

ORIGINAL RESEARCH

Gamma-glutamyl transferase to high-density lipoprotein cholesterol ratio as a novel predictor of long-term ischemic heart disease risk in overweight men: a nationwide population-based study

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Abstract

Background: The gamma-glutamyl transferase to high-density lipoprotein cholesterol (GGT/HDL-c) ratio is a novel composite index reflecting systemic oxidative stress and metabolic dysfunction. However, its prognostic value for long-term ischemic heart disease (IHD) risk among overweight men—a population with highly heterogeneous metabolic profiles—remains largely unexplored. This study investigated the association between the GGT/HDL-c ratio and incident IHD in this high-risk group. **Methods:** This retrospective, population-based cohort study utilized data from the Korean National Health Insurance Service. A total of 124,044 overweight men (body mass index ≥ 23.0 kg/m²) without a history of ischemic heart disease were included and stratified into quartiles according to their GGT/HDL-c ratios. Multivariate Cox proportional hazards regression models were used to estimate hazard ratios (HRs) for incident IHD. The incremental predictive value was evaluated using the C-index and net reclassification improvement (NRI). **Results:** Over a follow-up period of up to 20 years among the 124,044 participants, those in the highest GGT/HDL-c quartile (Q4) exhibited a significantly increased risk of IHD compared to the lowest quartile (Q1) (fully adjusted HR, 1.65; 95% confidence interval (CI), 1.49–1.83). A significant interaction with physical activity was observed ($p < 0.001$); the elevated IHD risk in Q4 was more pronounced among physically inactive men (HR, 1.82; 95% CI, 1.61–2.06) than among those engaging in regular exercise (HR, 1.42; 95% CI, 1.21–1.67). The addition of the GGT/HDL-c ratio to traditional risk models significantly improved risk reclassification (NRI = 0.058). **Conclusions:** An elevated GGT/HDL-c ratio is a potent and independent predictor of IHD in overweight men. Integrating this simple, cost-effective biomarker into routine assessments may improve clinical risk stratification. Furthermore, regular physical activity may serve as an important intervention to mitigate the elevated cardiovascular risk associated with this metabolic imbalance.

Keywords

Gamma-glutamyl transferase; High-density lipoprotein cholesterol; GGT/HDL-c ratio; Ischemic heart disease; Overweight; Oxidative stress; Physical activity; Cohort study

1. Introduction

The global prevalence of obesity and overweight has reached epidemic proportions over the past few decades, fundamentally altering the landscape of public health and contributing to a corresponding surge in cardiovascular diseases (CVD) [1, 2]. In the male population, weight gain is typically characterized by the accumulation of visceral adipose tissue rather than subcutaneous fat. This android fat distribution pattern is metabolically active and is intrinsically linked to systemic chronic inflammation, insulin resistance, and the accelerated progression of atherosclerosis [3]. However, clinical observations have

repeatedly demonstrated that cardiovascular risk is profoundly heterogeneous among individuals with identical body mass indices (BMI). This phenomenon highlights the significant limitations of traditional anthropometric measurements, such as BMI and waist circumference, which fail to distinguish between fat mass and lean muscle mass, nor can they accurately reflect the degree of ectopic fat deposition or subclinical metabolic dysregulation [4, 5]. Consequently, there is a critical need to identify robust, precise, and easily accessible metabolic markers that can better stratify cardiovascular risk, particularly among overweight men who may exhibit a deceptive “metabolically healthy” phenotype but remain at elevated risk for long-

term adverse outcomes.

In recent years, gamma-glutamyl transferase (GGT) and high-density lipoprotein cholesterol (HDL-c) have garnered substantial attention beyond their traditional diagnostic roles. GGT is an enzyme located on the external surface of plasma membranes and plays a pivotal role in the metabolism of extracellular glutathione, the principal intracellular antioxidant [6]. Elevated serum GGT activity is no longer viewed merely as a biomarker of alcohol consumption or hepatobiliary dysfunction. Instead, it is now recognized as a sensitive and early indicator of systemic oxidative stress and endothelial dysfunction. High GGT levels actively participate in the atherogenic process by promoting the oxidation of low-density lipoprotein (LDL) within the arterial plaque, thereby promoting plaque instability [7, 8]. Furthermore, elevated GGT levels are strongly correlated with non-alcoholic fatty liver disease (NAFLD), a condition that independently increases the risk of cardiovascular morbidity [9].

Conversely, HDL-c is universally recognized for its cardioprotective properties. It is primarily responsible for reverse cholesterol transport, removing excess cholesterol from peripheral tissues and macrophages within arterial walls, and transporting it back to the liver for excretion [10]. Beyond lipid transport, HDL-c possesses potent anti-inflammatory, antioxidant, and antithrombotic functions. A reduction in HDL-c levels is a hallmark of atherogenic dyslipidemia and metabolic syndrome, serving as a powerful independent predictor of adverse cardiovascular events, especially among men [11].

The GGT/HDL-c ratio (GHR) has recently been proposed as a novel and integrative metabolic index. By mathematically combining these two parameters, the GHR simultaneously captures two critical, opposing pathophysiological pathways: the exacerbation of oxidative stress and hepatic steatosis (represented by GGT) and the depletion of cardioprotective and antioxidant capacity (represented by HDL-c) [12]. Emerging short-term and cross-sectional studies have indicated that the GHR is a valuable predictor of adverse cardiometabolic outcomes, including type 2 diabetes mellitus and coronary heart disease [13, 14]. The physiological rationale suggests that a high GHR reflects a highly atherogenic metabolic milieu, making it a potentially ideal surrogate marker for uncovering hidden cardiovascular risks in overweight individuals.

Despite the biological plausibility and promising preliminary data, the prognostic utility of the GHR for long-term clinical outcomes remains largely unexplored. Most existing literature relies on cross-sectional designs or short-term follow-ups and often focuses on general populations rather than specific high-risk subgroups [15]. To date, no large-scale, long-term longitudinal studies have adequately investigated whether baseline GHR can reliably predict cardiovascular morbidity and mortality specifically in overweight men over a span of several decades.

Therefore, the primary objective of this study is to evaluate the clinical significance of the GHR as a predictive metabolic marker for long-term cardiovascular risk in overweight men, utilizing data from a large-scale cohort with a 20-year follow-up period. We hypothesized that an elevated baseline GHR is independently and strongly associated with an increased risk of incident ischemic heart disease (IHD), even after ad-

justing for traditional risk factors such as age, smoking, hypertension, and baseline glycemic status. By leveraging two decades of longitudinal data, this work aims to clarify the metabolic mechanisms driving the divergence in cardiovascular outcomes among overweight men and to determine whether the GHR can serve as a simple, cost-effective screening tool for risk stratification in routine clinical practice.

2. Materials and methods

2.1 Study design and data source

This retrospective, population-based cohort study was conducted using data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) of the Republic of Korea. The NHIS is a single-payer, mandatory universal health insurance system that covers approximately 97% of the Korean population. The NHIS-HEALS database contains anonymized, comprehensive medical records, including demographic profiles, socioeconomic status, claims data (diagnoses based on the International Classification of Diseases, Tenth Revision (ICD-10) codes), prescription records, and results from biennial national health screening examinations. The detailed cohort profile and data extraction protocols have been previously described in detail.

2.2 Study population

We initially extracted data for male participants aged 40 years or older who underwent a national health screening examination between 01 January 2002 and 31 December 2003 (defined as the baseline period). To specifically investigate the overweight and obese male population, we applied the Asia-Pacific regional criteria of the World Health Organization (WHO), defining overweight as a body mass index (BMI) ≥ 23.0 kg/m².

Participants were excluded if they met any of the following criteria: (1) missing data for baseline GGT, HDL-c, or other essential covariates; (2) a prior history of IHD before the baseline examination; (3) severe liver diseases (*e.g.*, liver cirrhosis, hepatocellular carcinoma) or excessive alcohol consumption (>30 g/day) to rule out primary hepatic causes of isolated GGT elevation; and (4) those who died within the first year of follow-up (to minimize reverse causality). A history of cerebrovascular disease (stroke) was not used as an exclusion criterion; rather, baseline stroke was retained and treated as a comorbid covariate in the adjusted models. After applying these criteria, a total of 124,044 overweight men were included in the final analysis.

2.3 Data collection and biochemical measurements

During the baseline health screening, comprehensive data were collected via standardized self-administered questionnaires, physical examinations, and blood tests. Anthropometric measurements, including height, weight, and waist circumference, were obtained by trained personnel. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²). Blood pressure (BP) was measured using a standardized sphygmomanometer after at least 5 minutes of

rest. Venous blood samples were drawn after an overnight fast of at least 8 hours. Serum biochemical parameters, including GGT, HDL-c, total cholesterol, triglycerides, and fasting blood glucose (FBG), were measured. According to the standardized national protocol, GGT was analyzed using an enzymatic colorimetric method, and HDL-c was measured using a homogeneous enzymatic method with standard automated analyzers at NHIS-certified local and regional clinical laboratories. Total cholesterol and triglycerides were measured by enzymatic colorimetric assays, and FBG was measured by the hexokinase method. All biochemical analyses followed a single standardized national protocol and were subject to internal and external quality-control programs, ensuring that identical measurement methods were applied uniformly to all participants. The GGT/HDL-c ratio (GHR) was calculated by dividing the serum GGT level (IU/L) by the HDL-c level (mg/dL). Regular physical activity was defined, based on the self-reported national health-screening questionnaire, as moderate-intensity exercise (*e.g.*, brisk walking) for at least 30 minutes per session on ≥ 5 days per week, or vigorous-intensity exercise for at least 20 minutes per session on ≥ 3 days per week; participants who did not meet this threshold were classified as physically inactive.

2.4 Definitions of outcomes

The primary outcome was incident ischemic heart disease (IHD), defined as a composite of acute myocardial infarction (AMI) and angina pectoris. IHD events were operationally ascertained using ICD-10 diagnostic codes from hospitalization and claims records and were defined as AMI (codes I21–I22) or angina pectoris (code I20). The study participants were followed longitudinally from the date of their baseline health screening until the first occurrence of the primary outcome, death, or the end of the follow-up period (31 December 2023), whichever came first, yielding a maximum follow-up duration of approximately 20 years.

2.5 Statistical analysis

Baseline characteristics of the study population were stratified by quartiles of the GHR. The GHR was categorized into quartiles, defined as Q1 (<0.91), Q2 ($0.91\text{--}1.45$), Q3 ($1.46\text{--}2.30$), and Q4 (≥ 2.31). Continuous variables were first tested for normality using the Kolmogorov–Smirnov test; normally distributed variables were presented as means $\pm$ standard deviations (SD) and compared using analysis of variance (ANOVA), whereas non-normally distributed variables were presented as medians with interquartile ranges (IQR) and compared using the Kruskal–Wallis test. In the present cohort, all continuous variables were approximately normally distributed and are therefore reported as means $\pm$ SD. Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test.

The cumulative incidence of IHD among the GHR quartiles was estimated using the Kaplan–Meier method and compared using the log-rank test. To evaluate the independent prognostic value of the GHR for long-term cardiovascular risk, multivariate Cox proportional hazards regression models were constructed. The models were sequentially adjusted for potential

confounders: Model 1 was unadjusted; Model 2 was adjusted for age; Model 3 was further adjusted for BMI, smoking status, alcohol consumption, and regular exercise; and Model 4 (fully adjusted) was additionally adjusted for systolic BP, FBG, total cholesterol, and use of antihypertensive or lipid-lowering medications. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Effect modification by physical activity was assessed on a multiplicative scale by introducing a cross-product term (GHR quartile $\times$ physical activity) into the fully adjusted Cox model, and the corresponding *p*-value for interaction was reported. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *p*-value of < 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics of the study population

A total of 124,044 overweight men were included in the final analysis. The baseline characteristics according to the GGT/HDL-c ratio quartiles are presented in Table 1. The mean GGT/HDL-c ratio was 1.72 ± 0.58 . Participants in the highest quartile (Q4) were generally older, had higher BMI, and showed a higher prevalence of hypertension and diabetes mellitus compared to those in the lowest quartile (Q1). Notably, the proportion of participants engaging in regular physical activity decreased as the GGT/HDL-c ratio increased (Q1: 31.0% vs. Q4: 21.0%; $p < 0.001$).

3.2 Association between GGT/HDL-c ratio and IHD risk

During the follow-up period of up to 20 years, 7815 (6.3%) incident cases of IHD were identified. The cumulative incidence of IHD increased progressively across the GGT/HDL-c ratio quartiles (4.5%, 5.2%, 6.5%, and 9.0% for Q1 to Q4, respectively; $p < 0.001$). Fig. 1 illustrates the Kaplan–Meier curves for the cumulative incidence of IHD, showing a significantly higher risk in the highest quartile than in the reference group (Log-rank $p < 0.001$).

In the multivariable Cox proportional hazards model (Table 2), the GGT/HDL-c ratio was independently associated with an increased risk of IHD. After adjusting for age, lifestyle factors, BMI, and comorbidities (Model 4), the hazard ratio (HR) for Q4 compared with Q1 was 1.65 (95% CI 1.49–1.83).

3.3 Subgroup analysis and interaction with physical activity

We observed a significant interaction between the GGT/HDL-c ratio and physical activity with respect to the risk of IHD (p for interaction < 0.001 ; Table 2). The association was more pronounced in the inactive group (Q4 HR: 1.82; 95% CI 1.61–2.06) than in the active group (Q4 HR: 1.42; 95% CI 1.21–1.67). Fig. 2 shows the restricted cubic spline analysis, which demonstrates a J-shaped relationship between the GGT/HDL-c ratio and IHD risk. Regular physical activity consistently miti-

TABLE 1. Baseline characteristics by GHR quartiles.

Variable	Total (N = 124,044)	Q1 (n = 31,011)	Q2 (n = 31,011)	Q3 (n = 31,011)	Q4 (n = 31,011)	p-value
GGT/HDL-c ratio	1.72 ± 0.58	0.65 ± 0.18	1.18 ± 0.25	1.82 ± 0.38	3.24 ± 1.15	<0.001
Clinical Outcomes, n (%)						
Total IHD	7815 (6.3)	1395 (4.5)	1613 (5.2)	2016 (6.5)	2791 (9.0)	<0.001
AMI	1985 (1.6)	310 (1.0)	372 (1.2)	527 (1.7)	776 (2.5)	<0.001
Angina Pectoris	5830 (4.7)	1085 (3.5)	1241 (4.0)	1489 (4.8)	2015 (6.5)	<0.001
Demographics						
Age (yr)	55.4 ± 9.1	54.2 ± 8.2	55.1 ± 8.4	55.8 ± 8.6	56.5 ± 8.8	<0.001
Height (cm)	171.2 ± 6.1	171.1 ± 6.0	171.3 ± 6.1	171.2 ± 6.2	171.2 ± 6.1	0.542
BMI (kg/m ²)	27.1 ± 2.1	26.1 ± 1.6	26.8 ± 1.9	27.4 ± 2.1	28.1 ± 2.4	<0.001
Laboratory Findings						
GGT (U/L)	64.8 ± 25.2	29.2 ± 11.5	46.4 ± 14.2	70.8 ± 23.5	112.8 ± 42.1	<0.001
HDL-c (mg/dL)	46.2 ± 10.2	51.8 ± 10.2	48.2 ± 9.5	44.5 ± 9.0	39.2 ± 8.2	<0.001
LDL-c (mg/dL)	118.5 ± 33.2	111.4 ± 27.5	117.8 ± 29.8	120.5 ± 31.4	124.3 ± 34.2	<0.001
Lifestyle & Activity, n (%)						
Current Smoker	48,377 (39.0)	9923 (32.0)	11,164 (36.0)	12,714 (41.0)	14,575 (47.0)	<0.001
Alcohol Drinker	68,224 (55.0)	12,404 (40.0)	14,575 (47.0)	18,606 (60.0)	22,638 (73.0)	<0.001
Physical Activity [†]	32,251 (26.0)	9613 (31.0)	8683 (28.0)	7443 (24.0)	6512 (21.0)	<0.001
Comorbidities, n (%)						
Hypertension	50,858 (41.0)	10,854 (35.0)	11,784 (38.0)	13,025 (42.0)	15,195 (49.0)	<0.001
Diabetes Mellitus	17,366 (14.0)	2481 (8.0)	3411 (11.0)	4652 (15.0)	6822 (22.0)	<0.001
Stroke	3101 (2.5)	682 (2.2)	713 (2.3)	806 (2.6)	900 (2.9)	<0.001
Chronic Kidney Disease	2481 (2.0)	558 (1.8)	527 (1.7)	651 (2.1)	745 (2.4)	<0.001

IHD, ischemic heart disease; AMI, acute myocardial infarction; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein; GGT, gamma-glutamyltransferase; BMI, body mass index. [†]Physical activity was defined as engaging in vigorous exercise at least once a week.

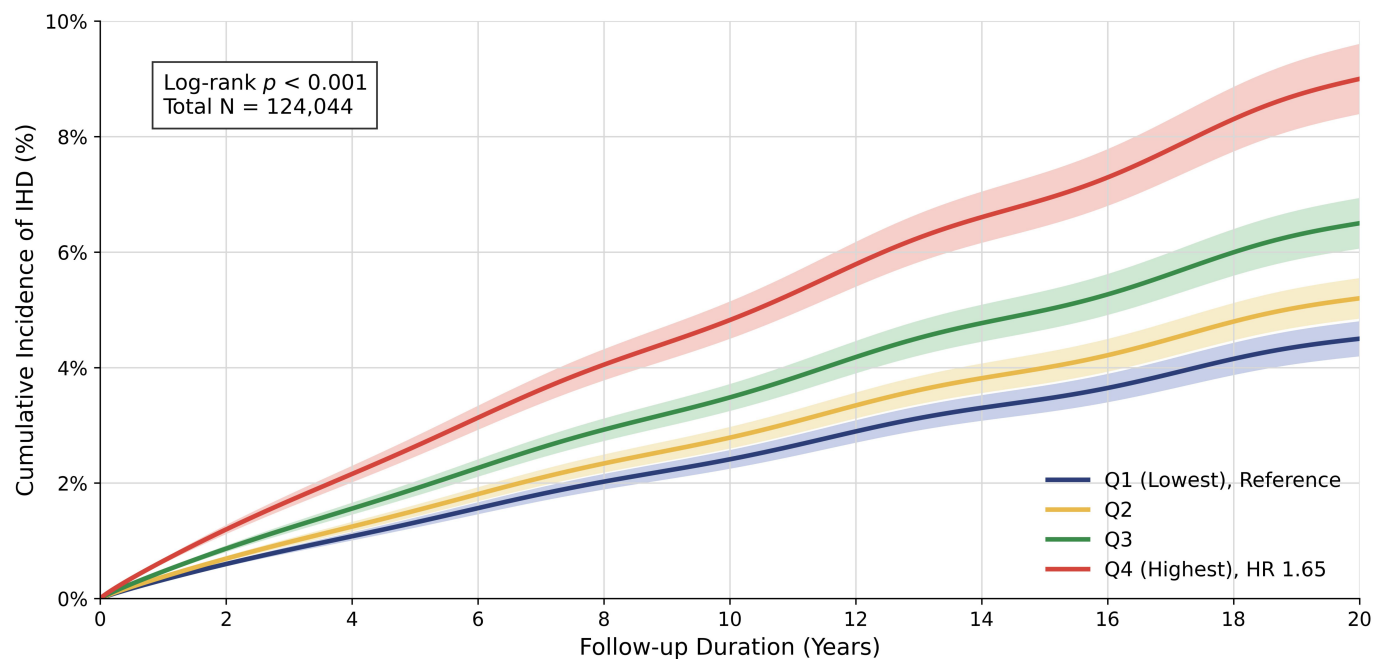


FIGURE 1. Kaplan-Meier cumulative incidence plot of IHD by GGT/HDL-c ratio quartiles in overweight men over a follow-up period of up to 20 years. IHD, ischemic heart disease; HR, hazard ratio.

TABLE 2. Hazard ratios and 95% confidence intervals for incident ischemic heart disease (IHD) according to GGT/HDL-c ratio (GHR) quartiles.

Variables	Q1 (Lowest)	Q2	Q3	Q4 (Highest)	<i>p</i> for trend	<i>p</i> -interaction
Total Population						
Model 1 (Unadjusted)	1.00 (Ref)	1.18 (1.06–1.32)	1.52 (1.37–1.68)	2.14 (1.93–2.37)	<0.001	-
Model 2 (Age adjusted)	1.00 (Ref)	1.14 (1.02–1.27)	1.41 (1.27–1.56)	1.92 (1.73–2.12)	<0.001	-
Model 3 (Lifestyle*)	1.00 (Ref)	1.11 (1.00–1.24)	1.35 (1.21–1.49)	1.78 (1.61–1.97)	<0.001	-
Model 4 (Fully adjusted†)	1.00 (Ref)	1.09 (0.98–1.21)	1.28 (1.15–1.43)	1.65 (1.49–1.83)	<0.001	-
Subgroup Analysis (Model 4)						
Physical Activity						
No (Inactive)	1.00 (Ref)	1.14 (1.01–1.28)	1.38 (1.22–1.56)	1.82 (1.61–2.06)	<0.001	<0.001
Yes (Active)	1.00 (Ref)	1.04 (0.88–1.22)	1.16 (0.99–1.36)	1.42 (1.21–1.67)	0.001	

*Model 3 adjusted for age, BMI, smoking, alcohol, and regular exercise.
†Model 4 additionally adjusted for systolic BP, FBG, total cholesterol, and anti-hypertensive/lipid-lowering medication use. Ref, reference.

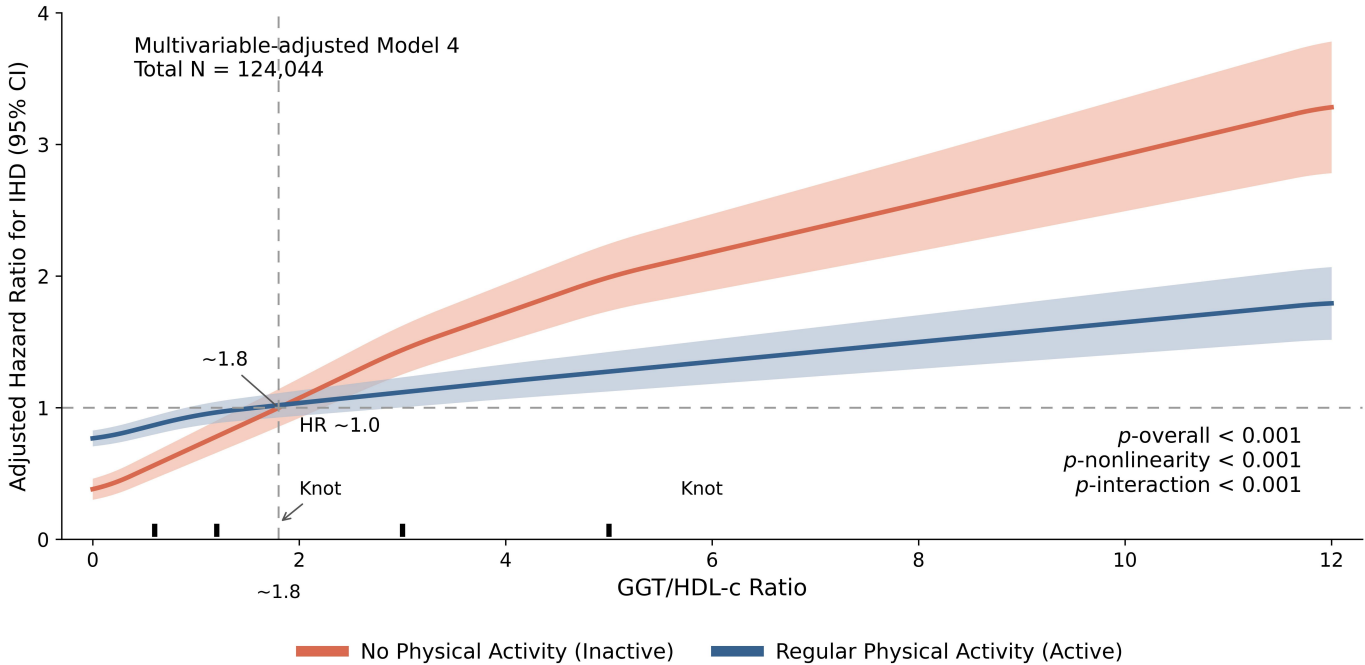


FIGURE 2. Restricted Cubic Spline Analysis of IHD Risk by GGT/HDL-c Ratio and Physical Activity. IHD, ischemic heart disease; CI, confidence interval; HR, hazard ratio; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol.

gated the risk of IHD across the entire range of the GGT/HDL-c ratio compared with the inactive group.

3.4 Incremental predictive value of the GGT/HDL-c ratio

The incremental predictive value of adding the GGT/HDL-c ratio to the baseline model (Model A) is shown in Table 3. The addition of the GGT/HDL-c ratio significantly improved the model’s discriminative ability, increasing the C-index from 0.742 to 0.765 ($p < 0.001$). Furthermore, the inclusion of the ratio resulted in a significant improvement in risk reclassification, with a Net Reclassification Improvement (NRI) of 0.058

and an Integrated Discrimination Improvement (IDI) of 0.007 (both $p < 0.001$).

4. Discussion

In this large-scale, nationwide population-based study of 124,044 overweight men, we demonstrated that the GGT/HDL-c ratio is a potent and independent predictor of long-term IHD risk. Over a follow-up period of up to 20 years, individuals in the highest GGT/HDL-c ratio quartile exhibited a 1.65-fold higher risk of incident IHD compared to those in the lowest quartile, even after rigorous adjustment for traditional cardiovascular risk factors. Notably, our study

TABLE 3. Incremental predictive value of GGT/HDL-c ratio for ischemic heart disease beyond traditional risk factors.

Models	C-index (95% CI)	p-value	NRI (95% CI)	IDI (95% CI)
Model A (Traditional Factors)	0.742 (0.731–0.753)	Ref	-	-
Model B (Model A + GGT)	0.746 (0.735–0.757)	0.084	0.015 (0.005–0.025)	0.001 (0.000–0.002)
Model C (Model A + HDL-c)	0.748 (0.737–0.759)	0.042	0.022 (0.012–0.032)	0.002 (0.001–0.003)
Model D (Model A + GGT/HDL-c)	0.765 (0.754–0.776)	<0.001	0.058 (0.046–0.070)	0.007 (0.005–0.009)

CI, confidence interval; NRI, net reclassification improvement; IDI, Integrated Discrimination Improvement; GGT, gamma-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; Ref, reference.

revealed a significant interaction between the GGT/HDL-c ratio and physical activity, suggesting that regular exercise may substantially mitigate the elevated cardiovascular risk associated with a high GGT/HDL-c ratio. Furthermore, the addition of this ratio to traditional risk models significantly improved risk reclassification, as evidenced by an NRI of 0.058.

The physiological significance of the GGT/HDL-c ratio lies in its ability to reflect the multifaceted nature of metabolic dysfunction and oxidative stress. Gamma-glutamyl transferase (GGT) is not merely a marker of hepatobiliary disease or alcohol consumption; it plays a crucial role in maintaining intracellular glutathione levels, the body's primary antioxidant [16]. Elevated GGT levels are increasingly recognized as a surrogate marker for systemic oxidative stress and subclinical inflammation, both of which are central to the pathogenesis of atherosclerosis [17]. In contrast, HDL-c is well-known for its role in reverse cholesterol transport and its anti-inflammatory, anti-thrombotic, and antioxidant properties [18]. Therefore, the GGT/HDL-c ratio serves as a composite index that captures the imbalance between pro-oxidant burden and protective lipid profiles, providing a more comprehensive metabolic signature than either marker alone.

Our findings in overweight men are particularly relevant given the “obesity paradox” and the heterogeneity of metabolic health among individuals with a high BMI. While BMI is a common screening tool, it fails to distinguish between metabolically healthy and unhealthy obesity. The GGT/HDL-c ratio appears to bridge this gap by identifying those at the highest risk within the overweight population. Notably, a recent multi-cohort Korean study reported that the prognostic value of the GGT/HDL-c ratio for incident cardiovascular disease was more evident in women than in men [19]; our findings, drawn from a larger male-only cohort with two decades of follow-up and a coronary-specific endpoint, extend this literature by demonstrating a robust and graded association in overweight men [14]. The J-shaped relationship observed in our restricted cubic spline analysis (Fig. 2) suggests a threshold effect, where the risk of IHD increases sharply once the GGT/HDL-c ratio exceeds approximately 1.8. This “metabolic red line” could serve as a practical trigger for more aggressive clinical intervention in primary care settings.

This J-shaped pattern is consistent with a recent analysis of 50,462 U.S. adults in the National Health and Nutrition Examination Survey (NHANES), which similarly reported a J-shaped association between the GGT/HDL-c ratio and cardiovascular

and all-cause mortality [15]. Biologically, the upturn in risk beyond this threshold may reflect a tipping point at which escalating oxidative stress and hepatic steatosis (reflected by elevated GGT levels) overwhelm the diminishing antioxidant and reverse-cholesterol-transport capacity of a depleted HDL pool, thereby accelerating endothelial dysfunction, LDL oxidation, and plaque instability. The relatively flat risk gradient below the threshold suggests that compensatory antioxidant reserves remain sufficient until the pro-oxidant burden crosses a critical level.

One of the most compelling findings of our study is the modulating effect of physical activity. The synergistic “double-hit” effect was evident: inactive men with a high GGT/HDL-c ratio faced nearly double the risk (HR 1.82) of IHD compared with the reference group, whereas this risk was significantly attenuated (HR 1.42) among those who engaged in regular physical activity. This interaction ($p < 0.001$) highlights the biological resilience afforded by exercise. Physical activity is known to enhance antioxidant defenses, improve insulin sensitivity, and promote more favorable HDL function, thereby counteracting the deleterious effects of high oxidative stress reflected by an elevated GGT/HDL-c ratio [20]. Clinically, this provides a powerful message for patient counseling: metabolic risk is not inevitable, and lifestyle modification remains a cornerstone of risk reduction even in high-risk individuals.

The clinical utility of a new biomarker is often judged by its incremental predictive value over established risk scores. Our results showed that adding the GGT/HDL-c ratio to a model containing age, BMI, smoking, and blood pressure significantly improved the C-index and, more importantly, the NRI (0.058). An NRI of 5.8% indicates that a substantial proportion of patients would be more accurately reclassified into appropriate risk categories using this ratio. In the context of our large cohort, this translates to a large number of individuals who could receive more timely and accurate preventive care. Given that both GGT and HDL-c are routinely measured in standard health check-ups at no additional cost, this ratio represents a cost-effective tool for refining risk stratification without the need for expensive genomic or imaging tests [21].

Several limitations of this study should be acknowledged. First, due to its observational nature, we cannot definitively establish a causal relationship. Second, although we adjusted for a wide range of confounders, the possibility of residual confounding by unmeasured factors remains. Third, the study population consisted exclusively of men; therefore, the findings may not be directly generalizable to women, who may exhibit different metabolic patterns. Fourth, the diagnosis of IHD was

based on ICD-10 codes from the NHIS database, which, while widely used in epidemiological research, may be subject to misclassification. Fifth, we did not perform internal or external validation (*e.g.*, bootstrapping or k-fold cross-validation) of the incremental predictive model; future studies should confirm the reproducibility of these estimates in independent cohorts. Finally, physical activity was assessed by self-report, which may be subject to recall and misclassification bias and could have attenuated or distorted the observed interaction.

Despite these limitations, the strengths of our study include the large sample size, the long-term follow-up duration, and the focus on a specific high-risk group (overweight men). To our knowledge, this is the first study to demonstrate the interaction between the GGT/HDL-c ratio and physical activity in a large-scale longitudinal cohort.

5. Conclusions

In conclusion, an elevated GGT/HDL-c ratio is a potent and independent predictor of long-term cardiovascular risk in overweight men, providing a simple and cost-effective tool for refining clinical risk stratification. Furthermore, our findings highlight that integrating this biomarker into routine assessments can effectively guide targeted lifestyle interventions, particularly emphasizing the critical role of regular physical activity in mitigating metabolic-related cardiovascular events.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available from the National Health Insurance Service (NHIS) of Korea. However, restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the NHIS.

AUTHOR CONTRIBUTIONS

UJ, EJ and HGK—conceptualization; resources; writing—review and editing; supervision; project administration. HKP, HYK and JYK—methodology; software and formal analysis. JYK, HYK and EJ—investigation; writing—original draft preparation. HYK and JYK—data curation; visualization. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (CNUH-EXP-2025-082). All research procedures were conducted in strict accordance with the ethical principles for medical research involving human subjects, as outlined in the 1964 Declaration of Helsinki and its subsequent amendments.

Given the retrospective design of this study and the use

of strictly anonymized, de-identified secondary clinical data provided by the National Health Insurance Service (NHIS) of Korea, the requirement for obtaining written informed consent from the participants was formally waived by the IRB of Chonnam National University Hospital.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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