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1 Association of triglyceride glucose-body mass index and hemoglobin glycation index with heart
2 failure prevalence in hypertensive populations: a study across different glucose metabolism status

3 Abstract

4 **Background:** The Triglyceride glucose-body mass index (TyG-BMI) and hemoglobin glycation index
5 (HGI) are well-established surrogate markers for insulin resistance. Nevertheless, the extent to which
6 these markers offer additive predictive value for heart failure (HF) prevalence in hypertensive
7 populations, and their predictive utility across various diabetic statuses, remains to be clarified.

9

8 Consequently, this study aimed to explore the independent and synergistic effects of TyG-BMI and
9 HGI on HF risk among individuals with different diabetic statuses.

10 **Methods:** Data from the study population (n = 9,847) were obtained from the National Health and
11 Nutrition Examination Survey (NHANES). Multivariable logistic regression models were employed to
12 estimate odds ratios (ORs) and 95% confidence intervals (CIs) to assess the combined associations
13 between TyG-BMI and HGI and the prevalence of HF across various diabetic statuses.

14 **Results:** In the total population, compared to the reference group (low TyG-BMI and low HGI), the OR
15 (95% CI) for HF prevalence was 1.30 (1.04, 1.64) for the combination of low TyG-BMI and high HGI,
16 2.40 (1.76, 3.29) for high TyG-BMI and low HGI, and 3.47 (2.41, 4.99) for high TyG-BMI and high
17 HGI. Interestingly, among normoglycemic individuals, higher TyG-BMI and HGI did not significantly
18 increase the prevalence of HF. Conversely, in the prediabetic population, the OR (95%CI) for HF
19 prevalence was 2.42 (1.69, 3.48) for the combination of high TyG-BMI and low HGI, and 4.30 (2.45,
20 7.54) for high TyG-BMI and high HGI. Similarly, in the diabetic population, the OR (95%CI) for HF
21 prevalence was 2.22 (1.43, 3.45) for low TyG-BMI and high HGI, 4.04 (2.43, 6.73) for high TyG-BMI
22 and low HGI, and 4.13 (2.25, 7.59) for high TyG-BMI and high HGI, compared to low TyG-BMI and

23 low HGI.

24 **Conclusion:** This study reveals that elevated TyG-BMI and HGI levels exert a synergistic impact on
25 the prevalence of HF in hypertensive adults, especially in those with prediabetes and diabetes.
26 Additionally, the presence of prediabetes and diabetes may amplify the detrimental combined effect of
27 TyG-BMI and HGI on HF prevalence.

28 **Keywords:** Heart failure, Triglyceride glucose-body mass index, Hemoglobin glycation index,
29 Diabetic status, Hypertension

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45 **Background**

46 Heart failure (HF) is a prevalent and serious cardiovascular condition associated with significant
47 morbidity and mortality worldwide[1]. Early identification of individuals at an high risk for HF is
48 crucial for timely interventions and the development of effective preventive strategies[2]. Hypertensive
49 adults with prediabetes and diabetes form a vulnerable population that experiences an increased risk of
50 HF due to the complex interplay of various shared mechanisms, such as insulin resistance (IR), cardiac
51 remodeling and fibrosis, inflammation, oxidative stress, vascular complications, and other common risk
52 factors[3-5].

53 Recently, there has been a growing interest in novel indices that integrate multiple metabolic
54 parameters to comprehensively assess cardiometabolic risk and predict adverse cardiovascular
55 outcomes. Notably, the triglyceride glucose-body mass index (TyG-BMI) and the hemoglobin glycation
56 index (HGI) stand out in this context[6, 7]. The TyG-BMI, a composite marker, is formulated through
57 the integration of measurements of insulin resistance (TyG) and BMI as a measure of adiposity[6, 8].
58 Research has demonstrated that elevated levels of TyG-BMI have been associated with an increased
59 risk of various cardiometabolic abnormalities, including IR, diabetes, dyslipidemia, obesity, and
60 cardiovascular disease (CVD)[9-11]. Concurrently, the HGI offers insights into the extent of
61 glycosylated hemoglobin (HbA1c) exceeding the levels anticipated based on glucose levels[12]. It has
62 been proposed as an indicator of glycemic variability and has shown associations with the risk of IR,
63 complications related to diabetes, and CVD[13-15].

64 Previous research has examined these indices in isolation, frequently neglecting their collective
65 influence, especially in hypertensive adults with prediabetes and diabetes. This oversight is significant,
66 as these populations are particularly vulnerable to HF due to interconnected metabolic, inflammatory,

67 and cardiovascular processes[16]. The study addresses this by assessing how the interplay between IR
68 (TyG-BMI) and glycemic control variability (HGI) contributes to HF risk, thus providing a more
69 comprehensive risk assessment tool for these high-risk groups[17, 18]. This approach not only fills a
70 critical gap in understanding the multifactorial nature of HF but also aids in the development of
71 targeted preventive and management strategies for HF in hypertensive individuals with varying diabetic
72 statuses. Moreover, the onset and progression of HF are influenced by various factors, including IR,
73 lipid metabolism, and adiposity, which are recognized as primary pathophysiological mechanisms[19,
74 20]. Therefore, investigating the combined effect of TyG-BMI and HGI on HF can provide valuable
75 insights into their synergistic effects on the development of HF and assist in identifying individuals at
76 the highest risk.

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77 The objective of this study is to examine the combined effect of TyG-BMI and HGI on the
78 prevalence of HF in hypertensive adults with prediabetes and diabetes. By assessing these biomarkers,
79 the goal is to enhance risk stratification and facilitate the development of personalized preventive and
80 management strategies for HF in this vulnerable population.

7 81 **Methods**

82 **Study population**

83 This study utilized data obtained from the National Health and Nutrition Examination Survey
84 (NHANES), a comprehensive program conducted by the Centers for Disease Control and Prevention
85 (CDC) and the National Centers for Health Statistics (NCHS) in the United States. NHANES is
1
86 designed to assess the health and nutritional status of the U.S. population, following the STROBE
87 guidelines for reporting observational studies. The NHANES study protocol was sanctioned by the
88 NCHS Research Ethics Review Board, and all participants provided written informed consent. Our

study extracted data¹² from the NHANES website (<https://www.cdc.gov/nchs/nhanes/index.htm>), which encompassed ten survey cycles conducted between 1999 and 2018. After excluding individuals with incomplete data, the final study population comprised 9,847¹⁴ adults aged 20 years or older who had been diagnosed with hypertension and had participated in NHANES across various survey cycles: 1999-2000 (n = 867), 2001-2002 (n = 943), 2003-2004 (n = 897), 2005-2006 (n = 816), 2007-2008 (n = 1077), 2009-2010 (n = 1102), 2011-2012 (n = 1006), 2013-2014 (n = 1085), 2015-2016 (n = 972), and 2017-2018 (n = 1082). The analysis focused on NHANES participants with hypertension,¹³ defined as having a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, taking antihypertensive medications, or having a self-reported history of hypertension[21].

Fig. 1 presents a flowchart illustrating the selection process of the study population.

Data collection and definitions

This study utilized a comprehensive set of covariates encompassing demographic information, medical history, and laboratory tests to comprehensively explore the research question. Demographic data, collected via self-report NHANES questionnaires, such as age, sex, racial/ethnic background, educational attainment, smoking status, and alcohol consumption. The calculation of BMI involved utilizing participants' weight and height measurements. Information reported by the participants was utilized to identify individuals with physician-diagnosed coronary heart disease (CHD), HF, as well as the use of hypoglycemic drugs, lipid-lowering drugs, and antihypertensive drugs.²⁷ Fasting venous blood samples were collected on-site during the survey⁴ and then sent to the Lipoprotein Analytical Laboratory at Johns Hopkins University School of Medicine. Lipid parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) concentrations, were measured using the Hitachi 704 Analyzer.

111 Fasting blood glucose (FBG) concentration was determined using a complete blood count (CBC)
 112 identification procedure. HbA1c levels, which provide a measure of long-term blood glucose control,
 113 were measured using high-performance liquid chromatography (HPLC) in a centralized laboratory.
 114 Hemoglobin concentrations were determined by analyzing whole blood with the Beckman Coulter
 115 MAXM instrument using a five-part differential complete blood count method. Albumin concentration
 116 was evaluated using specific antibodies that interact with albumin through an immunoturbidimetric
 117 assay. ¹⁷ The estimated glomerular filtration rate (eGFR) was determined by applying the simplified
 118 Modification of Diet in Renal Disease (MDRD) formula, which yields an estimate of kidney
 119 function[22].

³ The participants were classified into three groups based on their diabetic status using the criteria
 120 provided by the American Diabetes Association (ADA): normoglycemia, which included individuals
 121 with both FBG levels below ²³ 5.6 mmol/L and HbA1c levels below 5.7%, and no prescription of
 122 hypoglycemic drugs; prediabetes, which was defined by FBG levels ² ranging from 5.6 to 6.9 mmol/L or
 123 HbA1c levels between 5.7 and 6.4%, or both, and no prescription of hypoglycemic drugs. Diabetes was
 124 defined as ¹⁶ FBG levels equal to or greater than 7.0 mmol/L or HbA1c ¹⁶ levels equal to or greater than
 125 6.5%, or both. Additionally, individuals with a prescription of hypoglycemic drugs were classified as
 126 diabetic, irrespective of their FBG or HbA1c values[23].

² The TyG-BMI index was calculated using the formula: $\ln [TG (mg/dL) \times FBG (mg/dL)/2] \times BMI$ [6].
 128 The HGI value was determined by subtracting the predicted HbA1c value from the observed HbA1c
 129 value[7]. The predicted HbA1c in this study was calculated using a correlation regression equation
 130 based on the FBG and HbA1c values measured at baseline: Predicted HbA1c level = $3.212 + 0.431 \times$
 131 FBG (mmol/L) ($r = 0.826$; $P < 0.001$), as illustrated in **Fig. 2**. ²

133 **Ascertainment of outcome**

134 The occurrence of HF events in NHANES was determined using a combination of self-reported data
135 and clinical assessments. NHANES incorporates a comprehensive questionnaire component that
136 inquires about participants' medical history, including prior HF diagnoses. Participants are explicitly
137 queried regarding whether a healthcare professional has ever diagnosed them with HF. Upon
138 confirmation of the initial HF diagnosis, NHANES performs comprehensive medical examinations
139 encompassing various assessments associated with cardiovascular health. Additionally, NHANES may
140 obtain participants' medical records with their consent. This integrative approach, combining self-
141 reported data, clinical assessments, and the review of medical records, aims to enhance the accuracy
142 and validity of HF determination in NHANES.

143 **Statistical analysis**

144 This study adhered to the statistical analysis guidelines provided by the CDC, which ¹²can be accessed at
145 <https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx>. Given the ¹complex multistage stratified
146 ¹probability survey design employed in NHANES, our statistical analysis incorporated sample weights,
147 ¹clustering, and stratification to account for these factors. The baseline characteristics of the study
148 ¹population were presented according to their diabetes status (normoglycemia, prediabetes, diabetes)
149 and HF status (with HF, without HF). Survey-weighted means or medians were employed to report
150 continuous variables, whereas survey-weighted percentages were utilized for categorical variables.
151 ²⁰Receiver operating characteristic (ROC) analysis was utilized to identify the optimal thresholds of
152 ²⁰TyG-BMI and HGI for detecting HF prevalence in the total population and across different diabetes
153 statuses. Multivariable logistic regression models were used to estimate odds ratios (ORs) and their
154 ⁶corresponding 95% confidence intervals (CIs) to assess the independent and combined associations of

155 TyG-BMI and HGI with HF prevalence, both for the total population and within specific diabetic
156 subgroups. The selection of adjustment confounders was based on clinical relevance, candidate
157 variables with a ¹ *P*-value of <0.05 in univariate analysis, and the availability of events[24]. The
158 statistical ¹ analyses were performed using R version 4.0.2 and SPSS (IBM) version 23. ⁸ Statistical
159 significance was determined based on a two-tailed *P*-value below 0.05.

160 **Results**

161 **Baseline characteristics**

162 A total of 9,847 adults with hypertension ⁵ were included in this study, with a mean age of 58 years.
163 Among the participants, 51.4% were male, 32.3% had normoglycemia, 51.7% had prediabetes, 16%
164 had diabetes, and 5.4% had HF. ²⁴ The baseline characteristics of the study population are presented in
165 **Tables 1** and **Tables 2**, reflecting the participants' diabetes and HF statuses, respectively. **Tables 1**
166 demonstrates that patients with prediabetes and diabetes ²⁹ were older, more likely to be male, of Hispanic
167 ethnicity, less educated, and had a higher prevalence of obesity. Additionally, they exhibited elevated
168 levels of TG, FBG, TyG-BMI, HbA1c, predictive HbA1c, and HGI, as well as lower levels of HDL-C,
169 LDL-C, albumin, and eGFR. These patients also had higher rates of hypoglycemic drugs, lipid-
170 lowering drugs, and antihypertensive drugs, along with a higher prevalence of CHD and HF, compared
171 to those with normoglycemia (*P* <0.001). Furthermore, the hypertensive population with HF was
172 characterized by older age, lower educational attainment, higher TG, FBG, TyG, TyG-BMI, HbA1c,
173 predictive HbA1c, and HGI levels, as well as lower TC, ⁵ HDL-C, LDL-C, hemoglobin, albumin, and
174 eGFR levels, and a higher prevalence of hypoglycemic drugs, lipid-lowering drugs, antihypertensive
175 drugs, CHD, and diabetes when compared to individuals without HF (*P* <0.001) (**Table 2**).

176 **Determination of the optimal thresholds for TyG-BMI and HGI to detect HF**

177 Additional file 1: Table S1 displays the optimal thresholds for TyG-BMI and HGI as determined by
178 ROC analysis. In the total population, the optimal thresholds for detecting TyG-BMI and HGI for HF
179 were 342.89 and 0.25, respectively. Among hypertensive subjects with normoglycemia, the optimal
180 thresholds for TyG-BMI and HGI were determined as 194.27 and -0.19, respectively. In the prediabetic
181 group, the optimal threshold values for TyG-BMI and HGI were 326.08 and 0.47, respectively. In the
182 diabetic group, the optimal threshold values for TyG-BMI and HGI were 342.88 and 0.41, respectively.

183 ¹⁰ Association between TyG-BMI and HGI and the prevalence of HF

184 ¹⁰ The multivariate adjusted model presented in Table 3 depicts the respective associations of TyG-BMI
185 and HGI with the prevalence of HF. In the general population, individuals with high TyG-BMI
186 exhibited an elevated prevalence of HF (OR, 2.50; 95%CI, 1.95-3.20). Similarly, an increased
187 prevalence of HF was observed with high HGI (OR, 1.33; 95%CI, 1.08-1.63). Among individuals in
188 the normoglycemic group, elevated TyG-BMI and HGI did not significantly increase the prevalence of
189 HF when compared to those with low TyG-BMI or HGI levels. Among the prediabetic population,
190 ¹⁴ individuals with high TyG-BMI (OR, 2.60; 95%CI, 1.89-3.58) and high HGI (OR, 1.59; 95%CI, 1.15-
191 2.20) exhibited an elevated prevalence of HF. Likewise, diabetic patients with high TyG-BMI (OR,
192 2.76; 95%CI, 1.86-4.08) and high HGI (OR, 1.61; 95%CI, 1.14-2.28) displayed an increased
193 prevalence of HF.

194 Combined association of TyG-BMI and HGI with the prevalence of HF

195 ⁸ The multivariate-adjusted model presented in Table 4 illustrates the combined association of TyG-BMI
196 and HGI with the prevalence of HF. In the joint analysis, using low TyG-BMI and low HGI ²⁵ as the
197 ¹¹ reference, the OR and corresponding 95% CI for the combination of low TyG-BMI and high HGI, high
198 TyG-BMI and low HGI, and high TyG-BMI and high HGI in the total population were 1.30 (1.04,

1.64), 2.40 (1.76, 3.29), and 3.47 (2.41, 4.99), respectively. Furthermore, there was a gradual increase in the prevalence of HF across all four groups, as demonstrated in **Fig. 3A** (P for trend < 0.001). In the normoglycemic population, higher TyG-BMI and HGI, as well as their combination, did not elevate the prevalence of HF, as depicted in **Table 4** and **Fig. 3B**. However, among individuals with prediabetes, compared to the combination of low TyG-BMI and low HGI, a higher prevalence of HF was observed in the combination of high TyG-BMI and low HGI (OR, 2.42; 95% CI, 1.69-3.48) and the combination of high TyG-BMI and high HGI (OR, 4.30; 95% CI, 2.45-7.54) (**Fig. 3C**, P for trend < 0.001). Similarly, in the diabetic population, the combination of low TyG-BMI and high HGI, high TyG-BMI and low HGI, and high TyG-BMI and high HGI yielded ORs (95% CI) of 2.22 (1.43, 3.45), 4.04 (2.43, 6.73), and 4.13 (2.25, 7.59), respectively, in comparison to the combination of low TyG-BMI and low HGI. Notably, a significant trend towards an increased prevalence of HF was also observed in the combination group among the diabetic population (**Fig. 3D**, P for trend < 0.001).

7 Discussion

This study is the first to investigate the combined association of TyG-BMI and HGI with the prevalence of HF in a US representative hypertensive population, stratified based on diabetes status. The main findings are as follows: 1. Prediabetes and diabetes were characterized by unfavorable baseline factors, such as advanced age, a higher prevalence of obesity, and adverse metabolic profiles; 2. In the overall population, individuals with high TyG-BMI or high HGI had an increased prevalence of HF, with their combination demonstrating the highest prevalence; 3. Among normoglycemic populations, individuals with high TyG-BMI or high HGI did not show an increased prevalence of HF, and their combination did not result in cumulative risk effects; 4. Prediabetic and diabetic individuals with high TyG-BMI or high HGI were at a greater prevalence of HF. In the joint analysis, the combination of high TyG-BMI

221 and high HGI⁶ was significantly associated with a higher prevalence of HF compared to other
222 combinations.

223 Kiaw Er et al.[6] initially proposed the TyG-BMI and conducted a comparative analysis of TyG-BMI,
224 TyG, and lipid-related parameters in a non-diabetic population, revealing that TyG-BMI exhibited
225 superior diagnostic capabilities for IR. Subsequent studies have demonstrated² a positive correlation
226 between elevated TyG-BMI levels and an increased risk of various conditions, including prediabetes,
227 hypertension, hyperuricemia, metabolic syndrome, nonalcoholic liver disease, stroke, and
228 cardiovascular events[9, 11, 25-27]. Nevertheless, limited research has examined the impact of TyG-
229 BMI on occurrence of HF among hypertensive individuals with diabetes and prediabetes. The study
230 suggests that hypertensive individuals with elevated TyG-BMI levels may have a greater likelihood of
231 developing HF, with this association being influenced by the presence of diabetes. Moreover, this
232 connection was observed exclusively in individuals with prediabetes and diabetes. TyG-BMI
233 incorporates multiple factors into a single index, thereby offering a more comprehensive assessment of
234 metabolic health compared to relying solely on individual biomarkers. It captures the interplay among
235 lipid metabolism, glucose homeostasis, and adiposity, all of which⁹ play a crucial role in the
236 pathogenesis of HF[28, 29]. Moreover, the practicality, accessibility, and predictive value of TyG-BMI
237 further strengthen its utility in investigating the association with HF and potentially enhancing risk
238 assessment and management strategies in clinical settings.

239 HbA1c serves as the primary criterion for diagnosing diabetes and prediabetes[30]. However, the
240 HbA1c level measured by the analyzer reflects only 60% to 80% of the average blood glucose level,
241 and the remaining 20% to 40% of HbA1c variation may not be accounted for by the observed HbA1c
242 values[31-33]. To provide a comprehensive reflection of the blood glucose metabolic state, Hempe et al.

243 proposed HGI, which quantifies interindividual variations in HbA1c resulting from factors beyond
244 blood glucose concentration[34]. While previous ⁹ studies have established an association between
245 elevated HGI and an increased risk of prediabetes, diabetes, related complications, and CVD, ⁵ there is
246 limited research exploring the relationship between HGI and the risk of HF[13, 14]. Additionally, since
247 HGI serves as an indicator of blood glucose metabolism variations, its applicability may be influenced
248 by the individual's diabetes status[35]. Hence, it is imperative to evaluate the clinical significance of
249 HGI across various blood glucose states. This study is the first to examine the association between HGI
250 and HF across various diabetic states. The findings indicate that elevated HGI levels are linked to an
251 increased prevalence of HF among individuals with hypertension, although this relationship is
252 influenced by diabetes status. In particular, the positive association between HGI and the prevalence of
253 HF was observed exclusively in individuals with prediabetes and diabetes, while no such association
254 was found in those with normoglycemia. An examination of the relationship between HGI and HF
255 across different diabetic statuses enables clinicians to enhance their understanding of the cardiovascular
256 risk profile among patients with diabetes and adapt their management strategies accordingly. HGI
257 offers supplementary information beyond conventional glycemic markers and has the potential to
258 identify individuals in need of intensive monitoring and more aggressive interventions to prevent or
259 manage HF. Nevertheless, additional ²² research is necessary to validate these findings and ascertain the
260 optimal clinical utilization of HGI in the context of managing HF.

261 TyG-BMI and HGI were selected as combined variables due to several clinically relevant reasons.
262 First, TyG-BMI combines measurements of triglycerides, glucose, and BMI, all of which are
263 established prevalence factors for HF[36]. This compound variable enables a more comprehensive
264 evaluation of metabolic health and IR[37]. Moreover, HGI reflects the variability in glycemic control

265 and the glycation of hemoglobin[7]. By integrating these variables, researchers intend to encompass
266 multiple dimensions of metabolic dysfunction and assess their influence on the risk of HF. In addition,
267 the findings demonstrated an independent association between elevated TyG-BMI and HGI values and
268 an increased prevalence of HF. The simultaneous consideration of both variables allows clinicians to
269 achieve a more precise assessment of HF risk and customize management strategies accordingly.
270 Furthermore, examining the relationship between TyG-BMI, HGI, and HF across different diabetic
271 statuses facilitates the identification of high-risk subgroups. The findings indicate that individuals in a
272 prediabetic state who display anomalies in both metabolic markers may necessitate intensified
273 monitoring and early intervention to avert the onset of HF. The identification of individuals exhibiting
274 elevated combined TyG-BMI and HGI values empowers healthcare providers to introduce lifestyle
275 modifications, optimize glycemic control, and initiate preventive measures to mitigate the risk of HF.
276 Early intervention plays a vital role in enhancing outcomes and alleviating the burden of HF in
277 individuals with diabetes.

278 Notably, gender-related differences significantly influence the prognosis of patients with these
279 conditions. Studies, such as the one indicated by Calabrò P et al[38], have explored these differences,
280 highlighting how gender can affect disease manifestation, progression, and response to treatment. This
281 study, which examines the association of TyG-BMI and HGI with HF risk in hypertensive populations,
282 can benefit from acknowledging these differences. Especially, gender may modulate the risk factors
283 and predictive values of these indices, potentially influencing HF risk. Therefore, future research
284 should consider gender as a critical variable in understanding and managing cardiovascular and
285 metabolic diseases.

286 The biological mechanisms underlying the ³independent and combined associations of TyG-BMI and

287 HGI with the prevalence of HF, as well as the modifying effect of diabetes status, are complex and not
288 fully understood. However, there are several plausible explanations. First, TyG-BMI, which combines
289 measures of triglycerides, glucose, and BMI, is considered a marker of IR and metabolic
290 dysfunction[6]. IR, characterized by impaired insulin action and elevated glucose levels, leads to
291 dysregulated lipid metabolism, inflammation, endothelial dysfunction, and oxidative stress[39, 40].
292 These mechanisms contribute to the development and progression of HF[41, 42]. Elevated TyG-BMI
293 reflects these underlying metabolic abnormalities and can independently increase the prevalence of HF.
294 Second, HGI, which measures the variability in glycemic control and glycation of hemoglobin, reflects
295 long-term glycemic fluctuations and glycation patterns[7]. Chronic hyperglycemia in prediabetes and
296 diabetes can result in the formation of advanced glycation end products and increased oxidative stress,
297 promoting endothelial dysfunction, inflammation, fibrosis, and cardiac remodeling[43, 44]. These
298 pathological processes can contribute to the development and progression of HF. Higher HGI values,
299 indicating poorer glycemic control and increased glycation, have been associated with an independent
300 prevalence of HF. Third, the combined effect of TyG-BMI and HGI on HF suggests synergistic
301 interactions between IR, metabolic dysfunction, and glycemic variability. IR and hyperglycemia can
302 potentiate each other's deleterious effects, leading to a more pronounced cardiac damage[45]. This
303 synergy may result from the cumulative impact of dysregulated glucose and lipid metabolism,
304 oxidative stress, chronic inflammation, and endothelial dysfunction[46]. The combined effects of TyG-
305 BMI and HGI may amplify these underlying mechanisms, ultimately increasing the prevalence of HF.
306 Fourth, diabetes status, including prediabetes and established diabetes, can modify the relationship
307 between TyG-BMI, HGI, and HF. In individuals with prediabetes and diabetes, the presence of IR,
308 hyperglycemia, and chronic glycemic fluctuations further exacerbates the risk of HF[47]. The

309 modifying effect of diabetes status implies that the combined association of TyG-BMI and HGI may be²⁶
310 more pronounced in individuals with prediabetes or established diabetes compared to those with
311 normoglycemia. Overall, the explanations provided here are based on the current understanding of IR,
312 metabolic dysfunction, glycemic control, and cardiac pathology. Further studies are needed to unravel
313 the intricate interplay between these factors and to elucidate the underlying mechanisms in greater
314 detail.

315 ³Strengths and limitations

316 To the best of our knowledge, this study is the first to investigate the combined association of TyG-
317 BMI and HGI with the prevalence of HF, stratified by diabetes status. However, several limitations
318 should be noted. First,¹⁸ the cross-sectional design limits the ability to establish a cause-and-effect
319 relationship between TyG-BMI, HGI, and the prevalence of HF. It only allows for³⁰ the assessment of
320 associations at a single time point, without providing information on temporal relationships or the
321 possibility of reverse causality. Second, without longitudinal data, it is challenging to determine
322 whether TyG-BMI and HGI preceded the development of HF or were a consequence of it. Longitudinal
323 studies are better suited for reexamining temporal relationships. Third, despite a large sample size, the
324 generalizability of the findings may be limited to the US adults with hypertension under study. Fourth,
325 the NHANES study's limitation of only providing fasting glucose data without postprandial glucose. It
326 prevents us from fully differentiating between the prediabetes subcategories based on impaired glucose
327 tolerance (IGT). This finding primarily pertains to the impaired fasting glucose (IFG) aspect of
328 prediabetes, and caution should be exercised when generalizing the results to all prediabetic states.
329 Fifth, despite adjusting for enough confounding variables, the possibility of residual confounding and
330 known CVD effect remains. Unmeasured or inadequately measured factors could still influence the

331 observed associations. Finally, ¹ the study relied on self-reported data for recording outcomes, medical
332 history, lifestyle factors, and medication use. Self-reporting introduces potential recall bias and data
333 collection inaccuracies. However, NHANES employs rigorous quality control measures and
334 standardized protocols to ensure the reliability and accuracy of the collected data.

335 **Conclusions**

336 ³ In a nationally representative cohort of hypertensive US adults, the elevated TyG-BMI and HGI levels
337 were associated with an increased prevalence of HF. Notably, the concurrent elevation of TyG-BMI and
338 ⁶ HGI levels was associated with the highest prevalence of HF when compared to other combinations.
339 The relationships between TyG-BMI and HGI and the prevalences of HF were found to be influenced
340 by the presence of diabetes. Specifically, the adverse effects of TyG-BMI and HGI on HF prevalence
341 were observed solely in populations with prediabetes and diabetes. The clinical relevance of this study
342 lies in its demonstration that in hypertensive patients, particularly those with prediabetes and diabetes,
343 the combined assessment of TyG-BMI and HGI can serve as a significant predictive tool for HF risk,
344 thereby guiding more personalized and effective risk stratification and management strategies in
345 clinical practice.

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