



HOMA-IR and TyG index differ for their relationship with dietary, anthropometric, inflammatory factors and capacity to predict cardiovascular risk

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ABSTRACT

Background: HOMA-IR and the triglyceride-glucose index (TyG index) are surrogate indexes of insulin resistance. However, it remains to elucidate how HOMA-IR and the TyG index compare for their relationship with cardiometabolic health.

Aim: This study aimed at comparing HOMA-IR and the TyG index with regard to their relationship with anthropometric, dietary and inflammatory factors as well as ability to predict cardiovascular risk.

Methods: 438 subjects aged 55–80 years, underwent anthropometric, metabolic and nutritional characterisation. Spearman's correlation coefficient was used to evaluate the association between the parameters of interest. Predictors of HOMA-IR, the TyG index and the 10-year risk of cardiovascular events were investigated using stepwise multivariable regression analysis.

Results: HOMA-IR and TyG index correlated positively with body mass index, waist circumference, fat mass, systolic and diastolic blood pressure, interleukin-18 and C-reactive protein. However, only HOMA-IR correlated with dietary factors.

After adjusting for age and sex, waist circumference and interleukin-18 were stronger predictors of HOMA-IR compared to the TyG index. Instead, the TyG index, but not HOMA-IR, emerged as a predictor of cardiovascular risk.

Conclusions: The TyG index represents a better predictor of cardiovascular risk compared to HOMA-IR which, instead, exhibits a stronger relationship with anthropometric, inflammatory and nutritional variables.

1. Introduction

Insulin resistance is a pivotal determinant in shaping cardiometabolic health [1]. Indeed, it represents a crucial pathogenetic link between obesity and its comorbidities, such as the metabolic syndrome [2], type 2 diabetes [3], cardiovascular disease [4], metabolic dysfunction-associated steatotic liver disease (MASLD) [5], as well as neurodegenerative diseases like Alzheimer's [6] and Parkinson's disease [7]. Environmental factors such as unhealthy dietary habits and physical inactivity are central to the pathogenesis of insulin resistance [8]. They foster a positive energy balance leading to adipose tissue hypertrophic

expansion and dysfunction [9]. The latter, in turn, is pivotal in promoting insulin resistance by triggering lipotoxicity and low-grade chronic inflammation [10–12]. Additionally, specific nutrients like long-chain saturated fatty acids and sugar, as well as non-nutrients like advanced glycation end products, rather than calories per se, appear to be instrumental in promoting insulin resistance [12–14]. Currently, the gold standard for the assessment of insulin resistance is the euglycemic hyperinsulinemic clamp [15]. However, this technique is expensive, invasive and requires highly specialised personnel which makes its use in the clinical setting rather challenging. In light of these drawbacks, several surrogate indexes to assess insulin resistance were developed.

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[16]. The homeostasis model assessment for insulin resistance (HOMA-IR) and triglyceride-glucose (TyG) index are among the most widely used surrogate indexes of insulin resistance [17–19]. HOMA-IR is computed using fasting glucose and insulin levels and relies on the fact that hyperinsulinemia is an initial compensatory response to insulin resistance to maintain euglycemia as in the case of individuals with prediabetes or the metabolic syndrome [18]. The TyG index is also a static index of insulin resistance and is calculated using fasting glucose and triglyceride levels [20]. Contrarily to the HOMA-IR, the principle behind the TyG index is that both glucose and triglycerides increase in response to insulin resistance [21]. Furthermore, since TyG index does not require insulin measurement, it is more cost-effective than HOMA-IR and can be applied to all people, regardless of whether they are undergoing insulin treatment [22]. However, while it is well established that diet and body composition are both able to modulate insulin resistance [10,23], and subsequently affect cardiovascular health [24], the comparative relationships of HOMA-IR and TyG index with dietary factors, anthropometry as well as cardiometabolic health remain to be fully elucidated.

Thus, the aim of this study was to evaluate whether and to what extent dietary and anthropometric factors correlate with HOMA-IR and TyG index and if these surrogate indexes of insulin resistance differ for their relationship with cardiometabolic risk factors.

2. Subjects and methods

2.1. Study participants

Four hundred and thirty-eight subjects from PANGeA project [25] were considered for this study. Inclusion criteria were free-living subjects aged 55–80 years with the capability to walk 2 km independently. Individuals with cancer diagnosis, subjects with diabetes under insulin treatment or with diabetes complications, a history of hospitalization in the previous year, therapy with anticoagulants or lacking biochemical data were excluded. Study participants underwent anamnestic and nutritional interviews, anthropometric measurements and blood sampling.

Written informed consent was obtained from each participant. National Ethical Committee of the Slovenian Ministry of Health approved this study on April 17, 2012, under the acronym IR-aging 1200. This study was conformed to the ethical principles for medical research involving human subjects as required by the 2013 Review of the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

2.2. Dietary assessment

Food frequency and 24-hour recall questionnaires were administered to subjects by trained medical doctors with nutrition expertise.

Mediterranean Diet Adherence (MDA) was estimated considering the frequency consumption of 13 foods/food groups (milk and dairy products; cereals and grain products; vegetables; legumes; fruit, olive oil; white meat; red and processed meat; fish; sweets and desserts; nuts and seeds, and wine) according to the guidelines of the Mediterranean diet [26] as specified previously [25]. MDA ranged from 0 to 26 points.

To evaluate the dietary habits, the retrospective and quantitative 24-hour recall questionnaire was administered to the subjects twice, on the day of the visit and by telephone one month later. Total energy, macro- and micronutrients were estimated from the average of the data obtained from the analysis of the two 24-hour recalls using the nutrient analysis software Winfood R PRO 3.9.x (Medimatica Surl, Teramo, Italy).

2.3. Anthropometric measurements

Study participants wearing light clothing with no restrictive

underwear and no shoes, were subjected to the measure of body weight, height, waist and hip circumferences by trained medical doctors.

2.4. Bioelectrical impedance analysis (BIA)

Basal Metabolic Rate and Body composition were estimated using bioimpedance with a tetra-polar impedance-meter (BIA101, Akern, Florence, Italy). The subjects fasting for eight hours were lying down to perform the BIA according to manufacturer's instructions.

2.5. Biochemical analysis

Serum or plasma were collected from fasting blood samples centrifuged at 1600g for 15 min at 4 °C. Aliquoted samples were stored at –80 °C until use. Total Cholesterol (TC), HDL Cholesterol, triglycerides, glucose and insulin were assayed by standard enzymatic-colorimetric methods (24). High-sensitivity C-reactive protein (CPR) was assessed using the immune-turbidimetric kit CRP OSR6147 (Beckman Coulter, Brea, CA, USA). LDL Cholesterol was calculated by the Friedewald's formula (25). Insulin resistance was assessed using the Homeostasis model assessment index (HOMA-IR) and the Triglyceride glucose index (TyG) which was computed as follow:

$$\text{HOMA-IR} = [\text{glucose}(\text{mg/dl}) * \text{insulin}(\text{mU/l})] / 405$$

$$\text{TyGIndex} = \text{Ln}[\text{Triglyceride}(\text{mg/dL}) * \text{Glucose}(\text{mg/dL})] / 2$$

2.6. Evaluation of cardiovascular risk

The 10-year risk of fatal and non-fatal cardiovascular disease events was estimated using the algorithms SCORE2 (Systematic COronary Risk Evaluation) or SCORE2-OP (Systematic COronary Risk Evaluation Older Persons) respectively for individuals aged 40–69 years and over 70 years, without previous CVD events, for the cluster of countries at moderate risk [27,28]. The variables included in the calculation of those scores were: age, gender, smoking, TC, HDL-C, systolic blood pressure and diagnosis of diabetes.

2.7. Metabolic syndrome

Metabolic syndrome was defined according to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) and diagnosed in the presence of three or more of the following five criteria: (1) waist circumference ≥ 102 cm in men or ≥ 88 cm in women; (2) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or taking antihypertensive medications; (3) fasting triglycerides level ≥ 150 mg/dl or taking lipid lowering medications; (4) fasting HDL cholesterol ≤ 40 mg/dl in men or ≤ 50 mg/dl in women or pharmacological treatment for low HDL cholesterol; and (5) fasting blood glucose ≥ 100 mg/dl or taking hypoglycaemic medications. The metabolic syndrome Score ranged from 0 to 5 depending on the number of positive criteria.

2.8. Statistical analysis

Continuous variables were expressed as Mean \pm standard deviation (SD) and analyzed using Shapiro-Wilk tests to identify normally and non-normally distributed variables. Spearman's correlation coefficient was used to test the association between the parameters of interest. Stepwise multiple regression analysis was performed to reveal the independent predictors of HOMA-IR, TyG Index and the 10-year risk of cardiovascular disease events. Not normally distributed variables were log transformed for regression analysis. Data analysis was performed using SPSS Statistics for Windows, version 26.0 (SPSS, Inc., Chicago, IL) and a $p \leq 0.05$ was considered statistically significant.

Missing data for each variable of interest did not exceed 5 %.

3. Results

3.1. General characteristics of the study population

The metabolic and anthropometric characteristics of study participants are reported in [Table 1](#) which also include levels of the inflammatory biomarkers Interleukin-18 (IL-18) and C-reactive protein (CRP) as well as the Mediterranean Diet adherence score of the study cohort. In terms of the insulin resistance of the cohort, study participants displayed a HOMA-IR of 2.4 ± 0.1 (mean \pm SD) and a TyG index of 8.4 ± 0.1 (mean \pm SD) ([Table 1](#)).

3.2. The relationship between HOMA-IR, TyG index and cardiometabolic health

The TyG index has been reported to positively correlate with HOMA-IR [[29,30](#)], therefore it was first evaluated whether this relationship held true in the present study cohort. As expected, the TyG index positively correlated with HOMA-IR ([Table 2](#)). In order to evaluate how these surrogate indexes of insulin resistance compared with regard to their relationship with cardiometabolic risk, it was next investigated whether HOMA-IR and the TyG index correlated with anthropometric and metabolic variables as well as with the estimated 10-year primary risk of atherosclerotic cardiovascular disease. While HOMA-IR and the TyG index did not correlate with age, they, albeit to a different extent, positively correlated with BMI, fat mass, waist circumference, systolic and diastolic blood pressure, circulating triglycerides, IL-18 and CRP ([Table 2](#)). Similarly, both indexes correlated negatively with fat-free mass and HDL-cholesterol ([Table 2](#)). Conversely, HOMA-IR and the TyG index displayed an opposite behaviour in terms of their relationship with total and LDL-cholesterol. Indeed, while HOMA-IR correlated negatively with total cholesterol and did not correlate with LDL-

Table 1
Study participant characteristics.

Subjects, number	438
Female, number (%)	234 (53.4 %)
Age (years)	66 \pm 5
Systolic blood pressure (mmHg)	140 \pm 19
Diastolic blood pressure (mmHg)	85 \pm 10
Body mass index (kg/m ²)	26.7 \pm 3.8
Waist Circumference (cm)	92.9 \pm 10.4
Hip Circumference (cm)	98.2 \pm 9.6
Muscle Mass (Kg)	29.2 \pm 6.4
Fat Free Mass (%)	64.8 \pm 6.6
Fat Mass (%)	35.2 \pm 6.6
Glucose (mg/dL)	100.2 \pm 20.1
Insulin (U/L)	9.4 \pm 5.7
HOMA-IR	2.4 \pm 1.8
TyG index	8.4 \pm 0.5
Triglycerides (mg/dL)	100.9 \pm 44.7
Total Cholesterol (mg/dL)	216.2 \pm 38.5
Cholesterol HDL (mg/dl)	66.5 \pm 17.6
Cholesterol LDL (mg/dl)	129.5 \pm 33.9
IL-18 (pg/ml)	382.1 \pm 140.5
CRP (mg/dl)	0.2 \pm 0.3
Obesity, number (%)	156 (35.%)
Hypertension, number (%)	130 (29.7 %)
ic T2D subjects under metformin treatment, number (%)	16 (3.7 %)
Subjects with glucose > 126 mg/dl upon recruitment	19 (4.3 %)
Metabolic Syndrome, number (%)	74 (16.9 %)
Hypolipidemic treatment	77 (17.6 %)
Smoke, number (%)	41 (9.4 %)
Previous cardiovascular event	16 (3.7 %)
10-year risk of cardiovascular disease events	8.6 \pm 4.5

Data are expressed as mean \pm SD or as number (%) or N (%). SD, standard deviation; HOMA-IR, homeostatic model assessment for insulin resistance; TyG Index, Triglyceride glucose Index; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; IL-18, Interleukin-18; CRP, high-sensitivity C-reactive protein; T2D, Diabetes of type 2 diabetes.

Table 2

Spearman correlation between HOMA-IR and TyG Index with parameters of interest.

	HOMA-IR		TyG Index	
	Spearman's Rho	p-value	Spearman's Rho	p-value
TyG Index	0.492	<0.001		
Age (years)	0.057	0.236	0.072	0.134
Body mass index (kg/m ²)	0.529	<0.001	0.286	<0.001
Fat Free Mass (%)	-0.232	<0.001	-0.116	0.015
Fat Mass (%)	0.232	<0.001	0.116	0.015
Waist circumference (cm)	0.537	<0.001	0.270	<0.001
Systolic blood pressure (mmHg)	0.146	0.002	0.135	0.005
Diastolic blood pressure (mmHg)	0.125	0.009	0.130	0.007
Triglycerides (mg/dL)	0.369	<0.001	0.937	<0.001
Total Cholesterol (mg/dL)	-0.125	0.009	0.202	<0.001
LDL Cholesterol (mg/dL)	-0.074	0.12	0.248	<0.001
HDL Cholesterol (mg/dL)	-0.306	<0.001	-0.453	<0.001
Interleukin-18 (pg/mL)	0.272	<0.001	0.151	0.002
C-reactive protein (mg/L)	0.205	<0.001	0.158	0.001
10-year risk of cardiovascular disease events	0.173	<0.001	0.281	<0.001
Nutritional parameters				
Total calories (kcal/day)	-0,018	0,705	-0,048	0,322
Protein (g/day)	0,004	0,930	0,008	0,875
Lipid (g/day)	0,019	0,690	-0,047	0,327
Available carbohydrates (g/day)	-0,067	0,167	-0,039	0,422
Total fiber (g/day)	-0,171	0,001	-0,080	0,100
Cholesterol (mg/day)	0,126	0,009	0,054	0,269
MUFA/SFA ratio	-0,148	0,002	-0,081	0,093
Omega 3/Omega 6 ratio	-0,124	0,010	-0,06	0,217
Omega 3/SFA ratio	-0,155	<0,001	-0,087	0,074
Mediterranean Diet Adherence	-0,101	0,034	-0,080	0,096

HOMA-IR, homeostatic model assessment for insulin resistance; LDL, Low Density Lipoprotein; HDL, High Density Lipoprotein; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

cholesterol, the TyG index correlated positively with both total and LDL-cholesterol ([Table 2](#)). Finally, both indexes correlated positively with the estimated 10-year primary risk of atherosclerotic cardiovascular disease ([Table 2](#)).

3.3. Nutrient intake and adherence to the Mediterranean diet correlate with HOMA-IR but not the TyG index

Considering that diet is a crucial player in modulating insulin sensitivity [[23,31–33](#)], it was next assessed whether this would be reflected in the relationship between dietary variables, HOMA-IR as well as the TyG index. No relationship was observed between the TyG index and nutrient intake ([Table 2](#)). However, the TyG index tended to negatively correlate with the Mediterranean Diet adherence score as well as with the ratio between the intake of mono- and saturated fatty acids ([Table 2](#)). On the contrary, HOMA-IR correlated negatively with the intake of dietary fibre; the mono to saturated fatty acid, the omega-3s to omega-6s and the saturated to omega-3 fatty acid ratio as well as the Mediterranean Diet adherence score.

3.4. Anthropometric and inflammatory factors differently predict HOMA-IR and the TyG index

HOMA-IR and the TyG index displayed different correlation patterns with anthropometric, inflammatory and nutritional variables. In light of this, it was evaluated whether these surrogate indexes of insulin resistance could be differently predicted by variables known to affect insulin sensitivity, such as BMI, fat mass and waist circumference [[10,34,35](#)],

the pro-inflammatory cytokine IL-18 [36–38] and the intake of saturated fatty acids [12,32,39]. With regard to HOMA-IR, waist circumference emerged as the main predictor (Table 3). The predictive power of waist circumference for HOMA-IR was further implemented by IL-18 circulating levels, fat mass and BMI in model 2, 3 and 4, respectively (Table 3). However, all the dietary factors that displayed a relationship with HOMA-IR were excluded from the linear regression model, indicating they are not direct predictors of this surrogate index on IR. Instead, the only variables able to predict the TyG index were represented by waist circumference in model 1 and circulating IL-18 levels in model 2 (Table 4). Despite these variables being shared predictors for both HOMA-IR and the TyG index, their predictive power was higher for HOMA-IR (Table 3 & Table 4).

3.5. The TyG index but not HOMA-IR predicts cardiovascular risk

Despite HOMA-IR and the TyG index, being closely interrelated, they are differently predicted by known cardiometabolic risk factors. Given the central role of insulin resistance in the pathogenesis of cardiovascular disease [24,40] it was evaluated whether the differences between these two surrogate indexes of insulin resistance also apply to their ability to predict cardiovascular risk. While HOMA-IR was excluded from the linear regression model, the TyG index was able to increase the predictive power of waist circumference and fat mass for the estimated 10-year primary risk of atherosclerotic cardiovascular disease (Table 5).

4. Discussion

The data reported herein indicate that, albeit HOMA-IR and the TyG index having been reported to be reliable indicators of insulin resistance [16,18,21], they differ for their relationship with known anthropometric, dietary and inflammatory factors known to modulate IR which are more closely related to HOMA-IR. On the contrary, the TyG index, but not HOMA-IR, emerged as a predictor of cardiovascular risk.

Excess fat mass and particularly central adiposity are key drivers or insulin resistance [41]. In agreement with this, it is not surprising that both the surrogate indexes of insulin resistance assessed as part of this study correlated positively with BMI, fat mass and waist circumference. More importantly, however, HOMA-IR appeared to be more susceptible to changes in these anthropometric measures compared to the TyG index, with waist circumference representing the only shared predictor

Table 3
Multiple linear regression model indicating predictors of HOMA-IR.

Model	R ²	value model	Predictor	Unstandardized B coefficient	p value
1	0.238	<0.001	Constant	-0.885	<0.001
			Waist circumference (cm)	0.013	<0.001
2	0.267	<0.001	Constant	-1.067	<0.001
			Waist circumference (cm)	0.011	<0.001
			Log(Interleukin-18)	0.326	<0.001
3	0.290	<0.001	Constant	-2.379	<0.001
			Waist circumference (cm)	0.010	<0.001
			Log(Interleukin-18)	0.367	<0.001
4	0.303	<0.001	logFFM(%)	0.521	<0.001
			Constant	-12.166	<0.001
			Waist circumference (cm)	0.011	<0.001
			Log(Interleukin-18)	0.344	<0.001
5	0.317	<0.001	logFM(K%)	2.478	<0.001
			logFFM(%)	3.750	0.004
			Constan	-15.355	<0.0010.004
			tWaist circumference (cm)	0.006	<0.001
			Log(Interleukin-18)	0.341	<0.001
			logFM(%)	2.761	<0.001
			logFFM(%)	4.654	0.001
			logBMI	1.100	0.004

Parameters considered for this analysis: Age, Sex, Waist circumference; logBMI; logFFM(%); logFM (K%); logIL-18; logCRP; log(Mediterranean Diet Adherence); log(Omega 3/SFA ratio); log(Omega 3/Omega 6 ratio); log(MUFA/SFA ratio); logCholesterol; log(Total fiber).

FM, Fat Mass; FFM, Fat Free Mass; BMI, body mass index; CRP, high-sensitivity C-reactive protein; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

Table 4
Multiple linear regression model indicating predictors of TyG Index.

Model	R ²	value model	Predictor	Unstandardized B coefficient	p value
1	0.086	<0.001	Constant	0.864	<0.001
			Waist circumference (cm)	0.001	<0.001
2	0.095	<0.001	Constant	0.8310.001	<0.001
			Waist circumference (cm)		<0.001
			Log(Interleukin-18)	0.015	0.048

Parameters considered for this analysis: Age, Sex, Waist circumference; for logBMI; logFFM(%); logFM (K%); log(Interleukin-8); logCRP; log(Mediterranean Diet Adherence); log(Omega 3/SFA ratio); log(Omega 3/Omega 6 ratio); log(MUFA/SFA ratio); logCholesterol; log(Total fiber).

FM, Fat Mass; FFM, Fat Free Mass; BMI, body mass index; CRP, C-reactive protein; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

between these surrogate indexes of insulin resistance. In keeping with this, waist circumference alone explained 23.8 % of HOMA-IR variability, whereas this value dropped to 8.6 % when considering the TyG index. These findings are in agreement with previous reports which highlighted the role of central adiposity as a key risk factor for an increase in HOMA-IR [42]. Besides central adiposity, described herein by waist circumference, low-grade chronic inflammation is also pivotal in promoting insulin resistance [43,44]. In agreement with this, not only both HOMA-IR and TyG were positively correlated with CRP and IL-18, but IL-18 emerged as a predictor of both surrogate indexes of insulin resistance. However, again, the predictive power of this cytokine, known to alter insulin signalling [36,38], was significantly higher for HOMA-IR compared to TyG index variability. Thus, also considering the correlation coefficient of 0.424 between HOMA-IR and the TyG index, these surrogates of insulin resistance are not completely overlapping and may describe different aspects of cardiometabolic risk. Additionally, HOMA-IR appear to be more closely related to anthropometric variables and pro-inflammatory mediators known to interfere with insulin sensitivity. Thus, HOMA-IR may be to be more susceptible to the anthropometric variables and inflammatory mediators known to hamper insulin sensitivity and may therefore represent a better indicator, compared to

Table 5
Multiple linear regression model indicating predictors of 10-year risk of Cardiovascular disease events.

Model	R ²	value model	Predictor	Unstandardized B coefficient	p value
1	0.095	<0.001	Constant	0,267	0.006
			Waist circumference (cm)	0,007	<0.001
2	0,218	<0.001	Constant	1,5370,009	<0.001
			Waist circumference (cm)		<0.001
3	0,218	<0.001	logFM(%)	-0,975	<0.001
			Constantlog(TyG index)	-0.6700.008	0.124
			LogFM(%)	-0.997	<0.001
			Waist circumference (cm)	2.542	<0.001

Parameters considered for this analysis: logTyG index; logBMI; waist circumference; logFFM(%); logFM (K%); logInterleukin-18; logCRP; log (Mediterranean Diet Adherence); log(Omega 3/SFA ratio); log(Omega 3/Omega 6 ratio); log(MUFA/SFA ratio); logCholesterol; log (Total fiber); log(HOMA-IR).

BMI, body mass index; FM, Fat Mass; FFM, Fat Free Mass; CRP, C-reactive protein MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

the TyG index, to purely evaluate the relationship between insulin resistance, anthropometric and inflammatory variables. Another variable potentially contributing to lowering the correlation coefficient between HOMA-IR and the TyG index may be the genetic background of the study population. Indeed, the PNPLA3 rs738409 CC and GG genotypes significantly affected the relationship between HOMA-IR and the TyG index, with the GG genotype abolishing their correlation [45]. This effect may rely on the increase in liver fat content in the GG genotype carriers [46]. In line with this, while insulin resistance being one on the most common risk factors for the development of MASLD [5], genetic factors have also been implicated in the pathogenesis of fatty liver independently of insulin resistance [47]. However, from the data presented herein, also considering that study participants did not report an history of MASLD, it cannot be inferred whether the discrepancies between HOMA-IR and the TyG index may be driven by MADFLD also given that both surrogate indexes of insulin resistance are associated with fatty liver [48,49].

In further support of the discrepancies between HOMA-IR and the TyG index, only the first showed a significant relationship with dietary factors known to influence insulin sensitivity. Indeed, the intake of dietary fibre and the adherence to the Mediterranean diet, which have both been widely reported to improve insulin sensitivity [50,51], negatively correlated with HOMA-IR but not with the TyG index. The same applies when considering dietary fatty acids, with an increase in saturated fatty acid intake in the face of a lower consumption of unsaturated fatty acids negatively correlating with HOMA-IR only. This is in agreement with the fact that saturated fatty acids, as opposed to unsaturated and particularly mono e omega-3 polyunsaturated fatty acids, are able to disrupt insulin signal transduction thereby promoting insulin resistance [52,53]. Finally, dietary cholesterol which has also been previously associated with the onset of insulin resistance [54,55] correlated positively with insulin resistance assessed using HOMA-IR but not the TyG index. In light of this, HOMA-IR, as opposed to the TyG index, may represent a better surrogate to evaluate the relationship between insulin resistance and diet quality. Indeed, while, to our knowledge this was the first study comparing the relationship between these two surrogates of insulin resistance and dietary factors, the TyG index has already been shown not to relate with healthy dietary patterns [56,57]. On the contrary, HOMA-IR has been negatively associated with healthy dietary patterns [58,59], as it is the case of the adherence to the Mediterranean diet as part of this study. Additionally, besides dietary

patterns, HOMA-IR has been shown to have a close relationship with dietary fatty acid intake, with mono and polyunsaturated fatty acids improving this surrogate index of insulin resistance when replacing saturated fatty acids [60]. The relationship between dietary factors, HOMA-IR, and the TyG index may be explained by diet-induced changes in insulin circulating levels [61], which, in turn, largely drive HOMA-IR [62].

The fact that HOMA-IR and the TyG may describe different aspects of cardiometabolic risk is further corroborated by the fact that the TyG index was described as superior to HOMA-IR in predicting the metabolic syndrome [63,64]. The metabolic syndrome, in turn, is a constellation of metabolic aberrations which ultimately increase cardiovascular risk [65]. These notions are reflected in the data reported herein, with the TyG but not the HOMA-IR being able to increase the predictive power of waist circumference and fat mass for the estimated 10-year primary risk of atherosclerotic cardiovascular disease. In further support of this, the TyG has also been previously associated with cardiovascular disease [66,67] and described as a predictor of premature atherosclerotic cardiovascular disease [63]. The reason underpinning the discrepancy between HOMA-IR and the TyG in predicting cardiovascular disease may be explained by the fact that the latter exhibited a stronger positive correlation with non-HDL and particularly LDL-cholesterol which, in turn, is pivotal in promoting atherosclerotic cardiovascular disease [68]. Additionally, an increase in circulating triglycerides, and therefore of the TyG index, is strongly associated with a drop in HDL-cholesterol [69]. Indeed, the TyG index, relative to HOMA-IR, displayed a stronger negative correlation with HDL-cholesterol, which instead is inversely associated with CVD risk [70], even though it must be acknowledged that the protective effects of HDL-cholesterol on cardiovascular mortality is concentration dependent [71,72]. Finally, also fasting triglycerides, which are used to compute the TyG index, have been implicated in cardiovascular risk [73,74]. However, despite the fact that both fasting and non-fasting triglycerides having been associated with cardiovascular disease, the role of triglyceride lowering therapy on cardiovascular risk remains controversial with some [75] but not all reports [76] describing a decrease in atherosclerotic cardiovascular disease following the decrease in circulating triglycerides. Furthermore, the TyG index may better represent the cardiovascular risk associated with MASLD [77] with the latter contributing to increasing the TyG index by augmenting VLDL secretion [78]. However, despite this being tempting hypothesis, it is unlikely to hold true in this cohort as none of the study participants reported an history of liver dysfunction. Finally, the ability of the TyG index to predict CVD risk may also be explained by the relationship of this surrogate index of insulin resistance and key pathogenetic mechanisms underpinning CVD [79]. In this regard, the TyG index was positively associated with hypertension, endothelial dysfunction, oxidative stress, thrombosis [79]. Even though further studies are warranted in order to dissect the relationship between the TyG index and the aforementioned pathogenetic mechanisms, the present study confirmed the potential role of inflammation in linking the TyG index and CVD. Indeed, herein this surrogate of insulin resistance correlated positively with CRP and IL-18.

In light of the results reported herein, the TyG index may represent a tool to stratify subjects with medium to medium-high risk of cardiovascular disease. In particular this surrogate index of insulin resistance may be useful to identify subjects with medium risk among individuals generally classified as low risk such as those with normal weight but metabolically unhealthy. Thus, the TyG index constitutes an economical early risk stratification tool to be implemented, along with other risk variables [80], into the clinical practice in order to guide early therapeutic interventions to prevent cardiovascular disease.

A limitation of this study is its cross sectional design which does not allow to directly infer a cause effect relationship from the reported data. In line with this, nutritional information was collected using food frequency questionnaires and 24-hour recalls which do not allow to evaluate the causal effect of a nutritional intervention on the surrogate

indexes of insulin resistance investigated herein. In spite of these weaknesses, to our knowledge, this was the first study comparing HOMA-IR and TyG with regard to their relationship with anthropometric and nutritional factors as well as in terms of their predictive role for cardiovascular disease. In light of this, the present study provides novel insights into the differences between these two surrogate indexes of insulin resistance further highlighting that they describe different components of cardiometabolic health.

To conclude, HOMA-IR, compared to the TyG index, exhibits a stronger relationship with anthropometric, inflammatory and nutritional variables and may therefore be a better indicator to describe how these factors modulate insulin sensitivity. On the contrary, the TyG index, compared to HOMA-IR, represents a better predictor of cardiovascular risk given its close relationship with the circulating lipid profile. These findings highlight the complementary roles of these indices in evaluating metabolic and cardiovascular health, suggesting their potential combined use in clinical and research settings.

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CRedit authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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