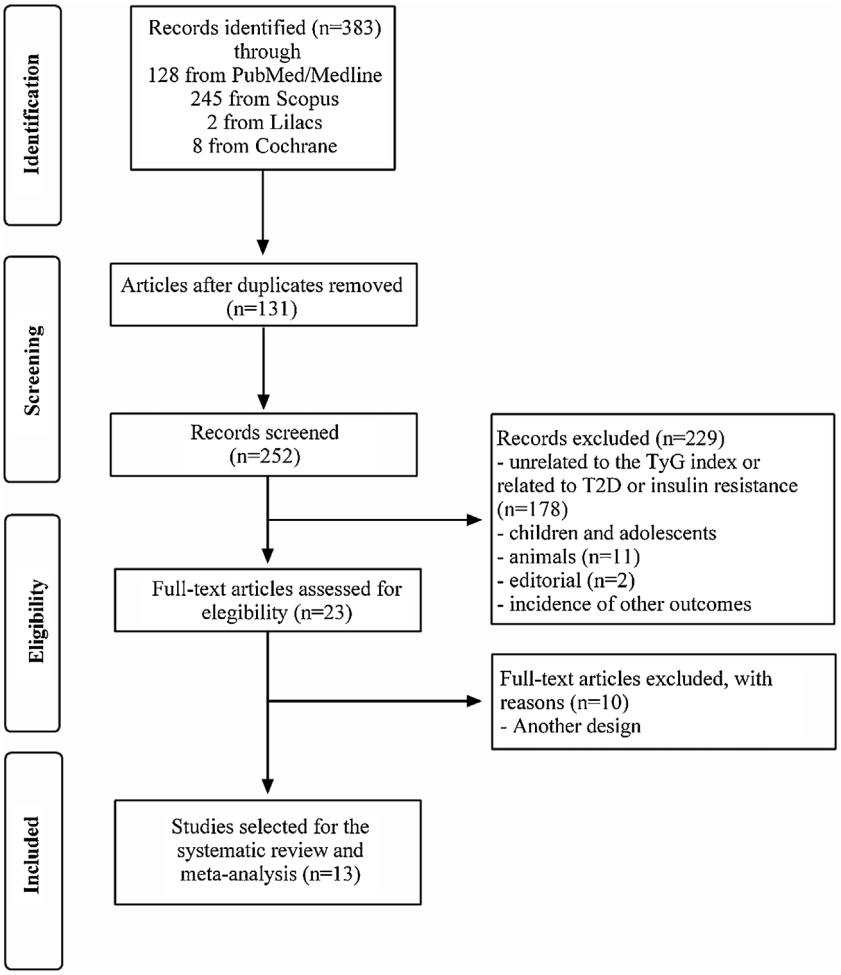

Fig. 1. Flow chart of the study search and selection for inclusion in the meta-analysis.

$p < 0.00001$) (Fig. 3). Still, visual inspection of funnel plots revealed significant publication bias.

4. Discussion

To the best of our knowledge, the present meta-analysis is the first in the literature to highlight the TyG index as a predictor of T2D development. We included 13 cohort studies in the meta-analysis, and we verified a positive and significant association of the TyG index with the T2D incidence in overall HR or RR meta-analysis. However, due to significant heterogeneity in the analysis, caution is necessary to extrapolate these results. On the other hand, in subgroup analysis, we observed an increased T2D risk across TyG index quartiles. The same results were observed in both sex and low evidence of heterogeneity was observed for some subgroup analysis. The studies show that subjects without diabetes but with a TyG index higher than 8.31 (for those reported in quartiles) have a higher T2D risk.

Metabolic mechanisms could justify the functionality of TyG index in the prediction of T2D. The elevated fasting plasma glucose and triglycerides concentrations are among the metabolic syndrome components, which are related to the IR state and development of chronic diseases. Characterized by the accumulation of blood glucose, the IR is the inability of insulin to stimulate glucose uptake and is related to obesity, where central and ectopic fat accumulation are involved [1]. On the other hand, triglycerides are related to IR, given that intramuscular lipids accumulation – one of the main storage sites of triglycerides – inhibits the translocation of the glucose transporter type 4 to the cell membrane, reducing the uptake of glucose by skeletal muscle [34,35]. Together, fasting glucose and triglycerides seem to be a useful marker to predict T2D development because of the link with the IR state. The hypothesis to explain the TyG index as a tool to predict T2D is that this marker is related to the cause and consequence of glucose homeostasis alteration. Considering that IR precedes T2D, possibly around 1 to 2 decades before diagnosis, the early identification of this condition is fundamental for the planning of health actions towards T2D prevention [4,36]. Other prospective studies have associated TyG index with hypertension [37,38] and cardiovascular disease incidence [37,39], showing metabolic alterations related to IR and associated with the TyG index.

The TyG index highlights mainly as a screening tool for IR evaluation and potentially for T2D since it uses simple and low-cost biomarkers often used in clinical practice (fasting triglycerideos and fasting glucose) [8,9]. Although the *euglycemic-hyperinsulinemic clamp* is the gold standard method for IR evaluation there are other good substitutive methods for IR evaluation, like the homeostasis model assessment of insulin resistance (HOMA-IR) [40] and the oral glucose tolerance test. However, these methods require insulin dosage, which increases the costs. Also, TyG index has been reported to have good sensibility and specificity compared to the gold standard method [9] and good sensitivity compared to HOMA-IR [8]. We emphasize that we do not compare the TyG index with the other methods in this meta-analysis, but we evaluate if the TyG index predicts T2D development. The *euglycemic-hyperynsulinemic* clamp, HOMA-IR, oral glucose toler-

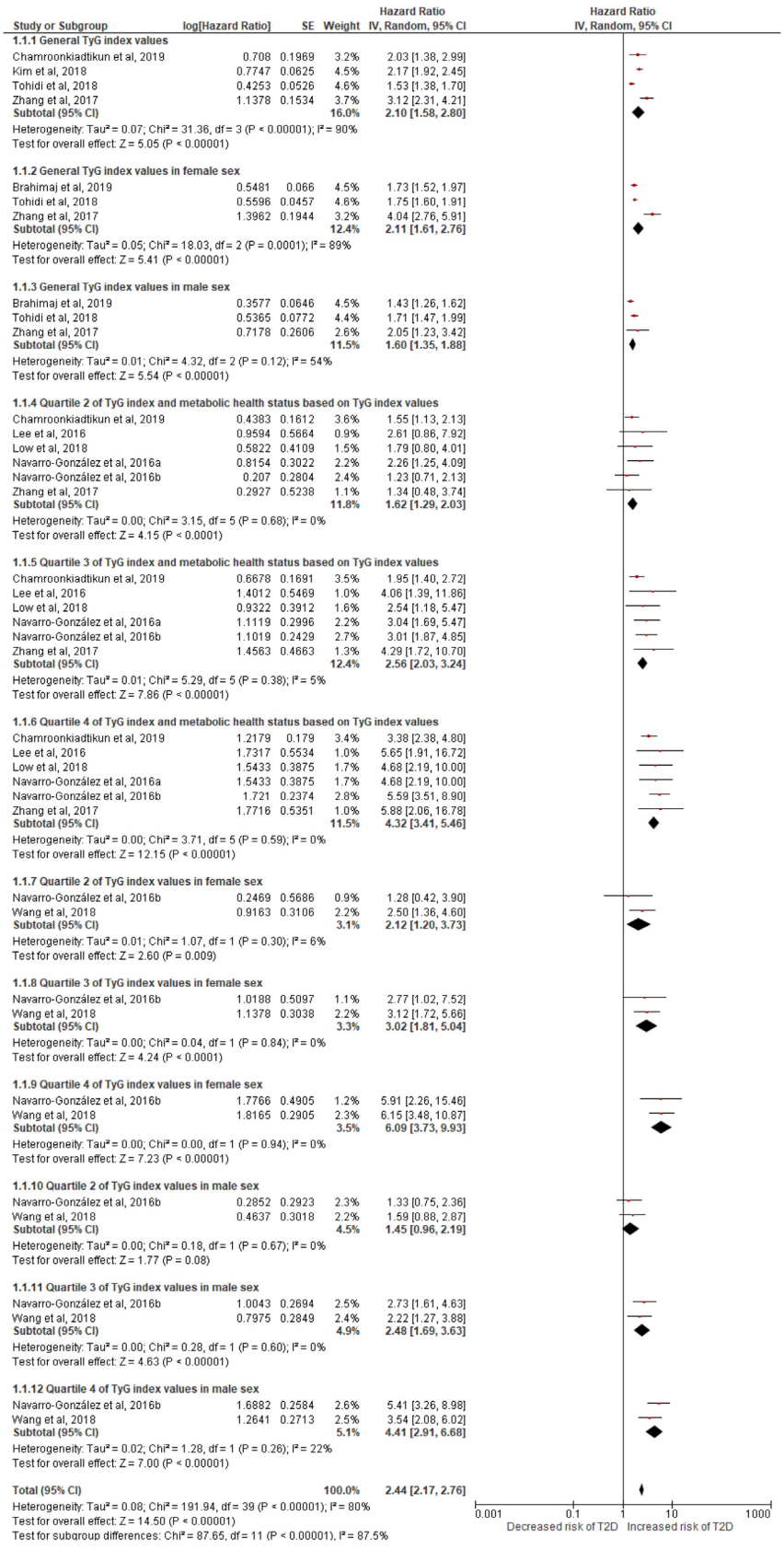

Fig. 2. Forest plot of hazard ratio for type 2 diabetes (T2D) associated with the TyG index.

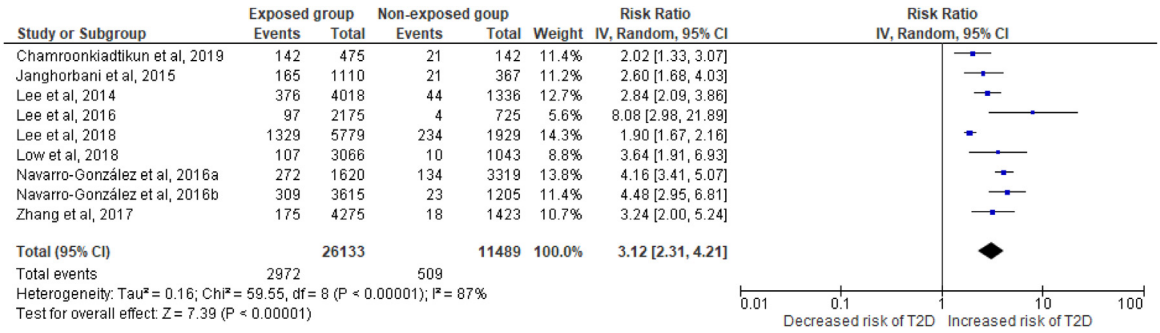

Fig. 3. Forest plot of risk ratio for type 2 diabetes (T2D) associated with the TyG index. *Non-exposed*: was considered as non-exposed the reference categories used in the multiple regression analysis. *Exposed group*: was considered as exposed the other categories used in the multiple regression analysis.

ance test, and other methods are used worldwide, however, we verified that the TyG index is associated with T2D risk and could be an applicable tool to use in clinical practice since that the TyG index is highlight as an easy and low-cost tool.

The T2D origin can be due to the set of genetic, clinical, or behavioural characteristics like the unhealthy diet, physical inactivity, and others. The diet consists of an important modifiable risk factor since excessive consumption of simple carbohydrates and fats is associated with the occurrence of hyperglycemia and dyslipidemia, affecting both components of the TyG index [41]. In our review, only one study was careful to use the energy intake as an adjustment [17]. Therefore, more studies are necessary to evaluate the relation of the TyG index with food consumption profile and if non- communicable chronic diseases are associated with the TyG index independently of this variable.

Our study is the first systematic review and meta-analysis that highlighted the relationship between the TyG index and T2D risk in adults and older adult subjects. Moreover, most of the studies evaluated (92.3%) presented high quality, showing that they attended the methodological criteria of selection, comparability, and assessment of the outcome of the cohorts. However, our review presented limitations, for example, we verified the statistical heterogeneity in the most analysis that may be caused by clinical (study population has hypertension and cardiovascular disease cases) and methodological (studies had proposed comparing tools that best predict the incidence of T2D, the adoption of different references to diagnosis T2D) differences between studies. Additionally, different weight from each study and other unknown study characteristics could affect the heterogeneity.

5. Conclusion

We verified through cohort studies a positive and significant association of the TyG index increase with the risk of T2D, regardless of socio-demographic and metabolic risk factors. Therefore, TyG index could become an applicable tool to identify subjects with T2D risk. However, due to the high heterogeneity evidenced in overall HR and RR analysis, more research is necessary to confirm this result. Besides, studies evaluating the TyG index use in other ethnicities, ages, comorbidities, and that summarize the accuracy of the TyG index compared to other methods for assessing IR at risk of T2D are also required. Thus, given the alarming expectations of the increase in type 2 diabetes incidence and the need for early identification to control and prevent comorbidities, the TyG index highlight like an easy and low-cost tool to identify those with type 2 diabetes risk.

Conflict of interests

None.

Author contributions

Search on databases and conception of the review was realized by Silva A. and Caldas A.P.S. Critical revisions, collection, and analysis of data were realized by Silva A., Caldas A.P.S., Rocha D.M.U.P., and Bressan J.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.pcd.2020.09.001.

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