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Association between the triglyceride-high-density lipoprotein-glucose-body index and new-onset cardiometabolic multimorbidity across blood pressure strata: a prospective cohort study

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Title

Association between the triglyceride-high-density lipoprotein-glucose-body index and new-onset cardiometabolic multimorbidity across blood pressure strata: a prospective cohort study

Running title

TyHGB and cardiometabolic multimorbidity across BP strata

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Abstract

Background Cardiometabolic multimorbidity (CMM), the coexistence of two or more cardiometabolic diseases, imposes a growing burden on middle-aged and older adults in China. Insulin resistance (IR) is a crucial modifiable contributor to this clustering. The triglyceride-glucose (TyG) index, a recognized IR surrogate, overlooks the protective role of high-density lipoprotein cholesterol (HDL-C) and the contribution of body mass index (BMI). The novel triglyceride-high-density lipoprotein-glucose-body index (TyHGB) integrates all four domains; however, its association with new-onset CMM, and whether this varies across blood pressure (BP) strata, remain unclear.

Methods Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS, 2011–2020). We included 7,830 participants free of CMM at baseline (fewer than two of heart disease, stroke, or diabetes) with classifiable BP status (normal, high-normal, or hypertension). Cox models with three incremental adjustment sets evaluated the TyHGB–CMM association; missing covariates were handled using multiple imputation by chained equations (m=20) with Rubin's rules. Multiplicative and additive (relative-excess-risk scale) interactions with BP status were tested. Restricted cubic splines explored non-linearity; incremental predictive value (change in 9-year time-dependent area under the curve, ΔAUC) was assessed within strata.

Results During approximately 9 years of follow-up, 803 (10.3%) incident CMM events were recorded. In the fully adjusted model, TyHGB was associated with higher CMM risk (hazard ratio [HR]=1.135 per unit, 95% CI: 1.115–1.155; per-SD HR=1.334, 1.282–1.388; quartile 4 versus 1 HR=4.268, 3.271–5.570). The association was consistent across BP strata (P for interaction=0.567), showed significant non-linearity (P for non-

linearity<0.001), and was predominantly expressed through diabetes-containing event combinations. The additive interaction between elevated TyHGB and hypertension did not persist after accounting for baseline cardiometabolic disease composition. Within-stratum predictive gains were modest (ΔAUC: 0.012–0.025).

Conclusions The TyHGB index was independently associated with new-onset CMM, with consistent strength across BP strata, expressed predominantly through diabetes-inclusive events. The co-occurrence of elevated TyHGB and hypertension identifies a jointly adverse phenotype with potential value for combined screening. These observational findings in middle-aged and older Chinese adults warrant external validation.

Trial registration Not applicable.

Keywords Cardiometabolic multimorbidity, TyHGB index, blood pressure stratification, insulin resistance, risk stratification

Highlights

- The TyHGB index integrates triglycerides, HDL-C, glucose, and adiposity into one marker.
- Higher TyHGB was prospectively associated with new-onset cardiometabolic multimorbidity.
- The association was consistent across normal, high-normal, and hypertensive strata.
- Elevated TyHGB combined with hypertension identified a jointly adverse phenotype.

Background

Cardiometabolic multimorbidity (CMM), the coexistence of two or more cardiometabolic diseases such as heart disease, stroke, and diabetes, is an escalating public health challenge among middle-aged and older adults. It is associated with substantially higher mortality risk than any single cardiometabolic condition [1, 2]. The prevalence of multimorbidity rises steeply with age and continues to grow globally [3]. China bears a particularly heavy and rising burden of cardiometabolic disease clustering amid rapid population aging [4, 5]. Insulin resistance (IR) is a core pathological basis underlying clustered metabolic risk factors, including hyperglycemia, dyslipidemia, and visceral adiposity, which jointly accelerate atherosclerosis and multi-organ damage [6, 7]. The hyperinsulinemic-euglycemic clamp, the gold standard for IR assessment, is complex and costly [8]. Simple, accessible surrogate markers of IR are therefore valuable tools for early screening and primary prevention of CMM.

The triglyceride-glucose (TyG) index has been widely established as a reliable surrogate marker for IR and is significantly associated with cardiovascular and cerebrovascular outcomes [9–11]. It relies solely on lipids and glucose, however, and therefore fails to account for the protective role of high-density lipoprotein cholesterol (HDL-C) and the contribution of body mass index (BMI) to cardiometabolic health [12]. HDL-C exerts anti-atherosclerotic effects via reverse cholesterol transport and anti-inflammatory pathways [13], whereas excess adipose tissue acts as an active endocrine organ that exacerbates systemic inflammation and insulin resistance [14]. To integrate these dimensions, the TyHGB index (triglyceride, HDL-C, glucose, BMI) was recently proposed as a quadri-dimensional composite indicator capturing glucotoxicity,

lipotoxicity, lipid protection, and obesity-related burden [15]. Validation across independent Chinese and US populations showed that TyHGB outperforms the traditional TyG index in identifying non-alcoholic fatty liver disease [16]. A longitudinal analysis of CHARLS further linked elevated TyHGB patterns to new-onset stroke [17]. Whether the TyHGB index is associated with incident CMM—the clustering outcome that most directly reflects systemic metabolic dysregulation—remains unexplored. Unlike the TyG-derived obesity composites evaluated to date, TyHGB uniquely incorporates a protective lipid dimension (HDL-C), making it the only member of this index family to capture both adverse and protective lipid pathways.

A second, largely overlooked question is whether blood pressure (BP) status modifies metabolic risk associations. Hypertension frequently coexists with insulin resistance and shares its upstream determinants, and elevated BP is itself a defining component of the cardiometabolic risk cluster [18, 19]. Recent work on combined metabolic phenotypes suggests that jointly adverse metabolic indices identify individuals at markedly elevated cardiovascular risk, and that quantifying their interaction on both multiplicative and additive scales is essential before claiming any synergy [20]. Most studies of metabolic indices, including the TyHGB analyses to date, have nonetheless reported single overall associations or focused on hypertensive subpopulations [21], and formal effect-modification testing across BP strata has largely been absent. Whether a metabolic marker performs equally in normotensive and hypertensive populations—and whether the two exposures jointly identify a high-risk phenotype suitable for combined screening—therefore remains unclear.

To address these gaps, we used data from the China Health and Retirement Longitudinal Study (CHARLS, 2011–2020). Specifically, we examined the longitudinal association between baseline TyHGB and new-onset CMM, tested whether baseline BP strata modified that association on both multiplicative and additive scales, and evaluated the incremental predictive value of TyHGB within each stratum. The findings may inform the value of multi-dimensional metabolic monitoring and joint metabolic–blood-pressure risk stratification for the primary prevention of CMM.

Methods

Study design and population

Data for this study were obtained from the China Health and Retirement Longitudinal Study (CHARLS) [22], a nationally representative longitudinal survey covering 450 communities and villages across 28 provinces in China. The survey was designed to collect health and socioeconomic data from adults aged 45 years and older. The study adhered to the principles of the Declaration of Helsinki and received approval from the Biomedical Ethics Review Board of Peking University (IRB00001052-11015 and IRB00001052-11014). All participants provided written informed consent.

Figure 1 details the participant selection process. A total of 17,708 participants from the 2011 baseline wave were initially screened. Participants were sequentially excluded based on the following criteria: (1) aged <45 years or with missing age (n=648); (2) having CMM (≥2 of heart disease, stroke, and diabetes) at baseline (n=589); (3) missing

baseline CMM status (n=275); (4) TyHGB not computable at baseline after extreme-value cleaning (TG, HDL-C, FBG, or BMI missing; n=8,093); (5) no follow-up CMM status across Waves 2–5 (n=216); and (6) baseline BP stratum not uniquely classifiable from observed diagnosis, medication, and measured blood pressure (n=57). Ultimately, 7,830 participants were included in the final analysis. Participants with exactly one baseline cardiometabolic disease were retained because incident CMM requires the accumulation of at least two diseases; these participants formed the baseline CMD=1 stratum in the stratified analyses below. Baseline characteristics of included versus excluded participants are compared in Table S9.

Exposures and outcome

Baseline (2011) triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), and body mass index (BMI) were used to derive the TyHGB index according to the previously established formula [15]: TyHGB = TG/HDL-C (mmol/L) + 0.7×FBG (mmol/L) + 0.1×BMI (kg/m²). Extreme values outside prespecified plausible ranges were set to missing before imputation rather than deleted at the person level; range checks were applied in the original measurement units (BMI 10–45 kg/m²; TG 20–1,000 mg/dL; FBG 40–500 mg/dL; HDL-C 5–150 mg/dL; SBP 70–260 mmHg; DBP 30–160 mmHg), with unit conversion to mmol/L applied afterwards for the TyHGB calculation. The comparator TyG index was computed as ln[TG (mg/dL)×FBG (mg/dL)/2] [9].

Baseline BP status was classified into three strata using all available observed information: hypertension was defined as self-reported physician diagnosis and/or current antihypertensive medication use and/or measured systolic blood pressure (SBP) ≥140

mmHg or diastolic blood pressure (DBP) ≥90 mmHg; high-normal BP was defined as measured SBP 120–139 mmHg or DBP 80–89 mmHg without meeting the hypertension definition; all remaining participants were classified as normal BP. Because any positive component uniquely determines hypertension, participants with partially missing BP components were retained whenever the stratum could still be uniquely determined (n=50); only participants whose stratum could not be uniquely classified were excluded (n=57, criterion 6 above).

The outcome was new-onset CMM, defined as the development of at least two of three physician-diagnosed conditions (heart disease, stroke, and diabetes) during follow-up (Waves 2–5, 2013–2020). Heart disease and stroke were ascertained by standardized questionnaire ("Have you been diagnosed with … by a doctor?") or current treatment for the condition; diabetes additionally incorporated laboratory criteria (FBG≥126 mg/dL or glycated hemoglobin [HbA1c] ≥6.5%). Due to the wave-based design of CHARLS, the exact date of disease onset was not available, resulting in interval-censored data. The event time was defined as the date of the interview at which the participant first met the CMM definition, and censored participants were right-censored at their last follow-up interview. Participants who reported a disease and later retracted it were conservatively treated as events ("once yes, always event"; 201 of 803 events, 25.0%). To address potential reverse causality arising from this interval-censored design, we performed an a priori sensitivity analysis excluding participants who developed CMM within the first 2 years of follow-up. Among the 803 incident CMM events, 601 (74.8%) included diabetes as one of the component diseases (heart disease and diabetes, n=435; stroke and diabetes,

n=127; heart disease and stroke, n=202; all three, n=39); this compositional feature is reported transparently and revisited in the sensitivity analyses and Discussion.

Data collection

We collected data on covariates encompassing sociodemographic characteristics (age, gender, marital status, educational background, and area of residence), lifestyle behaviors (smoking and drinking status), and laboratory indices (low-density lipoprotein cholesterol [LDL-C], C-reactive protein [CRP], and serum creatinine [Scr]). Categorical variables were coded as binary or ordinal categories as appropriate.

Statistical analysis

Descriptive analyses

Baseline characteristics were summarized across TyHGB quartiles as mean±standard deviation or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables. Between-quartile comparisons used one-way analysis of variance for continuous variables and Pearson's chi-square tests for categorical variables.

Main association analyses

The association between baseline TyHGB and incident CMM was evaluated using Cox proportional hazards regression models, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Three incremental adjustment sets were prespecified: Model 1 was unadjusted; Model 2 was adjusted for age, gender, marital status, education, residence, smoking, drinking, and BP strata; Model 3 (the primary model) was further

adjusted for LDL-C, CRP, and Scr. Total cholesterol was excluded from Model 3 because of structural collinearity with LDL-C (generalized variance inflation factor, GVIF^(1/(2df))=2.07, above the prespecified threshold). Diabetes was not included in Models 2–3 because it is a component of the CMM outcome (present in 74.8% of events); adjusting for an outcome component would constitute structural overadjustment. TyHGB was modeled as a continuous variable (per 1-unit and per-SD increase) and as quartiles (Q1 as reference).

Handling of missing data

Missing covariate data (all <2% per variable; Table S2 and Figure S4) were handled by multiple imputation by chained equations (MICE) [23] (m=20 imputations, maxit=10, seed=20260807). Predictive mean matching, logistic regression, and polytomous regression were used for continuous, binary, and multicategorical variables, respectively. The TyHGB index and observed BP strata were fixed and not imputed; all model estimates were pooled across imputations using Rubin's rules, except for descriptive baseline tables and cumulative-risk curves, which are presented as observed-data descriptions. MICE-based and complete-case estimates are compared in Table S3.

Effect modification and interaction analyses

Multiplicative effect modification by BP strata was tested by adding a continuous TyHGB×BP-strata interaction term to Model 3. The P for interaction was obtained from a joint Wald test pooled across imputations (the D1 statistic from the mice package). Additive interaction between elevated TyHGB (above vs below the sample median, 7.2818) and measured hypertension was quantified by the relative excess risk due to

interaction (RERI), attributable proportion (AP), and synergy index (SI) using the delta method [24, 25], under four incremental adjustment levels (Table S4). Because baseline cardiometabolic disease (CMD) composition differed across the four joint exposure groups, the additive analyses were repeated after excluding participants with baseline diabetes (n=6,814) and after excluding participants with any of the three baseline diseases (n=5,988), and were further stratified by baseline CMD status (CMD=0 vs CMD=1). Heterogeneity of the main association across baseline CMD strata was additionally evaluated on the multiplicative scale (Table S5).

Dose–response analyses

Restricted cubic spline (RCS) regression with four knots at the 5th, 35th, 65th, and 95th percentiles [26] was used to explore potential non-linear dose-response relationships between TyHGB and CMM risk, overall and within each BP stratum. Within each imputed dataset, log-hazard contrasts against the reference value were obtained from the fixed-knot spline basis and pooled pointwise using Rubin's rules. P values for non-linearity were derived from nested-model comparison pooled across imputations. RCS-derived inflection features are data-driven curve characteristics and are not interpreted as clinical thresholds.

Incremental predictive value

Incremental predictive value was evaluated within each BP stratum by comparing a basic model (the Model 3 covariate set without TyHGB) against the same model plus TyHGB, using 9-year time-dependent AUC with inverse probability of censoring weighting (IPCW) [27]. The net reclassification improvement (NRI) and integrated discrimination

improvement (IDI) [28] were also computed. Participant-level paired bootstrap resampling (B=8,000) was performed within each of the 20 imputed datasets and pooled with Rubin's rules. Decision curve analysis (DCA) [29] was used to assess clinical net benefit. All predictive performance is apparent (in-sample) and was not externally validated.

Mediation analyses

Exploratory bidirectional mediation analyses between TyHGB and hypertension were conducted on a landmark subsample (Wave 3 landmark; n=4,155) using the difference-method framework. Because both directions yielded non-significant average causal mediation effects, these analyses are reported in Table S6 only.

Sensitivity analyses and model diagnostics

Sensitivity analyses, each targeting a prespecified bias source, included: a Fine–Gray competing-risk model [30] treating death as the competing event (794 competing deaths; one death with a missing death date was excluded from this analysis); winsorizing TyHGB components at the 1st/99th percentiles; excluding participants with less than 2 years of follow-up; excluding participants with baseline diabetes (addressing the outcome-component composition); and two restricted-outcome variants probing the measurement overlap between fasting glucose (a TyHGB component) and the diabetes component of CMM: (i) censoring events whose qualifying disease combination included diabetes, restricting the outcome to heart disease–stroke pairs; and (ii) defining diabetes by self-reported diagnosis or medication use only. Sensitivity analyses also included excluding participants with CRP>10 mg/L. As a confounding control for the exclusion of

diabetes from the adjustment set, Model 3 was additionally refitted with baseline heart disease and stroke history included. The proportional hazards assumption was verified using Schoenfeld residuals within each imputed dataset (Table S8), and multicollinearity was assessed using GVIF (Table S7). Sensitivity results are summarized in Table S1 and Figure S1. All statistical analyses were performed using R software (version 4.5.2; packages survival, rms, cmprsk, mice, and survey), with data management in Python (pandas). A two-sided P-value<0.05 was considered statistically significant; interaction and predictive analyses were considered exploratory without formal multiplicity control.

Results

Baseline characteristics of participants

Table 1 summarizes the baseline characteristics of the 7,830 participants included in the analysis, stratified by TyHGB quartiles (cut-offs: 6.6196, 7.2818, and 8.3098). The overall mean age was 59.33±9.26 years, and 53.6% of participants were female. During follow-up, 803 (10.3%) incident CMM events were recorded, with a stepwise increase across TyHGB quartiles: 3.5% in Q1, 7.2% in Q2, 12.0% in Q3, and 18.4% in Q4 (P<0.001). Compared with the lowest quartile, participants in the highest quartile were slightly younger, more likely to be urban residents, and less likely to be current smokers or drinkers, yet presented a markedly more adverse cardiometabolic profile. This profile included higher systolic and diastolic blood pressure, FBG, HbA1c, and triglycerides, a higher prevalence of hypertension (53.1% vs 28.4% in Q1), and lower HDL-C levels.

Association between the TyHGB index and new-onset CMM

The TyHGB index was approximately normally distributed at baseline (median 7.2818; Fig. 2A). Descriptive cumulative-risk curves for the six TyHGB-by-BP-strata groups diverged early and remained separated throughout follow-up (log-rank χ^2=376.1, df=5, P<0.001; Fig. 2B). In Cox models pooled across 20 imputed datasets (Table 2), each 1-unit increase in TyHGB was associated with a higher risk of incident CMM in the unadjusted model (Model 1: HR=1.121, 95% CI: 1.105–1.138). The association persisted after incremental adjustment (Model 2: HR=1.115, 1.097–1.133; Model 3: HR=1.135, 1.115–1.155). Each SD increase in TyHGB was associated with a 33% higher risk in Model 3 (HR=1.334, 1.282–1.388). For scale context, one interquartile-range increase in TyHGB (≈1.69 units) corresponded to an estimated 24% higher risk of incident CMM. When modeled as quartiles, HRs increased monotonically in all three models: compared with Q1, the Model 3 HRs for Q2, Q3, and Q4 were 1.808 (1.351–2.419), 2.727 (2.072–3.591), and 4.268 (3.271–5.570), respectively.

Effect modification by BP strata on the multiplicative scale

The association between TyHGB and CMM was significant and of similar magnitude within each BP stratum (Table 2): normal BP (HR=1.144, 95% CI: 1.098–1.192 per unit), high-normal BP (1.132, 1.092–1.174), and hypertension (1.130, 1.103–1.158), with no evidence of multiplicative interaction (P for interaction=0.567). Within-stratum quartile analyses showed the same graded pattern, although the Q4 estimate in the high-normal stratum was imprecise owing to few reference-cell events (HR=9.648, 95% CI: 4.578–20.336; Q1 reference cell: 8 events/527 participants). Table 3 presents the joint exposure

analysis, using Low TyHGB and Normal BP as the reference. The Model 3 HR was 2.37 (1.69–3.33) for High TyHGB and Normal BP, 1.08 (0.71–1.62; P=0.728) for Low TyHGB and High-normal BP, 3.52 (2.57–4.82) for High TyHGB and High-normal BP, 2.73 (1.98–3.78) for Low TyHGB and Hypertension, and 5.88 (4.43–7.79) for the combined High TyHGB and Hypertension phenotype. The joint six-group pattern is visualized in Fig. 3. BP status thus acted as a strong parallel risk factor without modifying the strength of the TyHGB–CMM association on the multiplicative scale.

Additive interaction and baseline CMD heterogeneity

On the additive scale (Table 4; full detail in Table S4), the fully adjusted analysis of the four joint exposure groups yielded a statistically significant RERI of 1.175 (95% CI: 0.318–2.032; P=0.007), with AP=0.206 and SI=1.334. However, this signal attenuated after accounting for the compositional imbalance of baseline cardiometabolic disease (CMD) across the joint groups. After excluding participants with baseline diabetes (n=6,814), the RERI attenuated to 0.826 (−0.078 to 1.731; P=0.073); after excluding participants with any of the three baseline diseases (n=5,988), it disappeared entirely (RERI=−0.060, −1.333 to 1.212; P=0.926). Within baseline CMD strata, neither the CMD=0 (RERI=−0.060, −1.333 to 1.212; P=0.926) nor the CMD=1 subgroup (RERI=0.421, −0.167 to 1.009; P=0.160) showed a significant additive interaction. On the multiplicative scale (Table S5), the TyHGB–CMM association was stronger among participants free of any baseline cardiometabolic disease (CMD=0: HR=1.230, 1.172–1.291) than among those with one baseline disease (CMD=1: HR=1.042, 1.017–1.069; P for interaction=2.80×10^{-7}). The additive and multiplicative findings address different scales and are reported separately.

Dose-response relationship between TyHGB and CMM risk

Restricted cubic spline analyses revealed a significant non-linear dose-response relationship between baseline TyHGB and incident CMM in the overall population (P for non-linearity=5.72×10^{-14}; Fig. 4A) and within each BP stratum (normal: P=0.0048; high-normal: P=3.00×10^{-6}; hypertension: P=5.44×10^{-7}; Fig. 4B–D). Across all four panels, the estimated risk rose steeply over the lower range of TyHGB and the slope attenuated at higher levels, showing a saturation-like pattern that was directionally consistent across strata.

Subgroup and sensitivity analyses

Across the three BP strata, subgroup analyses by age, gender, education, residence, current smoking, and current drinking (18 subgroup-interaction tests in total) showed directionally consistent associations (Fig. 5). Seventeen of the 18 interaction tests were non-significant; the sole nominal signal was observed for high-normal BP×education (P for interaction=0.010). Sensitivity analyses, each targeting a prespecified bias source, confirmed the robustness of the primary association (Table S1, Figure S1): the continuous TyHGB estimate remained materially unchanged under a Fine–Gray competing-risk model treating death as the competing event (HR=1.134, 1.114–1.154), after winsorizing TyHGB components at the 1st/99th percentiles (1.201, 1.170–1.233), after excluding participants with less than 2 years of follow-up (1.134, 1.114–1.154), after excluding participants with baseline diabetes (1.195, 1.149–1.243), and after excluding participants with CRP>10 mg/L (1.141, 1.120–1.161). Two restricted-outcome analyses addressed the measurement overlap between fasting glucose (a TyHGB

component) and the diabetes component of CMM: censoring events whose qualifying disease combination included diabetes, restricting the outcome to heart disease–stroke pairs (202 events), fully attenuated the association (HR=0.979, 95% CI: 0.914–1.048; P=0.536), whereas defining diabetes by self-reported diagnosis or medication use only (757 events) left the estimate unchanged (HR=1.140, 1.119–1.160; P<0.001). As a confounding control for the deliberate exclusion of diabetes from the adjustment set, refitting Model 3 with baseline heart disease and stroke history left the TyHGB estimate essentially unchanged (1.147, 1.127–1.166), although both baseline conditions were themselves strong predictors (HR=3.914 and 3.580, respectively; both P<0.001). The proportional hazards assumption was not violated in any imputed dataset (global Schoenfeld P range 0.646–0.667; Table S8), and no problematic multicollinearity was detected (all GVIF within threshold; Table S7).

Incremental predictive value within BP strata

Adding TyHGB to the basic risk factor model yielded modest but statistically significant improvements in 9-year CMM discrimination within each BP stratum (Table 5): the time-dependent AUC increased from 0.640 to 0.662 in the normal stratum (ΔAUC=0.022, P=0.046), from 0.674 to 0.698 in the high-normal stratum (ΔAUC=0.025, P=0.012), and from 0.643 to 0.655 in the hypertension stratum (ΔAUC=0.012, P=0.022). The NRI was significant in the high-normal (0.402, P<0.001) and hypertension (0.230, P<0.001) strata but not in the normal stratum (0.159, P=0.215). The IDI reached significance only in the hypertension stratum (0.008, P=0.049). Incremental ROC and decision curve analyses are presented in Figures S2 and S3.

Discussion

To our knowledge, this is the first study to examine the longitudinal association between the novel TyHGB index and incident cardiometabolic multimorbidity. It is also the first to formally test whether this association is modified by baseline blood pressure strata. In this large, nationally representative CHARLS cohort, we found that baseline TyHGB was independently associated with new-onset CMM, with a clear dose-response gradient across quartiles. The association was consistent in strength across normal, high-normal, and hypertensive strata, with no multiplicative effect modification. The additive interaction between elevated TyHGB and hypertension did not persist once baseline cardiometabolic disease composition was accounted for. Adding TyHGB to basic risk factors provided modest but detectable incremental predictive value within each BP stratum.

The robust association between TyHGB and CMM is biologically plausible and likely reflects the convergence of insulin resistance, lipotoxicity, attenuated HDL-C-mediated protection, and obesity-related systemic inflammation [6, 7, 14, 31–33]. Each component of CMM (heart disease, stroke, and diabetes) shares this upstream metabolic soil. This shared soil may explain why a quadri-dimensional marker integrating triglycerides, glucose, HDL-C, and BMI captured the clustering outcome more strongly than single-pathway indicators typically do [34]. In our cohort, 74.8% of incident CMM events included diabetes as a component, and restricted-outcome analyses indicated that the association was predominantly carried by diabetes-containing event combinations; heart

disease–stroke clustering contributed little. The estimate was unchanged when diabetes was defined by self-reported diagnosis or medication use only, arguing against an artefact of laboratory-based ascertainment. Exploratory bidirectional mediation analyses between TyHGB and hypertension found no statistically significant mediating effect in either direction (Table S6), so the mechanistic interpretation above is best regarded as hypothesis-generating.

Our findings are consistent with recent evidence that composite metabolic indices (e.g., TyG-BMI, TyG-WHtR) outperform single biomarkers for cardiometabolic risk stratification [35–37]. They also extend the TyHGB literature, which has so far covered NAFLD identification [16] and stroke risk [17], to the multimorbidity setting. The absolute discriminative gains we observed were modest (ΔAUC 0.012–0.025), echoing prior evidence that individual blood-based biomarkers typically provide limited incremental performance for complex outcomes [38–40]. TyHGB is therefore best viewed as an adjunctive metabolic marker within multivariable risk frameworks, not a standalone predictive tool [41]. The clinical utility of these gains requires external validation [42] and decision-analytic confirmation.

A further contribution of this study is the formal, dual-scale evaluation of blood pressure as a candidate effect modifier. On the multiplicative scale, the TyHGB–CMM association was essentially identical across BP strata, indicating that TyHGB is a broadly applicable metabolic risk marker whose performance does not depend on BP status—stratified robustness, in other words, not effect modification. On the additive scale, the initially significant RERI disappeared after accounting for the compositional imbalance of baseline cardiometabolic disease across joint exposure groups. This pattern closely

mirrors recent joint-phenotype and BP-stratified analyses, in which the highest-risk combined group reflected the summation of two main effects without genuine synergy [20, 43]. The practical implication is therefore not synergy but a jointly adverse phenotype. Individuals with both elevated TyHGB and hypertension carried nearly six-fold the risk of the reference group. They represent a natural target for combined metabolic and blood-pressure screening. Among participants free of baseline cardiometabolic disease (CMD=0), the multiplicative association was stronger. This further suggests that TyHGB may be most informative early in the cardiometabolic disease course, before established disease dominates individual risk. An alternative explanation is that higher baseline risk leaves less room for additional discrimination once one cardiometabolic disease is established.

RCS analyses revealed significant non-linearity between TyHGB and CMM risk in the overall population and within each BP stratum, with risk rising steeply at lower TyHGB levels and the slope attenuating thereafter. Such saturation-like patterns have been widely reported for TyG-related indices in relation to cardiovascular outcomes [44–47]. These inflection features are model-dependent curve characteristics and serve as statistical reference values rather than clinical thresholds.

This study has several notable strengths, including a nationally representative cohort, a prespecified dual-scale interaction framework, multiple-imputation-based estimation with pooled inference, and a transparent accounting of outcome composition. Nevertheless, several limitations deserve mention. Cardiometabolic outcomes were partly based on self-report at discrete follow-up waves, and event times were approximated by interview dates. This introduces interval censoring and potential non-differential misclassification.

Self-reported incident stroke has shown satisfactory agreement with medical records in population-based cohorts [48]. Any residual non-differential misclassification typically biases hazard ratios toward the null, suggesting that the true association might be even stronger than observed [49]. Fasting glucose enters both the TyHGB formula and the laboratory definition of diabetes, and 74.8% of CMM events included diabetes; our findings therefore pertain to diabetes-inclusive CMM. All predictive analyses are apparent in-sample performance without external validation or optimism correction, and continuous NRI does not equate to clinical net benefit. The additive interaction and subgroup analyses were exploratory without formal multiplicity control. One nominal subgroup interaction (high-normal BP×education, P=0.010) among 18 tests should be read as hypothesis-generating. Within-stratum quartile cells with few events produced imprecise estimates. The study population consisted exclusively of middle-aged and older Chinese adults, and generalizability to other ethnic and regional populations requires further validation in diverse cohorts [50].

Conclusions

In this prospective cohort of middle-aged and older Chinese adults, the baseline TyHGB index was independently associated with new-onset cardiometabolic multimorbidity. The association was consistent in strength across normal, high-normal, and hypertensive blood pressure strata and showed a graded dose-response relationship. The absence of robust additive interaction indicates that elevated TyHGB and hypertension constitute a jointly adverse phenotype, identifiable through combined screening, rather than a

synergistic one. By integrating triglycerides, glucose, HDL-C, and adiposity, TyHGB provided modest incremental predictive value within each BP stratum and may serve as an adjunctive marker for metabolic risk stratification in primary prevention. These observational findings warrant external validation in diverse populations.

List of abbreviations

AP, attributable proportion; AUC, area under the curve; BMI, body mass index; BP, blood pressure; CHARLS, China Health and Retirement Longitudinal Study; CI, confidence interval; CMM, cardiometabolic multimorbidity; CMD, cardiometabolic disease; CRP, C-reactive protein; DCA, decision curve analysis; DBP, diastolic blood pressure; FBG, fasting blood glucose; GVIF, generalized variance inflation factor; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IDI, integrated discrimination improvement; IPCW, inverse probability of censoring weighting; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; MICE, multiple imputation by chained equations; NRI, net reclassification improvement; RCS, restricted cubic spline; RERI, relative excess risk due to interaction; SBP, systolic blood pressure; Scr, serum creatinine; SD, standard deviation; SI, synergy index; TG, triglycerides; TyG, triglyceride-glucose index; TyHGB, triglyceride-high-density lipoprotein-glucose-body index.

Declarations

Ethics approval and consent to participate This study was approved by the Biomedical Ethics Review Board of Peking University (approval numbers IRB00001052-11015 and IRB00001052-11014). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. All participants were informed of the purpose of the study, were assured of confidentiality, and provided written consent prior to participation.

Consent for publication Not applicable.

Availability of data and materials The datasets used in this investigation are available from the CHARLS project website (http://charls.pku.edu.cn/). The analysis code supporting the findings of this study is available from the corresponding author upon reasonable request.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions ZW and JW conceptualized the study. ZW developed the methodology, performed the formal analysis, curated the data, prepared the visualizations, and drafted the manuscript. SW contributed to the investigation, data curation, and review and editing. JW supervised the study, validated the work, and reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Additional files

Additional file 1 (.docx): Supplementary material — Tables S1–S9 and Figures S1–S4. Title: Supplementary tables and figures for the TyHGB–CMM cohort study. Description: prespecified sensitivity analyses; missing-data summary; multiple-imputation versus complete-case comparison; additive-interaction detail with composition-robustness analyses; CMD-stratified associations; exploratory mediation analyses; multicollinearity diagnostics; proportional-hazards tests; included-versus-excluded participant comparison; and supplementary figures S1–S4 (sensitivity forest plot, incremental ROC curves, decision curve analysis, missing-data pattern).

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References

1. Zhang D, Tang X, Shen P, et al. Multimorbidity of cardiometabolic diseases: prevalence and risk for mortality from one million Chinese adults in a longitudinal cohort study. BMJ Open. 2019;9:e024476.

2. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. JAMA. 2015;314:52–60.

519 3. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional
520 prevalence of multimorbidity in the adult population in community settings: a systematic
521 review and meta-analysis. EClinicalMedicine. 2023;57:101860.

522 4. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its
523 provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study
524 2017. Lancet. 2019;394:1145–58.

525 5. Wang L, Gao P, Zhang M, et al. Prevalence and ethnic pattern of diabetes and
526 prediabetes in China in 2013. JAMA. 2017;317:2515–23.

527 6. Li M, Chi X, Wang Y, et al. Trends in insulin resistance: insights into mechanisms and
528 therapeutic strategy. Signal Transduct Target Ther. 2022;7:216.

529 7. Hill MA, Yang Y, Zhang L, et al. Insulin resistance, cardiovascular stiffening and
530 cardiovascular disease. Metabolism. 2021;119:154766.

531 8. Baneu P, Vacarescu C, Dragan SR, et al. The triglyceride/HDL ratio as a surrogate
532 biomarker for insulin resistance. Biomedicines. 2024;12:1493.

533 9. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of
534 fasting glucose and triglycerides as surrogate for identifying insulin resistance in
535 apparently healthy subjects. Metab Syndr Relat Disord. 2008;6:299–304.

536 10. Ding X, Wang X, Wu J, Zhang M, Cui M. Triglyceride-glucose index and the
537 incidence of atherosclerotic cardiovascular diseases: a meta-analysis of cohort studies.
538 Cardiovasc Diabetol. 2021;20:76.

11. Lopez-Jaramillo P, Gomez-Arbelaez D, Martinez-Bello D, et al. Association of the triglyceride glucose index as a measure of insulin resistance with mortality and cardiovascular disease in populations from five continents (PURE study): a prospective cohort study. Lancet Healthy Longev. 2023;4:e23–33.

12. Lee J, Kim B, Kim W, et al. Lipid indices as simple and clinically useful surrogate markers for insulin resistance in the U.S. population. Sci Rep. 2021;11:2366.

13. Rohatgi A, Westerterp M, von Eckardstein A, Remaley A, Rye KA. HDL in the 21st century: a multifunctional roadmap for future HDL research. Circulation. 2021;143:2293–309.

14. Lee MJ, Kim J. The pathophysiology of visceral adipose tissues in cardiometabolic diseases. Biochem Pharmacol. 2024;222:116116.

15. Song S, Zhang Y, Qiao X, Duo Y, Xu J, Peng Z, et al. HOMA-IR as a risk factor of gestational diabetes mellitus and a novel simple surrogate index in early pregnancy. Int J Gynaecol Obstet. 2022;157:694–701.

16. Zhao E, Wang R, Chen Y, Xie H, Gao Y, Dong B, et al. Evaluation of a new TyG indicator, TyHGB, in predicting non-alcoholic fatty liver disease: evidence from two independent populations. Lipids Health Dis. 2025;24:342.

17. Lu A, Xu Q. Association between the triglyceride-high-density lipoprotein-glucose-body index and new-onset stroke risk: a prospective cohort study. Lipids Health Dis. 2026;25:143.

559 18. Mancusi C, Izzo R, di Gioia G, Losi MA, Barbato E, Morisco C. Insulin resistance
560 the hinge between hypertension and type 2 diabetes. High Blood Press Cardiovasc Prev.
561 2020;27:515–26.

562 19. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-kidney-metabolic
563 health: a presidential advisory from the American Heart Association. Circulation.
564 2023;148:1606–35.

565 20. Fan Y, Si Z, Wei M, Gu Y, Li X. Joint association of atherogenic index of plasma and
566 estimated glucose disposal rate with new-onset cardiovascular disease risk in individuals
567 with cardiovascular–kidney–metabolic syndrome stages 0–3: a 9-year nationwide
568 prospective cohort study. Cardiovasc Diabetol. 2026;25:184.

569 21. Huang Z, Ding X, Yue Q, et al. Triglyceride-glucose index trajectory and stroke
570 incidence in patients with hypertension: a prospective cohort study. Cardiovasc Diabetol.
571 2022;21:141.

572 22. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and
573 Retirement Longitudinal Study (CHARLS). Int J Epidemiol. 2014;43:61–8.

574 23. van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained
575 equations in R. J Stat Softw. 2011;45:1–67.

576 24. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating
577 measures of biological interaction. Eur J Epidemiol. 2005;20:575–9.

578 25. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect
579 modification and interaction. Int J Epidemiol. 2012;41:514–20.

26. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989;8:551–61.

27. Chambless LE, Diao G. Estimation of time-dependent area under the ROC curve for long-term risk prediction. Stat Med. 2006;25:3474–86.

28. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008;27:157–72.

29. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making. 2006;26:565–74.

30. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.

31. Lee YS, Olefsky J. Chronic tissue inflammation and metabolic disease. Genes Dev. 2021;35:307–28.

32. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542:177–85.

33. Schleh MW, Caslin HL, Garcia JN, et al. Metaflammation in obesity and its therapeutic targeting. Sci Transl Med. 2023;15:eadf9382.

34. Lin Y, Tao J, Wang H, Guan H, Liu X, Dong X, Gao W. The association of C-reactive protein–triglyceride–glucose index with cardiometabolic multimorbidity in middle-aged and older adults: evidence from two cohort studies. Cardiovasc Diabetol. 2026;25:90.

35. Zhang H, Tu Z, Liu S, et al. Association of different insulin resistance surrogates with all-cause and cardiovascular mortality among the population with cardiometabolic multimorbidity. Cardiovasc Diabetol. 2025;24:33.

36. Cui C, Qi Y, Song J, Shang X, Han T, Han N, et al. Comparison of triglyceride glucose index and modified triglyceride glucose indices in prediction of cardiovascular diseases in middle aged and older Chinese adults. Cardiovasc Diabetol. 2024;23:185.

37. Zhang F, Zhang B, Huang X, et al. Comparison of the TyG index, TyG-traditional obesity indices, and TyG-novel obesity indices: does increased complexity help in predicting cardiometabolic multimorbidity? Lipids Health Dis. 2025;25:33.

38. Rahmig J, Chanpura A, Schultz A, Barone FC, Gustafson D, Baird AE. Blood-based protein biomarkers during the acute ischemic stroke treatment window: a systematic review. Front Neurol. 2024;15:1411307.

39. Ding L, Liu Y, Meng X, Jiang Y, Lin J, Cheng S, et al. Biomarker and genomic analyses reveal molecular signatures of non-cardioembolic ischemic stroke. Signal Transduct Target Ther. 2023;8:222.

40. Li C, Zhang Z, Luo X, et al. The triglyceride-glucose index and its obesity-related derivatives as predictors of all-cause and cardiovascular mortality in hypertensive patients: insights from NHANES data with machine learning analysis. Cardiovasc Diabetol. 2025;24:47.

41. Zhang X-R, Zhong W-F, Liu R-Y, Huang J-L, Fu J-X, Gao J, et al. Improved prediction and risk stratification of major adverse cardiovascular events using an

622 explainable machine learning approach combining plasma biomarkers and traditional risk
623 factors. Cardiovasc Diabetol. 2025;24:153.

624 42. Collins GS, Moons KGM, Dhiman P, et al. TRIPOD+AI statement: updated guidance
625 for reporting clinical prediction models that use regression or machine learning methods.
626 BMJ. 2024;385:e078378.

627 43. Feng J, Cao S, Fan X, Li J, Geng Y, Shang S, Zhou J, Yuan Z. Atherogenic index of
628 plasma and stroke risk across blood pressure strata in Chinese adults. Sci Rep. 2026.
629 doi:10.1038/s41598-026-61906-8. Epub ahead of print.

630 44. Sun J, Meng X, Guo L, Nian C, Li H, Huang W. Association between modified
631 triglyceride glucose indices and stroke risk in middle-aged and older Chinese adults: a
632 prospective cohort study. Cardiovasc Diabetol. 2025;24:274.

633 45. Dang K, Wang X, Hu J, Zhang Y, Cheng L, Qi X, et al. The association between
634 triglyceride-glucose index and its combination with obesity indicators and cardiovascular
635 disease: NHANES 2003–2018. Cardiovasc Diabetol. 2024;23:8.

636 46. Yue Y, Li P, Sun Z, Murayama R, Li Z, Hashimoto K, et al. Association of novel
637 triglyceride-glucose-related indices with incident stroke in early-stage cardiovascular-
638 kidney-metabolic syndrome. Cardiovasc Diabetol. 2025;24:301.

639 47. Liu X, He G, Lo K, Huang Y, Feng Y. The triglyceride-glucose index, an insulin
640 resistance marker, was non-linear associated with all-cause and cardiovascular mortality
641 in the general population. Front Cardiovasc Med. 2021;7:628109.

642 48. Engstad T, Bønaa KH, Viitanen M. Validity of self-reported stroke: the Tromsø
643 Study. Stroke. 2000;31:1602–7.

644 49. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression
645 dilution bias. BMJ. 2010;340:c2289.

646 50. Zhao YC, Wu SQ, Li JK, et al. Predictive value of the combined triglyceride-glucose
647 and frailty index for cardiovascular disease and stroke in two prospective cohorts.
648 Cardiovasc Diabetol. 2025;24:318.

649 ## Figure legends

650 Figure 1. Flow chart of participant selection from the China Health and Retirement
651 Longitudinal Study (CHARLS), 2011–2020.

652 Figure 2. (A) Distribution of the baseline TyHGB index by blood-pressure status among
653 the 7,830 participants; dashed lines mark the quartile cut-offs (6.6196, 7.2818, and
654 8.3098). (B) Unadjusted descriptive cumulative hazard (Nelson–Aalen) of incident
655 cardiometabolic multimorbidity across the six groups defined by TyHGB (below/above
656 the median) and blood-pressure stratum, with numbers at risk (log-rank χ^2=376.1, df=5,
657 P<0.001).

658 Figure 3. Joint association of TyHGB (below/above the median) and blood-pressure
659 status with incident cardiometabolic multimorbidity: incidence and fully adjusted (Model
660 3) hazard ratios across the six joint exposure groups, with low TyHGB plus normal blood
661 pressure as the reference.

Figure 4. Restricted cubic spline curves for the association between the baseline TyHGB index and incident cardiometabolic multimorbidity (Model 3): (A) overall population; (B) normal blood pressure; (C) high-normal blood pressure; (D) hypertension. Shaded bands indicate 95% confidence intervals.

Figure 5. Subgroup analyses of the association between TyHGB (per 1-unit increase, Model 3) and incident cardiometabolic multimorbidity across the three blood-pressure strata, by age, gender, education, residence, current smoking, and current drinking. P int., P for interaction (degrees-of-freedom-1 Wald tests).

Tables

Table 1. Baseline characteristics of the study population by TyHGB quartiles.

Variable	Total (n=7830)	Q1 (<6.62) (n=1958)	Q2 (6.62–7.28) (n=1957)	Q3 (7.28–8.31) (n=1957)	Q4 (≥8.31) (n=1958)	P value
Age, years	59.33±9.26	60.19±9.81	59.17±9.25	59.17±9.15	58.78±8.74	<0.001
Gender						<0.001
Female	4195(53.58)	922(47.09)	1044(53.35)	1118(57.13)	1111(56.74)	
Male	3635(46.42)	1036(52.91)	913(46.65)	839(42.87)	847(43.26)	
Marital status						0.016
Married	6552(83.68)	1607(82.07)	1619(82.73)	1653(84.47)	1673(85.44)	
Other	1278(16.32)	351(17.93)	338(17.27)	304(15.53)	285(14.56)	
Education level						<0.001
Illiteracy	3949(50.43)	1063(54.29)	1012(51.71)	943(48.19)	931(47.55)	
Middle school below	1684(21.51)	428(21.86)	409(20.90)	432(22.07)	415(21.20)	
Middle	2197(28.06)	467(23.85)	536(27.39)	582(29.74)	612(31.26)	

school and above						
Residence						<0.001
Rural	6530(83.44)	1733(88.51)	1691(86.50)	1581(80.83)	1525(77.93)	
Urban	1296(16.56)	225(11.49)	264(13.50)	375(19.17)	432(22.07)	
Smoking status						<0.001
Never	4789(61.17)	1072(54.78)	1191(60.86)	1259(64.33)	1267(64.71)	
Former	685(8.75)	155(7.92)	158(8.07)	174(8.89)	198(10.11)	
Current	2355(30.08)	730(37.30)	608(31.07)	524(26.78)	493(25.18)	
Drinking status						<0.001
Never	4573(58.43)	1083(55.31)	1126(57.57)	1177(60.20)	1187(60.65)	
Former	638(8.15)	143(7.30)	160(8.18)	172(8.80)	163(8.33)	
Current	2615(33.41)	732(37.39)	670(34.25)	606(31.00)	607(31.02)	
SBP, mmHg	128.97±21.10	124.39±20.76	126.96±20.28	131.21±21.50	133.37±20.66	<0.001
DBP, mmHg	75.15±12.06	72.20±11.85	74.01±11.71	76.51±12.03	77.90±11.83	<0.001
WC, cm	85.12±10.03	77.90±7.26	82.99±8.10	88.18±8.96	91.40±9.94	<0.001
BMI, kg/m²	23.42±3.65	20.58±2.34	22.62±2.69	24.60±3.19	25.86±3.81	<0.001
FBG, mg/dL	107.88±30.01	91.75±9.23	100.59±8.69	106.05±11.48	133.14±48.54	<0.001
HbA1c, %	5.26±0.76	5.07±0.42	5.11±0.43	5.18±0.44	5.67±1.23	<0.001
TG, mg/dL	126.84±87.44	73.55±24.95	93.10±30.47	121.98±39.78	218.71±122.49	<0.001
TC, mg/dL	194.34±37.85	186.04±34.75	191.46±36.10	197.24±37.77	202.61±40.52	<0.001
HDL-C, mg/dL	51.67±15.16	62.60±14.81	55.35±12.89	48.62±11.47	40.11±11.21	<0.001
LDL-C, mg/dL	118.01±34.50	110.89±30.23	119.49±31.94	125.68±34.27	115.98±39.23	<0.001
CRP, mg/L	2.61±7.13	2.38±6.89	2.36±7.56	2.53±5.86	3.15±8.02	0.001
Scr, mg/dL	0.78±0.19	0.77±0.17	0.77±0.19	0.78±0.18	0.80±0.21	<0.001
Hypertension strata						<0.001
Normal BP	2604(33.26)	876(44.74)	752(38.43)	556(28.41)	420(21.45)	
High-normal BP	2067(26.40)	527(26.92)	540(27.59)	502(25.65)	498(25.43)	
Hypertension	3159(40.34)	555(28.35)	665(33.98)	899(45.94)	1040(53.12)	
Diabetes						<0.00

						1
No	6814(87.02)	1933(98.72)	1909(97.55)	1764(90.14)	1208(61.70)	
Yes	1016(12.98)	25(1.28)	48(2.45)	193(9.86)	750(38.30)	
CMM						<0.001
No	7027(89.74)	1890(96.53)	1817(92.85)	1722(87.99)	1598(81.61)	
Yes	803(10.26)	68(3.47)	140(7.15)	235(12.01)	360(18.39)	

Notes: Data are mean ± SD for continuous variables and n (%) for categorical variables. Between-quartile comparisons used one-way analysis of variance for continuous variables and Pearson's chi-square tests for categorical variables. BMI, body mass index; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Scr, serum creatinine; SD, standard deviation; TC, total cholesterol; TG, triglycerides; TyHGB, triglyceride–high-density lipoprotein–glucose–body index; WC, waist circumference.

Table 2. Association between baseline TyHGB and incident cardiometabolic multimorbidity, overall and by blood-pressure stratum.

TyHGB exposure	Events/N	Model 1, HR (95% CI); P	Model 2, HR (95% CI); P	Model 3, HR (95% CI); P
Overall (n=7,830)				
Continuous (per 1-unit increase)	803/7,830	1.121 (1.105–1.138); <0.001	1.115 (1.097–1.133); <0.001	1.135 (1.115–1.155); <0.001
Q1 (reference)	68/1,958	1 (Reference)	1 (Reference)	1 (Reference)
Q2 vs Q1	140/1,957	2.007 (1.501–2.682); <0.001	1.859 (1.390–2.487); <0.001	1.808 (1.351–2.419); <0.001
Q3 vs Q1	235/1,957	3.489 (2.663–4.572); <0.001	2.861 (2.175–3.762); <0.001	2.727 (2.072–3.591); <0.001
Q4 vs Q1	360/1,958	5.611 (4.328–7.274); <0.001	4.384 (3.363–5.716); <0.001	4.268 (3.271–5.570); <0.001
Normal blood pressure (n=2,604)				
Continuous (per 1-unit increase)	139/2,604	1.133 (1.091–1.176); <0.001	1.129 (1.087–1.172); <0.001	1.144 (1.098–1.192); <0.001
Q1 (reference)	25/876	1 (Reference)	1 (Reference)	1 (Reference)
Q2 vs Q1	32/752	1.459 (0.861–2.474); 0.159	1.486 (0.875–2.524); 0.141	1.462 (0.859–2.489); 0.160
Q3 vs Q1	45/556	2.829 (1.727–4.634); <0.001	2.825 (1.717–4.650); <0.001	2.804 (1.697–4.632); <0.001
Q4 vs Q1	37/420	3.179 (1.905–5.306); <0.001	3.301 (1.966–5.540); <0.001	3.375 (2.007–5.676); <0.001

High-normal blood pressure (n=2,067)				
Continuous (per 1-unit increase)	164/2,067	1.103 (1.068–1.139); <0.001	1.103 (1.068–1.140); <0.001	1.132 (1.092–1.174); <0.001
Q1 (reference)	8/527	1 (Reference)	1 (Reference)	1 (Reference)
Q2 vs Q1	31/540	3.771 (1.723–8.253); 0.001	3.880 (1.769–8.507); <0.001	3.748 (1.707–8.229); 0.001
Q3 vs Q1	56/502	7.271 (3.447–15.339); <0.001	7.825 (3.694–16.577); <0.001	7.302 (3.439–15.506); <0.001
Q4 vs Q1	69/498	9.250 (4.424–19.343); <0.001	9.893 (4.706–20.799); <0.001	9.648 (4.578–20.336); <0.001
Hypertension (n=3,159)				
Continuous (per 1-unit increase)	500/3,159	1.107 (1.084–1.130); <0.001	1.115 (1.090–1.140); <0.001	1.130 (1.103–1.158); <0.001
Q1 (reference)	35/555	1 (Reference)	1 (Reference)	1 (Reference)
Q2 vs Q1	77/665	1.700 (1.139–2.538); 0.010	1.637 (1.095–2.447); 0.016	1.603 (1.072–2.398); 0.022
Q3 vs Q1	134/899	2.280 (1.570–3.311); <0.001	2.109 (1.447–3.074); <0.001	2.016 (1.381–2.943); <0.001
Q4 vs Q1	254/1,040	3.928 (2.756–5.598); <0.001	3.663 (2.556–5.248); <0.001	3.517 (2.452–5.044); <0.001

Notes: HRs and 95% CIs are from Cox proportional hazards models pooled across 20 multiply imputed datasets. Model 1: unadjusted. Model 2: adjusted for age, gender, marital status, education, residence, smoking, drinking, and blood-pressure strata (overall analysis only). Model 3: Model 2 further adjusted for LDL-C, CRP, and Scr. Continuous estimates are per 1-unit increase in TyHGB; per-SD estimates are reported in the main text. Quartile cut-offs: 6.6196, 7.2818, and 8.3098. BP, blood pressure; CI, confidence interval; CMM, cardiometabolic multimorbidity; CRP, C-reactive protein; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; TyHGB, triglyceride–high-density lipoprotein–glucose–body index.

Table 3. Joint association of TyHGB and blood-pressure status with incident cardiometabolic multimorbidity (Model 3).

Group	N	Events	Incidence, %	HR (95% CI)	P
Low TyHGB + Normal BP (reference)	1,628	57	3.5	1 (Reference)	—
High TyHGB + Normal BP	976	82	8.4	2.37 (1.69–3.33)	<0.001
Low TyHGB + High-normal BP	1,067	39	3.66	1.08 (0.71–1.62)	0.728
High TyHGB	1,000	125	12.5	3.52 (2.57–	<0.001

+ High-normal BP				4.82)	
Low TyHGB + Hypertension	1,220	112	9.18	2.73 (1.98–3.78)	<0.001
High TyHGB + Hypertension	1,939	388	20.01	5.88 (4.43–7.79)	<0.001

Notes: TyHGB was dichotomized at the sample median (7.2818). HRs are from Model 3 (adjusted for age, gender, marital status, education, residence, smoking, drinking, LDL-C, CRP, and Scr), pooled across 20 multiply imputed datasets. BP, blood pressure; CI, confidence interval; CMM, cardiometabolic multimorbidity; HR, hazard ratio; TyHGB, triglyceride–high-density lipoprotein–glucose–body index.

Table 4. Additive interaction between elevated TyHGB and hypertension on incident cardiometabolic multimorbidity.

Adjustment level	Measure	Estimate (95% CI)	P
Unadjusted			
	RERI	1.646 (0.701 to 2.592)	<0.001
	AP	0.252 (0.121 to 0.383)	—
	SI	1.424 (1.111 to 1.737)	—
Age–sex adjusted			
	RERI	1.481 (0.588 to 2.374)	0.001
	AP	0.241 (0.108 to 0.374)	—
	SI	1.405 (1.092 to 1.718)	—
Core model			
	RERI	1.327 (0.450 to 2.205)	0.003
	AP	0.224 (0.087 to 0.361)	—
	SI	1.369 (1.060 to 1.678)	—
Fully adjusted			
	RERI	1.175 (0.318 to 2.032)	0.007
	AP	0.206 (0.065 to 0.347)	—
	SI	1.334 (1.030 to 1.638)	—

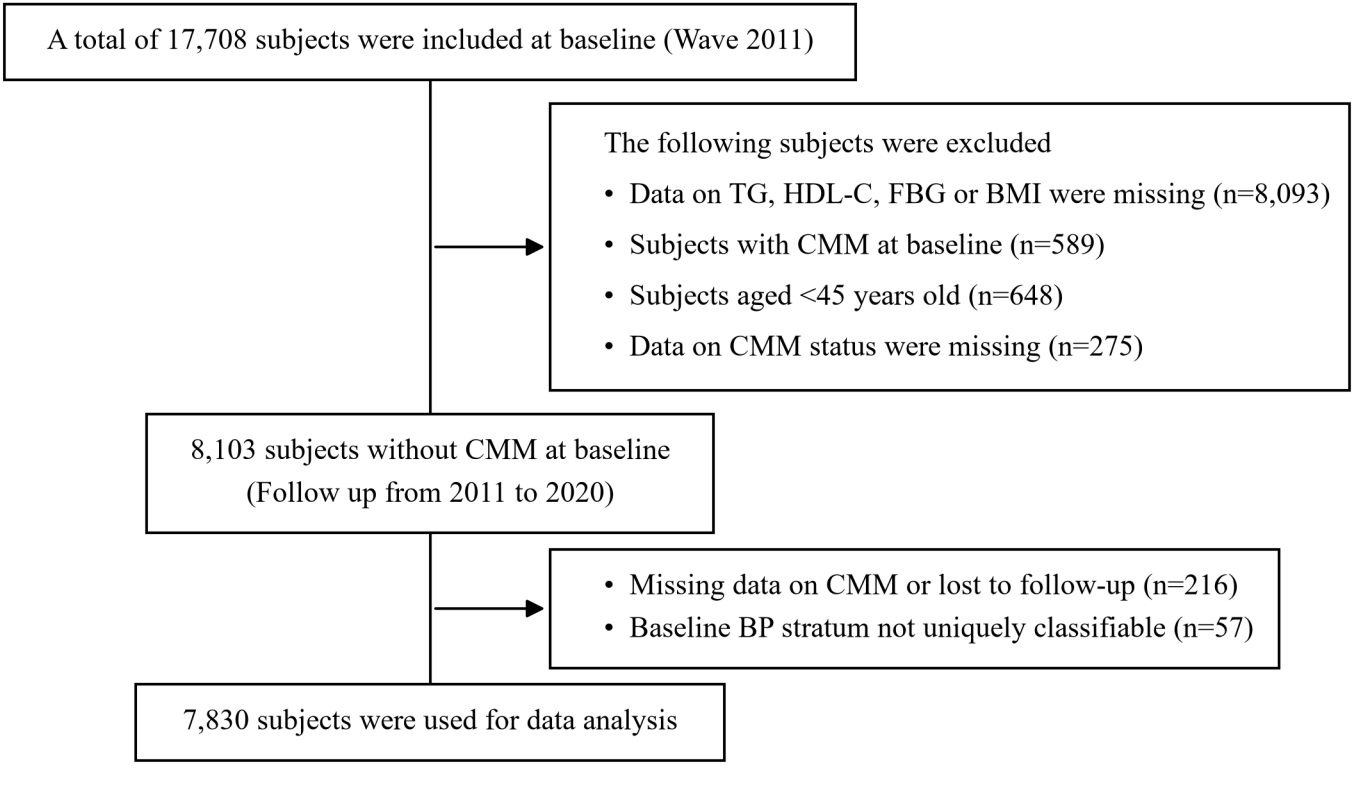
Notes: Additive interaction between elevated TyHGB (above vs below the sample median, 7.2818) and hypertension was quantified using the delta method (n=7,830; 803 events). Adjustment levels follow the incremental covariate sets of Models 1–3: unadjusted; age–sex adjusted; core model (age, gender, marital status, education, residence, smoking, drinking, and BP strata); fully adjusted (core model plus LDL-C, CRP, and Scr). P values are available for RERI only. AP, attributable proportion due to interaction; BP, blood pressure; CI, confidence interval; CMM, cardiometabolic

multimorbidity; RERI, relative excess risk due to interaction; SI, synergy index; TyHGB, triglyceride–high-density lipoprotein–glucose–body index.

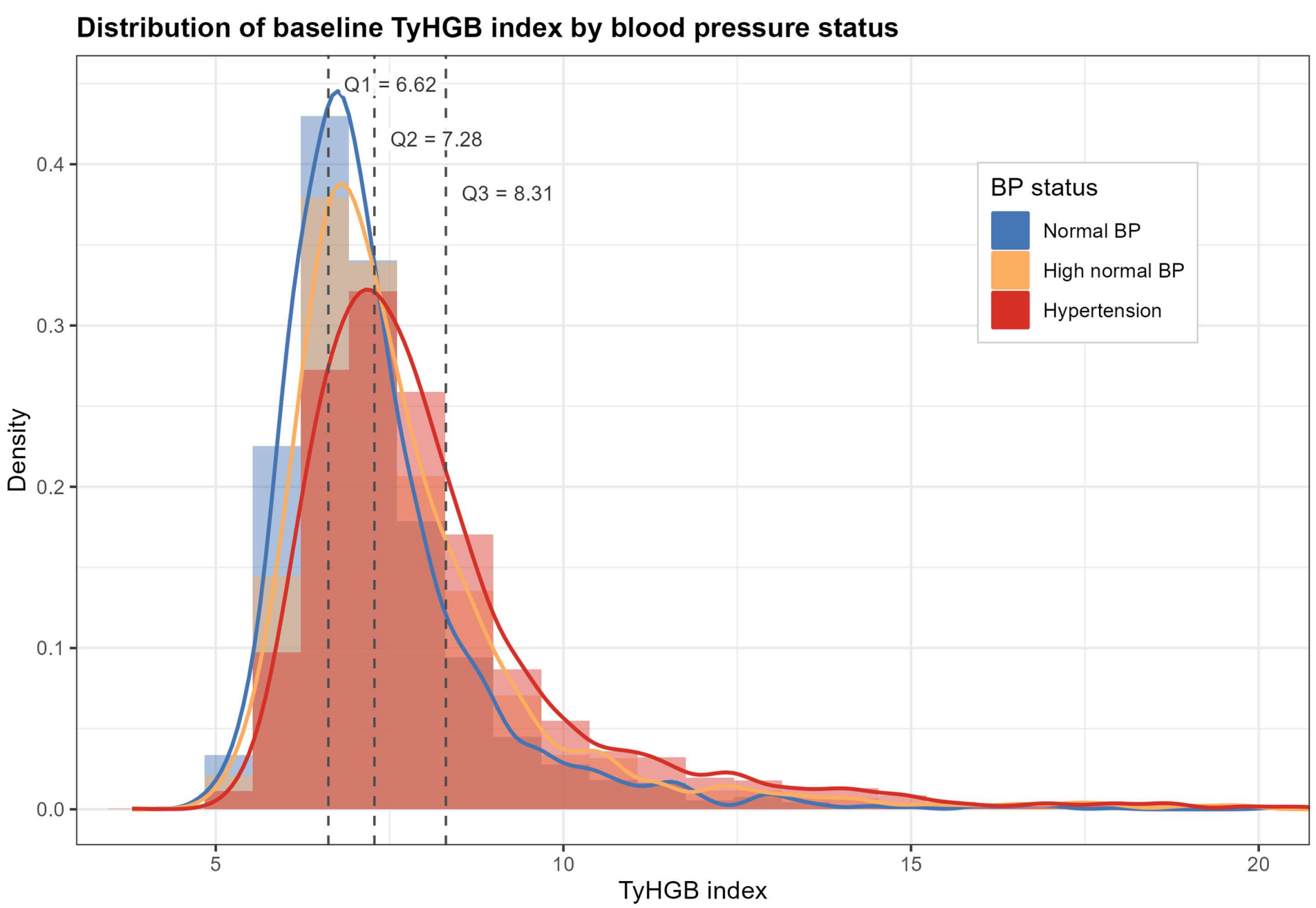
Table 5. Incremental predictive value of TyHGB for 9-year cardiometabolic multimorbidity within blood-pressure strata.

BP stratum	Model	N	9-year events	AUC (95% CI)	ΔAUC (95% CI); P	NRI (95% CI); P	IDI (95% CI); P
Normal blood pressure	Basic model	2,604	125	0.640 (0.589 to 0.692)	—	—	—
	+ TyHGB			0.662 (0.614 to 0.710)	0.022 (0.000 to 0.043); 0.046	0.159 (−0.092 to 0.409); 0.215	0.008 (−0.002 to 0.017); 0.107
High-normal blood pressure	Basic model	2,067	149	0.674 (0.630 to 0.717)	—	—	—
	+ TyHGB			0.698 (0.657 to 0.740)	0.025 (0.005 to 0.044); 0.012	0.402 (0.197 to 0.608); <0.001	0.006 (−0.005 to 0.017); 0.311
Hypertension	Basic model	3,159	471	0.643 (0.614 to 0.673)	—	—	—
	+ TyHGB			0.655 (0.627 to 0.684)	0.012 (0.002 to 0.022); 0.022	0.230 (0.118 to 0.343); <0.001	0.008 (0.000 to 0.015); 0.049

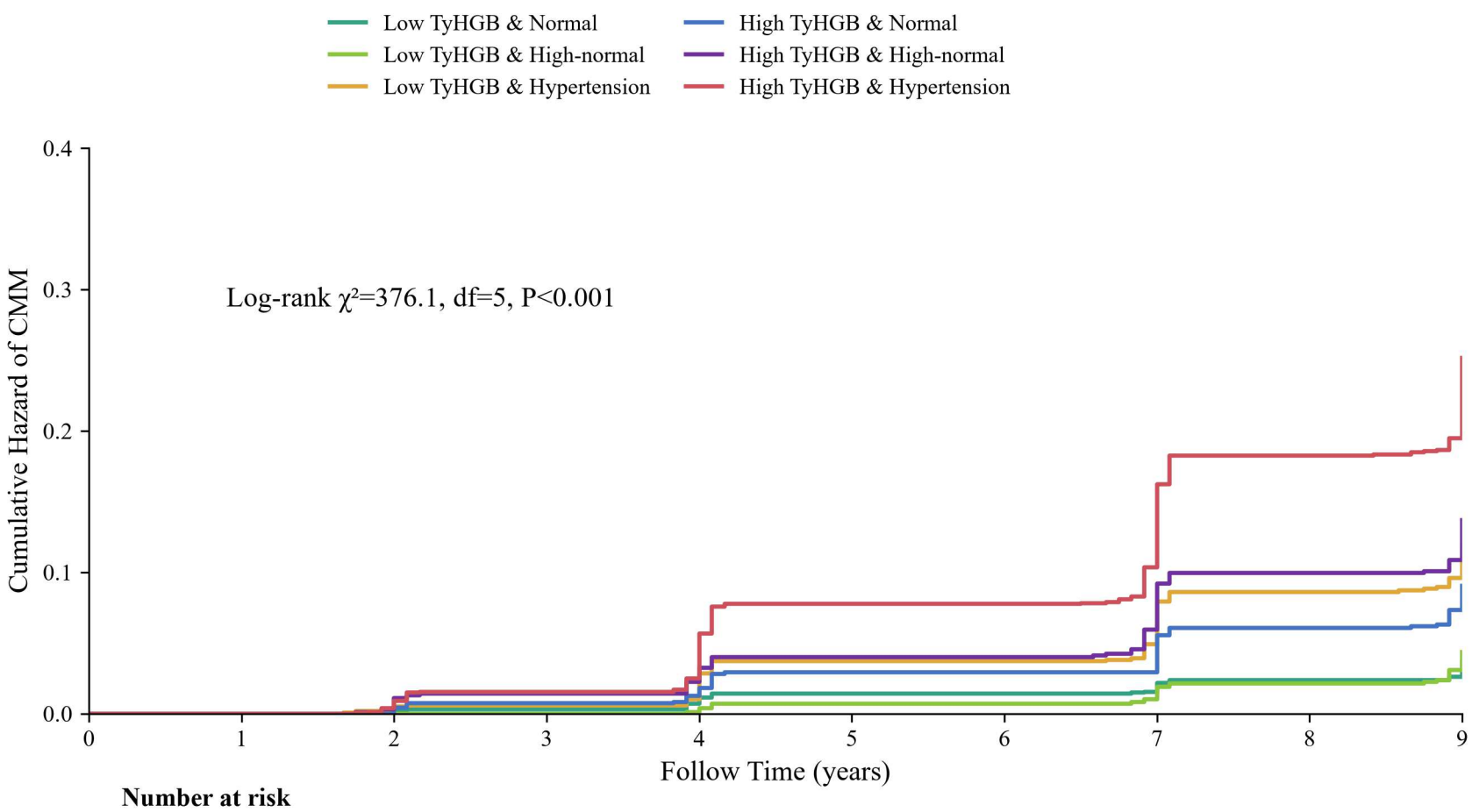
Notes: The basic model comprises the Model 3 covariate set without TyHGB (age, gender, marital status, education, residence, smoking, drinking, LDL-C, CRP, and Scr); + TyHGB adds the continuous TyHGB index. Discrimination was assessed by 9-year time-dependent AUC with inverse probability of censoring weighting; ΔAUC, NRI, and IDI compare the + TyHGB model against the basic model within each stratum. Estimates were obtained by participant-level paired bootstrap resampling (B=8,000) within each of the 20 imputed datasets and pooled with Rubin's rules. All metrics are apparent (in-sample) performance without external validation. AUC, area under the receiver operating characteristic curve; BP, blood pressure; CI, confidence interval; CMM, cardiometabolic multimorbidity; IDI, integrated discrimination improvement; NRI, net reclassification improvement; TyHGB, triglyceride–high-density lipoprotein–glucose–body index.


A total of 17,708 subjects were included at baseline (Wave 2011)
The following subjects were excluded
• Data on TG, HDL-C, FBG or BMI were missing (n=8,093)
• Subjects with CMM at baseline (n=589)
• Subjects aged <45 years old (n=648)
• Data on CMM status were missing (n=275)
8,103 subjects without CMM at baseline
(Follow up from 2011 to 2020)
• Missing data on CMM or lost to follow-up (n=216)
• Baseline BP stratum not uniquely classifiable (n=57)
7,830 subjects were used for data analysis

A

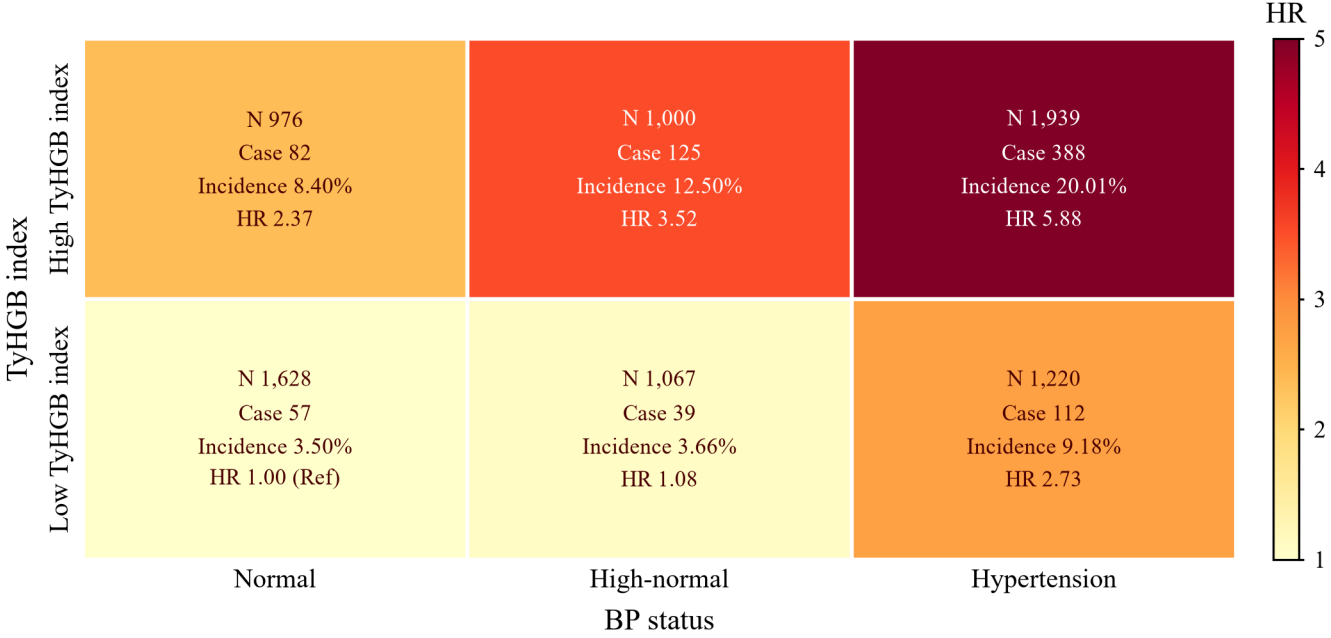


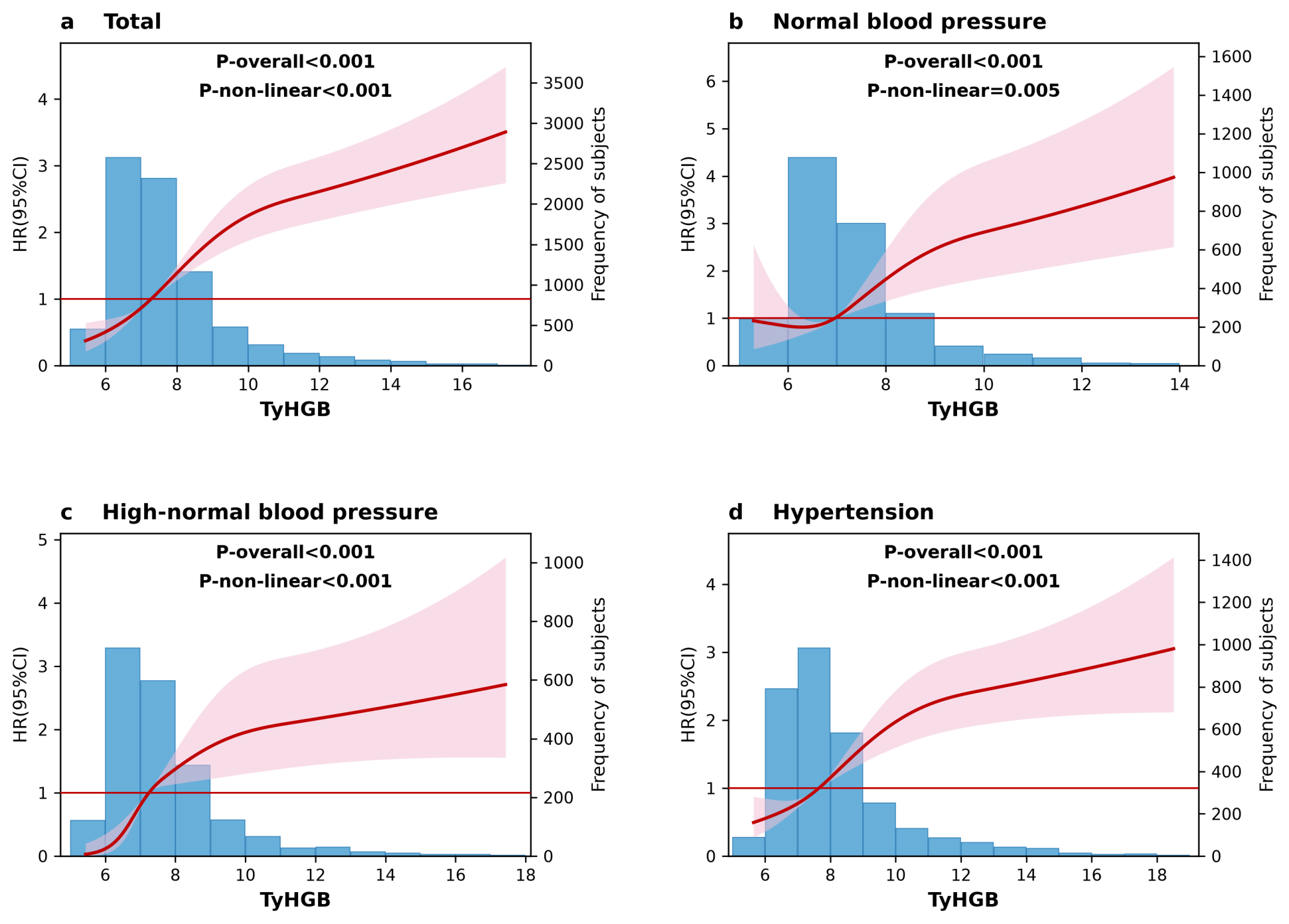
B



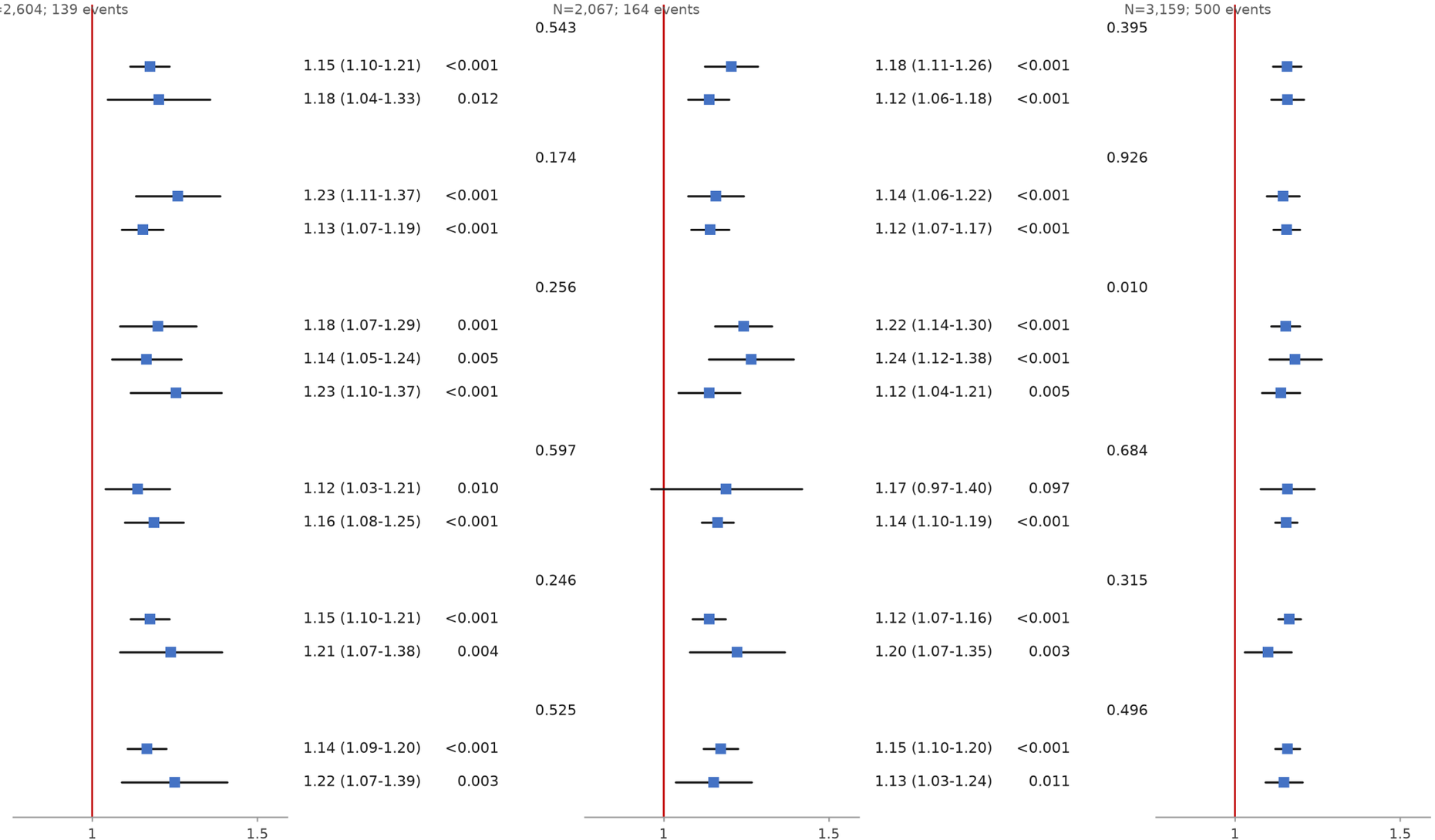
Number at risk

Low TyHGB & Normal	1628	1628	1613	1576	1546	1482	1482	1461	1389	1067
Low TyHGB & High-normal	1067	1067	1057	1022	996	946	946	926	877	639
Low TyHGB & Hypertension	1220	1220	1203	1142	1103	999	999	960	877	633
High TyHGB & Normal	976	976	969	937	923	875	875	870	807	641
High TyHGB & High-normal	1000	1000	994	957	932	887	887	860	780	607
High TyHGB & Hypertension	1939	1939	1902	1811	1754	1571	1571	1494	1291	985


TyHGB index
High TyHGB index
Low TyHGB index
N 976
Case 82
Incidence 8.40%
HR 2.37
N 1,000
Case 125
Incidence 12.50%
HR 3.52
N 1,939
Case 388
Incidence 20.01%
HR 5.88
N 1,628
Case 57
Incidence 3.50%
HR 1.00 (Ref)
N 1,067
Case 39
Incidence 3.66%
HR 1.08
N 1,220
Case 112
Incidence 9.18%
HR 2.73
Normal
High-normal
Hypertension
BP status
HR
5
4
3
2
1


a Total
P-overall<0.001
P-non-linear<0.001
HR(95%CI)
Frequency of subjects
TyHGB
b Normal blood pressure
P-overall<0.001
P-non-linear=0.005
HR(95%CI)
Frequency of subjects
TyHGB
c High-normal blood pressure
P-overall<0.001
P-non-linear<0.001
HR(95%CI)
Frequency of subjects
TyHGB
d Hypertension
P-overall<0.001
P-non-linear<0.001
HR(95%CI)
Frequency of subjects
TyHGB

Subgroup	Normal	HR (95%CI)	P value	P int.	High-normal	HR (95%CI)	P value	P int.	Hypertension	HR (95%CI)	P value	P int.
	N=2,604; 139 events				N=2,067; 164 events				N=3,159; 500 events			
Age (Years)				0.543				0.395				0.707
<60		1.15 (1.10-1.21)	<0.001			1.18 (1.11-1.26)	<0.001			1.14 (1.10-1.18)	<0.001	
>=60		1.18 (1.04-1.33)	0.012			1.12 (1.06-1.18)	<0.001			1.14 (1.09-1.18)	<0.001	
Gender (%)				0.174				0.926				0.549
Male		1.23 (1.11-1.37)	<0.001			1.14 (1.06-1.22)	<0.001			1.12 (1.08-1.17)	<0.001	
Female		1.13 (1.07-1.19)	<0.001			1.12 (1.07-1.17)	<0.001			1.14 (1.10-1.17)	<0.001	
Education (%)				0.256				0.010				0.585
Illiteracy		1.18 (1.07-1.29)	0.001			1.22 (1.14-1.30)	<0.001			1.13 (1.09-1.17)	<0.001	
Middle school below		1.14 (1.05-1.24)	0.005			1.24 (1.12-1.38)	<0.001			1.16 (1.09-1.24)	<0.001	
Middle school and above		1.23 (1.10-1.37)	<0.001			1.12 (1.04-1.21)	0.005			1.12 (1.07-1.17)	<0.001	
Residence (%)				0.597				0.684				0.813
Urban		1.12 (1.03-1.21)	0.010			1.17 (0.97-1.40)	0.097			1.14 (1.06-1.22)	<0.001	
Rural		1.16 (1.08-1.25)	<0.001			1.14 (1.10-1.19)	<0.001			1.13 (1.10-1.17)	<0.001	
Current smoker				0.246				0.315				0.145
No		1.15 (1.10-1.21)	<0.001			1.12 (1.07-1.16)	<0.001			1.14 (1.11-1.18)	<0.001	
Yes		1.21 (1.07-1.38)	0.004			1.20 (1.07-1.35)	0.003			1.08 (1.02-1.15)	0.006	
Current drinker				0.525				0.496				0.490
No		1.14 (1.09-1.20)	<0.001			1.15 (1.10-1.20)	<0.001			1.14 (1.10-1.17)	<0.001	
Yes		1.22 (1.07-1.39)	0.003			1.13 (1.03-1.24)	0.011			1.13 (1.08-1.18)	<0.001	



HR of incident CMM per 1-unit increase in TyHGB (Model 3, MICE + Rubin pooling); P int. = P for interaction (D1 Wald)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS4.tif
- FigureS3.tif
- FigureS1.tif
- FigureS2.tif
- Additionalfile1SupplementaryMaterial.docx