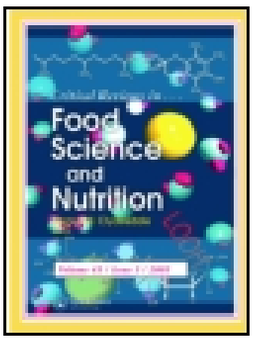

Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Predictive capacity of triglyceride-glucose (TyG) index for insulin resistance and cardiometabolic risk in children and adolescents: a systematic review

Alice Divina Melo de Brito , Helen Hermana Miranda Hermsdorff , Mariana De Santis Filgueiras , Lara Gomes Suhett , Sarah Aparecida Vieira-Ribeiro , Sylvia do Carmo Castro Franceschini & Juliana Farias de Novaes

To cite this article: Alice Divina Melo de Brito , Helen Hermana Miranda Hermsdorff , Mariana De Santis Filgueiras , Lara Gomes Suhett , Sarah Aparecida Vieira-Ribeiro , Sylvia do Carmo Castro Franceschini & Juliana Farias de Novaes (2020): Predictive capacity of triglyceride-glucose (TyG) index for insulin resistance and cardiometabolic risk in children and adolescents: a systematic review, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1788501

To link to this article: https://doi.org/10.1080/10408398.2020.1788501

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1788501

Taylor & Francis
Taylor & Francis Group

REVIEW

Predictive capacity of triglyceride-glucose (TyG) index for insulin resistance and cardiometabolic risk in children and adolescents: a systematic review

Alice Divina Melo de Brito, Helen Hermana Miranda Hermsdorff, Mariana De Santis Filgueiras, Lara Gomes Suhett, Sarah Aparecida Vieira-Ribeiro, Sylvia do Carmo Castro Franceschini, and Juliana Farias de Novaes

Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Brazil

ABSTRACT

Insulin resistance (IR) in childhood plays a key role in the development of metabolic changes in adulthood, therefore, it is important to diagnose it early. We aimed to investigate studies that evaluated the TyG index for prediction of IR risk and other cardiometabolic risk factors, as well as, the proposed cutoff points in childhood and adolescence. This is a systematic review elaborated according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA). The search was performed in Lilacs, PubMed and CAPES Journal Portal, using the terms "TyG index OR triglyceride-glucose index OR triglyceride and glucose index AND children OR adolescent*". Eight articles were included in this review. All were cross-sectional studies with individuals aged ≥2 and ≤20 years old, from the United States, Korea, Mexico, Brazil, and Iran. We concluded that the TyG index was positively associated with other IR prediction methods and appears to be advantageous for predicting IR risk and other cardiometabolic risk factors in children and adolescents (review registration: PROSPERO CRD42018100726).

KEYWORDS

Adolescent; biomarkers; child; insulin resistance

Introduction

The prevalence of obesity in children and adolescents has been increasing worldwide. In 2016, according to data from the World Health Organization (WHO), over 340 million children and adolescents from 5 to 19 years old were overweight or obese, which can cause serious consequences in childhood and adulthood, such as hypertension, dyslipidemia, metabolic syndrome (MetS), nonalcoholic fatty liver disease, psychosocial complications, insulin resistance (IR) and diabetes mellitus (DM) (Han, Lawlor, and Kimm 2010; Kim et al. 2016; Güngör 2014; WHO 2017).

Insulin resistance (IR) is a metabolic state in which the responsiveness of target-tissues to normal insulin concentrations is reduced and plays a key role in these outcomes, especially in type 2 DM and MetS (Sesti 2006; Vasques et al. 2011). Therefore, evaluate the IR and diagnose it early is of great interest in childhood (Sesti 2006; Vasques et al. 2011). An emerging assessment method, especially in adults, is the triglyceride-glucose index (TyG), a product of the triglyceride (TG) and fasting glucose (Verduci et al. 2015). Compared to the gold standard (hyperinsulinemic-euglycemic (HE clamp)) and homeostatic model assessment for insulin resistance (HOMA-IR), the TyG index has been shown to be useful for estimating the risk of IR in adults (Vasques et al. 2011; Guerrero-Romero et al. 2010; Irace et al. 2013; Du et al. 2014). In addition, it is a considered a risk marker for the development of type 2 DM, MetS and cardiovascular diseases, such as atherosclerosis (Irace et al. 2013; Du et al. 2014; Unger et al. 2014).

The TyG index has low cost and, hence, has easier access at an outpatient and population level, however, there is no consensus about its cutoff points to predict IR and other cardiometabolic risk factors in childhood and adolescence. To date, no other systematic reviews have been found that investigated these factors, according to our knowledge. In order to know the existing evidences with this new IR marker in childhood and adolescence, we aimed to investigate the studies that evaluated the TyG index to predict the IR risk and other cardiometabolic risk factors, as well as the cutoff points already proposed for this population.

Methods

Identification and selection of studies

This systematic review was elaborated from the research question: "Could the TyG index be used to predict the IR risk and other cardiometabolic risk factors in children and adolescents?" This systematic review was conducted from August 2018 to January 2019, in accordance with the recommendations of the Preferred Reporting Items for Systematic

CONTACT Juliana Farias de Novaes jnovaes@ufv.br Department of Nutrition and Health, Universidade Federal de Viçosa, Avenida P.H. Rolfs, Centro de Ciências Biológicas II, Campus Universitário, s/n, Viçosa, Minas Gerais 36570-900, Brazil.

Supplemental data for this article can be accessed at https://doi.org/10.1080/10408398.2020.1788501.

Reviews and Meta-Analyzes (PRISMA) (Moher et al. 2009) and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO) by registration number CRD42018100726.

The search was performed using the databases: Latin American and Caribbean System on Health Sciences (Lilacs), PubMed and CAPES Journal Portal. The search included papers written in English, Portuguese and Spanish, without geographic and date of publication limitation, and using the following search strategy with the terms: ("TyG index" OR "triglyceride-glucose index" OR "triglyceride and glucose index") AND ("children" OR "adolescent*"). The eligibility criteria adopted were:

- Inclusion: published observational studies evaluating the use of the TyG index to predict the risk of IR and/or cardiometabolic risk in individuals aged ≥2 and ≤20 years old. The TyG index should be compared to other IR prediction methods, such as the HE clamp (gold standard) and HOMA-IR, and MetS criteria, as Cook et al. (2003), De Ferranti et al. (2004), International Diabetes Federation (IDF) (Zimmet et al. 2007) and National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), or other cardiometabolic risk markers (single or pooled), such as blood pressure, fasting blood glucose (FBG), total cholesterol, high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), and triglycerides.
- Exclusion: children and adolescents hospitalized and/or with special characteristics that could interfere with the normal functioning of the organism, such as autism, Down syndrome, kidney diseases; duplicate studies; gray literature; reviews and meta-analyzes; conference abstracts; books and book chapters; monographs, dissertations and theses.

Initially, the titles and abstracts of the articles were read, which, if it met the initial selection criteria, the full text reading was proceeded (Figure 1). To verify the eligibility of the articles, a standard form was used (Moher et al. 2009).

Data extraction

Data were extracted independently, using a standard spreadsheet in the Microsoft Excel® program. Information gathered about the selected papers were author and year of publication; study design; sample origin (country); age group; number of participants; inclusion and exclusion criteria; independent, dependent, and confounding variables; TyG formula used by authors; main results; and cut-off points.

Evaluation of study quality

The risk of bias was evaluated by the National Heart, Lung, and Blood Institute (NHLBI), Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. This tool assesses studies by the presence (yes) or absence (no) of 14 criteria, in which the criteria 10 (repeated exposure assessment), 12 (blinding outcome evaluators) and 13 (follow-up rate) did not apply (NA) to any of the studies in this review, since covered only cross-sectional observational studies. In the end, the studies were classified as good, fair or bad, according to the sum of the criteria evaluated as "yes" (National Heart, Lung and Blood Institute. Quality Assessment Tool for Observational and Cross-Sectional Studies, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

The bias risk analysis was presented in Table 1. All studies presented a satisfactory sum in the quality assessment.

Results

Selection and description of studies

Twenty-eight articles were identified in all databases. After reading titles, abstracts, and full text and submitting to the standard eligibility form, eight articles were included in the present systematic review (Figure 1).

The descriptive characteristics of the articles are presented in Table 2. All studies had cross-sectional design, were published between 2015 and 2019, conducted with children and adolescents of both sexes, healthy, obese or with metabolic alterations, aged ≥2 and ≤20 years old. The sample size ranged from 221 to 8,037 participants, with American (Mohd Nor et al. 2016; Moon, Park, and Ahn 2017), Korean (Kim et al. 2016; Moon, Park, and Ahn 2017; Kang et al. 2017), Mexican (Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017; Simental-Mendía et al. 2017), Brazilian (Vieira-Ribeiro et al. 2018) and Iranian (Angoorani et al. 2018) children and adolescents. Table 3 presents the methodologies and main results of the studies selected for this review.

TyG index and insulin resistance

Half (n = 4) of the eight studies selected evaluated the ability of the TyG index to predict the IR risk. Some studies carried out correlation analysis to evaluate the relationship between TyG index and the HE clamp, a gold standard method for assessing insulin sensitivity (Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero, 2017; Mohd Nor et al., 2016). These studies have found an inverse correlation between TyG index and the HE clamp in obese, with prediabetes or type 2 DM children (Mohd Nor et al., 2016) and in black and white Mexican pubertal and prepubescent children (Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero, 2017). Kang et al. (2017) compared the TyG index and the HOMA-IR in the predictive ability for IR risk and found a positive correlation. Additionally, Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero (2017) identified high agreement between the TyG index and the HOMA-IR in pubertal and prepubescent boys and girls.

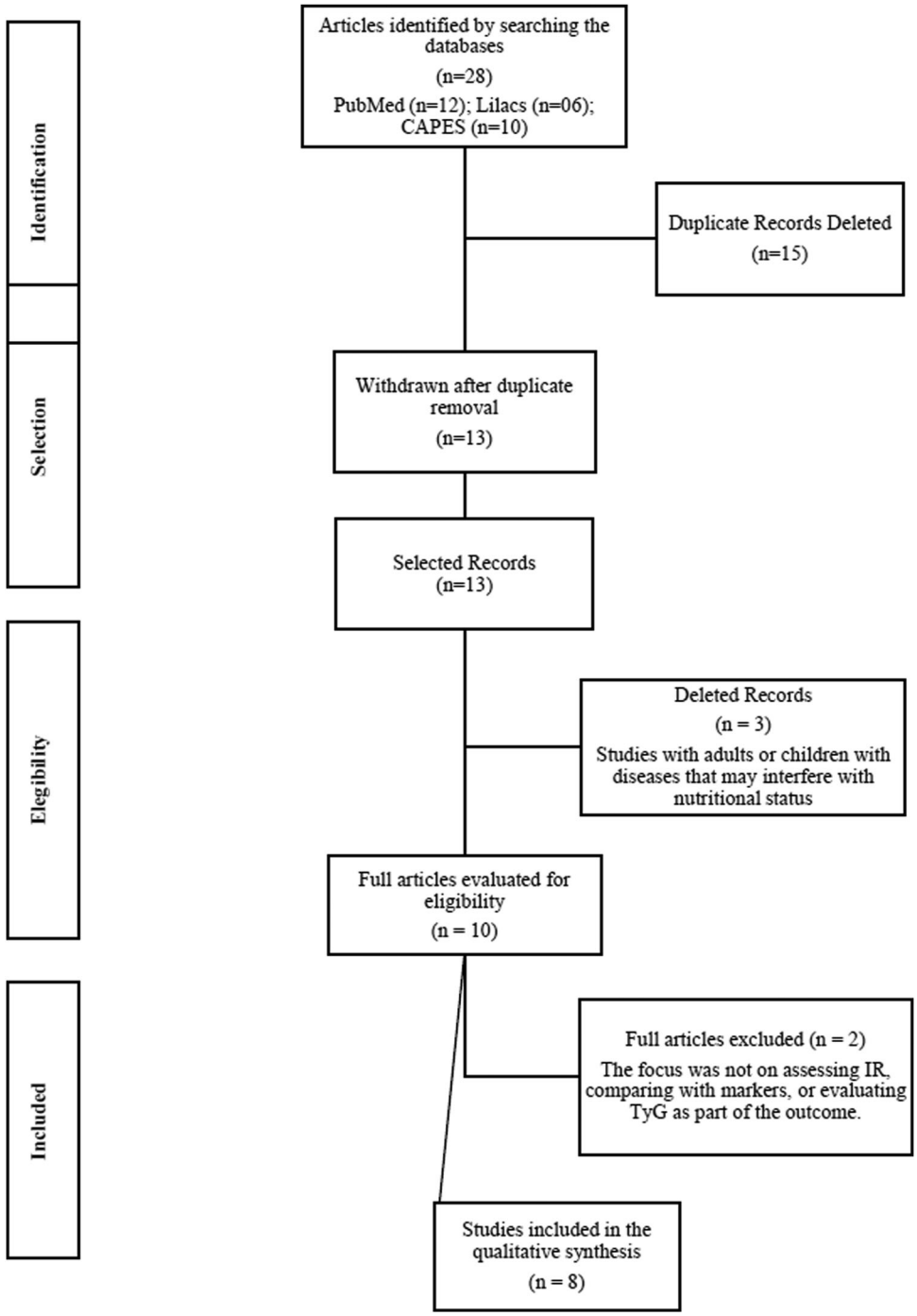

Figure 1. Flowchart of article selection.

The main factors related to increased TyG index values according to the data analyzed in the studies were: unhealthy eating pattern, physical inactivity, obesity, pre-diabetes and type 2 diabetes mellitus, hyperglycemia, elevated HOMA-IR and dyslipidemia (Figure 2).

TyG index and other cardiometabolic risk factors

To determine MetS in children and adolescents, Cook et al. (2003), De Ferranti et al. (2004), International Diabetes Federation (IDF) (Zimmet et al. 2007) and National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) criteria were used. Regardless of the method, the TyG index showed good ability to predict MetS. Moon, Park, and Ahn (2017) evaluated Korean and American adolescents (Mexican-Americans, non-Hispanic whites, non-Hispanic blacks) aged 12–19 by the first three criteria above. TyG values for black non-Hispanic adolescents were lower compared to other ethnicities, but there was no significant difference between Mexican-Americans and non-Hispanic whites, with TyG values for Korean adolescents slightly smaller than those. Kim et al. (2016), when evaluating

Table 1. Bias risk analysis by quality assessment tool for observational cohort and cross-sectional studies—NHLBI, NIH.

Questions/Studies	Mohd Nor et al. (2016)	Kim et al. (2016)	Kang et al. (2017)	Moon et al. (2017)	Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero (2017)	Simental-Mendía et al. (2017)	Vieira-Ribeiro et al. (2019)	Angoorani et al. (2018)
1. Search Question	Y	Y	Y	Y	Y	Y	Y	Y
2. Study population	Y	Y	Y	Y	Y	Y	Y	Y
3. Population elegibility rate	Y	Y	Y	Y	Y	Y	N	N
4. Recruited groups from the same population and uniform eligibility criteria	Y	Y	Y	Y	Y	Y	Y	Y
5. Justification of sample size	N	N	N	N	N	N	N	N
6. Exposure assessed before result measurement	N	N	N	N	N	N	N	N
7. Enough time to see an effect	N	N	N	N	N	N	N	N
8. Different exposure levels of interest	Y	Y	N	Y	Y	Y	Y	Y
9. Exposure measures and assessment	Y	Y	Y	Y	Y	Y	Y	Y
10. Exposure Assessment Repeat	NA	NA	NA	NA	NA	NA	NA	NA
11. Result measures	Y	Y	Y	Y	Y	Y	Y	Y
12. Blinders of result evaluators	NA	NA	NA	NA	NA	NA	NA	NA
13. Tracking Rate	NA	NA	NA	NA	NA	NA	NA	NA
14. Adjusted Statistical Analysis	Y	N	N	Y	Y	Y	Y	Y
SUM (Total = 11)	8	7	6	8	8	8	7	7
Quality Assessment	Fair	Fair	Fair	Fair	Fair	Fair	Fair	Fair

Y-Yes; N-No; NA-Not applicable.

Korean adolescents aged 10 to 18 years old, found that the TyG index was better at predicting MetS by the criteria of Cook et al. (2003), De Ferranti et al. (2004) and IDF (Zimmet et al. 2007) than HOMA-IR. Angoorani et al. (2018), determining MetS by the NCEP/ATP III criteria in Iranian children, concluded that this index was clinically useful for its diagnosis in this age group.

In the study by Simental-Mendía et al. (2017), participants with higher cardiovascular risk (occurrence of at least one of the following: systolic blood pressure and/or diastolic blood pressure $\geq$ 90th percentile; triglycerides $\geq$100 mg/dl; HDL-c $\leq$ 40 mg/dl; and fasting blood glucose $\geq$100 mg/dl) had higher TyG index values compared to those without cardiovascular risk. Furthermore, participants in the largest quintiles of TyG index had higher fasting blood glucose and triglycerides, and lower HDL-c, compared to those in the lowest quintiles, as well as high TyG index was significantly associated with hyperglycemia, hypertriglyceridemia, and low HDL-c. Other studies have found significant associations between the TyG index and some cardiometabolic risk factors, such as total and central body adiposity (Vieira-Ribeiro et al. 2018), obesity and glucose tolerance level (normal, pre-DM and type 2 DM) (Mohd Nor et al. 2016).

In addition to these cardiometabolic risk factors, the TyG index was positively associated with greater adherence to the "unhealthy" dietary pattern and negatively associated with physical activity level (Vieira-Ribeiro et al. 2018).

Cutoff points

In seven of the eight articles included, the receiver operating characteristic (ROC) curve was used to determine the cutoff point for the TyG index. Four studies predicted the IR risk: two studies evaluated TyG index versus *clamp* (Mohd Nor et al. 2016; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017) and the other two (Kang et al. 2017; Vieira-Ribeiro et al. 2018) versus HOMA-IR. Three studies predicted de risk of MetS: two evaluated TyG index versus Cook et al. (2003), De Ferranti et al. (2004) and IDF (Zimmet et al. 2007; Kim et al. 2016; Moon, Park, and Ahn 2017) and one versus ATP III criteria (Angoorani et al. 2018). Among those papers which stratified the TyG index cutoff points by sex, the values ranged from 4.75 to 8.47 for girls and 4.70 to 8.47 for boys. When stratified by MetS determination criteria, values ranged from 8.35 to 8.55 for Cook et al. (2003), 8.15 to 8.45 for De Ferranti et al. (2004) and 8.15 to 8.66 for the IDF (Zimmet et al. 2007). Considering all cutoff points established by the included studies, regardless of stratification, the lowest cutoff point was 4.65 and the highest was 8.66.

Discussion

Answering the research question of this review, we observed that the use of TyG index is advantageous to predict the IR risk and other cardiometabolic risk factors, since higher values of the TyG index were found in obese, pre-diabetic or

Table 2. Descriptive characteristics of the selective studies for the systematic review.

Study	Design	Sample origin	Age	Number of participants	Inclusion criteria	Exclusion criteria
Angoorani et al. (2018)	Cross-sectional	Children and adolescents from CASPIAN (2015) study—Irã	7–18 years old	3,843 (2,010 boys and 1,833 girls)	Children and adolescents with complete biochemical exams	No biochemical tests
Vieira-Ribeiro et al. (2019)	Cross-sectional	Children of a Retrospective Birth Cohort (PROLAC)—Viçosa, Minas Gerais, Brazil	4–7 years old	403 (221 boys and 181 girls)	Presence of identifying data to locate children; date of birth compatible between 4 and 7 years old at time of study	Not found after three attempts. Not authorized by those responsible. Incomplete study steps. Problems that prevented your participation. Incomplete data on food intake and/or biochemical tests.
Simental-Mendía et al. (2017)	Cross-sectional	Children and adolescents—Durango, México	6–15 years old	2,117 (1,036 boys e 1,081 girls)	Seemingly healthy children and adolescents of normal weight and aged 6 to 15 years	Obesity, smoking, alcohol intake, pregnancy, previous diagnosis of DM, kidney, liver, endocrine, drug ingestion or any kind of medical treatment
Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero (2017)	Cross-sectional	Children and adolescents—Durango, México	7–17 years old	2,779 (1,299 boys and 1,480 girls); 124 subsample	Healthy kids and teens aged 7 to 17 years	Chronic or acute illness, pregnancy, smoking and alcohol consumption, and inadequate clinical/laboratory tests
Moon et al. (2017)	Cross-sectional	Adolescents from NHANES (1999 a 2012) e KNHANES (2005 e 2013)—USA and South Korea	12–19 years old	8.037 (4.263 boys and 3.774 girls)	Adolescents with 12–19 years old	Incomplete or inadequate data, pregnant women using steroids, hormones or medications for dyslipidemia, DM, cancer or asthma.
Kang et al. (2017)	Cross-sectional	Children and adolescents (2014) –North Korea	9–13 years old	221 (168 boys and 53 girls)	Non-diabetic children and adolescents	Inadequate blood test data. Diabetics.
Kim et al. (2016)	Cross-sectional	Children and adolescents of the 4th 5th KNHANES (2007–2010)—South Korea	10–18 years old	3.313 (1.756 boys and 1.557 girls)	Children and adolescents from 10 to 18 years old	Individuals with missing anthropometric data or incomplete blood test results
Mohd Nor et al. (2016)	Cross-sectional	Obese children and youth—Pittsburgh, Pennsylvania, USA	10–20 years old	225 (114 boys and 111 girls)	Children and adolescents with BMI $\geq$ P95 and complete fasting lipid, OGTT, and insulin-stimulated Rd data from HE clamp. Tanner Stage II to V	Children with normal weight. DM2 patients with HbA1c$>$ 8.5%

Caption: DM–Diabetes Mellitus; CASPIAN–Childhood and Adolescent Surveillance and Prevention of Noncommunicable Diseases of Adults; HE–hyperinsulinemic-euglycemic clamp; KNHANES–Korean National Health and Nutrition Examination Survey; NHANES–National Health and Nutrition Research; PROLAC–Lactation Support Program; OGTT–Oral glucose tolerance test.

obese children and adolescents with diagnosed type 2 DM, with IR assessed by HOMA-IR, which presented accumulation of cardiovascular risk factors. The same was observed for those with greater adherence to an unhealthy dietary pattern, sedentary lifestyle, with higher values of triglycerides and fasting serum glucose, and lower values of HDL-c.

Disregarding non-modifiable risk factors such as ethnicity, puberty and rare genetic or acquired conditions characterized by lipodystrophy, obesity is the most important trigger for the development of IR (Maffeis and Morandi 2018), which correlates with clinical and metabolic alterations, especially in children and adolescents with excess weight (Romualdo, Nóbrega, and Escrivão 2014). Thus, children with IR had a greater predisposition for the future development of MetS, type 2 DM and cardiovascular diseases (Agrawal and Gensure 2018).

Romualdo, Nóbrega, and Escrivão (2014), using the HOMA-IR to assess the IR of obese individuals aged 5 to 14 years, have demonstrated that insulin-resistant individuals had higher BMI, waist circumference, triglycerides and lower

Table 3. Variables and main results of the studies included in the systematic review.

Author/year	Group	Independent Variables (IV), Dependent (DV) and Confounding Factors (CF)	Formula	Main results	Cutoff point
Angoorani et al. (2018)	Age groups: 7–12 years 13–18 years	**IV:** BMI, WC, RC, NC, WC/S, BP, FBG, TC, TG, HDL-c, LDL-c, TyG index; **DV:** MetS (ATP III -at least three of the following: TG $\geq$ 150mg/dL; HDL-c $\leq$ 40mg/dL; FBG $\geq$100mg/dL; abdominal obesity: WtHR$>$ 0,5 e SBA or DBA $>$ P90 (for age, sex and height)	Ln[Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	Mean TyG index in children with NW, SW, Ob was 8.19; 8.25; 8.21 (7–12 years) and 8.20; 8.23; 8.20 (13 to 18 years), respectively	Total: 8.33 (S: 87%; Spe:68%) M: 8.47 (S:77%; Spe: 78%) F: 8.33 (S:90%; Spe:67%) 7–12 years old: Total: 8.47 (S:75%; Spe:78%) M: 8.39 (S:80%; Spe:73%) F: 8.33 (S:91%; Spe:68%) 13–18 years old: Total: 8.34 (S:89%; Spe:68%) M: 8.47 (S:81%; Spe:78%) F: 8.35 (S:88%; Spe:68%
Vieira-Ribeiro et al. (2018)	4–7 years	**IV:** BMI, %BF, WC/S, central fat, WC, TG, FBG, FI (sub-sample of 141 children), HOMA-IR (sub-sample), Dietary patterns, age, per capita, screen time, physical activity level, EMT **DV:** Increased TyG index.	Ln[Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	5 DPs identified: "Traditional", "Unhealthy", "Chocolate Milk and Milk", "Snacks", "Healthy"; $>$ "unhealthy" PD adherence positively associated with TyG; AF was negatively associated with the index; $\uparrow$ of 1 pcs in the 4 IACs evaluated $>$ TyG	7.88 (S:80%; Spe:53.2%)
Simental-Mendía et al. (2017)	CRF; No-CRF e 6–9 years (children); 10–15 years (adolescents)	**IV:** Sociodemographic characteristics; High TyG (4.65 and 4.72 in children and adolescents respectively.); BMI, age, WC, Sex, BP, FBG, CT, HDL-c, TG; **DV:** Presence of CVR (occurrence of at least one of the following: SBP or DBP $\geq$ P90 according to age, sex and height; TG $\geq$ 100mg / dl; HDL-c $\leq$ 40mg / dl; and FBG $\geq$100mg / dl; **CF:** age, sex, BMI, WC	Ln [Fasting triglycerides (mg/dL) $\times$ fasting glucose (mg/dL)]/2	TyG $>$ quintile participants had higher FBG, TG and lower HDL vs. lower quintiles; Significant association between TyG index, $\uparrow$ TG, $\downarrow$ HDL-C and FBG.	–
Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero (2017)	*Tanner* stage: Pré-pubertal (stage 1) ou Pubertal (stage 2–4).	**VI:** HE clamp (subsample), TyG, HOMA-IR, BMI, TG, FBG, FI, TMGT; **DV**: IR by Clamp: TMGT $\geq$ 125mg / m2min; IR by HOMA-IR:$>$ P95 according to age and gender.	Ln [Fasting triglycerides (mg/dL) $\times$ fasting glucose (mg/dL)]/2	Coef. Pearson's correlation between TyG and TMGT: $-$0.725 ($<$0001) prepubertal and $-$0.695 (p $<$0.0005) pubertal Correlation between TyG and TMGT was similar between girls (-0.726) and boys (-0.733) and nOB (-0.785) and Ob (-0.910); K-statistic between TyG and HOMA-IR: high agreement for prepubertal F and M	Pré-pubertal group: 4.65 (S:83.1%; Spe:74.5%); Pubertal group: F: 4.75 (S:88.5%; Spe:78.1%) M: 4.70 (S:88%; Spe:76.8%)

(*continued*)

Table 3. Continued.

Author/year	Group	Independent Variables (IV), Dependent (DV) and Confounding Factors (CF)	Formula	Main results	Cutoff point
				(0.910 and 0.902) and pubertal (0.932 and 0.925)	
Moon et al. (2017)	Mexican-American (MA), White non-Hispanics (WNH), Black non-Hispanics (BNH), Koreans (KO)	WC, BP, TG, HDL-c, FBG, TyG index. **VD:** MetS (Cook et al. (2003), De Ferranti et al. (2004) and IDF (2007); **CF:** sex, ethnicity.	Ln [Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	TyG index of BNH and KO was lower vs. MA and WNH; Modest correlation between TyG and HOMA-IR;	Cook et al.: 8.55 (MA; WNH); 8.35 (BNH; KO): 8.35 S: 89.4–97.3% Spe: 76.6–86.7% (min-max) De Ferranti et al.: 8.45 (MA e WNH); 8.15 (BNH); 8.35 (KO) S:85.1–93.8% Spe: 72.6–84.6% IDF: 8.65 (MA e WNH); 8.15 (BNH) and 8.55 (KO) S: 82.1–91.1% Spe: 73.2–87.7%
Kang et al. (2017)	Insulin-resistant (IR) and non-insulin-resistant (non-IR)	**IV:** Age, sex, WC, BP, BMI, %BF e LM (BIA), FBG, FI, TC, TG, HDL-c, LDL-c, HOMA-IR; TyG, TG/HDL-c; **DV:** Age, sex, WC, BP, BMI, %BF e LM (BIA), FBG, FI, TC, TG, HDL-c, LDL-c, HOMA-IR; TyG, TG/HDL-c;	Ln [Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	TyG index was higher in group IR vs. non-IR group (8.43 ± 0.45 vs. 8.05 ± 0.41); HOMA-IR correlated positively with TyG index ($r = 0.41$, $p < 0.001$) and TG / HDL-C ($r = 0.40$, $p < 0.001$), similarly TyG and TG / HDL-C had a strong positive correlation. ($r = 0.84$, $p < 0.001$);	TyG: 8.18 (S:77.4%; Spe:64.8%) TG/HDL: 1.16 (S:72.7%; Spe:61.8%)
Kim et al. (2016)	MetS by Cook et al. (2003), De Ferranti et al. (2004) and IDF (2007)	**IV:**Age, WC, BMI, BP, FBG, TG, HDL-c, FI, HOMA-IR, TyG index; **DV:** MetS (Cook et al. (2003), De Ferranti et al. (2004) and IDF (2007).	Ln [Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	HOMA-IR average: 2.97 total, 2.92M and 3.03F. TyG average: 8.13 total, 8.11M and 8.15F	HOMA-IR and TyG index, respectively: Cook et al.: Total: 3.29; 8.48 F: 3.49; 8.48 M: 2.98; 8.48. S: 73.3–76.5%; 94.4–96.3% Spe: 66.2–75.4%; 78.8–81.1% Ferranti et al.: Total: 2.96; 8.41; F: 2.96; 8,38; M: 2,86; 8,40. S: 71.1–74.9%; 85–88.2% Spe: 61.3–64.7%; 76.3–81.8% IDF: Total: 3.54; 8.66; F: 3.69; 8.61; M: 3.54; 8.66. S: 79.2–82.1%; 89.3–95.8% Spe: 77.7–79.3%; 84.1–86.5%
Mohd Nor et al. (2016)	156 OB-NGT; 37 OB-preDM; 32 OB-T2DM	**IV:** Z-score BMI, WC, race, gender, serum lipids (TC, LDL-c, HDL-c, TG), FBG and insulin. 2h OGTT. 3h HE clamp. **DV**: IR: Insulin stimulated Rd <4.9mg/kg/min. IR Markers: TyG Index, TG/HDL, 1/FI **CF** Age, Tanner	Ln [Fasting triglycerides (mg/dL) x fasting glucose (mg/dL)/2]	TyG average: 8.5 ± 0.5; TyG > in OB-T2DM and OB-preDM, white and M; OB-NGT < TG / HDL-c ratio> 1/FI; Coef. Spearman's correlation between TyG and Rd in blacks was −0.366 ($p < 0.0001$) and in whites −0.530 (p	8.52 (S:69.1%; Spe:71.7%)

(*continued*)

Table 3. Continued.

Author/year	Group	Independent Variables (IV), Dependent (DV) and Confounding Factors (CF)	Formula	Main results	Cutoff point
		Stage, Sex, BMI (z-score), glycemic group.		<0.0001); 51.4% of the variance in Rd (p <0.0001) was explained by TyG, BMI, gender, glycemic group, and race.;	

FA: daily time spent on active activities; HE clamp: Hyperinsulinemiceuglycemic clamp; EBF: Exclusive breastfeeding; WNH: Non-Hispanic Whites; KO: Koreans; TC: total cholesterol; DM: Diabetes Melittus; F: Female; CF: Confounding factors; FBG: Fasting blood glucose; IAC: indicators of body adiposity; BMI: Body Mass Index; FI: Fasting insulin; BNH: Non-Hispanic Blacks; M: Male; MA: Mexican American; LM: lean mass; BIA: bioimpedance; Ob: Obesity; OB-NGT: Obese with normal TOG; OB-preDM: Obese with pre-diabetes; OB-T2DM: Obese with type 2 DM; BP: blood pressure; S: sensitivity; Spe: specificity; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: Waist circumference; HC: Hip Circumference; NW: normal weight; IR: Insulin resistance; CVR: Cardiovascular risk; WHtR: waist/height ratio; MetS: metabolic syndrome; SP: Overweight; TOG: oral glucose tolerance; TG: Triglycerides; TMGT: Total Glucose Metabolism Rate; TTOG: Oral Glucose Tolerance Test; IV: Independent variables; DV: Dependent variables; % GC: Percentage of body fat.

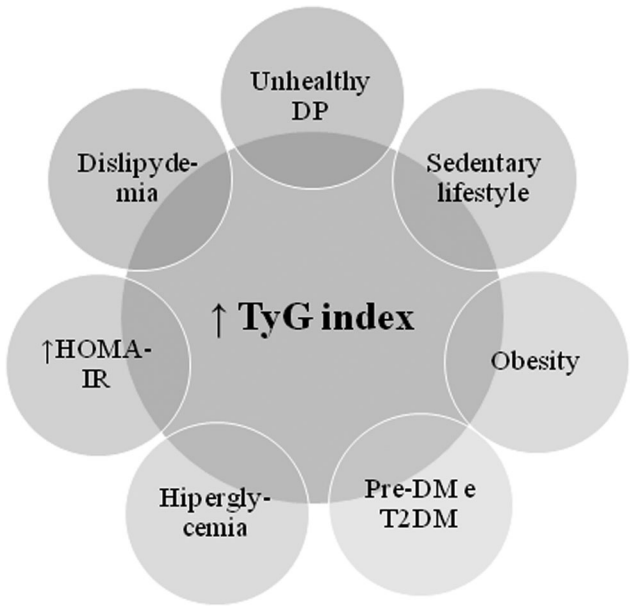

Figure 2. Risk factors related to higher TyG index values.
DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; HOMA-IR: Homeostasis Model of Assessment; DP: dietary pattern.

HDL-c concentrations, which corroborates with the relationship among obesity, IR and dyslipidemia in this age group.

In addition to all these factors, an unhealthy diet and lifestyle contribute to the development of obesity, IR, type 2 DM and other chronic diseases. Unhealthy dietary patterns, characterized by lower consumption of fresh or minimally processed foods and higher processed and ultra-processed foods, are one of the main causes of obesity and type 2 DM (Perkison, Adekanye, and de Oliveira Otto 2018). A Brazilian study with children aged 4 to 7 years have shown a positive association of "unhealthy" and "traditional" dietary patterns with indicators of body adiposity (BMI and total body fat) and central adiposity (WtHR and central fat) (Vieira-Ribeiro et al. 2019).

According to the ROC curve cutoff analysis for prediction of IR and MetS, TyG index values ranged from 4.65 to 8.66 in all groups (Kim et al. 2016; Mohd Nor et al. 2016; Moon, Park, and Ahn 2017; Kang et al. 2017; Vieira-Ribeiro et al. 2018, Angoorani et al. 2018). We highlight that the specificity for the cutoff points established was mostly lower in relation to the sensitivity (Kim et al. 2016; Mohd Nor et al. 2016; Moon, Park, and Ahn 2017; Kang et al. 2017; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017; Vieira-Ribeiro et al. 2018, Angoorani et al. 2018), noting the importance of performing other more specific tests to confirm the diagnosis, if the IR risk is determined by the TyG index (Vieira-Ribeiro et al. 2018).

The studies included in this review used different formulas to obtain the TyG index values. The original formula is Ln [fasting triglycerides (mg/dL) x fasting glucose (mg/dL)]/2 (Simental-Mendía, Rodríguez-Morán and Guerrero-Romero 2008), which generates results close to 4. However, most of the studies (Angoorani et al. 2018; Kang et al. 2017; Kim et al. 2016; Mohd Nor et al. 2016; Moon, Park, and Ahn 2017; Vieira-Ribeiro et al. 2018) calculated the Ln after dividing the product of triglycerides and fasting glucose by 2, which result in values around 8. Moreover, the values of the TyG index can be influenced by several characteristics, mainly by ethnicity (Mohd Nor et al. 2016; Moon, Park, and Ahn 2017; Kang et al. 2017; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017), degree of sexual maturation (Kim et al. 2016; Mohd Nor et al. 2016; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017) and sex (Mohd Nor et al. 2016; Angoorani et al. 2018), which explains the variation in the cutoff points found by the studies. Therefore, TyG index cutoff points already proposed in the literature should be carefully evaluated in clinical practice and epidemiological studies, and it is necessary to consider the kind of formula used, ethnicity, sex and the degree of puberty when choosing a reference value.

Few studies have used the HE clamp method as a reference for analysis (Mohd Nor et al. 2016; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017), and a negative correlation between the TyG index and the clamp evaluation units have been demonstrated. It is noteworthy that the implementation of this gold standard method to determine IR is laborious, time-consuming, expensive, and invasive, especially when used in child public(Chiarelli and

Marcovecchio 2008; Levy-Marchal et al. 2010). For this reason, many studies have used HOMA-IR as a reference method to determine cutoff points (Kim et al. 2016; Moon, Park, and Ahn 2017; Kang et al. 2017; Vieira-Ribeiro et al. 2018, Angoorani et al. 2018).

When compared to other IR predictors such as triglycerides/HDL-c ratio and HOMA-IR, TyG index presented strong correlation with TG/HDL-c ratio, high agreement and moderate positive correlation with HOMA-IR (Moon, Park, and Ahn 2017; Kang et al. 2017; Rodríguez-Morán, Simental-Mendía, and Guerrero-Romero 2017). The TyG index has the advantage of being based on fasting glucose levels, which has been shown to be directly related to the development of IR, beta cell dysfunction, pre-DM and type 2 DM in young adults. Thus, the fasting glycemic component of the TyG index may potentiate it for the prediction of diabetes in relation to lipid ratio (Kang et al. 2017; Nguyen et al. 2010; O'Malley et al. 2010).

The TyG index is easier to measure than the HOMA-IR, based on the components of its mathematical formulas. The TyG index appears to mainly reflect on muscle IR, since a possible increase in plasma triglycerides may be able to interfere in the normal muscle glucose metabolism, causing reduced insulin sensitivity.In contrast, HOMA-IR seems to reflect hepatic IR, asit expresses the ability of basal insulin to suppress hepatic glucose production in fasting situations (Irace et al. 2013; Kelley, Goodpaster, and Storlien 2002; Lee et al. 2014). The main limitation of this review is the lack of studies evaluating the TyG index in children/adolescents with different ethnicities and degrees of puberty. The lack of consensus on the definition of MetS, especially in children under 9 years of age, is also a limiting factor. In addition, due to the heterogeneity of the studies regarding the age, ethnicity, and methods of investigation of the variables, it was not possible to perform a meta-analysis of the data. Nevertheless, this review adds new information to literature, has the advantage of being based on the PRISMA guidelines, peer-review, and having a study quality assessment through the NHLBI method.

We concluded that the use of the TyG index to predict the IR risk and other cardiometabolic risk factors appears to be advantageous, as it is a noninvasive method that uses common components to clinical practice, making it accessible and low cost. Also, because it has a positive association with other methods, it is considered an important predictor for the IR risk and can be used to screen children and adolescents for the prevention of cardiovascular disease in adulthood.

Acknowledgements

We thank CAPES Foundation, Brazil (CAPES, Finance code 001) and *Fundação de Amparo a Pesquisa do Estado de Minas Gerais* (FAPEMIG) for granting master and doctoral scholarships for A.D.M.B., M.S.F. and L.G.S. HHM Hermsdorff has a Research Fellowship from CNPq (1D-level).

ORCID

Alice Divina Melo de Brito http://orcid.org/0000-0002-6698-4802
Helen Hermana Miranda Hermsdorff http://orcid.org/0000-0002-4441-6572
Mariana De Santis Filgueiras http://orcid.org/0000-0003-1932-6126
Lara Gomes Suhett http://orcid.org/0000-0002-2497-1587
Sarah Aparecida Vieira-Ribeiro http://orcid.org/0000-0002-0304-2711
Sylvia do Carmo Castro Franceschini http://orcid.org/0000-0001-7934-4858
Juliana Farias de Novaes http://orcid.org/0000-0003-3616-5096

References

Agrawal, S., and R. Gensure. 2018. Commentary on the impact of obesity on pediatric diabetes. *Clinical Therapeutics* 40 (10):1631–7. doi: 10.1016/j.clinthera.2018.08.006.

Angoorani, P., R. Heshmat, H.-S. Ejtahed, M. E. Motlagh, H. Ziaodini, M. Taheri, T. Aminaee, A. Goodarzi, M. Qorbani, and R. Kelishadi. 2018. Validity of triglyceride-glucose index as an indicator for metabolic syndrome in children and adolescents: The CASPIAN-V study. *Eating and Weight Disorders : EWD* 23 (6):877–83. doi: 10.1007/s40519-018-0488-z.

Chiarelli, F., and M. L. Marcovecchio. 2008. Insulin resistance and obesity in childhood. *European Journal of Endocrinology* 159 (Suppl_1):S67–S74. doi: 10.1530/EJE-08-0245.

Cook, S., M. Weitzman, P. Auinger, M. Nguyen, and W. H. Dietz. 2003. Prevalence of a metabolic syndrome phenotype in adolescents: Findings from the third National Health and Nutrition Examination Survey, 1988–1994. *Archives of Pediatrics & Adolescent Medicine* 157 (8):821–7. doi: 10.1001/archpedi.157.8.821.

De Ferranti, S. D., K. Gauvreau, D. S. Ludwig, E. J. Neufeld, J. W. Newburger, and N. Rifai. 2004. Prevalence of the metabolic syndrome in American adolescents: Findings from the Third National Health and Nutrition Examination Survey. *Circulation* 110 (16): 2494–7. doi: 10.1161/01.CIR.0000145117.40114.C7.

Du, T., G. Yuan, M. Zhang, X. Zhou, X. Sun, and X. Yu. 2014. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovascular Diabetology* 13:146. doi: 10.1186/s12933-014-0146-3.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 2001. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment Panel III). *Journal of the American Medical Association* 285:2486–97. doi: 10.1001/jama.285.19.2486.

Guerrero-Romero, F., L. E. Simental-Mendía, M. González-Ortiz, E. Martínez-Abundis, M. G. Ramos-Zavala, S. O. Hernández-González, O. Jacques-Camarena, and M. Rodríguez-Morán. 2010. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *The Journal of Clinical Endocrinology & Metabolism* 95 (7):3347–51. doi: 10.1210/jc.2010-0288.

Güngör, N. K. 2014. Overweight and obesity in children and adolescents. *Journal of Clinical Research in Pediatric Endocrinology* 6 (3): 129–43. doi: 10.4274/Jcrpe.1471.

Han, J. C., D. A. Lawlor, and S. Y. Kimm. 2010. Childhood obesity. *The Lancet* 375 (9727):1737–48. doi: 10.1016/S0140-6736(10)60171-7.

Irace, C., C. Carallo, F. B. Scavelli, M. S. De Franceschi, T. Esposito, C. Tripolino, and A. Gnasso. 2013. Markers of insulin resistance and carotid atherosclerosis. A comparison of the homeostasis model assessment and triglyceride glucose index. *International Journal of Clinical Practice* 67 (7):665–72. doi: 10.1111/ijcp.12124.

Kang, B., Y. Yang, E. Y. Lee, H. K. Yang, H.-S. Kim, S.-Y. Lim, J.-H. Lee, S.-S. Lee, B.-K. Suh, and K.-H. Yoon. 2017. Triglycerides/glucose index is a useful surrogate marker of insulin resistance among

adolescents. *International Journal of Obesity* 41 (5):789–92. doi: 10.1038/ijo.2017.14.

Kelley, D. E., B. H. Goodpaster, and L. Storlien. 2002. Muscle triglyceride and insulin resistance. *Annual Review of Nutrition* 22:325–46. doi: 10.1146/annurev.nutr.22.010402.102912.

Kim, J. W., S. H. Park, Y. Kim, M. Im, and H.-S. Han. 2016. The cutoff values of indirect indices for measuring insulin resistance for metabolic syndrome in Korean children and adolescents. *Annals of Pediatric Endocrinology & Metabolism* 21 (3):143–8. doi: 10.6065/apem.2016.21.3.143.

Lee, S.-H., H.-S. Kwon, Y.-M. Park, H.-S. Ha, S. H. Jeong, H. K. Yang, J.-H. Lee, H.-W. Yim, M.-I. Kang, W.-C. Lee, et al. 2014. Predicting the development of diabetes using the product of triglycerides and glucose: The chungju metabolic disease cohort (CMC) study. *PLoS One.* 9 (2):e90430. doi: 10.1371/journal.pone.0090430.

Levy-Marchal, C., S. Arslanian, W. Cutfield, A. Sinaiko, C. Druet, M. L. Marcovecchio, and F. Chiarelli. 2010. Insulin resistance in children: Consensus, perspective, and future directions. *The Journal of Clinical Endocrinology and Metabolism* 95 (12):5189–98. doi: 10.1210/jc.2010-1047.

Maffeis, C., and A. Morandi. 2018. Body composition and insulin resistance in children. *European Journal of Clinical Nutrition* 72 (9): 1239–45. doi: 10.1038/s41430-018-0239-2.

Mohd Nor, N. S., S. Lee, F. Bacha, H. Tfayli, and S. Arslanian. 2016. Triglyceride glucose index as a surrogate measure of insulin sensitivity in obese adolescents with normoglycemia, prediabetes, and type 2 diabetes mellitus: Comparison with the hyperinsulinemic–euglycemic clamp. *Pediatric Diabetes* 17 (6):458–65. doi: 10.1111/pedi.12303.

Moher, D., A. Liberati, J. Tetzlaff, and D. G. Altman, and PRISMA Group. 2009. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine* 6 (7): e1000097 doi: 10.1371/journal.pmed.1000097.

Moon, S., J.-S. Park, and Y. Ahn. 2017. The cut-off values of triglycerides and glucose index for metabolic syndrome in american and korean adolescents. *Journal of Korean Medical Science* 32 (3):427–33. doi: 10.3346/jkms.2017.32.3.427.

Nguyen, Q. M., S. R. Srinivasan, J. H. Xu, W. Chen, and G. S. Berenson. 2010. Fasting plasma glucose levels within the normoglycemic range in childhood as a predictor of prediabetes and type 2 diabetes in adulthood: The bogalusa heart study. *Archives of Pediatrics and Adolescent Medicine* 164:124–8.

O'Malley, G., N. Santoro, V. Northrup, E. D'Adamo, M. Shaw, S. Eldrich, and S. Caprio. 2010. High normal fasting glucose level in obese youth: A marker for insulin resistance and beta cell dysregulation. *Diabetologia* 53 (6):1199–209. doi: 10.1007/s00125-010-1693-0.

Perkison, W. B., J. A. Adekanye, and M. C. de Oliveira Otto. 2018. Dietary interventions and type 2 diabetes in youth: A fresh look at the evidence. *Current Nutrition Reports* 7 (4):227–34. doi: 10.1007/s13668-018-0241-2.

Rodríguez-Morán, M., L. E. Simental-Mendía, and F. Guerrero-Romero. 2017. The triglyceride and glucose index is useful for recognising insulin resistance in children. *Acta Paediatrica (Oslo, Norway : 1992)* 106 (6):979–83. doi: 10.1111/apa.13789.

Romualdo, M. C. S., F. J. Nóbrega, and M. A. M. S. Escrivão. 2014. Insulin resistance in obese children and adolescents. *Jornal de Pediatria* 90 (6):600–7. doi: 10.1016/j.jped.2014.03.005.

Sesti, G. 2006. Pathophysiology of insulin resistance. *Best Practice & Research. Clinical Endocrinology & Metabolism* 20 (4):665–79. doi: 10.1016/j.beem.2006.09.007.

Simental-Mendía, L. E., M. Rodríguez-Morán, and F. Guerrero-Romero. 2008. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metabolic Syndrome and Related Disorders* 6 (4):299–304. doi: 10.1089/met.2008.0034.

Simental-Mendía, L. E., G. Hernández-Ronquillo, R. Gómez-Díaz, M. Rodríguez-Morán, and F. Guerrero-Romero. 2017. The triglycerides and glucose index is associated with cardiovascular risk factors in normal-weight children and adolescents. *Pediatric Research* 82 (6): 920–5. doi: 10.1038/pr.2017.187.

Unger, G., S. F. Benozzi, F. Perruzza, and G. L. Pennacchiotti. 2014. Triglycerides and glucose index: A useful indicator of insulin resistance. *Endocrinologia y Nutricion : Organo de la Sociedad Espanola de Endocrinologia y Nutricion* 61 (10):533–40. doi: 10.1016/j.endoen.2014.11.006.

Vasques, A. C. J., F. S. Novaes, M. S. Oliveira, J. R. M. Souza, A. Yamanaka, J. C. Pareja, M. A. Tambascia, M. J. A. Saad, and B. Geloneze. 2011. TyG index performs better than HOMA in a Brazilian population: A hyperglycemic clamp validated study. *Diabetes Research and Clinical Practice* 93 (3):e98–e100. doi: 10.1016/j.diabres.2011.05.030.

Verduci, E., C. Lassandro, R. Giacchero, V. L. Miniello, G. Banderali, and G. Radaelli. 2015. Change in metabolic profile after 1-year nutritional-behavioral intervention in obese children. *Nutrients* 7 (12):10089–99. doi: 10.3390/nu7125520.

Vieira-Ribeiro, S. A., P. C. A. Fonseca, C. S. Andreoli, A. Q. Ribeiro, H. H. M. Hermsdorff, P. F. Pereira, S. E. Priore, and S. C. C. Franceschini. 2018. The TyG index cutoff point and its association with body adiposity and lifestyle in children. *Jornal de Pediatria* 95 (2):217–23. doi: 10.1016/j.jpedp.2018.03.010.

Vieira-Ribeiro, S. A., C. S. Andreoli, P. C. A. Fonseca, H. H. M. Hermsdorff, P. F. Pereira, A. Q. Ribeiro, S. E. Priore, and S. C. C. Franceschini. 2019. Dietary patterns and body adiposity in children in Brazil: A cross-sectional study. *Public Health* 166:140–7. doi: 10.1016/j.puhe.2018.10.002.

WHO. 2017. Overweight and obesity. Acessed March 27, 2020. http://www.who.int/gho/ncd/risk_factors/overweight_adolescents_text/en/.

Zimmet, P., G. Alberti, F. Kaufman, N. Tajima, M. Silink, S. Arslanian, G. Wong, P. Bennett, J. Shaw, and S. Caprio. 2007. The metabolic syndrome in children and adolescents. *The Lancet* 369 (9579): 2059–61. doi: 10.1016/S0140-6736(07)60958-1.