Non-HDL Cholesterol as a Predictor for Incident Type 2 Diabetes in Community-dwelling Adults: Longitudinal Findings Over 12 Years

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Abstract

Background

Non-high-density lipoprotein cholesterol (non-HDL cholesterol) is a simple measure to analyze the total amount of proatherogenic lipoproteins in the blood and to predict development of cardiovascular disease. However, it is unclear whether non-HDL cholesterol has a relationship with incident type 2 diabetes. This study aimed to evaluate the association between non-HDL cholesterol and incident type 2 diabetes with a large-sample, community-based Korean cohort over a 12-year period.

Methods

Among the 10,038 total participants, 7,608 (3,662 men and 3,946 women) without diabetes were selected from the Korean Genome and Epidemiology Study (KoGES). Their non-HDL cholesterol level was calculated as [total cholesterol – HDL cholesterol] mg/dL and divided into quartiles. Newly developed type 2 diabetes was defined as any of the following: a fasting plasma glucose level ≥ 126 mg/dL; a plasma glucose level ≥ 200 mg/dL at two hours after a 75-g oral glucose tolerance test; a glycosylated hemoglobin level ≥ 6.5%; or current treatment with oral anti-diabetic medications or insulin therapy. The hazard ratios (HRs) with 95% confidence intervals (CIs) for incident type 2 diabetes were calculated using multivariate Cox proportional hazards regression models after adjusting for potentially confounding variables.

Results

In total, 1,442 individuals (18.9%: 1442 of 7608) developed type 2 diabetes during the 12-year follow up period, with an incident rate of 3.0–5.0. Compared to the reference first quartile, the HRs (95% CIs) of incident type 2 diabetes for the second, third, and fourth quartiles increased in a dose-response manner after adjusting for potentially confounding variables, including the HOMA-IR insulin resistance marker.

Conclusion

Non-HDL cholesterol level at baseline can be a useful predictor of new-onset type 2 diabetes.

Background

Type 2 diabetes has emerged as a global epidemic and leads to increased mortality and various comorbidities and constitutes a crucial challenge to human health. The number of patients with type 2 diabetes among 20–70-year-old adults worldwide is expected to increase from 382 million in 2013 to 592 million in 2035 [1]. Similarly, in South Korea, the prevalence of type 2 diabetes has increased from 8.6% in 2001 to 13.7% in 2016 [2]. Type 2 diabetes increases medical expenditures, which are 2.3 times higher in people with type 2 diabetes than in those without diabetes [3]. In addition, type 2 diabetes is a significant risk factor for cardiovascular disease (CVD) and is associated with higher all-cause and CVD mortality

rates [4-8]. In 2018, type 2 diabetes was the sixth leading cause of death in South Korea [9]. Therefore, it is a critical public health concern to predict and prevent type 2 diabetes in at-risk populations.

Type 2 diabetes results from dysfunction in insulin secretion and development of insulin resistance due to uncontrolled metabolism of carbohydrates, lipids, and protein [1]. Previous studies have shown that lipid abnormalities are observed prior to the onset of type 2 diabetes [10-12] and suggest that dysregulation in glucose and lipid metabolism has a close relationship. Among the many lipid profile parameters, the non-high-density lipoprotein cholesterol (non-HDL cholesterol) has been suggested as a simple way to analyze the total amounts of proatherogenic lipoproteins containing apolipoprotein B (apoB), very low-density lipoproteins and their metabolic remnants, intermediate-density lipoproteins, lipoprotein (a), and low-density lipoproteins [13]. Non-HDL cholesterol predicts the development of CVD [14] and is a component of recommended United States (US) and European guidelines for CVD risk estimation [15, 16].

However, no large-scale prospective cohort studies have investigated the relationship between non-HDL cholesterol and incident type 2 diabetes independent of baseline insulin resistance status. Therefore, we prospectively examined the association between non-HDL cholesterol and incident type 2 diabetes using a large, community-based Korean cohort that was observed over a 12-year period.

Methods

Study population

The dataset used in this study (Ansan-Ansung cohort) was obtained after review and evaluation of our research plan by the Korea Centers for Disease Control and Prevention (http://www.cdc.go.kr/CDC/eng/main.jsp). This study used data from the Korean Genome and Epidemiology Study (KoGES), a longitudinal prospective cohort study conducted by the Korean Centers for Disease Control and Prevention (KCDC) to examine the prevalence of and risk factors for chronic diseases in Korea. The KoGES consists of six large prospective cohort studies categorized into population-based and gene-environment model studies. All data in this study were derived from the KoGES Ansan and Ansung study, one of the population-based KoGES cohort studies. All participants enrolled in the study voluntarily, and all provided written informed consent. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Korean Health and Genomic Study at the Korea National Institute of Health. Details of the KoGES and its sampling method have been reported elsewhere. The KoGES included men and women who were 40–69 years old and lived in Ansan (urban area) or Ansung (rural area) during the baseline survey period from 2001–2002. The cohort was surveyed biennially until 2013–2014. Among the 10,030 participants in the baseline survey, we excluded 1,351 (13.5%) who had been previously diagnosed with type 2 diabetes or satisfied the American Diabetes Association (ADA) diagnostic criteria for type 2 diabetes on the baseline survey. Of the remaining participants, we excluded those who were lost to follow-up (n = 888). We also excluded participants who satisfied one or more of the following criteria: missing data or current

use of lipid-lowering medication (n = 183). After these exclusions, 7,608 participants (3,662 men and 3,946 women) were included in the final analysis. A flow chart of the selection process is shown in Figure 1.

Study definitions and outcomes

The fasting plasma glucose, glycosylated hemoglobin (HbA1c), and post two-hour plasma glucose levels after a 75-g oral glucose tolerance test (OGTT) were evaluated biennially in all participants until 2013–2014. Based on the ADA criteria, new-onset type 2 diabetes was defined as any of the following: a fasting plasma glucose level ≥ 126 mg/dL; a plasma glucose level ≥ 200 mg/dL at two hours after a 75-g OGTT; an HbA1c ≥ 6.5%; or current treatment with oral anti-diabetic medications or insulin therapy. Non-HDL cholesterol level was calculated as [total cholesterol – HDL cholesterol] mg/dL. The formula for Homeostasis model assessment of insulin resistance (HOMA-IR) was as follows: [fasting glucose (mg/dL) * fasting insulin (μIU/mL)/405].

Measurement of anthropometric and biochemical parameters

Participant height and body weight were measured to the nearest 0.1 cm and 0.0 kg, respectively, while they wore light indoor clothing without shoes. Their smoking status, drinking behaviors, and physical activity levels were obtained from self-reported questionnaires that all study participants completed during the interview period. Smoking status was divided into three categories: current smokers, ex-smokers, and never smokers. We categorized alcohol drinking status as current drinker or not. Regular exercise was defined as moderate-intensity physical exercise at least three times a week. We defined one episode of exercise as any physical activity that lasted for at least 30 minutes. The systolic and diastolic blood pressure values were assessed three times in the right upper arm using a standard mercury sphygmomanometer (Baumanometer, Baum, Copiague, NY, USA), and the mean of the second and third blood pressure readings was used for analysis.

Biochemical parameters, including fasting serum glucose, HbA1c, 60-minute OGTT, 120-minute serum glucose, and lipid levels (total cholesterol, triglycerides [TG], and HDL-C) were measured enzymatically using a 747 Chemistry Analyzer (Hitachi 7600, Tokyo, Japan). The HbA1c level was assessed using high-performance liquid chromatography (VARIANT II; Bio-Rad Laboratories, Hercules, CA). The plasma insulin concentration level was determined using a radioimmunoassay (LINCO kit, St. Charles, MO, USA).

Statistical analysis

Non-HDL cholesterol quartiles were categorized as follows: Q1, ≤121 mg/dL; Q2, 122–142 mg/dL; Q3, 143–166 mg/dL; and Q4, ≥ 167 mg/dL. Depending on the normality of the distributions of continuous variables, the baseline characteristics of the study population according to non-HDL cholesterol quartile were compared using one-way analysis of variance or the Kruskal-Wallis test. The chi-square test was used to compare categorical variables. The continuous data are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical data are shown as frequency. The lowest quartile

(Q1) was defined as the reference group. The hazard ratio (HR) with 95% confidence interval (CI) for incident type 2 diabetes was calculated using multivariate Cox proportional hazards regression models after adjusting for potentially confounding variables. The cumulative incidence of type 2 diabetes was represented using a Kaplan-Meier curve. Log-rank tests were conducted to determine the differences in the cumulative incidence of type 2 diabetes among the groups. All analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Table 1 shows the baseline characteristics of the 7608 participants without diabetes at baseline according to non-HDL cholesterol quartile. The following cardiometabolic variables increased proportionally with increased non-HDL cholesterol quartile: the mean values of age, body mass index, waist circumference, systolic and diastolic blood pressure, HbA1C, fasting glucose, and total cholesterol. The median values of insulin, HOMA-IR, and TG significantly increased with non-HDL cholesterol quartile. In addition, the proportion of current smoking, an unfavorable lifestyle habit, increased with non-HDL cholesterol quartile. However, HDL cholesterol and frequency of regular exercise tended to decrease proportionally with non-HDL cholesterol quartile.

Table 1
Baseline characteristics of the study population according to non-HDL cholesterol quartiles

	Non-HDL cholesterol quartiles					
	Total n = 7,608	Q1 n = 1,987	Q2 n = 1,906	Q3 n = 1,876	Q4 n = 1,839	P value*
Non-HDL cholesterol (mg/dl)	143.9 ± 33.2	≤ 121	122–142	143–166	≥ 167	
Age (years)	51.7 ± 8.8	51.1 ± 9.1	51.3 ± 8.7	52.3 ± 8.7	52.3 ± 8.6	< 0.001
Male sex (%)	46.9	43.7	45.8	47.2	51.1	<0.001
Body mass index (kg/m^2)	24.4 ± 3.1	23.4 ± 3.1	24.2 ± 3.0	24.8 ± 3.0	25.4 ± 2.9	< 0.001
Waist circumference (cm)	82.1 ± 8.7	79.3 ± 8.6	81.5 ± 8.8	83.1 ± 8.4	84.9 ± 8.0	< 0.001
Systolic blood pressure (mmHg)	120.5 ± 17.9	118.5 ± 18.1	119.2 ± 17.9	121.5 ± 17.5	122.9 ± 17.8	< 0.001
Diastolic blood pressure (mmHg)	79.9 ± 11.3	78.0 ± 11.3	79.3 ± 11.4	80.4 ± 10.9	82.1 ± 11.4	< 0.001
Mean arterial pressure (mmHg)	93.4 ± 12.9	91.5 ± 13.0	92.6 ± 12.9	94.1 ± 12.4	95.7 ± 12.8	< 0.001
Fasting plasma glucose (mg/dl)	82.6 ± 8.5	80.7 ± 7.8	81.8 ± 8.1	83.4 ± 8.5	84.8 ± 9.0	< 0.001
2-h postprandial plasma glucose (mg/dl)	113.9 ± 30.2	108.5 ± 28.8	110.8 ± 29.6	115.8 ± 30.8	120.7 ± 30.1	< 0.001
Hemoglobin A1c (%)	5.5 ± 0.3	5.45 ± 0.33	5.51 ± 0.34	5.58 ± 0.35	5.64 ± 0.34	< 0.001
Total cholesterol (mg/dL)	188.9 ± 33.9	150.7 ± 16.4	177.6 ± 11.7	198.0 ± 11.9	232.6 ± 21.7	< 0.001
Triglyceride (mg/dl)	130 (97–181)	103 (83–138)	124 (95–164)	142 (108–192)	165 (122–229)	< 0.001
HDL-cholesterol (mg/dl)	44.9 ± 10.0	46.2 ± 10.7	45.1 ± 10.2	44.0 ± 9.6	44.3 ± 9.3	< 0.001
Serum insulin (mg/L)	6.9 (5.1–9.5)	6.7 (5.0-8.9)	6.9 (5.2–9.4)	6.9 (5.1–9.5)	7.3 (5.3–9.9)	< 0.001

Data are expressed as the mean ± SD or percentage. *P-values were calculated using ANOVA or the chi-squared test. †Alcohol intake ≥ twice/week. ‡Moderate intensity physical exercise ≥ three times/week.

	Non-HDL cholesterol quartiles					
HOMA-IR (mU/L)	1.39 (1.03–1.92)	1.33 (0.97–1.79)	1.37 (1.02–1.89)	1.41 (1.04–1.95)	1.52 (1.08–2.08)	< 0.001
Current smoker (%)	25.1	26.9	23.2	22.2	27.9	< 0.001
Alcohol drinking (%)†	47.8	49.7	47.2	46.9	47.3	0.004
Regular exercise (%)‡	25.3	27.5	25.8	24.4	23.3	0.077
Family history of diabetes (%)	10.1	9.3	10.2	10.2	10.6	0.588

Data are expressed as the mean ± SD or percentage. *P-values were calculated using ANOVA or the chi-squared test. †Alcohol intake ≥ twice/week. ‡Moderate intensity physical exercise ≥ three times/week.

The incidence of type 2 diabetes during the 12 years of follow-up is presented in Table 2. During the follow-up period, the incidence rate of diabetes was calculated biennially. A total of 1,442 individuals (18.9%: 1442 of 7608) developed type 2 diabetes during this 12-year follow-up period. The incidence rate per 2 years over the 12-year follow-up period was highest from 2005–2006 at 5.0 and lowest in 2013–2014 at 3.0.

Table 2
Incidence of type 2 diabetes during the follow-up study

Year range	Follow-up	n	Incidence cases (n)	Incidence rate over 2 years
2001–2002	Baseline	7608		
2003–2004	2 years	7129	270	3.8
2005–2006	4 years	6366	321	5.0
2007–2008	6 years	5708	248	4.3
2009–2010	8 years	5706	262	4.6
2011–2012	10 years	5383	189	3.5
2013–2014	12 years	5104	152	3.0

The cumulative incidence of type 2 diabetes according to non-HDL cholesterol quartile is shown in Fig. 2 as a Kaplan-Meier curve. As the non-HDL cholesterol quartile increased, the cumulative incidence of type 2 diabetes over 12 years also significantly increased (log-rank test $p < 0.001$).

Further analyses using the multivariate Cox proportional hazards regression analysis were performed to predict type 2 diabetes according to non-HDL cholesterol quartile (Table 3). In Model 1, the HRs were

calculated after adjusting for age, sex, and waist circumference. In Model 2, lifestyle habits, such as smoking status, alcohol intake, and physical activity, were included in the analysis. In Model 3, we included the following additional potential confounding variables: mean arterial blood pressure and family history of diabetes. Finally, we analyzed the incidence rate of type 2 diabetes according to non-HDL cholesterol quartile by adjusting the HOMA-IR in Model 4. Compared to the reference first quartile of non-HDL cholesterol, the HR of incident type 2 diabetes for the second, third, and fourth quartiles increased in a dose-response manner. The HR of incidence of type 2 diabetes for the fourth quartile of non-HDL cholesterol was 1.62 (1.38–1.88) in Model 1, 1.60 (1.36–1.87) in Model 2, 1.56 (1.33–1.8) in Model 3, and 1.53 (1.31–1.79) in Model 4 compared to the reference first quartile.

Table 3
Hazard ratios and 95% confidence intervals for incident type 2 diabetes according to non-HDL cholesterol quartiles

	Non-HDL cholesterol quartiles			
	Q1 n = 1,987	Q2 n = 1,906	Q3 n = 1,876	Q4 n = 1,839
Non-HDL cholesterol, mg/dl	≤ 121	122–142	143–166	≥ 167
New cases of diabetes, n	261	340	403	438
Mean follow-up, years	9.2 ± 3.6	9.3 ± 3.5	9.0 ± 3.7	8.7 ± 3.8
Person-years of follow-up	18,345	17,665	16,794	15,984
Incidence rate/1000 person - years	14.2	19.3	24.0	27.4
Model 1	1.00 (reference)	1.25 (1.06–1.47)	1.48 (1.26–1.73)	1.62 (1.38–1.88)
Model 2	1.00 (reference)	1.27 (1.07–1.49)	1.48 (1.26–1.73)	1.60 (1.36–1.87)
Model 3	1.00 (reference)	1.26 (1.07–1.48)	1.47 (1.25–1.72)	1.56 (1.33–1.83)
Model 4	1.00 (reference)	1.25 (1.05–1.46)	1.46 (1.24–1.71)	1.53 (1.31–1.79)

Model 1: adjusted for age, sex, and waist circumference

Model 2: adjusted for age, sex, waist circumference, smoking status, alcohol intake, and physical activity

Model 3: adjusted for age, sex, waist circumference, smoking status, alcohol intake, physical activity, mean arterial blood pressure, and family history of diabetes

Model 4: adjusted for age, sex, waist circumference, smoking status, alcohol intake, physical activity, mean arterial blood pressure, family history of diabetes, and HOMA-IR

Discussion

In this large, community-based, 12-year prospective cohort study, non-HDL cholesterol level was related positively and independently to incident type 2 diabetes independent of baseline insulin resistance (measured as HOMA-IR) after adjusting for potential confounding variables. Our findings are consistent with the results of previous epidemiological studies that have shown a link between ratios including HDL cholesterol and incident type 2 diabetes. Seo et al. reported that the total cholesterol/HDL cholesterol ratio and the apolipoprotein B (apoB)/HDL cholesterol ratio were significantly associated with new-onset type 2 diabetes over four years. These HDL-cholesterol-including ratios also showed higher odds ratio for development of type 2 diabetes compared with the traditional lipid profiles [17]. In addition, the non-HDL cholesterol/HDL cholesterol ratio was suggested as a better predictor of development of metabolic syndrome and insulin resistance [18]. Hwang et al. showed the importance of non-HDL cholesterol for predicting incident type 2 diabetes over three years [19]. These authors also reported that non-HDL cholesterol was a more powerful predictive marker for development of type 2 diabetes than is fasting glucose or glycated hemoglobin level [20]. Although previous results are compatible with our findings regarding the role of non-HDL cholesterol in predicting type 2 diabetes, those studies had several limitations. For example, in one study, the mean follow-up duration was up to four years, and the biggest HR was only 1.27 (95% CI: 1.24–1.29). Furthermore, previous studies adjusted their statistical model using an insufficient number of confounding variables and therefore caused a possible residual confounding effect; thus, non-HDL cholesterol was not powerful enough as a predictor of type 2 diabetes. To the best of our knowledge, the current study is the first to reveal a positive relationship between non-HDL cholesterol and incidence risk of type 2 diabetes regardless of baseline insulin resistance (such as HOMA-IR) in a long-term follow-up cohort study (12 years) with a large sample population. Moreover, non-HDL cholesterol level can be obtained in routine clinical practice without regard for patient fasting status.

The most conceivable hypothesis for the pathophysiology of the relationship between non-HDL cholesterol and type 2 diabetes is insulin resistance. Although other mechanisms (excluding insulin resistance) behind the relationship between non-HDL cholesterol and type 2 diabetes remain unclear, pancreatic β cell dysfunction might be the strongest candidate. Cholesterol accumulation in pancreatic β cells causes β cell dysfunction and decreases their ability to secrete insulin. Cholesterol accumulation in β cells alters the micro-domains on the cell membranes that are important for signaling events [21]. This change attenuates glucagon-like peptide 1 receptor (GLP-1R)-mediated generation of cAMP and blunts insulin secretion in pancreatic β cells [22]. In addition, impairments in the mitochondrial function of β cells caused by cholesterol accumulation induce dysfunction in these pancreatic β cells. This cholesterol accumulation produces mitochondrial reactive oxygen species and alters mitochondrial architecture [22]. Furthermore, the mechanism of the accumulation of cholesterol in pancreatic β cells might be a decrease in the efflux of cholesterol due to the consequent lower HDL cholesterol level [23]. This series of mechanisms indicates a relationship between non-HDL cholesterol and incident type 2 diabetes independent of insulin resistance.

Our current study had several limitations that must be considered. We used a large prospective cohort dataset for this study. However, all participants came from a Korean population. Therefore, our results might not be generalized to other populations. Second, the cohort data had the potential for selection bias, as participation was voluntary and limited to specific geographic regions. Despite these limitations, we suggest that our results could have clinical importance for prediction of type 2 diabetes in East Asian patients.

Conclusions

In conclusion, non-HDL cholesterol predicted new-onset type 2 diabetes independent of other associated variables in community-dwelling Koreans in a large prospective study.

Abbreviations

Non-HDL cholesterol: Non-high-density lipoprotein cholesterol

KoGES: the Korean Genome and Epidemiology Study

HRs: Hazard ratios)

CIs: Confidence intervals

CVD: Cardiovascular disease

apoB: Apolipoprotein B

US: United States

KCDC: the Korean Centers for Disease Control and Prevention

ADA: American Diabetes Association

HbA1c: Glycosylated hemoglobin

OGTT: Oral glucose tolerance test

DS: Standard deviation

IQR: Interquartile range

GLP-1R: Glucagon-like peptide 1 receptor

Declarations

Ethical standards

The Ansan-Ansung study protocol was reviewed and approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention, and all study participants submitted written informed consent. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (IRB number: 3-2018-0348).

Consent for publication

Not applicable

Availability of data and materials

The dataset used in this study (Ansan-Ansung cohort) is available from the Korea Centers for Disease Control and Prevention (http://www.cdc.go.kr/CDC/eng/main.jsp) upon request.

Competing interests

No potential conflicts of interest relevant to this article were reported.

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Authors' contributions

I.H. Seo and Y.J. Lee formed the study concept and designed the study; collected, analyzed, and interpreted the data; wrote the first draft; and revised later drafts of the article. I.H. Seo, D.H Son, and H.S. Lee analyzed and interpreted the data and performed the statistical analysis. Y.J. Lee revised the article. All authors have approved the final manuscript.

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Figures

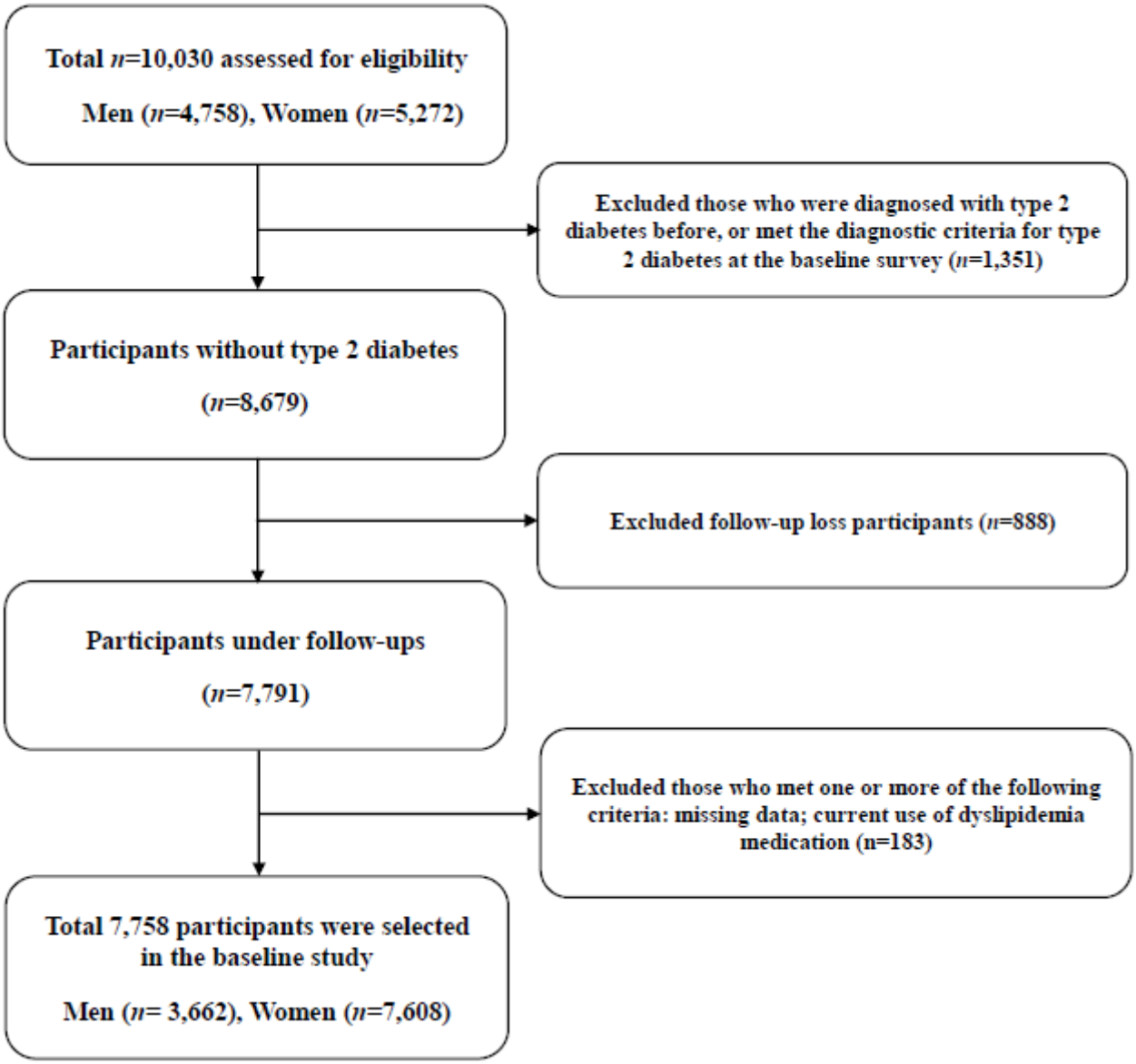

Figure 1

Flow chart of the study population selection.

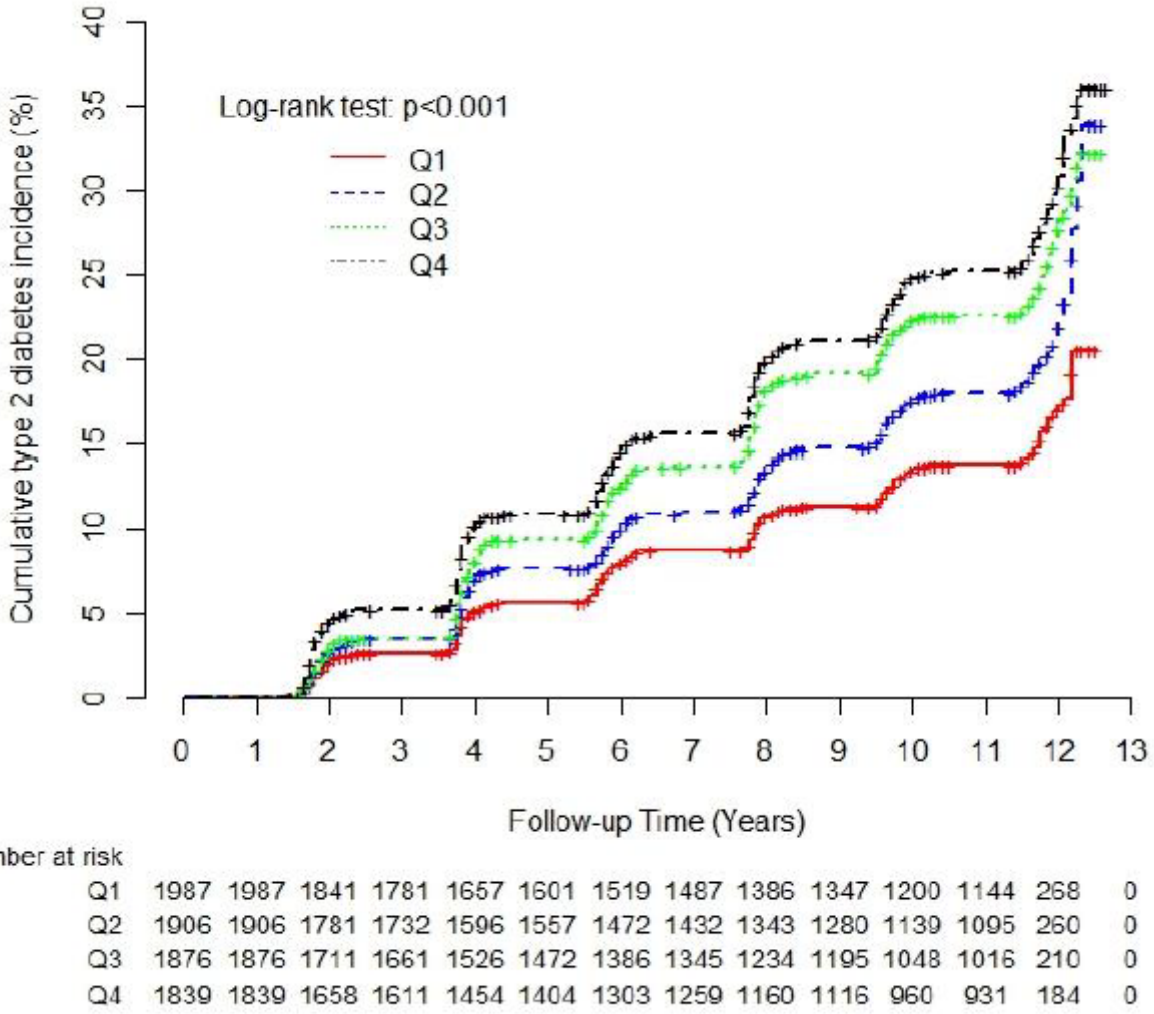

Figure 2

Cumulative incidence of type 2 diabetes according to quartiles of non-HDL cholesterol level.