

Relationship Between the Triglyceride-glucose Index and Incident Ischemic Heart Disease Risk: A Prospective Study Using National Health Insurance Data

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Abstract

Background: Ischemic heart disease (IHD) without diabetes is considered an important challenge to human health and is associated with a poor prognosis as well as a lack of health awareness. Until now, the association between early insulin resistance and IHD among nondiabetic adults has been poorly understood. We prospectively investigated the relationship between the triglyceride-glucose (TyG) index, a surrogate marker of early insulin resistance, and incident IHD risk in a large cohort of nondiabetic adults using National Health Insurance data.

Methods: We assessed 16,455 participants (8,426 men and 8,029 women) without diabetes using data from a health risk assessment study (HERAS) and Korea Health Insurance Review & Assessment (HIRA) data. The participants were divided into four groups according to TyG index quartiles, calculated as $\ln[\text{fasting triglycerides (mg/dL)} \times \text{fasting plasma glucose (mg/dL)} / 2]$. We prospectively assessed hazard ratios (HRs) with 95% confidence intervals (CIs) for IHD, using multivariate Cox proportional-hazards regression models, over a 50-month period that followed the baseline survey.

Results: During the follow-up period, 322 (2.0%) participants developed IHD. HRs of IHD for TyG index quartiles 1–4 were 1.00, 1.63 (95% CI, 1.06–2.49), 1.88 (95% CI, 1.23–2.87), and 2.35 (95% CI, 1.53–3.61), respectively, after adjusting for age, sex, body mass index, smoking status, alcohol intake, physical activity, high sensitivity C-reactive protein, and mean arterial blood pressure.

Conclusion: A higher TyG index precedes and significantly predicts future IHD among nondiabetic Koreans. Accordingly, a high TyG index may be a useful additional measure in assessing cardiovascular risks for apparently healthy adults in clinical practice.

Background

Ischemic heart disease (IHD) can cause premature morbidity and mortality among middle-aged and older individuals, and it is an important challenge to human health in both developing and developed countries [1]. The burden of premature IHD in an ageing population cannot be underestimated, considering it is a factor that decreases the quality of life and increases social burden [2]. Accordingly, assessing and identifying potential risks for IHD in the preclinical stage among apparently healthy individuals is worthwhile for facilitating disease prevention and slowing the progression of IHD.

Accumulating evidence suggests that the triglyceride-glucose (TyG) index, a simple and widely accessible measure, is a novel and surrogate marker for early insulin resistance [3, 4]. Epidemiological studies conducted in the Korean population have shown that the TyG index is a better indicator of metabolic syndrome and type 2 diabetes than the homeostasis model assessment of insulin resistance (HOMA-IR) [5, 6]. Koreans are a group of East Asians with ethnic homogeneity with a lower overall body mass index (BMI) than Westerners. Regarding the total energy intake, the proportion of carbohydrate intake was much higher among Koreans than Westerners [7]. The prevalence of both hypertriglyceridemia and

impaired fasting glucose was 20–30% among Korean adults, according to data from the Korea National Health and Nutrition Examination Survey (KNHANES) [8, 9].

The TyG index has been associated with subclinical atherosclerosis symptoms such as arterial stiffness and preclinical coronary arterial calcification [10–12]. Meanwhile, prospective studies to evaluate the predictive value of TyG index in cardiovascular diseases (CVDs) have been focused mainly on preexisting coronary arterial disease or diabetes mortality [13, 14]. Furthermore, nondiabetic individuals with IHD tend to have a poorer prognosis than do diabetic patients without IHD [15, 16]. Therefore, we prospectively investigated the relationship between the TyG index and IHD incidence within a large-scale, community-dwelling, nondiabetic adult cohort using National Health Insurance data.

Methods

Study participants

This study is based on a health risk assessment study (HERAS) that aimed to characterize cardiovascular risk factors and explore surrogate markers of CVD in Korean adults. The study cohort consisted of 20,530 individuals aged ≥ 20 years who voluntarily visited the Health Promotion Center, Gangnam Severance Hospital, Yonsei University College of Medicine, for regular health examinations between November 2006 and June 2010. Among 20,530 participants initially assessed, 1,590 (7.7%) participants with a history of IHD or ischemic stroke, a previous diagnosis of type 2 diabetes or a fasting plasma glucose level ≥ 126 mg/dL were excluded. We also excluded participants who met at least one of the following criteria: age <30 years, missing data, current use of dyslipidaemia medication or aspirin, high-sensitivity C-reactive protein (hsCRP) level ≥ 10 mg/L ($N = 2,485$). After exclusion criteria were applied, 16,455 participants (8,426 men and 8,029 women) were included in our final analysis.

Data collection

Each participant completed a lifestyle and medical history questionnaire that included information regarding cigarette smoking, alcohol consumption, and physical activity.

Smoking status was defined using the following categories: non-smoker, ex-smoker, and current smoker. Questions regarding alcohol intake included information regarding consumption frequency on a weekly basis. Regular alcohol consumption was defined as alcohol consumption \geq two times per week. Participants were asked about their level of physical exercise on a weekly basis, and regular exercise was defined as exercise \geq three times per week. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light indoor clothing without shoes. BMI was calculated as an individual's weight in kilograms divided by the square of his/her height in metres (kg/m^2). Systolic blood pressure and diastolic blood pressure were measured on the patient's right arm using a standard mercury sphygmomanometer in the sitting position after 10 min of rest (Baumanometer, W.A. Baum Co Inc., Copiague, NY, USA). All blood samples were obtained from the antecubital vein after overnight fasting for 12 h. Fasting plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol

levels were measured via enzymatic methods using a Hitachi 7600 automated chemistry analyser (Hitachi Co.; Tokyo, Japan). hsCRP concentrations were measured with a Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN, USA) using a latex-enhanced immunoturbidimetric method with a low limit of detection of 0.09 mg/L. Hypertension was defined as systolic blood pressure \geq 140 mmHg, diastolic blood pressure \geq 90 mmHg, or current use of hypertension medication. Chronic kidney disease (CKD) was defined either as renal tissue damage or reduced renal functioning, as determined by an eGFR value $<$ 60 mL/min/1.73 m² or proteinuria 1+ or greater [17].

Study outcomes

The primary outcome assessed was IHD, which consisted of angina pectoris (ICD-10 codes I20) or acute myocardial infarction (ICD-10 codes I21) that occurred after initial study enrolment. To define baseline and post-survey outcomes, we linked a personal, 13-digit identification number that was assigned to each subject with Korea Health Insurance Review & Assessment (HIRA) data, which is a repository of claims data collected in the process of reimbursing healthcare providers, between November 2006 and December 2010. Participants that were found to have had IHD or ischemic stroke (ICD-10 codes I20, I21, and I63) at the time of their initial assessment were excluded before the final analysis.

Statistical analysis

The TyG index values were categorised into quartiles, as follows: Q1 (\leq 8.08), Q2 (8.09–8.45), Q3 (8.46–8.85), and Q4 (\geq 8.86). All data are presented as means with standard deviations or percentages. The baseline characteristics of the study population according to the TyG index quartiles were compared using an analysis of variance (ANOVA) model for continuous variables and the chi-squared test for categorical variables. Kaplan–Meier curves were used to assess the cumulative incidence of IHD. The log-rank test was used to determine whether the distributions of cumulative IHD incidence differed among groups. Pairwise comparisons of receiver-operating characteristic (ROC) curves were used to contrast area under the ROC curve (AUC) of IHD incidence based on TyG index, fasting plasma glucose, and serum triglyceride levels. Further, AUC values were used to test the sensitivity and specificity of biomarkers for predicting IHD. For multivariate analysis, after setting the lowest TyG index value quartile as a reference group, hazard ratios (HRs) and 95% confidence intervals (CIs) for incident IHD were calculated using the Cox proportional-hazards regression model after adjusting for potential confounding variables. All analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was set at $P < 0.05$.

Results

Table 1 shows the baseline characteristics of the study population (n = 16,455; 8,426 men and 8,029 women) according to TyG index quartiles. The mean age and BMI of the study population were 46.1 ± 9.5 years and 23.4 ± 3.0 kg/m², respectively. The mean fasting plasma glucose concentration was

determined to be 91.4 ± 9.8 mg/dL, the mean triglycerides level was 124.2 ± 84.9 mg/dL, and the mean TyG index value was 8.49 ± 0.56 .

The mean BMI, mean arterial pressure, total cholesterol, and hsCRP values were highest and the mean HDL-cholesterol levels were lowest in the highest TyG index quartile group. The greatest proportions of current smokers and alcohol drinkers were members of the fourth TyG index quartile, whereas the proportion of individuals who participated in regular exercise was highest in the first TyG index quartile. The higher TyG index groups had a significantly elevated cumulative incidence of IHD over a 50-month period that followed the baseline survey (log-rank test, $P < 0.001$) (Figure 1).

Using a pairwise comparison of ROC analyses of incident IHD, the AUC of TyG index data was significantly higher than that of fasting plasma glucose ($P = 0.016$), and was marginally significant when compared with the AUC produced using serum triglyceride level data ($P = 0.058$). The sensitivity, specificity, AUC of TyG index for classifying IHD was 80.8%, 37.2%, and 0.613, respectively (Table 2).

Table 3 shows results of the multivariate Cox proportional-hazards regression analysis for the prediction of IHD according to TyG index quartile. A total of 322 individuals (2.0%, 322/16,455) developed IHD during the follow up period. The incidence rate (per 1,000 person years) of IHD increased proportionally as TyG index quartile increased. Compared with the first TyG index quartile, the HRs of incident IHD for the second, third, and fourth quartiles increased in a dose-responsive manner. The HRs of incident IHD were 1.63 (95% CI, 1.06–2.49), 1.88 (95% CI, 1.23–2.87), and 2.35 (95% CI, 1.53–3.61) for the second, third and fourth TyG index quartiles, respectively, after adjusting for age, sex, BMI, smoking status, alcohol intake, physical activity, mean arterial blood pressure, hsCRP, and CKD (Model 3).

Discussion

Among community dwelling Korean adults without diabetes, we found that elevated TyG index values were positively and independently associated with IHD incidence in this large-scale, prospective cohort study that included a 50-month follow-up. Our study showed that the association between TyG index and IHD persisted after further adjustment for lifestyle factors, inflammation, and mean arterial blood pressure.

In a prospective study that considered patients with stable coronary artery disease, Jin et al. showed that the TyG index may be a useful predictive marker of cardiovascular events [13]. Ma et al., in a longitudinal study of 766 patients who underwent percutaneous coronary intervention, reported that subgroups within the top tertile of the TyG index had a 2.17-fold higher risk of adverse cardiovascular outcomes over a median follow-up period of 30 months, compared with the referent first tertile [14]. To our knowledge, one previous longitudinal study has examined the relationship between the TyG index and incident IHD within a population-based cohort. Sanchez-Inigo et al. performed a study that included 5,014 Caucasian men and women with a mean age of 55.51 ± 13.68 and 53.72 ± 12.84 , respectively. The work revealed a positive association between the TyG index and CVD throughout a median period of 10 years. However, the study performed by Sanchez-Inigo et al. included an older age group, and also included patients with

diabetes and current users of anti-aggregation medication [18]. That study did not identify a relationship between the TyG index and incident CVD in participants with type 2 diabetes at baseline, which may have been due to effects of medication or the adoption of healthier habits by participants.

Meanwhile, some studies have reported that the TyG index is associated with subclinical coronary atherosclerosis not only in diabetic patients but also in the general population [11, 19]. From an epidemiological standpoint, nondiabetic individuals with myocardial infarction have been reported to have a poorer prognosis than diabetic patients without myocardial infarction [15, 16, 20, 21]. To predict future CVD, a health risk assessment over a 5-year period has become as important as that over a 10-year period over the past few decades [22, 23]. This study revealed for the first time an association between the TyG index and incident IHD among apparently healthy individuals using an assessment period that did not exceed five years in an East Asian population, despite the fact that the incidence of IHD was relatively low. Some possible explanations for the observed association deserve consideration. The TyG index has been known to be one of the best indices that can be used for identifying individuals with early insulin resistance [3]. In a prospective study of non-obese Chinese adults, Zhang et al. suggested that the TyG index may be valuable for predicting type 2 diabetes [24]. Further, TyG index was determined to be superior to well-known predictive biomarkers of type 2 diabetes such as HOMA-IR in a study that assessed 5,354 Korean subjects without diabetes with a mean age of 61.6 years and a mean BMI of 24.2 kg/m² [25]. Additionally, the TyG index has been suggested to be a useful surrogate marker of overall metabolic health status according to KNHANES, a nationwide survey representing the entire Korean population [26]. Finally, chronic inflammation could contribute to the association between the TyG index and IHD. In the present study, serum hsCRP levels gradually increased with the TyG index quartile, which supports the idea that TyG index is closely linked to underlying low-grade inflammation.

Some strengths and limitations require careful consideration and may affect the interpretation of the results of the present study. A major strength of the work was that we conducted a prospective cohort study using a large number of Korean individuals that was linked to HIRA data, derived from the universal coverage system in Korea. As a result, there was a very low chance that data was missing [27]. This study had some limitations that should also be acknowledged. First, because the study cohort was composed of volunteers that visited a clinic for health promotion screenings conducted at a single hospital, patients appeared to be slightly healthier than most community-based cohorts previously assessed. Second, some diabetic individuals may have been included in the study population because glycated haemoglobin A1c and 2-h oral glucose tolerance tests were not performed at the beginning of the study.

Conclusions

In conclusion, an elevated TyG index precedes and significantly predicts future IHD among community dwelling nondiabetic Koreans. Moreover, the TyG index was found to be a more powerful predictive indicator of IHD than fasting glucose or triglyceride levels alone. Accordingly, a high TyG index may be a useful additional measure in assessing cardiovascular risks for apparently healthy adults in clinical

practice. Large-scale prospective studies are necessary to elucidate the mechanism for the association between the TyG index and IHD.

Abbreviations

IHD: ischemic heart disease; TyG: triglyceride glucose; HERAS: health risk assessment study; HIRA: Korea Health Insurance Review & Assessment; HRs: hazard ratios; CIs: confidence intervals; HOMA-IR: homeostasis model assessment of insulin resistance; BMI: body mass index; KNHANES: Korea National Health and Nutrition Examination Survey; CVD: cardiovascular diseases; hsCRP: high sensitivity C-reactive protein; CKD: chronic kidney disease; ANOVA: analysis of variance; ROC: receiver-operating characteristic; AUC: area under the receiver-operating characteristic curve.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BP, YJL, and DHJ designed the study; BP, YJL, and DHJ assisted with data acquisition and interpretation; BP, YJL and HSL performed statistical analyses; BP, YJL, HSL, and DHJ contributed to the discussion; BP and YJL drafted the manuscript; and DHJ revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of the study population according to TyG index quartiles

	Quartile of TyG index					<i>P</i> value
	Total	Q1	Q2	Q3	Q4	
	n = 16,456	n = 4,140	n = 4,119	n = 4,096	n = 4,100	
TyG index	8.49 ± 0.56	≤ 8.08	8.09– 8.45	8.46– 8.85	≥8.86	
Age (years)	46.1 ± 9.5	44.0 ± 8.9	46.0 ± 9.5	47.5 ± 9.7	46.8 ± 9.4	< 0.001
Male sex (%)	51.2	27.7	43.3	58.4	75.8	< 0.001
Body mass index (kg/m ²)	23.4 ± 3.0	21.6 ± 2.5	22.7 ± 2.7	23.9 ± 2.8	25.2 ± 2.8	< 0.001
Systolic blood pressure (mmHg)	121.9 ± 15.5	115.0 ± 13.9	119.8 ± 14.8	124.1 ± 14.9	128.8 ± 14.8	< 0.001
Diastolic blood pressure (mmHg)	76.2 ± 10.1	71.5 ± 9.1	74.7 ± 9.5	77.7 ± 9.6	80.9 ± 9.7	< 0.001
Mean arterial pressure (mmHg)	91.5 ± 11.5	86.0 ± 10.3	89.8 ± 10.9	93.2 ± 11.0	96.9 ± 11.0	< 0.001
Fasting plasma glucose (mg/dl)	91.4 ± 9.8	85.8 ± 7.8	90.2 ± 8.3	92.9 ± 9.1	96.8 ± 10.3	< 0.001
Total cholesterol (mg/dL)	190.3 ± 33.3	175.7 ± 29.6	185.6 ± 29.7	195.5 ± 32.1	204.4 ± 34.4	< 0.001
Triglyceride (mg/dL)	124.2 ± 84.9	58.9 ± 10.7	87.3 ± 11.6	123.5 ± 17.9	227.9 ± 109.2	< 0.001
HDL-cholesterol (mg/dL)	53.2 ± 12.6	61.3 ± 12.4	55.8 ± 11.9	50.7 ± 10.7	45.1 ± 9.2	< 0.001
High sensitivity C-reactive protein (mg/L)	1.0 ± 1.3	0.7 ± 1.2	0.9 ± 1.3	1.2 ± 1.4	1.3 ± 1.4	< 0.001
Current smoker (%)	24.7	11.2	19.3	27.1	41.1	< 0.001
Alcohol drinking (%)	43.3	35.2	39.2	44.6	54.3	< 0.001
Regular exercise (%)	30.9	33.4	32.7	31.2	26.3	< 0.001
Hypertension (%)	20.3	9.1	15.5	23.4	33.5	< 0.001
Chronic kidney disease (%)	1.9	1.5	1.7	2.2	2.3	0.011

Data are expressed as the mean \pm SD or percentage

Table 2. TyG index versus fasting glucose and serum triglyceride levels for predicting ischemic heart disease

	Pairwise comparison of AUC			TyG index for classifying ischemic heart disease			
	Difference	95% CI	<i>P</i> value	Sensitivity (%)	Specificity (%)	AUC	<i>P</i> value
TyG index vs fasting plasma glucose	0.04	0.01 to 0.08	0.016				
TyG index vs serum triglyceride levels	0.01	0.00 to 0.01	0.058				
Fasting plasma glucose vs serum triglyceride levels	0.04	0.00 to 0.07	0.072				
TyG index				80.8	37.2	0.613	< 0.001
Fasting plasma glucose				50.0	70.7	0.571	< 0.001
Serum triglyceride levels				67.1	50.6	0.607	< 0.001

ROC, receiver operating characteristic; *AUC*, area under the receiver operating characteristic curve; TyG index, triglyceride-glucose index

Table 3. Hazard ratios and 95% confidence intervals for new-onset ischemic heart diseases according to TyG index quartiles

	TyG index quartiles			
	Q1	Q2	Q3	Q4
	n = 4,140	n = 4,119	n = 4,096	n = 4,100
New cases of ischemic heart disease, n	41	70	93	118
Mean follow-up, years	2.4 ± 1.1	2.4 ± 1.1	2.4 ± 1.1	2.4 ± 1.1
Pearson-years of follow-up	9878	9745	9651	9756
Incidence rate/1000 person - years	4.2	7.2	9.6	12.1
Model 1	1.00 (reference)	1.41 (0.96–2.08)	1.67 (1.15–2.42)	2.13 (1.48–3.06)
Model 2	1.00 (reference)	1.61 (1.05–2.48)	1.85 (1.21–2.81)	2.29 (1.50–3.51)
Model 3	1.00 (reference)	1.63 (1.06–2.49)	1.88 (1.23–2.87)	2.35 (1.53–3.61)
Model 1: adjusted for age and sex				
Model 2: adjusted for age, sex, body mass index, smoking status, alcohol intake, and physical activity				
Model 3: adjusted for age, sex, body mass index, smoking status, alcohol intake, physical activity, high sensitivity C-reactive protein, and mean arterial blood pressure, C-reactive protein level, and chronic kidney disease				

Figures

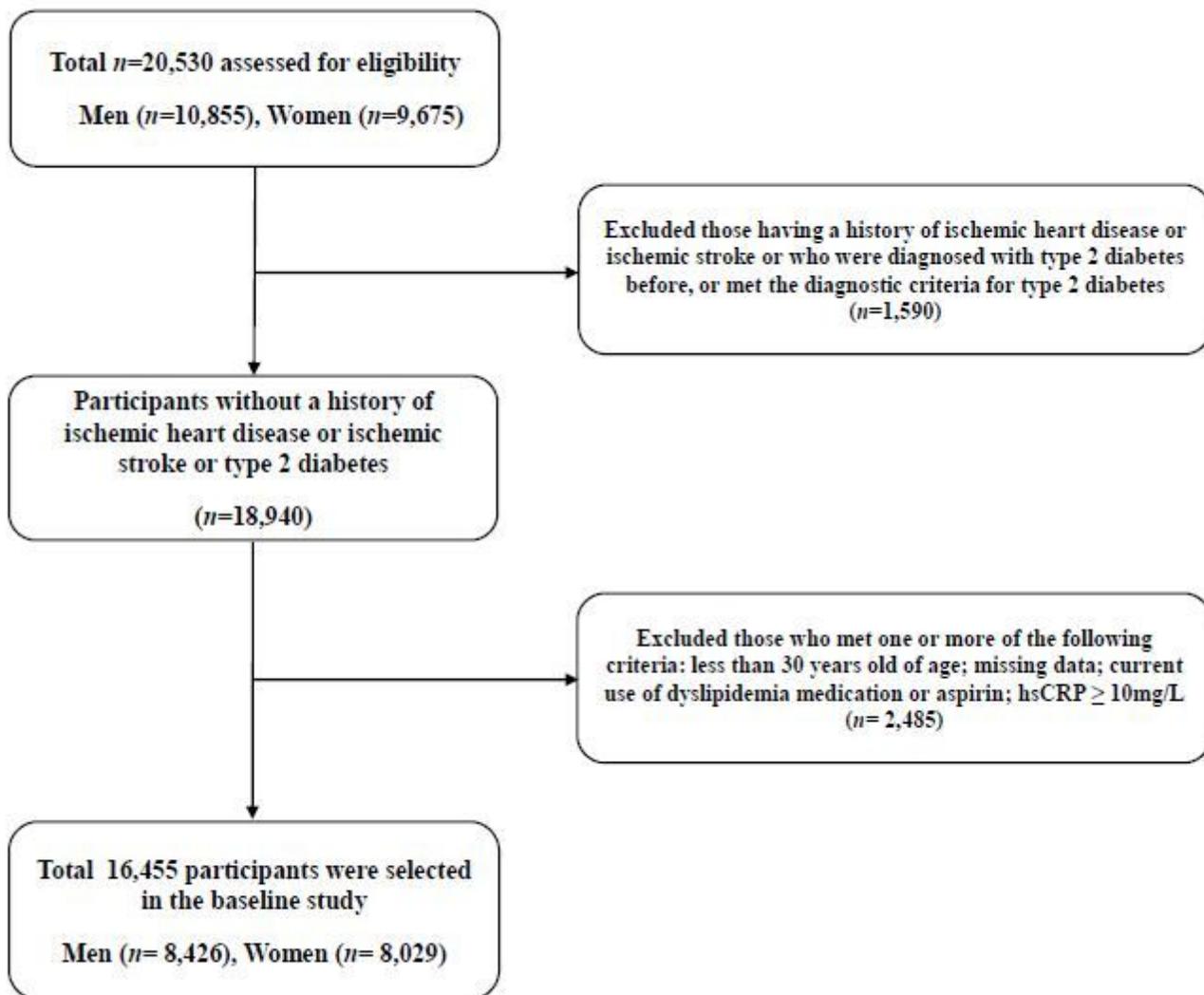
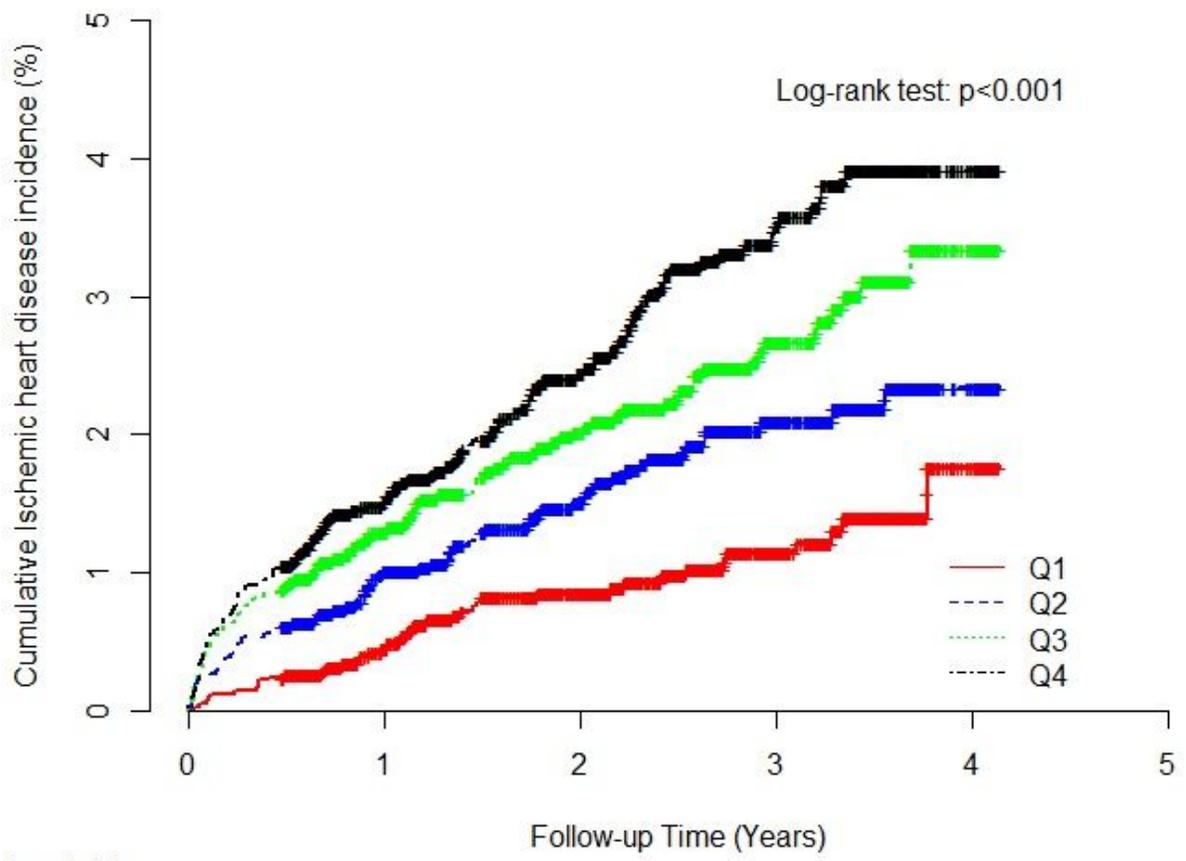


Figure 1

Flowchart for the selection of study participants.



Number at risk		Follow-up Time (Years)				
	0	1	2	3	4	5
Q1	4140	3523	2668	1455	149	0
Q2	4119	3508	2591	1433	140	0
Q3	4096	3479	2505	1441	160	0
Q4	4100	3548	2546	1433	173	0

Figure 2

Kaplan–Meier plots indicating the cumulative probability of being diagnosed with ischemic heart disease after the baseline survey.