Triglyceride-glucose index in the development of peripheral artery disease: findings from the Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background

It remains unclear whether triglyceride-glucose (TyG) index, a surrogate marker of IR, was prospectively associated with incident PAD.

Methods

We included 12573 ARIC (Atherosclerosis Risk in Communities Study) participants free of PAD at baseline (1987–1989). The TyG index was determined using ln(fasting triglycerides [mg/dL] × fasting glucose [mg/dL]/2), and measured during 5 visits between 1987 and 2013. Incident PAD was defined as the first hospitalization with PAD diagnosis. We quantified the association of both baseline and trajectories of TyG index with incident PAD using Cox regression and logistic regression analysis, respectively.

Results

Over a median follow-up of 23 years, there were 1331 cases of incident PAD. After adjustment for traditional PAD risk factors, each 1-SD (0.58) increase in TyG index was associated with an 18.9% higher risk of incident PAD (hazard ratio, 1.189 [95% CI, 1.106–1.278]). Results were similar when individuals were categorized by TyG index quartiles (hazard ratio, 1.363 [95% CI, 1.125–1.652]; comparing extreme quartiles). Four distinct trajectories of TyG index were identified (low-increasing [43.0%], moderate-stable [22.3%], moderate-decreasing [27.6%], and high-decreasing [7.1%]). Trajectories of elevated TyG index levels had greater incident PAD after multivariable adjustment for potential cardiovascular risks. Compared with moderate-stable group (reference), high-decreasing group was associated with the highest risk of future incident PAD (odds ratio, 2.314 [95%CI, 1.687–3.175]).

Conclusion

Higher TyG index is independently associated with incident PAD. Long-term trajectories of TyG index help identify individuals at a higher risk of future PAD who deserve appropriate follow-up to detect asymptomatic disease.

Background

Lower extremity peripheral artery disease (PAD) is an important manifestation of systemic atherosclerosis affecting an estimated over 200 million people worldwide [1, 2]. It is associated with significant cardiovascular morbidity and mortality, with a variable spectrum of symptoms from none to severe when patients present with claudication or critical limb ischemia [3]. Despite its high prevalence

and well-described adverse outcomes, the pathobiology of PAD is incompletely understood. There is a need to identify potential biomarkers that could predict the risk of PAD, and guide targeted screening to facilitate timely intervention at early stages of atherosclerosis.

Insulin resistance (IR), a pathophysiological state characterized by the attenuated insulin sensitivity of peripheral tissues, is the key feature of metabolic syndrome and type 2 diabetes [4]; and contributes significantly to the development of atherosclerotic cardiovascular disease [5]. However, the role of IR in PAD has been inadequately explored, compared with that of other atherogenic mechanisms such as inflammation [6–8]. Moreover, risk factors for PAD have not been as thoroughly investigated as those for coronary artery disease [9]. The triglyceride glucose (TyG) index, which is calculated using fasting triglycerides and fasting glucose, is a reliable measure of IR [10, 11]. Growing evidence has demonstrated that the TyG index is related to morbidity and mortality of cardiovascular disease in the general population, patients with and those without diabetes [12, 13] This is possibly because elevated TyG index by itself contributes to systemic arterial atherosclerosis, including carotid atherosclerosis and coronary artery calcification, an established marker of subclinical atherosclerosis [14, 15]. However, long-term specific prospective studies on the relationship between the TyG index and PAD have not been performed.

We hypothesized that dynamic changes over the decades in IR, either improved or exacerbated, might modify the development of PAD. Accordingly, we used the data from the Atherosclerosis Risk in Communities (ARIC) study to evaluate the association of the TyG index with PAD and to determine the influence of baseline TyG index and different trajectories of its change over 20 years on the development of PAD.

Methods

Study population

The ARIC Study is a prospective cohort study that enrolled 15792 participants aged 45 to 64 years from 4 US communities (Forsyth County, North Carolina; Jackson, Mississippi; eight northern suburbs of Minneapolis, Minnesota; and Washington County, Maryland), aimed at investigating the natural history, etiology, and clinical manifestations of atherosclerotic disease in black and white men and women. The participants were recruited between 1987 to 1989 (visit 1). Four subsequent visits were conducted: visit 2 (1990-1992), visit 3 (1993-1995), visit 4 (1996-1998), and visit 5 (2011-2013). The details about the study design have been previously described [16]. Written informed consent was obtained from all ARIC participants, and the ARIC study was approved by the institutional review boards at each site.

We excluded participants who had PAD diagnosis at baseline (n=613); those who had missing data regarding PAD (n=555); and those who had missing data regarding other covariates of interest (n=1785). We also excluded participants who had no follow-up information on PAD (n=266). This resulted in a final sample of 12573 participants for the analysis of association between baseline TyG index and incident PAD. We further excluded those participants with fewer than three valid TyG index during follow-up visits;

the remaining 9296 participants were included in the analysis of association between TyG index group-based trajectory and incident PAD (Figure 1).

Data collection at baseline

Trained interviewers collected information using standardized questionnaires on demographic, lifestyle, and detailed medical information at visit 1. Age, sex, race, educational level, physical activity, alcohol consumption, and smoking status were self-reported. Educational attainment was categorized as basic (less than high school), intermediate (high school graduate or vocational school), and advanced (college, graduate school, or professional school). Smoking and alcohol drinking status were classified as current, former, or never. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Seated blood pressure represented the mean of the last two of three measurements using a random-zero sphygmomanometer after a 5-minute rest. Hypertension was defined as systolic blood pressure readings ≥140 mmHg or diastolic blood pressure readings ≥90 mmHg, or use of antihypertensive drugs in the previous two weeks. Diabetes was defined as fasting glucose level ≥126 mg/dL (≥7.0 mmol/L), non-fasting glucose level ≥200 mg/dL (≥11.1 mmol/L), self-reported physician diagnosis of diabetes, or use of antidiabetic drugs. Prevalent cardiovascular diseases such as coronary heart disease and stroke were determined according to both participants' self-report and measurements at visit 1. Blood samples were obtained from participants who were asked to fast for 12 hours and stored at -70°C according to standardized protocols until laboratory analysis [17]. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using automated enzymatic procedures, and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation when the concentration of triglycerides is < 400 mg/dL [18]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [19]. Medications were determined through self-reported usage in the previous two weeks and inspection of medication containers that participants brought to the visit.

The triglyceride-glucose (TyG) index was calculated as ln(fasting triglycerides [mg/dL]×fasting glucose [mg/dL]/2). Group-based trajectory analysis is designed to identify clusters of individuals with similar patterns of change over time. Trajectory groups were identified and then qualitatively examined and named to describe a visual pattern of change.

Ascertainment of incident PAD

Based on previous literature [8, 20, 21], PAD-related hospitalizations were identified by the following International Classification of Diseases Ninth Revision (ICD-9) discharge codes: peripheral vascular disease, unspecified (443.9); atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); chronic total occlusion artery extremities

(440.4); atherosclerosis of other specified arteries (440.8); coexisting leg amputation (84.11, 84.12, 84.15, 84.17); leg artery revascularization (38.18, 39.25, 39.29, 39.50); lower extremity ulcer and gangrene (707.1x). Incident PAD was defined as if a documented PAD-related hospitalization or a measured ankle-brachial index <0.90 during follow-up visits in patients not diagnosed with PAD at visit 1 [3]. Critical limb ischemia (CLI), the severe form of PAD, was based on the discharge codes (84.11, 84.12, 84.15, 84.17, 707.1x).

Statistical Analysis

Normally distributed continuous data were expressed as mean±SD, and the non-normally distributed continuous data, otherwise, were expressed as the median (interquartile range). Categorical data were expressed as numbers (percentage). Differences among groups were evaluated using analysis of variance (ANOVA) or Kruskal-Wallis *h*-test when appropriate for the continuous variables, and the χ^2 test for the categorical variables. The follow-up period was set as the time from visit 1 (baseline) to the incident of PAD, or loss to follow-up, or September 30, 2015, whichever came first. Kaplan-Meier estimates were used to compute cumulative incidence of incident PAD by TyG index quartiles and the differences in estimates were compared using the log-rank procedure. Cox proportional hazards regression model was used to calculate hazard ratios and 95% CIs between TyG index and time to incident PAD. Three multivariate models with progressive degrees of adjustment were used to adjust for potential confounders. Model 1 adjusted for age, sex, and race. Model 2 further adjusted for antihypertensive drugs, body mass index, coronary heart disease, cholesterol-lowering drugs, diastolic blood pressure, diabetes, drinking status, education level, hypertension, physical activity during leisure time, systolic blood pressure, smoking status, sport during leisure time, stroke. Model 3 was additionally further adjusted for eGFR, insulin, LDL cholesterol and total cholesterol. We further used a restricted cubic spline regression model with 3 knots to assess the nonlinear dose-response association between TyG index and incident PAD. Subgroup analyses were performed stratifying by age, sex, race, smoking status, body mass index, hypertension, and diabetes at baseline, respectively. Moreover, we used latent class models to identify different patterns of longitudinal change in TyG index during follow-up. Models were fit using R 3.6.1 based on R package tidyLPA. Group-based trajectory analysis was designed to identify clusters of individuals with similar patterns of change over time [22]. The optimal number of trajectory groups was determined using a combination of Bayesian information criterion and number of observations in each group. Participants were assigned to the trajectory group for which they had the greatest posterior predictive probability. To estimate the association of trajectory groups with incident PAD, trajectory groups was included as an independent variable in a logistic regression model examining predictors of follow-up incident PAD.

All analyses were conducted in SPSS version 23 (SPSS, Inc, Chicago, Illinois). A two-sided *P* value of < 0.05 was considered statistically significant.

Results

Baseline characteristics according to quartiles of TyG index

The average age of all the participants was 54.2±5.7 years, 5784 (46.0%) were men, 3202 (25.5%) were current smokers, and 5298 (42.1%) were hypertensive. The mean TyG index was 8.7±0.6 (Table I in the Data Supplement). We categorized the included population into four groups based on the quartiles of baseline TyG index (Table 1). Participants with a higher TyG index were older, male, and white; had higher levels of body mass index, systolic and diastolic blood pressures, total cholesterol, LDL cholesterol, triglycerides, insulin and fasting plasma glucose; had lower rates of current drinkers, lower levels of education, physical activity score, HDL cholesterol, and eGFR. Likewise, participants in a higher TyG index quartile had a higher prevalence of hypertension, diabetes, coronary heart disease, stroke; and were more prone to take antihypertensive drugs, and cholesterol-lowering drugs. Compared with the analytic cohort, excluded participants were more likely to be female, black, current smokers and non-current drinkers; have lower levels of education, physical activity score and HDL cholesterol; have higher levels of body mass index, systolic and diastolic blood pressures, fasting plasma glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, and eGFR, have correspondingly higher rates of hypertension, diabetes, coronary heart disease, stroke (Table I in the Data Supplement).

Association between baseline TyG index and incident PAD

During a follow-up period of 23.0 (14.7, 25.5) years, 1331 incident cases (10.6%) of PAD were observed. As Table 1 shows, the risk of incident PAD increased with increasing quartiles of TyG index (quartiles 1-4: 228 [7.3%] versus 287 [9.1%] versus 369 [11.7%] versus 447 [14.2%]; *P* for trend<0.001). A similar trend in prevalence of incident CLI was observed. Both unadjusted and adjusted models yielded identical results. The highest risk of incident PAD was found in participants in the highest TyG index quartile (Table 2). In the multivariate model that measured TyG index as a continuous variable, a 1-SD increase (corresponding to 0.58) in TyG index was associated with an 18.9% higher risk of incident PAD (hazard ratio, 1.189 [95% CI, 1.106, 1.278]; *P*<0.001; Table 2). Results were similar when we categorized individuals by TyG index quartiles: the highest risk of incident PAD was observed in the participants with the highest TyG index, in both unadjusted and adjusted models (*P*<0.05, Table 2). In the final model, the hazard ratios (95%CIs) for incident PAD comparing the second, third, fourth quartiles of TyG index to the first quartile were 1.059 (95% CI, 0.888-1.264), 1.224 (95% CI, 1.029-1.457), and 1.363 (95% CI, 1.125-1.652), respectively (Table 2; Figure 2). Figure 3 shows the restricted cubic splines of the risk of incident PAD across levels of TyG index. Consistent with the analysis using quartiles of sample distribution, the risk of incident PAD increased in participants with a higher TyG index. However, there was no significant difference for risk of incident PAD in participants with TyG index <8.6 (Figure 3).

When participants were stratified by age (≤54 or >54 years), sex (male or female), race (white or black), smoking status (current, former or never), body mass index (<30 or ≥30 kg/m^2), hypertension (yes or no), and diabetes (yes or no), the association between TyG index and incident PAD remained consistent (Figure 4).

Association between TyG index trajectories and incident PAD

9296 participants were included for further trajectory analysis (Figure 1), and four discrete trajectories in TyG index from visit 1 to visit 5 were identified (Figure 5); i.e., 43.0% of the cohort (n=3998) had long-term low TyG index values, with a slight increase in later life (low-increasing), 22.3% (n=2075) maintained fairly stable moderate TyG index values all along the follow-up (moderate-stable), 27.6% (n=2567) had long-term moderate TyG index values with a slight decrease in later life (moderate-decreasing), and 7.1% (n=656) had long-term high TyG index values with a slight decrease in later life (high-decreasing) throughout the follow-up. As shown in Figure 6, the prevalence of incident PAD was 7.8%, 10.3%, 13.9% and 20.9%in moderate-stable, low-increasing, moderate-decreasing and high-decreasing TyG index groups, respectively (*P* for trend=0.001). In multivariable analysis, compared with moderate-stable, the odds ratios (95% CIs) for low-increasing, moderate-decreasing, and high-decreasing were 1.118 (95% CI, 0.914-1.368), 1.507 (95% CI, 1.202-1.890), and 2.314 (95% CI, 1.687-3.175), respectively (Table 3).

Discussion

In this large-scale, community-based prospective cohort of middle-aged adults, we show for the first time that higher levels of TyG index are significantly associated with an increased risk of PAD over a median follow-up of 23 years. Furthermore, we identify that four distinct trajectories of TyG index confer different risk of PAD, and two-decade trajectory with elevated TyG index carries greater risk of future incident PAD. These findings suggest a potential role for long-term trajectory with high IR in the pathogenesis of PAD.

IR has been considered as an important risk factor for cardiovascular disease [23, 24]. Methods to directly measure IR are invasive, complex, and costly [10, 11]. Therefore, a number of surrogate markers of IR have been proposed and compared with the gold standard of the hyperinsulinemic-euglycemic clamp [25]. Homeostatic model assessment of IR (HOMA-IR), which is calculated by fasting insulin and glucose, is commonly used for assessing IR. However, the insulin concentrations are not routinely measured in clinical settings. As for the ARIC cohort, there were many missing insulin values due to low detection rate and absence of no insulin measurement at visit 2 and visit 3. Therefore, in this large-scale, community-based prospective cohort study, we utilized the TyG index as a biomarker of IR. The TyG index has been proved to be highly correlated with the euglycemic-hyperinsulinemic clamp test [10], and thus has a validity similar to HOMA-IR [11]. The immense advantage of using such a simple method of IR identification is obviously that it is easily accessible in any clinical settings, making our findings immediately usable by clinicians.

Among the multiple pathological consequences of atherosclerosis, PAD has generally been paid far less attention than coronary diseases or stroke. Based on the updated estimates of PAD prevalence at global regional levels in 2015, 236.62 million (5.56%) people aged 25 years and older had PAD, among whom 73% were in low-income and middle-income countries [26]. However, only about 10% of patients with PAD demonstrate the typical symptomatology of intermittent claudication; and the majority of patients with PAD are thus asymptomatic and underdiagnosed [27]. Therefore, it is of great importance to regularly

measure markers of risk for PAD and take preventive measures at an earlier clinical stage. In addition to age, significant atherosclerotic risk factors for PAD include cigarette smoking, dyslipidemia, and diabetes [28]. It has been well-established that IR and coexisting hyperinsulinemia are implicated in the development of dyslipidemia, hypertension, hypercoagulability, and atherosclerosis [29, 30]. However, there is a paucity of prospective data regarding the association between IR assessed by HOMA-IR and PAD [31, 32]. A cross-sectional study of 3242 adults from data in the National Health and Nutrition Examination Survey has identified a positive association between IR and PAD [31]. Only one community-based longitudinal study, which enrolled 4208 participants over the age of 65 years in the Cardiovascular Health Study, showed that IR was associated with a higher risk of clinical PAD [32]. In line with previous studies, our study of larger sample size showed that the metabolic risk factors such as hypertension, diabetes, and hyperlipidemia, were more obvious with higher quartiles of TyG index. Meanwhile, individuals in the highest quartile of baseline TyG index had a 2.15-fold higher risk of PAD incidence compared to those with the lowest quartile. After adjusting all the aforementioned PAD risk factors, this positive association attenuated but remained significant. These findings suggested that clinical management of TyG index may bring additional effect on PAD development even under vigorous control of traditional risk factors. Further studies are needed to unravel this aspect. Most previous studies based on the TyG index measured at a single time point, which may not reflect long-term exposure because of variation of the TyG index level over time [12, 13]. Therefore, measurements of long-term trajectories of TyG index provide more reliable and robust results. Our study is the first, to our knowledge, to investigate the impact of long-term patterns of IR assessed by TyG index on future PAD incidence. Latent class modeling, as used in our analyses, has allowed identification of different patterns of IR changes as separate trajectory groups, which provides a more realistic understanding of long-term trends in IR as compared to population mean levels. Data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study involving 2414 individuals showed that high-increasing IR (assessed by HOMA-IR) trajectory over 25 years was associated with impaired diastolic function compared with low-decreasing IR trajectory [33]. Another post-analyses by using CARDIA Study data also demonstrated that high-increasing HOMA-IR (referent: low-stable) was associated with greater prevalent diabetes in participants with non-alcoholic fatty liver disease [34]. We highlighted the fact that within the ARIC population there were heterogeneous patterns of trends in TyG index. Our results further suggest that those trajectory groups with long-term moderate and high TyG indexes beginning in midlife are at a greater risk of incident PAD over 20 years, despite the minor reduction of TyG index observed in later life.

Higher TyG index, a surrogate marker of IR, which induce an imbalance in glucose metabolism that generates chronic hyperglycemia, and can also alter lipid metabolism and lead to dyslipidemia [35]. Although the potential mechanisms responsible for the association of the TyG index with the risk of PAD have not been elucidated, our findings at least in part support the important role that metabolic disturbances, including hyperglycemia and hypertriglyceridemia, in the pathophysiology of PAD [36]. Many studies have indicated that IR could promote atherosclerosis not only through mechanisms that involve systemic factors, such as dyslipidemia, hypertension, and a proinflammatory state, but also

through the effect of perturbed insulin signaling at the level of the intimal cells [30, 37]. Therefore, further studies are warranted to elucidate the precise mechanism for the association.

Study Limitations

Several limitations of this investigation are worth noting. The study included only whites and blacks aged 45–64 years at baseline, results may differ outside this age range and in other ethnicities. Due to the shortage of records on insulin in the ARIC study, we cannot compare trajectories of TyG index with HOMA-IR for predicting incident PAD. Similarly, because of the missing data of endothelial function, we cannot explore the potential role of endothelial dysfunction in the association between TyG index and PAD, which was demonstrated to be at least one possible biological pathway between IR and atherosclerosis [38, 39]. Moreover, as for the nature of any observational studies, we cannot exclude the possibility of residual confounders despite our careful adjustment for the well-known and suspected risk factors.

Conclusion

Higher TyG index is associated with incident PAD, which is independent of other traditional atherosclerotic risk factors; suggesting that metabolic dysfunction is actually involved in the pathophysiology of PAD. Trajectories denoting long-term exposure to high IR assessed by TyG index provide additional information about the cumulative burden of risk for future PAD.

Abbreviations

ARIC: Atherosclerosis Risk in Communities Study; CARDIA: Coronary Artery Risk Development in Young Adults; CLI: critical limb ischemia; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; IR: insulin resistance; LDL: low-density lipoprotein; PAD: peripheral artery disease; TyG: triglyceride-glucose.

Declarations

Authors' contributions

JWG, QYH and PML contributed to the study concept, and drafted the manuscript. JWG and QYH has full access to the data and performed the analyses; JWG and QYH assisted in data interpretation; MG, KZ and XZL helped in the data methods and presentation; JWG, DAV, SLZ and PML critically revised the manuscript. JFW and PML supervised the study analyses. All authors read and approved the final manuscript

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study was approved by the institutional review boards at all field centers of ARIC study, and informed consent was obtained from all participants.

Consent for publication

The consent to publish was obtained from all participants in this study.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics of study participants by quartiles of TyG index

Characteristics	Quartile 1 (n=3143)	Quartile 2 (n=3145)	Quartile 3 (n=3142)	Quartile 4 (n=3143)	*P* value
TyG index	8.0±0.2	8.4±0.1	8.8±0.1	9.4±0.4	<0.001
Age, years	53.1±5.7	54.1±5.7	54.7±5.7	55.1±5.7	<0.001
Male, %	1171 (37.3%)	1347 (42.8%)	1565 (49.8%)	1701 (54.1%)	<0.001
White, %	2187 (69.6%)	2360 (75.0%)	2473 (78.7%)	2500 (79.5%)	<0.001
BMI, kg/m^2	25.6±4.8	27.0±5.1	28.1±5.2	29.7±5.1	<0.001
SBP, mmHg	117.3±18.9	119.3±18.4	121.5±17.9	125.1±18.3	<0.001
DBP, mmHg	72.4±11.5	72.9±11.2	73.8±10.9	74.8±10.9	<0.001
Smoking status, %					<0.001
Current smoker	711 (22.6%)	846 (26.9%)	853 (27.1%)	792 (25.2%)	
Former smoker	931 (29.6%)	992 (31.5%)	1052 (33.5%)	1175 (37.4%)	
Never smoker	1501 (47.8%)	1307 (41.6%)	1237 (39.4%)	1176 (37.4%)	
Drinking status, %					<0.001
Current drinker	1873 (59.6%)	1814 (57.7%)	1767 (56.2%)	1736 (55.2%)	
Former drinker	496 (15.8%)	569 (18.1%)	628 (20.0%)	664 (21.1%)	
Never drinker	774 (24.6%)	762 (24.2%)	747 (23.8%)	743 (23.6%)	
Education level, %					<0.001
Basic education	601(19.1%)	695 (22.1%)	701 (22.3%)	836 (26.6%)	
Intermediate education	1220 (38.8%)	1264 (40.2%)	1351 (43.0%)	1334 (42.4%)	
Advanced education	1322 (42.1%)	1186 (37.7%)	1090 (34.7%)	973 (31.0%)	
Physical activity score					
Sport during leisure time	2.5±0.8	2.5±0.8	2.5±0.8	2.4±0.8	0.002
Physical activity during leisure time	2.4±0.6	2.4±0.6	2.4±0.6	2.3±0.6	<0.001
Incident PAD, %	228 (7.3%)	287 (9.1%)	369 (11.7%)	447 (14.2%)	<0.001
Incident CLI, %	22 (0.7%)	20 (0.6%)	41 (1.3%)	103 (3.3%)	<0.001

Hypertension, %	979 (31.1%)	1170 (37.2%)	1370 (43.6%)	1779 (56.6%)	<0.001
Diabetes, %	57 (1.8%)	129 (4.1%)	232 (7.4%)	984 (31.3%)	<0.001
Coronary heart disease, %	67 (2.1%)	122 (3.9%)	175 (5.6%)	247 (7.9%)	<0.001
Stroke, %	66 (2.1%)	67 (2.1%)	96 (3.1%)	123 (3.9%)	<0.001
Antihypertensive medication, %	586 (18.6%)	800 (25.4%)	976 (31.1%)	1370 (43.6%)	<0.001
Cholesterol-lowering medication, %	32 (1.0%)	77 (2.4%)	102 (3.2%)	140 (4.5%)	<0.001
FPG, mg/dL	94.2±8.6	98.9±11.5	103.7±17.7	133.8±63.1	<0.001
Insulin, μIU/mL	6.0 (4.0, 9.0)	8.0 (6.0, 12.0)	10.0 (7.0, 15.0)	14.0 (10.0, 23.0)	<0.001
HDL-C, mg/dL	62.9±17.7	54.6±15.6	47.8±13.9	41.7±12.3	<0.001
LDL-C, mg/dL	121.4±34.1	136.3±37.4	146.2±38.1	145.5±40.4	<0.001
TC, mg/dL	197.0±36.0	209.8±38.0	220.4±39.4	229.4±43.3	<0.001
Triglycerides, mg/dL	63.6±12.4	94.7±13.2	131.7±20.9	211.2±62.8	<0.001
eGFR, mL/min/1.73m^2	105.6±14.8	102.5±14.5	100.9±15.4	99.9±16.5	<0.001

Values are mean±SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%).

BMI body mass index, *CLI* critical limb ischemia; *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *PAD* peripheral artery disease, *SBP* systolic blood pressure, *TC* total cholesterol.

Table 2. Risk of incident PAD for baseline TyG index

TyG index	Events/No. at risk	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value	Model 3 HR (95% CI)	*P* value
Quartile 1	228/3143	Reference	1.0	Reference	1.0	Reference	1.0
Quartile 2	287/3145	1.271 (1.067, 1.513)	0.007	1.110 (0.931, 1.323)	0.246	1.059 (0.888, 1.264)	0.524
Quartile 3	369/3142	1.648 (1.395, 1.946)	<0.001	1.297 (1.093, 1.539)	0.003	1.224 (1.029, 1.457)	0.023
Quartile 4	447/3143	2.150 (1.829, 2.528)	<0.001	1.327 (1.108, 1.588)	0.002	1.363 (1.125, 1.652)	0.002
Per 1 SD (0.58)	1331/12573	1.376 (1.307, 1.449)	<0.001	1.141 (1.072, 1.214)	<0.001	1.189 (1.106, 1.278)	<0.001

Model 1: Adjusted for age, race, sex.

Model 2: Adjusted for model 1 covariates plus antihypertensive medication, body mass index, coronary heart disease, cholesterol-lowering medication, diastolic blood pressure, diabetes, drinking status (current, former, never), education level (basic, intermediate, advanced education), hypertension, physical activity during leisure time, systolic blood pressure, smoking status (current, former, never), sport during leisure time, stroke.

Model 3: Adjusted for model 2 covariates plus estimated glomerular filtration rate, insulin, low-density lipoprotein cholesterol and total cholesterol.

HR hazard ratio, *CI* confidential interval.

All abbreviations as in Table 1.

Table 3. Risk of incident PAD for TyG index trajectory groups

TyG index trajectories	Model 1 OR (95% CI)	*P* value	Model 2 OR (95% CI)	*P* value	Model 3 OR (95% CI)	*P* value
Moderate-stable	Reference	1.0	Reference	1.0	Reference	1.0
Low-increasing	1.396 (1.152, 1.691)	0.001	1.204 (0.986, 1.469)	0.068	1.118 (0.914, 1.368)	0.279
Moderate-decreasing	2.009 (1.648, 2.450)	<0.001	1.510 (1.215, 1.877)	<0.001	1.507 (1.202, 1.890)	<0.001
High-decreasing	3.184 (2.480, 4.087)	<0.001	2.017 (1.508, 2.697)	<0.001	2.314 (1.687, 3.175)	<0.001

Model 1: Adjusted for baseline age, race, sex.

Model 2: Adjusted for model 1 covariates plus antihypertensive medication, body mass index, coronary heart disease, cholesterol-lowering medication, diastolic blood pressure, diabetes, drinking status, education level (basic, intermediate, advanced education), hypertension, physical activity during leisure time, systolic blood pressure, smoking status, sport during leisure time, stroke.

Model 3: Adjusted for model 2 covariates plus estimated glomerular filtration rate, insulin, low-density lipoprotein cholesterol and total cholesterol.

OR odds ratio, *CI* confidential interval.

All abbreviations as in Table 1.

Figures

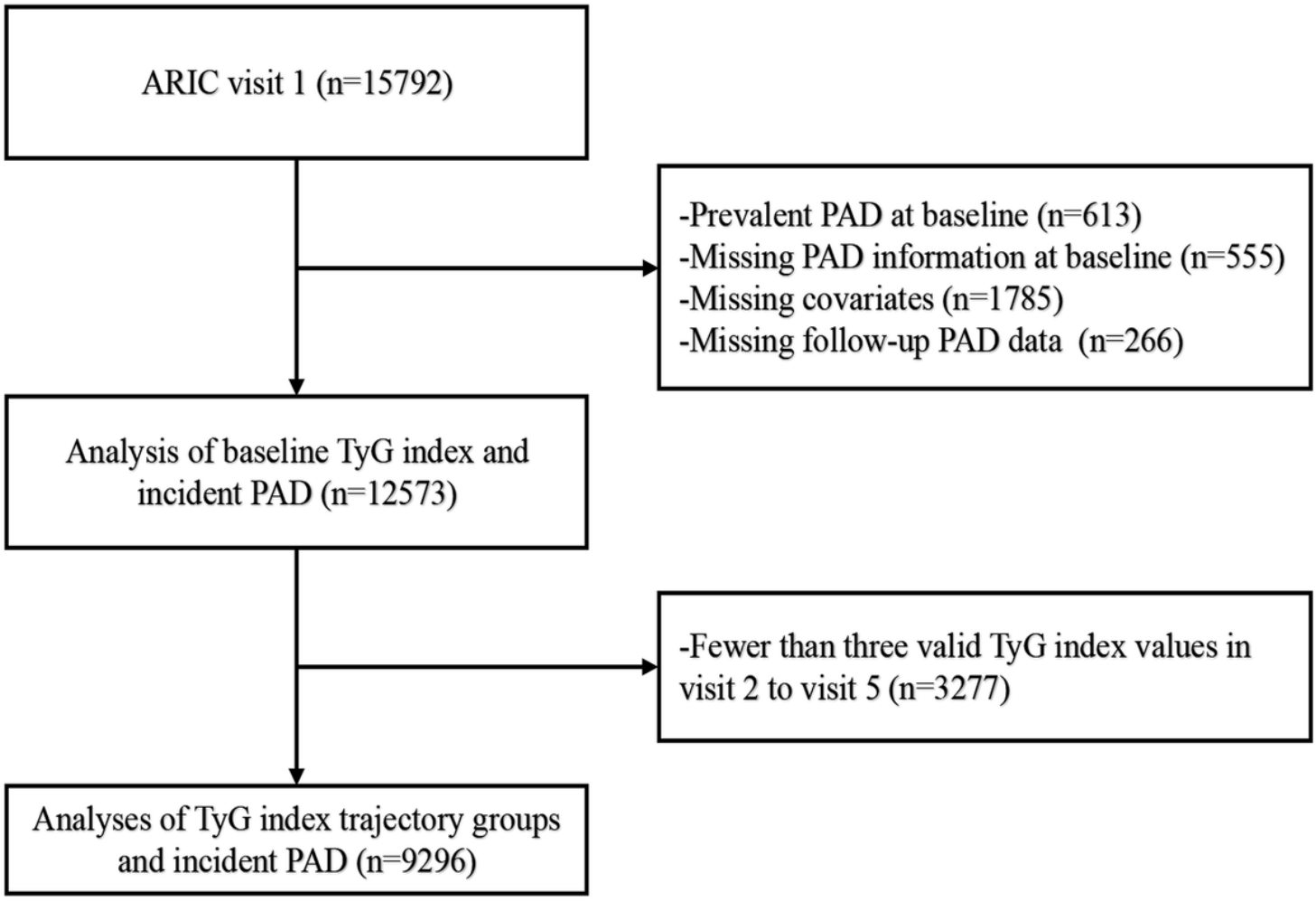

Figure 1

Flowchart for selecting the Atherosclerosis Risk in Communities (ARIC) participants for analysis.

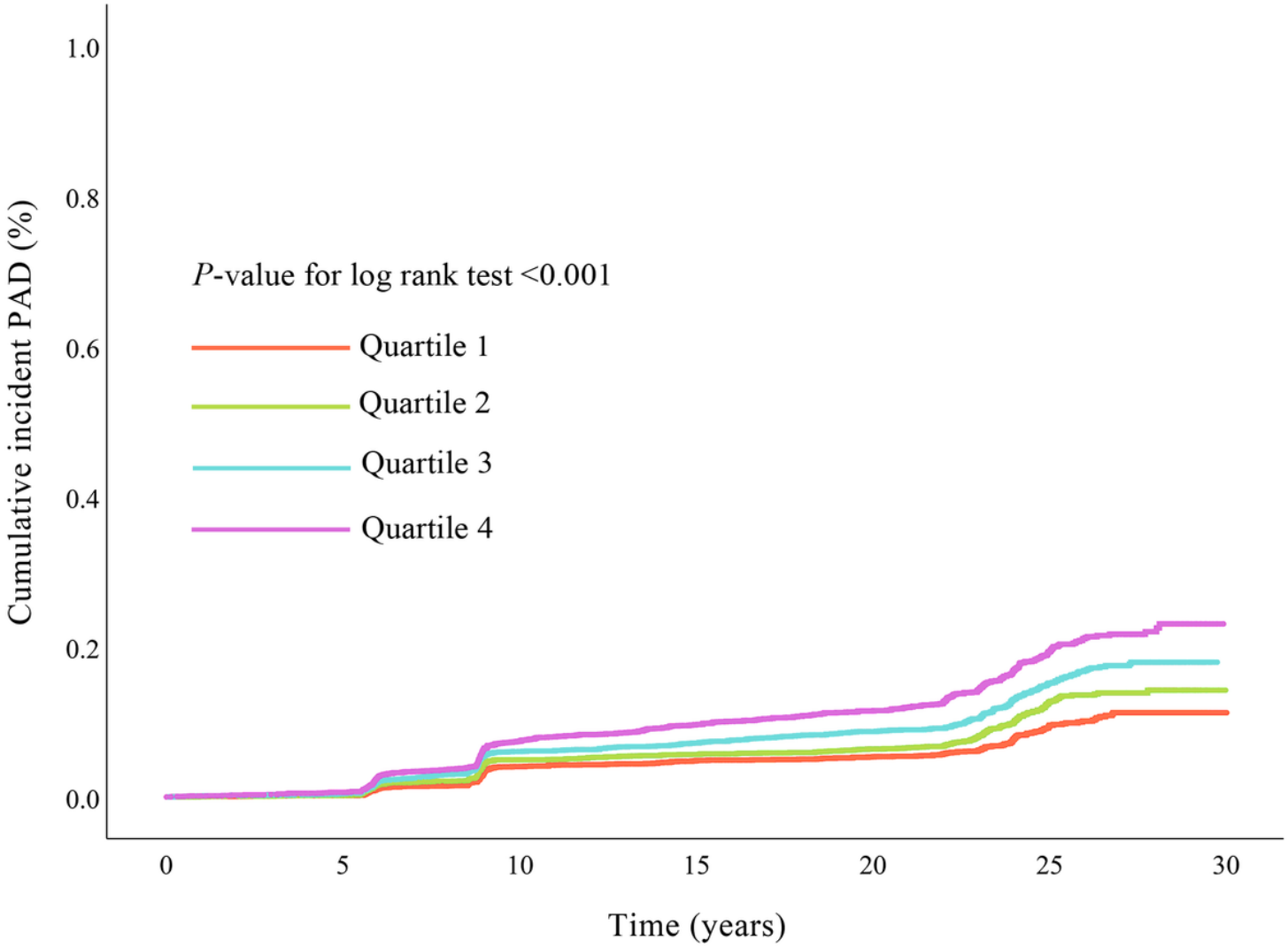

Figure 2

Cumulative incidence of incident PAD by quartiles of baseline TyG index. Cumulative incidence curves are statistically different (log-rank P <0.001).

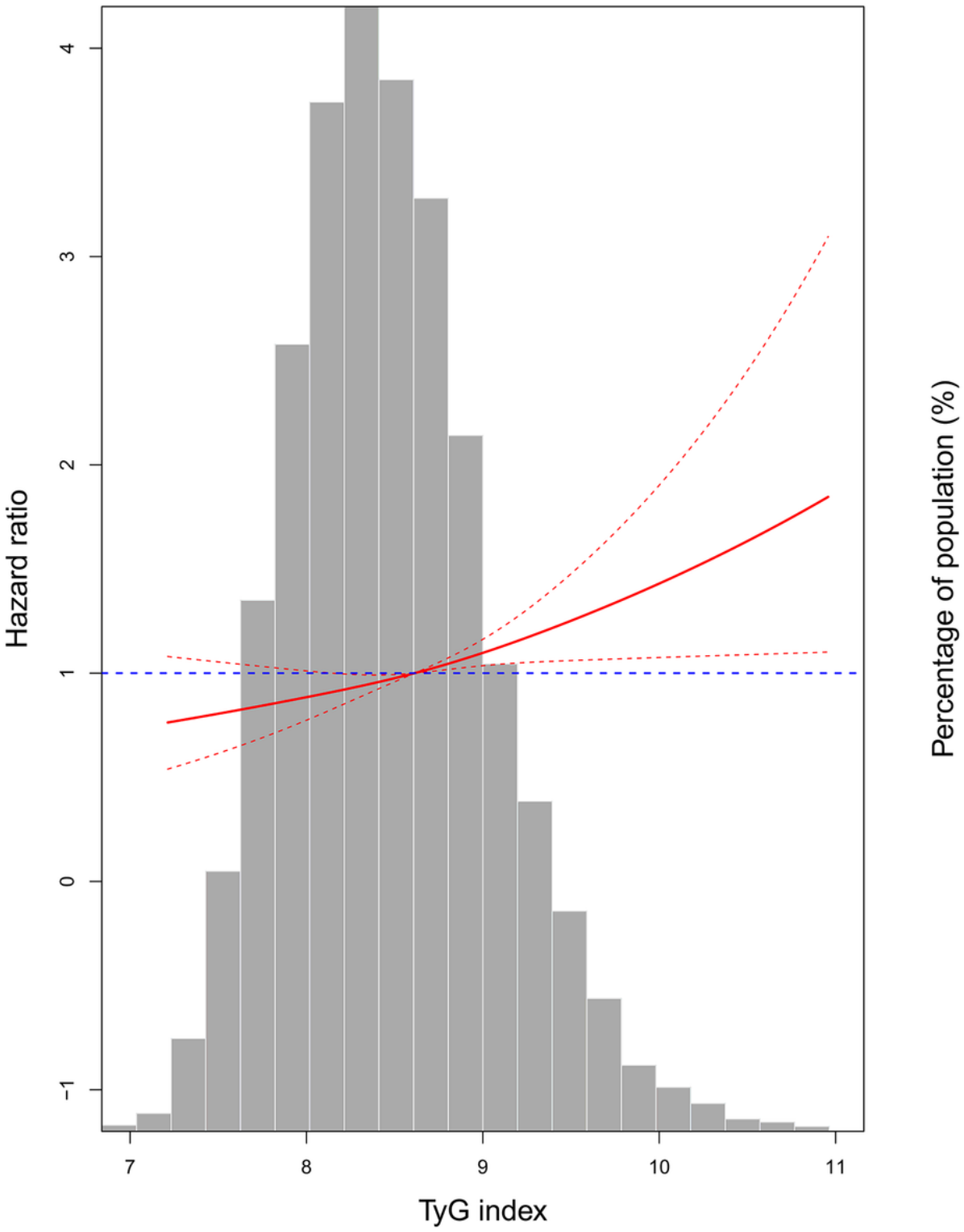

Figure 3

Adjusted hazard ratios of incident peripheral artery disease (PAD) by baseline triglyceride-glucose (TyG) index. Each hazard ratio was computed with a TyG index level of 8.6 as the reference. The hazard ratio was adjusted for age, sex, race, antihypertensive medication, body mass index, coronary heart disease, cholesterol lowering medication, diastolic blood pressure, diabetes, drinking status, education level, hypertension, physical activity during leisure time, systolic blood pressure, smoking status, sport during

leisure time, stroke, estimated glomerular filtration rate, insulin, low-density lipoprotein cholesterol and total cholesterol. Red solid line represents the hazard ratio of TyG index across the whole range. Red dotted lines represent the 95% CI. Blue dotted line is the reference line as hazard ratio=1. Histograms represent the frequency distribution of TyG index.

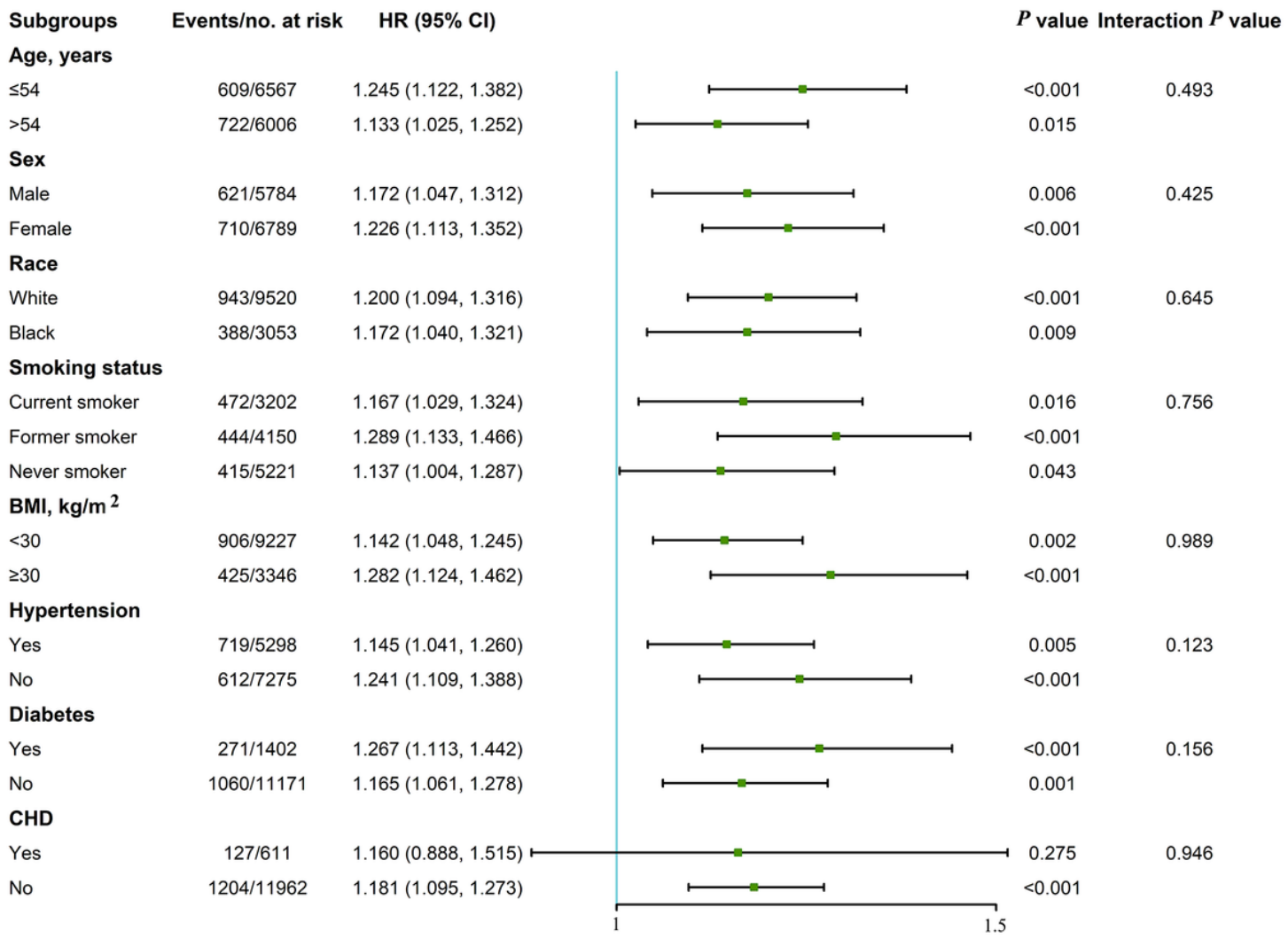

Figure 4

Subgroup analysis of the association between baseline TyG index and incident PAD. Cox regression after adjustment for antihypertensive medication, cholesterol-lowering medication, coronary heart disease, diastolic blood pressure, drinking status, education level, hypertension, physical activity during leisure time, systolic blood pressure, sport during leisure time, stroke, estimated glomerular filtration rate, insulin, low-density lipoprotein cholesterol and total cholesterol was performed in subgroups according to age (≤54 or >54 years), gender (male or female), race (White or black), smoking status (current or former or never), body mass index (BMI; <30 or ≥30 kg/m2), hypertension (yes or no), and diabetes (yes or no).

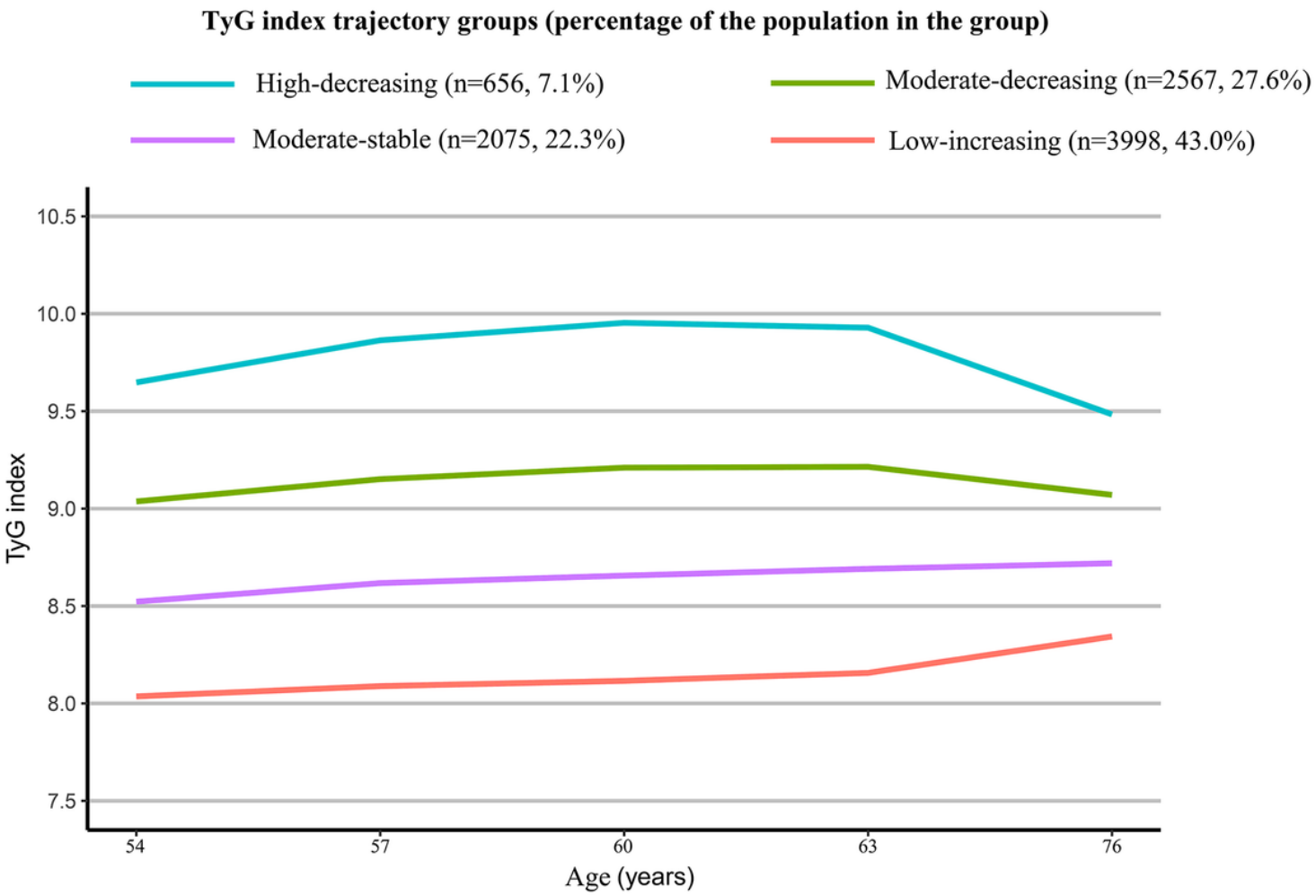

Figure 5

Trajectories by TyG index in the Atherosclerosis Risk in Communities (ARIC) Study.

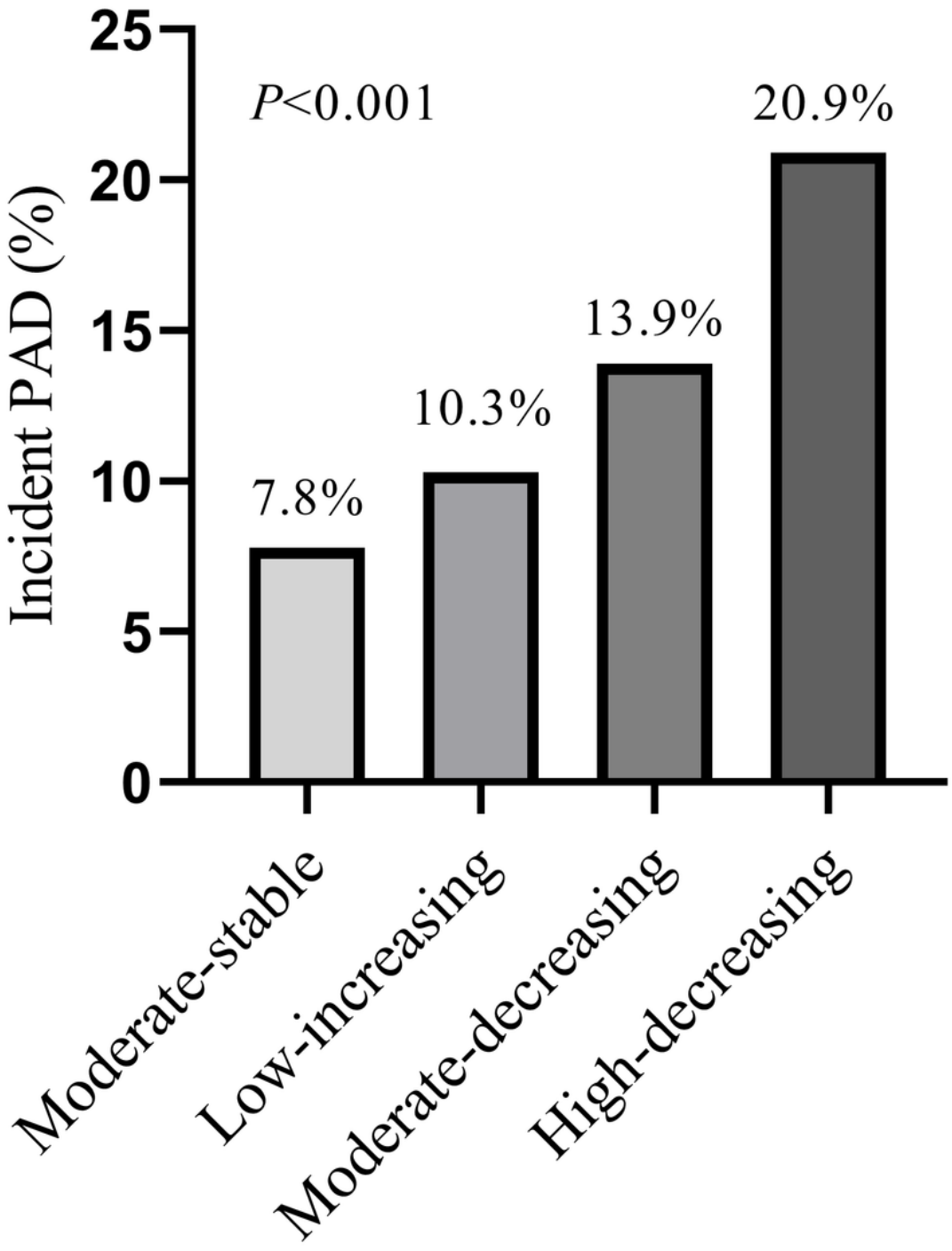

Figure 6

Prevalence of incident PAD across the TyG index trajectory groups.

Supplementary Files

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- SupplementaryMaterial.docx