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Triglyceride/HDL cholesterol ratio and lipoprotein insulin resistance Score: Associations with subclinical atherosclerosis and incident cardiovascular disease

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ABSTRACT

Background: The triglyceride/HDL cholesterol (TG/HDL-C) ratio and the Lipoprotein Insulin Resistance (LP-IR) score are lipid markers of insulin resistance. Their associations with carotid intima media thickness (cIMT; subclinical atherosclerosis) and incident cardiovascular disease (CVD) have not been thoroughly investigated.
Methods: In a cross-sectional cohort (89 subjects without type 2 diabetes (T2D) and 81 subjects with T2D we determined cIMT (ultrasound), homeostasis model assessment of insulin resistance (HOMA-IR) and the TG/HDL-C ratio. The LP-IR score, based on 6 lipoprotein characteristics determined by nuclear magnetic resonance spectroscopy, was measured in 123 participants. A prospective study was carried out among 6232 participants (Prevention of REnal and Vascular ENd-stage Disease study).
Results: Cross-sectionally, the adjusted associations of HOMA-IR, the TG/HDL-C ratio and the LP-IR score with cIMT were approximately similar (standardized β = 0.34 (95 % CI 0.19–0.48), 0.24 (95 % CI 0.09–039) and 0.41 (95 % CI 0.23—0.59), respectively). Prospectively, 507 new cases of CVD were observed after a median follow-up of 8.2 (interquartile range 7.5–8.8) years. HOMA-IR, the TG/HDL-C ratio and LP-IR were each associated with incident CVD independent of potential confounders (HR 1.12, 95 % CI 1.02–1.24;1.22, 95 % CI 1.11–1.35 and 1.15. 95 % CI 1.01–1.31, respectively). The association of the TG/HDL-C ratio with incident CVD was somewhat stronger than that of HOMA-IR.
Conclusion: Lipoprotein-based markers of insulin resistance are at least as strongly associated with subclinical atherosclerosis and clinical atherosclerosis development as HOMA-IR, obviating the need to measure insulin to determine the impact of insulin resistance. For practical purposes, the easily obtainable TG/HDL-C ratio may suffice.

1. Introduction

The prevalence of insulin resistant conditions such as type 2 diabetes (T2D) and the metabolic syndrome are increasing exponentially worldwide in parallel with the global obesity epidemic [1,2]. The effects of insulin resistance on glucose and fatty acid metabolism are widely understood to play an important pathogenic role in the development of these conditions [3–6]. Evidence is accumulating that the triglyceride/high density lipoprotein cholesterol (TG/HDL-C) ratio is closely related to insulin resistance as measured by either plasma insulin, steady state

Abbreviations: BMI, body mass index; cIMT, carotid intima media thickness; CI, confidence interval; CV, coefficient of variation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; EDTA, ethylenediaminetetraacetic acid; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycated haemoglobin; HDL, high density lipoproteins; HR, hazard ratio; LDL, low density lipoproteins; LP-IR score, Lipoprotein Insulin Resistance score; MACE, major adverse cardiovascular events; m, men; NMR, nuclear magnetic resonance; PREVEND, prevention of renal and vascular end-stage disease; SD, standard deviation; std.β, standardized regression coefficient; TG/HDL-C ratio, triglyceride/HDL cholesterol ratio; T2D, type 2 diabetes; TRL, triglyceride rich lipoproteins; UAE, urinary albumin excretion; VLDL, very low density lipoproteins.

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plasma glucose during an insulin suppression test or Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)[7–12]. Such relationships of the TG/HDL-C ratio with insulin resistance measures have been observed in men and women, in various age and obesity groups[7–12] though not in African Americans [13], whereas little is known about this relationship in subjects with pre-existent T2D.

More recently, nuclear magnetic resonance spectroscopy (NMR) has become a valuable laboratory tool to measure plasma concentrations of very low density lipoproteins (VLDL- also designated as TRL or triglyceride-rich lipoproteins), low density lipoproteins (LDL) and high density lipoproteins (HDL) and their subfractions in human plasma [14–18]. Using this NMR spectrometry method, an algorithm has been developed based on 6 lipoprotein measures called the Lipoprotein Insulin Resistance (LP-IR) score, which is more closely related to HOMA-IR and the glucose disposal rate during a euglycemic hyperinsulinemic clamp than the individual lipoprotein fractions and sizes that comprise the algorithm [16].

HOMA-IR [19–21], the TG/HDL-C ratio [21,22] and LP-IR [17] have been shown to predict the development of new onset T2D. Notably, the TG/HDL-C ratio is associated with carotid artery intima media thickness (cIMT) and carotid artery plaque [23–25], established proxies of subclinical atherosclerosis with predictive ability for future coronary heart disease (CHD) [26]. Moreover, it has been suggested that the TG/HDL-C ratio is prospectively associated with cardiovascular disease (CVD) and mortality in women with T2D, in women with high CVD risk [21,27,28]. Indeed, a *meta*-analysis showed that the TG/HDL-C ratio is independently associated with incident CVD [29]. Additionally, another *meta*-analysis demonstrated that HOMA-IR predicts non-fatal major adverse cardiovascular (MACE) events [21]. However, it is currently unclear whether the association of cIMT with the TG/HDL-C ratio remains present when taking account of HOMA-IR. It is also uncertain whether the association of the TG/HDL-C ratio with adverse CVD outcome taking account of the LP-IR, nor has it been established whether the LP-IR score is associated with (subclinical) atherosclerosis.

The aims of the present study were i) to cross-sectionally evaluate the associations of HOMA-IR, the TG/HDL-C ratio and the LP-IR score with cIMT in a cohort of non-T2D and T2D subjects, and ii) to prospectively determine the strength of the associations of HOMA-IR, the TG/HDL-C ratio and the LP-IR score with incident non-fatal and fatal CVD events in the population-based Prevention of Renal and Vascular ENd-stage Disease (PREVEND) cohort study.

2. Materials and methods

2.1. Study design and participants

2.1.1. Cross-sectional study

The Groningen cohort included non-insulin treated T2D patients and non-T2D control subjects, aged > 18 years. T2D patients were recruited via primary care physicians. None of the subjects with or without T2D in this study had clinically manifest CVD, renal insufficiency (estimated glomerular filtration rate (eGFR) < 60 mL/1.73 m^2 or proteinuria), used lipid lowering medication or were current smokers. They were studied after an overnight fast. We determined the relationship of the TG/HDL-C ratio with insulin resistance using HOMA-IR as the read out and sought to find relationships with ultrasonography-determined cIMT. In a subset of participants, we also determined NMR-measured lipoprotein subfractions and the LP-IR scores [30].

cIMT was measured by ultrasonography in the supine position as published previously [30–32]. High-resolution B-mode ultrasound images were scanned (ACUSON 128 XP, Mountain View, CA, USA) with a 7.5 MHz linear array transducer. Three arterial wall segments of each carotid artery were imaged from a fixed lateral transducer angle at the far wall. The segments scanned were: the segment 1 cm proximal to the carotid dilatation (common carotid artery), the segment between the carotid dilatation and carotid flow divider (carotid bulb) and a 1 cm segment distal to the flow divider (internal carotid artery). The scans were recorded on S-VHS tape and analysed off-line by an image analyst who was unaware of subject's characteristics. B-mode image analyses were digitized with a frame grabber (DT286 l; Data Translation Inc.; Marlboro, MA, USA). The image analysis software was developed using an algorithm as described [32,33]. The mean cIMT of 6 carotid artery segments was calculated and used for analysis. At a mean cIMT of 0.80 mm, inter-sonographer variability was 0.05 mm, with an image analyst variability < 0.03 mm, corresponding to a total coefficient of variation (CV) between 6.3 and 7.3 % [32]. Body mass index BMI) was calculated as weight divided by length squared.

2.1.2. Prospective study

The PREVEND study is a population-based cohort study, performed among inhabitants (aged between 28 and 75 years) of the city Groningen, The Netherlands, as detailed elsewhere [34]. In short, after exclusion of individuals using insulin and pregnant women, 7768 subjects with urinary albumin concentration ≥ 10 mg/L and 2592 individuals with urinary albumin concentration < 10 mg/L were invited to participate in the study. The PREVEND study initially included 8592 subjects (1997–1998). The second screening (2001–2003) was the starting point of the current study (2001–2003) and included 6892 subjects. Individuals with missing data on CVD at baseline and follow-up and those with missing NMR or covariate data at baseline were excluded, leaving 6232 participants for the present analysis. Follow-up time was defined as the period between baseline and first CVD event, loss to follow-up, or the end of follow up time (01–01-2011), whichever came first. If a person had moved to an unknown destination, the date on which the person was dropped from the municipal registry was used as the census date. The International Classification of Diseases, the Ninth Revision (ICD-9) was used for data until 01–01-2009, after this date, data were coded according to the Tenth Revision (ICD-10). CVD was defined as the combined endpoint of incident cardiovascular morbidity and mortality which includes the following events: myocardial infarction, ischemic heart disease, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, subarachnoid haemorrhage, intracerebral haemorrhage, other and unspecified intracranial haemorrhage, occlusion and stenosis of precerebral arteries, occlusion and cerebral arteries, carotid desobstruction, aorta peripheral bypass surgery and percutaneous transluminal femoral angioplasty.

BMI was calculated as weight divided by length squared. HOMA-IR was calculated as fasting plasma insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5) [35]. Urinary albumin excretion (UAE) was measured in two consecutives 24-hour urine collections (PREVEND study) and the results were averaged. T2D was defined as a fasting serum glucose level > 7.0 mmol/L, a non-fasting plasma glucose level > 11.1 mmol/L, self-report of a physician diagnosis or the use of glucose lowering drugs, retrieved from a central pharmacy registry. eGFR was calculated using the combined creatinine cystatin C-based Chronic Kidney Disease Epidemiology Collaboration equation [36].

2.1.3. Ethics

The Groningen cohort study was approved by the medical ethics committee of the University of Groningen, The Netherlands (METC020.164). The PREVEND study was approved by the local medical ethics committee, University Medical Center Groningen (approval number: MEC96/01/022). Both studies were performed according to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent.

2.1.4. Laboratory methods

Total cholesterol, HDL cholesterol and triglycerides were assayed by routine automated methods as described [32,37]. Plasma glucose was measured by dry chemistry (Eastman Kodak, Rochester, NY, USA). HbA1c was measured by high performance liquid chromatography (Bio-Rad, Veenendaal, The Netherlands; diabetes threshold 6.5 % (43 mmol/

mol). Insulin was measured with an immunoturbidometric assay (Diazyme Laboratories, Poway, CA, USA). Serum creatinine and cystatin C were measured by an enzymatic method (Roche Modular analyser, Roche Diagnostics) and using reagents from Gentian (Cystatin C Immunoassay (Gentian AS) on a Roche modular analyser (Roche Diagnostics), respectively. Urinary albumin was measured by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Ethylenediaminetetraacetic acid **(**EDTA)- anticoagulated plasma samples were stored at −80 ^{0}C until analysis. Plasma insulin was measured with a microparticle enzyme immuno-assay (AxSYM insulin assay; Abbott Laboratories, Abbott Park, IL).

Frozen plasma aliquots were sent to LipoScience/Labcorp Inc., Morrisville, North Carolina, USA for determination of lipoprotein particle profiles by NMR spectroscopy [14–18]. VLDL (TRL), LDL and HDL particle concentrations, subfractions and sizes were quantified from the amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Diameter range estimates were for VLDL (including chylomicrons if present): >60 nm to 29 nm, for LDL: 29 nm to 18 nm, and for HDL: 14 nm to 7.3 nm. The VLDL, LDL and HDL particle concentrations were calculated as the sum of the respective lipoprotein subclasses. The intra-assay CVs for the lipoprotein parameters are: VLDL concentration (11.0 %), LDL concentration (4.1 %), HDL concentration (2.0 %) and amount to 6.6–27.9 % for the various VLDL, LDL and HDL subfractions [3,4]. Mean VLDL, LDL and HDL sizes were calculated using the weighted averages of the diameters of their various subfractions. The LP-IR scores were calculated using 6 NMR-measured lipoprotein variables: weighted average sizes of VLDL, LDL and HDL, combined with the concentrations of large VLDL, small LDL and large HDL particles [16]. LP-IR scores vary between 0 and 100; the higher the score the more insulin resistant the individual [16,17].

2.1.5. Statistical analyses

Data are expressed as mean (and SD) or median (and interquartile range) for normally distributed and non-normally distributed data, respectively. Nominal data are presented as n (with percentage (%)). Non-parametrically distributed data, e.g., HOMA-IR and the TG/HDL-C ratio, were $\log_e$ transformed to achieve approximately normal distributions. for statistical analysis. Between-group differences in continuous variables and in dichotomous variables were determined by unpaired T-tests and by χ^2-analysis, respectively. Univariable relationships were assessed using Pearson correlation coefficients. Cross-sectionally, multivariable linear regression analyses were applied to disclose the independent associations of HOMA-IR, the TG/HDL-C ratio and the LP-IR score with cIMT. Standardized regression coefficients (βs) are shown with 95 % confidence intervals. HOMA-IR (homeostasis model of insulin resistance) and the TG/HDL-C ratio are log transformed. Standardized regression coefficients (std. βs) are given. Longitudinal associations with incident cardiovascular disease were analysed using Kaplan-Meier survival analysis with log rank test and uni- and multivariable Cox regression analyses. The Cox proportional hazard assumption was tested through the evaluation of independence between scaled Schoenfeld residuals with time for each variable and for every model as a whole; this assumption was met, with no indication of violation. Hazard ratios (HRs) are expressed per 1 SD increase with 95 % confidence intervals (CIs). Statistical significance was set at two-tailed *P*-values < 0.05. SPSS (IBM SPSS Statistics for Windows, Version 26.0. IBM Corp. Armonk, NY, USA) was used for cross-sectional data analysis. Prospective analysis was performed with R language for statistical computing software, v. 4·0·3 (2020), (Vienna, Austria).

3. Results

3.1. Cross-sectional analysis: Groningen cohort

This cohort as comprised of 89 participants without T2D and 81 T2D participants (median diabetes duration 5 (4.0–7.4) years) in whom conventional lipoproteins and cIMT were measured (Table 1). Patients with T2D were treated for glycaemic control with metformin and sulfonylurea, alone or in combination. Other glucose lowering drugs were not used. All participants were White. NMR-derived lipoprotein variables and the LP-IR scores were measured in 56 non-T2D subjects and in 67 patients with T2D.

T2D patients were older (59 ± 9 vs. 55 ± 9 years), had higher BMI (28.6 ± 4.8 vs. 3.9 kg/m^2), blood pressure (143 ± 20 vs. 131 ± 19 mmHg), cIMT (0.883 ± 0.195 vs. 0.808 ± 0.147 mm), plasma glucose (8.8 ± 2.3 vs. 5.6 ± 0.6 mmol/L), HbA1c (6.8 ± 1.1 % vs. 5.3 ± 0.4 %), plasma insulin (10.8 [7.0–15.3] vs. 6.5 [4.7–8.6] mU/L) and HOMA-IR (3.9 [2.4–6.5] vs. 1.6 [1.1–2.23] mU*mmol/L^2/22.5) values than non-T2D subjects. Triglycerides were higher (1.7 [1.2–2.2] vs. 1.3 [0.9–2.0] mmol/L), HDL cholesterol was lower (1.3 ± 0.4 vs. 1.5 ± 0.4 mmol/L), and the TG/HDL-C ratio and LP-IR scores were higher in T2D patients (1.32 [0.87–2.22] vs. 0.89 [0.47–1.72] and 60 ± 23 vs. 45 ± 27, respectively). VLDL (TRL), LDL and HDL particle concentrations were not different between the groups but the averaged size of VLDL was greater and HDL was smaller in T2D patients (51.2 [45.8–58.0] vs. 44.3 [41.8–52.2] nm and 8.8 [8.6–9.2] vs. 9.2 [8.7–9.6] nm, respectively). The TG/HDL-C ratio and the LP-IR score were strongly and positively correlated with HOMA-IR. Expectedly strong positive correlations were also found between the TG/HDL-C ratio and triglycerides and inversely with HDL cholesterol. The TG/HDL-C ratio was also correlated positively with the VLDL (TRL) particle concentration and size, with LDL particle concentration, and inversely with LDL size, HDL particle concentration and HDL size. Except for the HDL particle concentration, such relationships were also found with HOMA-IR. Essentially similar relationships were found in subjects with and without T2D separately (**Suppl. Table 1**).

cIMT was correlated with HOMA-IR, the TG/HDL-C ratio and the LP-IR score (Table 1). In multivariable linear regression analysis, adjusting for age, sex, diabetes status, systolic blood pressure and plasma total cholesterol, HOMA-IR, the TG/HDL-C ratio and the LP-IR score were each independently associated with cIMT in separate models (Table 2**; models A, B and C**). In these models, the association of cIMT with HOMA-IR and the TG/HDL-C ratio was comparable, whereas that with the LP-IR score appeared to be somewhat stronger, both in the crude (Std. β 0.41 (95 % CI 0.23, 0.59) $p < 0.001$) and the fully adjusted model (Std. β 0.30 (95 % CI 0.12, 0.49) $p = 0.001$). Notably, there was no significant association of cIMT with T2D taking account of either HOMA-IR, the TG/HDL-C ratio or the LP-IR score.

3.2. Cross-sectional and prospective analyses: PREVEND cohort

During a median follow-up of 8.2 (7.5 – 8.8) years 507 of the 6232 participants experienced a CVD event. 373 participants had T2D at baseline. Table 3 shows clinical and laboratory variables in all participants and in those who did and did not experience a CVD event during follow up. Participants who experienced CVD during follow-up were predominantly men (71.2 %), presented higher systolic and diastolic blood pressure (140 ± 21 vs. 125 ± 18 mmHg and 78 ± 10 vs 73 ± 9 mmHg, respectively); and had T2D more frequently (15.2 % vs 5.2 %). They were more obese (BMI: 28.0 ± 4.1 vs. 26.6 ± 4.4 kg/m^2), had lower eGFR and higher UAE (79 ± 19.7 vs. 93.2 ± 16.5 mL/min/1.73 m^2 and 15.2 [8.0–43.8] vs. 8.5 [6.0–14.9] mg/24 h, respectively), higher plasma insulin (10.6 [7.7–15.6] vs. 8.1 [5.7–12.1] mU/L) and HOMA-IR (2.45 [1.70–3.93] vs. 1.7 [1.2–2.7] mU*mmol/L^2/22.5), higher triglycerides (1.4 [1.0–1.9] vs. 1.1 [0.8–1.6] mmol/L), lower HDL cholesterol (1.1 ± 0.3 vs. 1.3 ± 0.3 mmol/L), a higher TG/HDL-C ratio (1.22 [0.82–1.92] vs. 0.90 [0.59–1.45]) and a higher LP-IR score (52.00 [32.00–71.00] vs. 40.00 [21.00–61.00]) (Table 3**).** VLDL (TRL) and LDL particle concentrations were higher (53 [34–78] vs. 46 [28–66] nmol/L and 1152.00 [913.00–1422.00] vs. 1039.00 [810.00–1288.00] nmol/L, respectively), whereas the HDL particle concentration was lower in participants who experienced a CVD (29 [26–33] vs. 31

Table 1
Clinical and laboratory variables and univariable correlations in the Groningen cohort (89 subjects without T2D and 81 patients with Type 2 diabetes (T2D)).

	Subjects with T2D (n = 81)	Subjects without T2D (n = 89)	Correlation coefficients with log_e HOMA-IR (all participants combined)	Correlation coefficients with log_e TG/HDL-C ratio (all participants combined; n = 170)	Correlation coefficients with LP-IR score (all participants combined; n = 123)
Age (years)	59 ± 9[a]	55 ± 9	0.11	−0.04	0.05
Sex (men; n (%))	50 (61 %)	49 (55.0)	−0.02	0.18[a]	0.34[c]
BMI (kg/m^2)	28.6 ± 4.8[c]	25.9 ± 3.9	0.61[c]	0.39[c]	0.46[c]
Systolic blood pressure (mm Hg)	143 ± 20[c]	131 ± 19	0.35[c]	0.05	0.21[a]
Diastolic blood pressure (mm Hg)	87 ± 9[b]	83 ± 11	0.32[c]	0.22[b]	0.34[c]
cIMT (mm)	0.883 ± 0.195[b]	0.808 ± 0.147	0.27[c]	0.24[b]	0.38[c]
Glucose (mmol/L)	8.8 ± 2.3[c]	5.6 ± 0.6	0.63[c]	0.32[c]	0.31[c]
HbA1c (%)	6.8 ± 1.1[c]	5.3 ± 0.4	0.50[c]	0.27[c]	0.27[b]
Insulin (mU/L)	10.8 (7.0,15.3)[c]	6.5 (4.7,8.6)	0.94[c]	0.48[c]	0.58[c]
HOMA-IR (mU*mmol/L^2/22.5)	3.9 (2.4,6.5)[c]	1.6 (1.1,2.3)		0.50[c]	0.58[c]
Total cholesterol (mmol/L)	5.4 ± 1.0[a]	5.7 ± 1.0	−0.07	0.27[c]	0.12
HDL cholesterol (mmol/L)	1.3 ± 0.4[c]	1.5 ± 0.4	−0.48[c]	−0.80[c]	−0.82[c]
Triglycerides (mmol/L)	1.7 (1.2,2.2)[a]	1.3 (0.9,2.0)	0.44[c]	0.96[c]	0.79[c]
TG/HDL-C ratio	1.32 (0.87,2.22)[b]	0.89 (0.47,1.72)	0.50[c]		0.88[c]
VLDL (TRL) particle concentration (nmol/L)	71 (47,91)	62 (52,102)	0.18[a]	0.68[c]	0.53[c]
LDL particle concentration (nmol/L)	1264 (1024,1497)	1142 (942,1370)	0.30[c]	0.57[c]	0.55[c]
HDL particle concentration (μmol/L)	33 (29,37)	34 (32,36)	−0.13	−0.34[c]	−0.25[b]
VLDL (TRL) size (nm)	51.2 (45.8,58.0)[c]	44.3 (41.8,52.2)	0.50[c]	0.772[c]	0.80[c]
LDL size (nm)	20.8 (20.4,21.3)	21.3 (20.9,21.5)	−0.44[c]	−0.76[c]	−0.79[c]
HDL size (nm)	8.8 (8.6,9.2)[b]	9.2 (8.7,9.6)	−0.47[c]	−0.66[c]	−0.81[c]
LP-IR score	60 ± 23[c]	45 ± 27	0.58[c]	0.88[c]	

Data in mean ± SD or in median (interquartile range and numbers). Pearson correlation coefficients are shown. For comparisons between subjects with and without T2D and for correlation analyses insulin, HOMA-IR, triglycerides and the TG/HDL-C ratio are log_e transformed. NMR-derived variables including the LP-IR score were measured in 67 T2D patients and in 56 non-T2D subjects. Abbreviations: cIMT, carotid artery intima media thickness; HbA1c, glycated haemoglobin; HDL, high density lipoproteins; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low density lipoproteins; LP-IR score, lipoprotein insulin resistance score; m, men; TG/HDL-C ratio, triglycerides/HDL cholesterol ratio; VLDL, very low density lipoproteins; TRL, triglyceride-rich lipoproteins. [a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$.

Table 2
Associations of homeostasis model assessment of insulin resistance (HOMA-IR), triglycerides/HDL cholesterol (TG/HDL-C) ratio and lipoprotein insulin resistance (LP-IR) score with carotid artery intima media thickness (cIMT) by multivariable linear regression analysis in the Groningen cohort (170 subjects; 81 patients with T2D and 89 subjects without T2D; the LP-IR score was measured in 123 subjects).

	Model A		Model B		Model C	
	cIMT (n = 170)	***P*-value**	**cIMT** (n = 170)	***P*-value**	**cIMT** (n = 123)	***P*-value**
Crude	0.34 (0.19, 0.48)	<0.001	0.24 (0.09, 0.39)	0.02	0.41(0.23, 0.59)	<0.001
Adjusted*	0.26 (0.12, 0.40)	<0.001	0.19 (0.05, 0.33)	0.008	0.30 (0.12, 0.49)	0.001

Standardized regression coefficients (std. βs) are shown with 95 % confidence intervals. HOMA-IR (homeostasis model of insulin resistance) and the TG/HDL-C (triglycerides/high density lipoprotein cholesterol) ratio are log_e transformed.
Model A: Association of cIMT with HOMA-IR.
Model B: Association of cIMT with the TG/HDL-C ratio.
Model C: Association of cIMT with the LP-IR score.
* Adjusted for age, sex, diabetes status, systolic blood pressure and total cholesterol.

[28–35] μmol/L). The averaged size of VLDL (TRL) was greater (49.6 [44.4–55.7] vs. 48.9 [44.1–54.6] nm) and that of LDL and HDL was smaller in participants who experienced a CVD (20.8 [20.3–21.3] vs. 21.1 [20.6–21.5] nm and 8.9 [8.5–9.4] vs. 9.1 [8.7–9.6] nm, respectively). Correlations between clinical and laboratory variables with HOMA-IR, the TG/HDL-C ratio and the LP-IR score were comparable to those found in the Groningen cohort. The HDL particle concentration was inversely correlated with HOMA-IR, the TG/HDL-C ratio and the LP-IR score (Table 3), with little differences between those who did and did not experience CVD during follow-up (**Suppl. Table 2**). Again, strong correlations between HOMA-IR, the TG/HDL-C ratio and the LP-IR score were observed (Table 3, Fig. 1**A–C**).

Fig. 2 shows Kaplan-Meier curves for the association of HOMA-IR (**panel A**) the TG/HDL-C ratio (**panel B**) and the LP-IR score (**panel C**) (each in tertiles) with incident CVD. CVD incidence has highest in the highest tertile of HOMA-IR, the highest tertile of the TG/HDL-C ratio, as well as in the highest tertile of the LP-IR score (log rank test: $P < 0.001$ for each). Cox-proportional hazard analysis showed that HOMA-IR, the TG/HDL-C ratio and the LPIR scores were each associated with incident CVD (Table 4). All these associations of incident CVD with HOMA-IR, the TG/HDL-C ratio and the LP-IR score remained after adjustment for age and sex (models 1), after further adjustment for total cholesterol, systolic blood pressure, smoking, presence of T2D, antihypertensive and lipid lowering medication (models 2), as well as after further adjustment

Table 3
Clinical and laboratory variables and univariable correlations in the PREVEND cohort (5232 participants).

	All participants (n = 6232)	No CVD during follow-up (n = 5725)	CVD during follow-up (n = 507)	Correlation coefficients with log_e HOMA-IR (all participants; n = 6232)	Correlation coefficients with log_e TG/HDL-C ratio (all participants; n = 6232)	Correlation coefficients with LP-IR score (all participants; n = 6232)
Age (years)	54 ± 12	53 ± 12[c]	64 ± 10	0.2[c]	0.14[c]	0.10[c]
Sex (men; n, %)	3090 (49.6 %)	2729 (47.7 %)[c]	361 (71.2 %)	−0.09[c]	−0.29[c]	−0.31[c]
BMI (kg/m^2)	26.7 ± 4.4	26.6 ± 4.4[c]	28.0 ± 4.1	0.47[c]	0.36[c]	0.38[c]
Systolic blood pressure (mm Hg)	126 ± 19	125 ± 18[c]	140 ± 21	0.27[c]	0.27[c]	0.27[c]
Diastolic blood pressure (mm Hg)	73 ± 9	73 ± 9[c]	78 ± 10	0.20[c]	0.27[c]	0.28[c]
Type 2 diabetes (n, %)	374 (6.0 %)	297 (5.2 %)[c]	77 (15.2 %)	0.21[c]	0.27[c]	0.1[c]
Current smokers (n, %)	1817 (29.2 %)	1648 (28.8 %)[c]	169 (33.3 %)			
Statin use (n, %)	448 (7.2 %)	343 (6.0 %)[c]	105 (20.7 %)			
Antihypertensive medication use (n, %)	1188 (19.1 %)	965 (16.9 %)[c]	223 (44.0 %)			
Glucose (mmol/L)	4.8 (4.4, 5.3)	4.7 (4.4, 5.3)[c]	5.20 (4.60, 5.90)	0.49[c]	0.25[c]	0.26[c]
Insulin (mU/L)	8.3 (5.9, 12.3)	8.1 (5.7, 12.1)[c]	10.6 (7.7, 15.6)	0.74[c]	0.38[c]	0.40[c]
HOMA-IR (mU*mmol/L^2/22.5)	1.8 (1.2, 2.8)	1.7 (1.2, 2.7)[c]	2.45 (1.70, 3.93)	–	0.34[c]	0.35[c]
eGFR (mL/min/1.73 m^2)	92.0 ± 17.2	93.2 ± 16.5[c]	79.0 ± 19.7	−0.19[c]	−0.17[c]	−0.10[c]
UAE (mg/24 h)	8.8 (6.1, 15.92	8.5 (6.0, 14.9)[c]	15.2 (8.0, 43.8)	0.10[c]	0.09[c]	0.07[c]
Total cholesterol (mmol/L)	5.5 ± 1.0	5.4 ± 1.0[b]	5.6 ± 1.1	0.11[c]	0.27[c]	0.16[c]
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.3 ± 0.3[c]	1.1 ± 0.3	−0.27[c]	−0.70[c]	−0.58[c]
Triglycerides (mmol/L)	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)[c]	1.4 (1.0, 1.9)	0.31[c]	0.81[c]	0.65[c]
TG/HDL-C ratio	0.93 (0.60, 1.49)	0.90 (0.59, 1.45)[c]	1.22 (0.82, 1.92)	0.30[c]	–	0.61[c]
VLDL (TRL) particle concentration (nmol/L)	46 (29, 67)	46 (28, 66)[c]	53 (34, 78)	0.22[c]	0.71[c]	0.44[c]
LDL particle concentration (nmol/L)	1049.00 (817.00, 1300.00)	1039.00 (810.00, 1288.00)[c]	1152.00 (913.00, 1422.00)	0.22[c]	0.4[c]	0.42[c]
HDL particle concentration (μmol/L)	31 (28, 34)	31 (28, 35)[c]	29 (26, 33)	−0.16[c]	−0.34[c]	−0.17[c]
VLDL (TRL) size (nm)	49.0 (44.2, 54.7)	48.9 (44.1, 54.6)[c]	49.6 (44.4, 55.7)	0.22[c]	0.47[c]	0.66[c]
LDL size (nm)	21.1 (20.6, 21.5)	21.1 (20.6, 21.5)[c]	20.8 (20.3, 21.3)	−0.11[c]	−0.23[c]	−0.25[c]
HDL size (nm)	9.1 (8.7, 9.6)	9.1 (8.7, 9.6)[c]	8.9 (8.5, 9.4)	−0.31[c]	−0.68[c]	−0.67[c]
LP-IR score	41.00 (22.00, 62.00)	40.00 (21.00, 61.00)[c]	52.00 (32.00, 71.00)	0.42[c]	0.84[c]	–

Data in mean ± SD or in median (interquartile range) and numbers (percentages). Pearson correlation coefficients are shown. For comparisons between participant who did and did not experience a cardiovascular event during follow-up and for correlation analyses insulin, HOMA-IR, triglycerides and the TG/HDL-C ratio are log_e transformed. Abbreviation: eGFR, estimated glomerular filtration rate; HDL, high density lipoproteins; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low density lipoproteins; LP-IR score, lipoprotein insulin resistance score; m, men; TG/HDL-C ratio, triglycerides/HDL cholesterol ratio; VLDL, very low density lipoproteins; TRL, triglyceride-rich lipoproteins; UAE, urinary albumin excretion; [a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$.

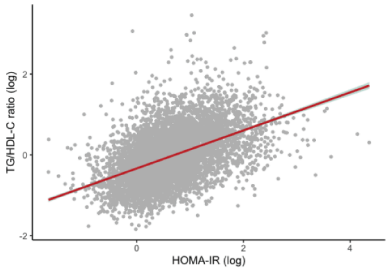
for eGFR and urinary albumin excretion (models 3). Notably, when the associations of HOMA-IR, the TG/HDL-C ratio and the LP-IR score with incident CVD were mutually adjusted, (models 5 and 6) the association of HOMA-IR with incident CVD lost significance, whereas the association of the TG/HDL-C ratio remained after adjustment for the LP-IR score. Conversely, the association of the LP-IR score was lost after adjustment for HOMA-R or the TG/HDL-C.

4. Discussion

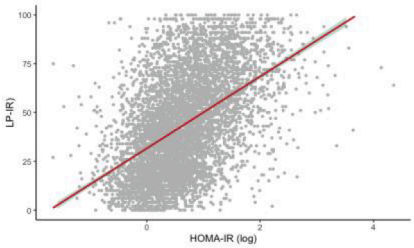
The present study demonstrates that the TG/HDL-C ratio is not only related to higher plasma triglycerides and lower HDL-C but also to higher (VLDL) TRL, higher LDL and lower HDL particle concentrations, greater TRL size and smaller LDL and HDL sizes, and a higher LP-IR score. Notably, in a mixed cohort of non-T2D subjects and T2D patients, the cross-sectional associations of the TG/HDL-C ratio, HOMA-IR and the LP-IR score with cIMT were approximately similar. In a population-based cohort, HOMA-IR, the TG/HDL-C ratio and the LP-IR score were each prospectively associated with incident CVD, independent of conventional risk factors. A somewhat stronger association was found for the TG/HDL-C ratio. Combined, the current results underscore the premise that both early manifestations of atherosclerosis (cIMT) and the development of clinically manifest CVD are associated with lipoprotein-based measures of insulin resistance.

Compared to non-T2D subjects, the currently studied T2D patients in the Groningen cohort had higher TG and lower HDL-C levels, expectedly resulting in a higher TG/HDL-C ratio [10,18,32,38]. Moreover, in line with previous findings using NMR spectroscopy and other methods [17,39–43], the VLDL (TRL) and LDL particle concentrations tended to be increased whereas the HDL particle concentration tended to be decreased in T2D, together with changes in averaged lipoprotein sizes contributing to the higher LP-IR score in T2D [16]. Compared to individuals who had not experienced a CVD event during follow-up, participants who experienced CVD had a greater LP-IR score. Besides robust interrelationships with HOMA-IR and the LP-IR index, the TG/HDL-C was also related to VLDL (TRL), LDL and HDL particle concentrations

Panel A: Relationship of log_e triglycerides/HDL cholesterol (TG/HDL-C) ratio with log_e transformed homeostasis model assessment of insulin resistance (HOMA-IR) in 6232 PREVEND participants (r=0.30, *P*<0.001).



Panel B: Relationship of lipoprotein insulin resistance (LP-IR) score with log_e transformed homeostasis model assessment of insulin resistance (HOMA-IR) in 6232 PREVEND participants (r=0.42, *P*<0.001).



Panel C: Relationship of lipoprotein insulin resistance (LP-IR) score with log_e transformed triglycerides/HDL cholesterol (TG/HDL-C) ratio in 6233 PREVEND participants (r= 084, *P*<0.001).

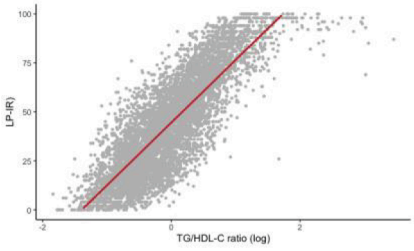


Fig. 1. Panel A: Relationship of log_e triglycerides/HDL cholesterol (TG/HDL-C) ratio with log_e transformed homeostasis model assessment of insulin resistance (HOMA-IR) in 6232 PREVEND participants (r = 0.30, $P < 0.001$). **Panel B**: Relationship of lipoprotein insulin resistance (LP-IR) score with log_e transformed homeostasis model assessment of insulin resistance (HOMA-IR) in 6232 PREVEND participants (r = 0.42, $P < 0.001$). **Panel C**: Relationship of lipoprotein insulin resistance (LP-IR) score with log_e transformed triglycerides/HDL cholesterol (TG/HDL-C) ratio in 6233 PREVEND participants (r = 084, $P < 0.001$).

and the averaged sizes of these lipoprotein fractions, with similar relationships in T2D and non-T2D individuals. Such relationships were also found among PREVEND participants.

The VLDL (TRL), LDL and HDL particle concentrations represent clinically relevant lipid biomarkers of atherosclerosis development [44–47]. In the current study, cIMT was greater in T2D patients compared to non-T2D individuals, but the difference disappeared after either taking account of HOMA-IR, the TG/HDL-C ratio or the LP-IR score. This would underscore the relevance of non-insulin-based lipid biomarkers of insulin resistance in explaining early atherosclerosis development in T2D. To our knowledge, neither the association of cIMT with the TG/HDL-C ratio nor the LP-IR score has been previously determined taking account of HOMA-IR, nor has the association of the TG/HDL-C ratio and the LP-IR score with future development of clinically manifest CVD been determined together. A potentially important novel finding of our study is that the strength of the association of cIMT with the TG/HDL-C ratio was similar compared to that with HOMA-IR, while that with the LP-IR score was as least as strong. Prospectively, HOMA-IR, the TG/HDL-C ratio and the LP-IR index were each independently associated with incident CVD in the PREVEND population. This is in accordance with a *meta*-analysis comprising 8 studies involving over 17.000 individuals, in which HOMA-IR predicted incident non-fatal CVD [21]. However, in this analysis, HOMA-IR values were variably reported using specific cut-off points, per 1 SD increment or according to quartiles of highest vs. lowest HOMA-IR values. The prospective association of the TG/HDL-C index in the PREVEND cohort also aligns with other studies [21,27–29]. In our prospective analysis, the association of the TG/HDL-C ratio with incident CVD was somewhat stronger than that of HOMA-IR. With both cIMT and incident CVD as endpoints, the association with the TG/HDL-C ratio was at least as strong as that with HOMA-IR. In the cross-sectional study 48 % of participants had T2D with inherent higher LP-IR scores, while only 6 % of PREVEND participant had T2D, possible the affecting the strength of the association with cIMT and newly manifest CVD with the LP-IR score as compared with the TG/HDL-C ratio.

Several methodological considerations of the present report need to be discussed. We were able to document relationships of the TG/HDL-C ratio with detailed NMR-based lipoprotein measures and the LP-IR index in two independent and extensively phenotyped cohorts, and found similar relationships of lipoprotein variables with the TG/HDL-C ratio,

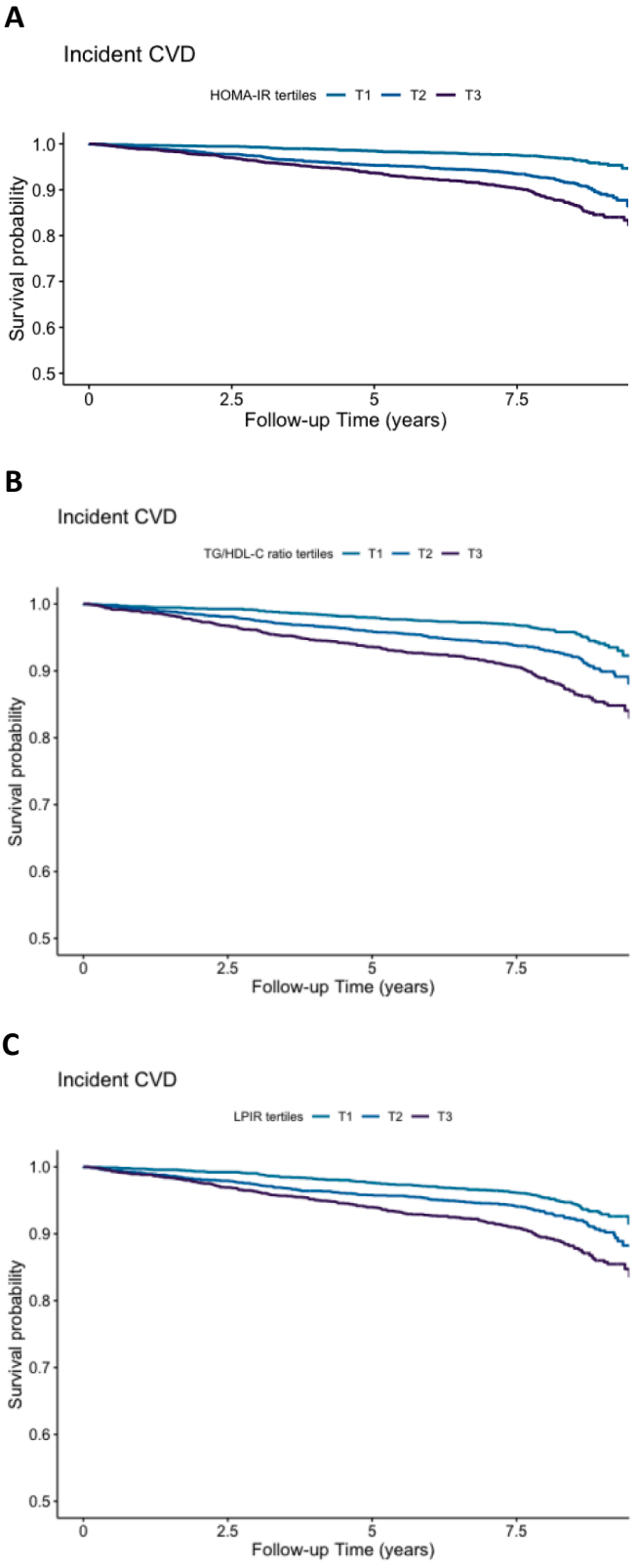


Fig. 2. Kaplan Meijer curves for the association of HOMA-IR (**panel A**), the TG/HDL-C ratio **(panel B**), and the LP-IR score (**panel C**) with incident CVD. Tertiles of the TG/HDL-C ratio and the LP-IR score are given.

Table 4
Cox proportional hazard analyses of HOMA-IR, the triglycerides/HDL cholesterol ((TG/HDL-C) ratio) and the lipoprotein insulin resistance (LP-IR) score with incident cardiovascular disease (n = 507) in the PREVEND cohort (n = 6232). Hazard ratios (HRs) are given per 1 SD increase with 95 % confidence intervals (CI).

	A *p*-value	B *p*-value	C *p*-value
Crude	1.59 [1.46;1.75] < 0.001	1.55 [1.43;1.68] < 0.001	1.63 [1.41;1.87] < 0.001
Models 1	1.25 [1.13;1.38] < 0.001	1.39 [1.27;1.52] < 0.001	1.33 [1.15;1.53] < 0.001
Models 2	1.13 [1.02;1.25] 0.01	1.22 [1.11;1.34] < 0.001	1.15 [1.00;1.31] 0.04
Models 3	1.12 [1.02;1.24] 0.02	1.22 [1.11;1.35] < 0.001	1.15 [1.01;1.31] 0.04
Models 4	**NA**	1.21 [1.09;1.33] < 0.001	1.12 [0.98;1.28] 0.11
Models 5	1.08 [0.98;1.19] 0.13	**NA**	1.06 [0.93;1.20] 0.40
Models 6	1.09 [0.98;1.21] 0.11	1.39 [1.18;1.62] < 0.001	**NA**

HOMA-IR and the TG/HDL-C ratio are $\log_e$ transformed.
A: with HOMA-IR as independent variable.
B: with the TG/HDL-C ratio as independent variable.
C: with the LP-IR score as independent variable.
Models 1: adjusted for age and sex.
Models 2: Models 1 + adjustment for total cholesterol, systolic blood pressure, smoking, presence of T2D, antihypertensive and lipid lowering medication
Models 3: Models 2 + adjustment for eGFR and urinary albumin excretion
Models 4: Models 3 + adjustment for HOMA-IR (B,C).
Models 5: Models 3 + adjustment for the TG/HDL-C ratio (A, C).
Models 6: Models 3 + adjustment for the LP-IR score (A, B).

thereby strengthening the robustness of our observations, However, the observational nature of our study precludes conclusions regarding causality. Furthermore, the participants of both cohorts were predominantly White individuals recruited from the northern part of The Netherlands. This would preclude extrapolating our findings to people with other backgrounds, although the LP-IR index method that we used Lipoprofile (LabCorp) shows in general sufficient agreement with HOMA-IR across various ethnicities [16]. It is also worth noting that there are multiple methods of using NMR for quantifying lipoprotein particles. In comparison with another NMR method (AXINON® lipoFIT® method; The Numares AG (Am Biopark 9, 93,053 Regensburg, Germany): both methods show close agreement for LDL cholesterol and HDL cholesterol compared to β quantification, as well as for triglycerides [48]. However, VLDL, LDL and HDL particle concentrations differ between the two NMR methods, and except for lipoprotein sizes, lipoprotein subspecies cannot be directly compared due to different categorization, especially with respect to the diameter ranges of the lipoprotein subspecies [48].

In conclusion, lipoprotein-based markers of insulin resistance are at least as strongly associated with subclinical atherosclerosis and with newly developing atherosclerotic manifestations than HOMA-IR. This would essentially obviate insulin measurement to determine the impact of insulin resistance on (sub)clinical atherosclerosis. For practical purposes, the easily obtainable TG/HDL-C ratio may suffice.

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CRediT authorship contribution statement

José L. Flores-Guerrero: Writing – review & editing, Writing – original draft, Formal analysis. **Riemer A. Been:** . **Irina Shalaurova:** Writing – review & editing. **Margery A. Connelly:** Writing – review & editing. **Peter R. van Dijk:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Robin P.F. Dullaart:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2023.117737.

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