High hemoglobin glycation index is associated with increased systemic arterial stiffness independent of hyperglycemia in real-world Japanese population: A cross-sectional study

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Abstract

Aims: To investigate the association of metabolic parameters including hemoglobin glycation index (HGI, observed HbA1c – predicted HbA1c) with systemic arterial stiffness assessed by cardio-ankle vascular index (CAVI).

Subjects: We analyzed the cross-sectional data from 22,696 subjects (mean age 48.0 years, mean FPG 88 mg/dL, mean HbA1c 5.5%) with or without past history of metabolic disorders including diabetes.

Results: Men had higher body mass index (BMI), CAVI, blood pressure (BP), FPG, HbA1c, total cholesterol and triglyceride; and lower age, HGI and HDL-cholesterol. After stratifying subjects into HGI quartiles, the highest quartile (Q4) group showed higher age, female ratio, and frequencies of obesity, hypertension, diabetes, and dyslipidemia. Furthermore, bivariate logistic regression model revealed that the Q4 of HGI was a significant predictor of high CAVI (≥9.0) independent of the presence of diabetes.

Conclusion: High HGI is associated with systemic arterial stiffening independent of hyperglycemia. This index is therefore expected to be not only a predictor of hypoglycemia, but also a therapeutic guide for atherosclerosis.

Keywords

Glycemic parameters, hemoglobin glycation index, arterial stiffness, cardio-ankle vascular index

Introduction

Diabetes is associated with an increased risk of cardiovascular disease (CVD) by at least two- to three-fold compared with nondiabetic subjects. On the other hand, the susceptibility to developing macrovascular complications differs between patients, even when they have similar levels of hyperglycemia evaluated by glycated hemoglobin (HbA1c). HbA1c is a measure of mean glycemia over the preceding 1 to 2 months, and is considered the gold standard for assessing the compensation and treatment of diabetes. However, only 60% to 80% of the variance in HbA1c level could be explained by the mean blood glucose (MBG) level. The remaining variance in HbA1c is presumed to be affected by interindividual variations in biological factors involved in glucose metabolism, genetic factors and passive hemoglobin glycation rates, or in red cell survival among different ethnic groups. For this reason, the hemoglobin glycation index (HGI) was established to quantify the variance. HGI is defined as the measured HbA1c levels minus predicted HbA1c calculated from a linear regression of blood glucose versus HbA1c levels. Therefore, HGI indicates the degree of nonenzymatic glycation of hemoglobin. Since patient with high HGI has higher HbA1c value compared to blood glucose level, if the patient’s diabetes treatment is intensified (further blood glucose reduction) based on HbA1c, the risk of hypoglycemia is...
increased. Furthermore, high HGI has been reported to be associated with increased risks of CVDs, obesity-related metabolic disorders and carotid atherosclerosis in nondiabetic individuals.

Arterial stiffness is a feature of vascular aging and a predictor of CVDs. Increased arterial stiffness corresponds to lower vascular distensibility, and may be a potential therapeutic target for cardiometabolic complications. Recently, the cardio-ankle vascular index (CAVI) has been developed as a blood pressure (BP)-independent parameter for arterial stiffness. CAVI has adequate reproducibility for clinical use, and is associated with diabetes and other CVD risk factors. Severe of CVD severity assessed by CAVI in diabetic patients. In other words, CAVI reflects impaired glucose tolerance-induced arterial stiffening that can be improved by appropriate therapeutic interventions. However, the relationship between HGI and arterial stiffness is unclear.

On these premises, the primary aim of this cross-sectional study was to investigate in detail the relationship of the metabolic parameters including HGI with arterial stiffness assessed by CAVI in real-world Japanese population.

Materials and methods

Design

We performed a retrospective cross-sectional study in Japanese who underwent health screening between April 2010 and March 2019 in Japan. This study was approved by the Institutional Review Board and Ethics Committee of Sakura Hospital, School of Medicine, Toho University (No. S-19066). Written informed consent was obtained from the participants.

Data collection and laboratory assay methods

The population-based sample used in the present analysis comprised 76,720 Japanese subjects residing in major cities nationwide, who participated in the CVD and cancer screening program organized by the Japan Health Promotion Foundation. Duplicate subjects were weeded out. Participants were volunteers who were not paid and were not recruited for this study (unlike subjects of a clinical trial). We also recruited subjects taking any medication and/or having a history of heart disease, treatment for hypertension, stroke, diabetes or gout, and excluded those with insufficient data. Finally, 22,696 subjects were enrolled.

All parameters were evaluated using standardized methods. Height and body weight (BW) were measured, and body mass index (BMI) was calculated as follows: BW (kg) divided by square of height (m). Obesity was defined as BMI ≥ 25 kg/m², according to the Examination Committee of Criteria for Obesity Disease in Japan.

Blood was collected from the antecubital vein in the morning after 12 h of fasting to measure fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and serum uric acid level. All the blood levels were determined according to standard procedures.

Dyslipidemia was defined as hyper-cholesterolemia (TC ≥ 220 mg/dL), hypo-HDL cholesterol (HDL-C < 40 mg/dL) and/or hypertriglyceridemia (TG ≥ 150 mg/dL), or treatment with lipid-lowering agents. Hyperuricemia was diagnosed by serum uric acid ≥ 7.0 mg/dL, treatment with uric acid-lowering agents or past history of gout attack. HbA1c (%) measured by the Japan Diabetes Society (JDC) method was converted to NGSP value (%) using the following formula: HbA1c (NGSP) (%) = 1.019 × HbA1c (JDS) (%) + 0.30%. A combination of ≥6.5% HbA1c with ≥126 mg/dL FPG was adopted to detect diabetes. Participants receiving antidiabetic agents were also diagnosed as diabetes. To estimate the interindividual variance in HbA1c levels, the HGI was calculated using HbA1c and FPG levels. The linear relationship between HbA1c and FPG was estimated from linear regression analysis of the data of the subject population (regression equation: HbA1c = 0.0251 × FPG + 3.311, r = 0.718 and p < 0.001). Predicted HbA1c level was then calculated from the regression equation using each subject’s FPG value. HGI was defined as the difference between the measured HbA1c and the predicted HbA1c (HGI = measured HbA1c − predicted HbA1c). Besides, Non-HDL-C was defined as TC minus HDL-C. We also evaluated the triglycerides and glucose (TyG) index as a marker of insulin resistance, calculated as ln(TG (mg/dL) × FPG (mg/dL))/2.

BP was measured simultaneously with CAVI, and hypertension was diagnosed by systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, or treatment with BP-lowering agents.

Measurement of CAVI

CAVI was measured automatically using VaSera VS-1500 (Fukuda Denshi Co Ltd, Tokyo, Japan). With the subject lying supine and the head held in midline position, cuffs were wrapped bilaterally around both upper arms and both ankles. Electrocardiography electrodes were placed on both wrists, and a microphone was attached over the sternum to detect heart sounds.

CAVI was calculated according to the following formula:

$$CAVI = a \times (2\rho\Delta P) \times \ln(Ps/Pd) \times PWV^2 + b,$$

where Ps is systolic blood pressure; Pd is diastolic blood pressure; $\Delta P$ is Ps − Pd; $\rho$ is blood density; PWV is cardio-ankle pulse wave velocity, and a and b are constants.
The details of CAVI have been described previously.\textsuperscript{25} Right and left CAVI were measured, and the higher value was used for analysis. Subjects with ankle-brachial indices lower than 0.90 were excluded, because patients with severe arterial occlusive diseases may give falsely low CAVI.

**Statistical analysis**

All data are expressed as mean ± standard deviation (SD). The SPSS software (version 11.5, Chicago, IL, USA) was used for statistical processing. Mann-Whitney \(U\) test or Fisher’s exact test was used to compare male and female subjects.

**Results**

**Clinical and biochemical characteristics of male and female participants**

In this cross-sectional study, a total of 22,696 Japanese urban residents (10,586 men and 12,110 women, mean age 48.0 years, mean FPG 88 mg/dL, mean HbA1c 5.5%) were enrolled. Table 1 compares the clinical characteristics of male and female participants.

Compared with women, men had significantly higher BMI, CAVI, BP, FPG, HbA1c, Non-HDL-C, TG, TyG index, and uric acid level; and lower age, TC, HGI, and HDL-C. The frequencies of obesity, hypertension, diabetes, dyslipidemia, and hyperuricemia were higher in males.

### Table 1. Clinical and biochemical characteristics of male and female participants.

| Variables | All (Mean ± SD) | Male (Mean ± SD) | Female (Mean ± SD) | \(p\) value |
|-----------|----------------|-----------------|-------------------|-----------|
| Number of subjects | 22,696 | 10,586 | 12,110 | – |
| Age (years) | 48.0 ± 15.3 | 47.1 ± 14.6 | 48.7 ± 15.8 | <0.001 |
| Old age (≥65 years) | 18.9% | 15.7% | 21.8% | <0.001* |
| Height (cm) | 1.63 ± 0.09 | 1.70 ± 0.06 | 1.57 ± 0.06 | <0.001 |
| Body weight (kg) | 59.4 ± 12.2 | 67.8 ± 10.5 | 52.0 ± 8.3 | <0.001 |
| BMI (kg/m²) | 22.2 ± 3.4 | 23.4 ± 3.2 | 21.2 ± 3.3 | <0.001 |
| Obesity (≥25 kg/m²) | 18.2% | 25.8% | 11.5% | <0.001* |
| CAVI | 7.75 ± 1.03 | 7.80 ± 1.00 | 7.69 ± 1.01 | <0.001 |
| High CAVI (≥9) | 14.2% | 15.2% | 13.4% | <0.001* |
| SBP (mmHg) | 123 ± 17 | 127 ± 15 | 120 ± 18 | <0.001 |
| DBP (mmHg) | 72 ± 11 | 75 ± 11 | 69 ± 11 | <0.001 |
| Hypertension | 22.5% | 25.9% | 19.6% | <0.001* |
| FPG (mg/dL) | 88 ± 16 | 90 ± 18 | 85 ± 13 | <0.001 |
| HbA1c (%) | 5.51 ± 0.53 | 5.55 ± 0.62 | 5.48 ± 0.44 | <0.001 |
| Diabetes | 4.8% | 6.8% | 3.1% | <0.001* |
| HGI (%) | 0.00 ± 0.37 | −0.03 ± 0.41 | 0.02 ± 0.33 | <0.001 |
| TC (mg/dL) | 209 ± 37 | 208 ± 36 | 210 ± 37 | <0.001 |
| TG (mg/dL) | 101 ± 83 | 122 ± 103 | 82 ± 54 | <0.001 |
| HDL-C (mg/dL) | 67 ± 17 | 61 ± 15 | 73 ± 17 | <0.001 |
| Non-HDL-C (mg/dL) | 142 ± 37 | 147 ± 37 | 137 ± 37 | <0.001 |
| TyG index | 8.19 ± 0.63 | 8.41 ± 0.63 | 8.01 ± 0.56 | <0.001 |
| Dyslipidemia | 44.9% | 48.6% | 41.7% | <0.001* |
| Uric acid (mg/dL) | 5.2 ± 1.4 | 6.1 ± 1.2 | 4.4 ± 1.0 | <0.001 |
| Hyperuricemia | 11.8% | 23.8% | 1.3% | <0.001* |

BMI: body mass index; CAVI: cardio-ankle vascular index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HGI: hemoglobin glycation index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; TyG index: triglycerides and glucose index.

Data are presented as mean ± standard deviation. Mann-Whitney \(U\) test and Fisher’s exact test were used to compare male and female subjects.
**Table 2. Correlation of CAVI with clinical variables analyzed by multiple regression model.**

| Variable          | \( \beta \) coefficient | SE  | \( p \) value |
|-------------------|---------------------------|-----|--------------|
| Male gender       | 0.089                     | 0.009 | \(<0.001 \) |
| Age (years)       | 0.813                     | 0.000 | \(<0.001 \) |
| BMI (kg/m²)       | −0.140                    | 0.001 | \(<0.001 \) |
| SBP (mmHg)        | 0.106                     | 0.000 | \(<0.001 \) |
| HbA1c (%)         | 0.052                     | 0.007 | \(<0.001 \) |
| Non-HDL-C (mg/dL) | 0.007                     | 0.000 | \(<0.001 \) |
| HDL-C (mg/dL)     | −0.015                    | 0.000 | \(<0.001 \) |
| Uric acid (mg/dL) | 0.039                     | 0.003 | \(<0.001 \) |

CAVI: cardio-ankle vascular index; BMI: body mass index; SBP: systolic blood pressure; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein-cholesterol; SE: standard error.

**Correlation of CAVI with clinical variables analyzed by multiple regression model**

Next, we examined the factors associated with CAVI (Table 2). The multiple regression model for the correlation of CAVI with clinical variables (Model; \( r^2 = 0.760, \ p < 0.001 \)) revealed that age was the major independent predictor of CAVI (\( \beta \) coefficient = 0.813). Additionally, a weak correlation between CAVI and BMI (\( \beta = −0.140 \)) or SBP (\( \beta = 0.106 \)) was observed.

**Correlation of HGI with clinical variables analyzed by multiple regression model**

Factors related to HGI by gender were also examined (Table 3). The coefficient of determination of the HGI-related multiple regression model using clinical variables was low for both men and women (Model; \( r^2 = 0.040 \) in men, 0.058 in women, \( p < 0.001 \)). However, a weak correlation between HGI and BMI in both gender (\( \beta = 0.121 \) in men, 0.110 in women); or age (\( \beta = 0.118 \)) or FPG (\( \beta = −0.195 \)) in women.

**Characteristics of participants stratified by quartile of HGI**

The subjects were stratified by HGI into four groups: lowest quartile (Q1), Q2, Q3, and highest quartile (Q4). Table 4 compares their clinical characteristics.

Compared with Q1 group, Q4 group had significantly higher age, BMI, CAVI, HbA1c, TC, TG, and Non-HDL-C; and significantly lower male ratio and HDL-C. Furthermore, the frequencies of obesity, hypertension, diabetes, and dyslipidemia were higher in Q4 group compared to Q1 group.

**Bivariate logistic regression model for high CAVI (≥9.0)**

Furthermore, we examined the factors associated with high CAVI (≥9.0) using bivariate logistic regression analysis of dichotomous variables (Table 5). In addition to the highest HGI quartile (Q4), gender and major cardiovascular risk factors were entered into the model. The analysis identified all of the variables including male gender, old age, obesity, dyslipidemia, hypertension, diabetes and, hyperuricemia to be associated with high CAVI, respectively.

Notably, highest HGI quartile (Q4) was a significant predictor for high CAVI independent of the presence of diabetes.

**Correlation of HGI with HbA1c**

Finally, the relationship between HGI and HbA1c was investigated (Figure 1). A highly significant statistical positive correlation was observed between HGI and HbA1c (\( r = 0.681, \ p < 0.001 \)).

**Discussion**

In the present study of a real-world Japanese population of 22,696 subjects, gender, age, BMI, and SBP were major independent confounders of CAVI. Additionally, the highest HGI quartile was associated with high CAVI independent of the presence of diabetes. This may be the first report to demonstrate the association of HGI with arterial stiffness.
Increased arterial stiffness along with increase in HGI is consistent with the finding in the Diabetes Control and Complications Trial (DCCT) that HGI is a predictor for progression of diabetic angiopathy.26 As for the possible mechanisms for the relationship between high HGI and systemic arterial stiffening, there are several hypotheses. The first assumed mechanism is increased formation of advanced glycation end products (AGEs), which cause both insulin

### Table 4. Characteristics of participants stratified by quartile of hemoglobin glycation index.

| Variables          | Quartile of hemoglobin glycation index (HGI) | p value |
|--------------------|---------------------------------------------|---------|
|                    | Q1 (Lowest) | Q2 | Q3 | Q4 (Highest) |       |
| Number of subjects | 5673        | 5609 | 5675 | 5739         | –       |
| Male               | 55.2%       | 48.0% | 42.1% | 41.3%†       | <0.001a |
| Age (years)        | 47.2 ± 15.2 | 47.3 ± 15.4 | 46.9 ± 15.3 | 50.4 ± 14.9† | <0.001b |
| Old age (≥65 years)| 16.9%       | 18.6% | 18.1% | 22.1%†       | <0.001b |
| BMI (kg/m²)        | 22.2 ± 3.1  | 22.0 ± 3.2 | 21.9 ± 3.3 | 22.7 ± 3.9† | <0.001b |
| Obesity (≥25 kg/m²)| 16.9%       | 15.7% | 16.6% | 23.4%†       | <0.001a |
| CAVI               | 7.72 ± 0.99 | 7.71 ± 1.00 | 7.68 ± 1.00 | 7.88 ± 1.03† | <0.001b |
| High CAVI (≥9)     | 12.9%       | 13.2% | 13.1% | 17.7%        | <0.001a |
| SBP (mmHg)         | 125 ± 17    | 123 ± 17 | 121 ± 17 | 123 ± 18†    | <0.001b |
| DBP (mmHg)         | 74 ± 11     | 72 ± 11 | 71 ± 11 | 72 ± 12†     | <0.001b |
| Hypertension       | 24.5%       | 20.8% | 19.5% | 25.2%†       | 0.003a  |
| HbA1c (%)          | 5.2 ± 0.3   | 5.4 ± 0.3 | 5.5 ± 0.3 | 5.9 ± 0.8†    | <0.001b |
| Diabetes           | 3.2%        | 1.5%  | 1.8%  | 12.6%        | <0.001a |
| FPG (mg/dL)        | 92 ± 16     | 87 ± 10 | 85 ± 11 | 87 ± 22†     | <0.001b |
| TC (mg/dL)         | 206 ± 36    | 209 ± 36 | 208 ± 36 | 212 ± 38†    | <0.001 |
| TG (mg/dL)         | 104 ± 92    | 98 ± 86 | 94 ± 68 | 106 ± 84     | <0.001b |
| HDL-C (mg/dL)      | 68 ± 17     | 68 ± 17 | 67 ± 17 | 65 ± 17†     | <0.001b |
| Non-HDL-C (mg/dL)  | 138 ± 36    | 141 ± 36 | 141 ± 37 | 147 ± 39†    | <0.001b |
| TyG index          | 8.27 ± 0.63 | 8.17 ± 0.59 | 8.11 ± 0.59 | 8.22 ± 0.63 | <0.001b |
| Dyslipidemia       | 42.9%       | 43.4% | 42.7% | 50.6%†       | <0.001a |
| Uric acid (mg/dL)  | 5.3 ± 1.4   | 5.2 ± 1.4 | 5.1 ± 1.4 | 5.2 ± 1.4†    | <0.001b |
| Hyperuricemia      | 13.3%       | 12.0% | 10.7% | 11.1%†       | 0.002a  |

BMI: body mass index; CAVI: cardio-ankle vascular index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; HGI: hemoglobin glycation index; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; TyG index: triglycerides and glucose index.

Data are presented as mean ± standard deviation.

*p < 0.005, Cochran-Q test, Q1 versus Q4.

†p < 0.001, Bonferroni test, Q1 versus Q4.

*Cochran-Armitage test.

bANOVA, p value for trend.

### Table 5. Bivariate logistic regression model for high CAVI (≥9.0).

| Variables         | Odds ratio | 95% CIs | p value |
|-------------------|------------|---------|---------|
| Male gender       | 1.86       | 1.66–2.07 | <0.001 |
| Old age           | 26.2       | 23.6–29.2 | <0.001 |
| Obesity           | 0.499      | 0.438–0.569 | <0.001 |
| Dyslipidemia      | 1.54       | 1.39–1.70 | <0.001 |
| Hypertension      | 3.56       | 3.21–3.95 | <0.001 |
| Diabetes          | 2.89       | 2.41–3.46 | <0.001 |
| Hyperuricemia     | 1.29       | 1.11–1.51 | 0.001 |
| Highest HGI quartile (Q4) | 1.20 | 1.07–1.34 | 0.002 |

CI: confidence interval; HGI: hemoglobin glycation index.

Akaike’s Information Criterion: 10,825, residual deviance: 10,807, p < 0.001.

**Figure 1.** Correlation of HGI with HbA1c. The scatter plot shows the distribution of HGI with HbA1c. HGI: hemoglobin glycation index; HbA1c: glycated hemoglobin.
resistance and atherosclerosis. A previous study has found an association between increased HGI and high levels of AGEs in diabetic patients. It is therefore possible that subjects with high HGI have a propensity to glycate other proteins and macromolecules leading to a higher risk of developing vascular complications. Furthermore, Marini et al. reported that high HGI was associated with obesity-related metabolic disorders including high triglycerides, uric acid, and fasting insulin, together with low insulin-stimulated glucose disposal, independent of confounders such as age and gender in non-diabetic individuals. Similar findings are confirmed in our study (Table 4), which may indicate that HGI is a useful tool to identify a subset of subjects with high risk of CVD. On the other hand, in the present study, the prevalence of hyperuricemia was almost equal between HGI quartile groups, which might be influenced by decreased male gender ratio with increasing HGI quartile.

Another explanation for the association of HGI with systemic arterial stiffening is the influence of postprandial hyperglycemia that could not be detected by HGI in our study. Unlike previous studies using MBG for the calculation of HGI, we used only FPG. While HbA1c is mainly contributed by FPG and postprandial glucose, calculation of HGI from FPG alone may omit the contribution of postprandial hyperglycemia. However, previous studies have shown that HGI calculated from MBG correlates highly with that obtained using FPG alone. Furthermore, previous studies have also revealed that HGI calculated from FPG is adequately useful to verify the clinical implications for diabetes, as well as to assess the risk of hypoglycemia and inflammatory status. Therefore, it seems reasonable to calculate HGI from FPG instead of MBG, considering convenience. In any case, HGI is a risk factor for atherosclerosis independent of hyperglycemia, and may be useful as a therapeutic target in addition to assessing the risk of hypoglycemia during intensive diabetes treatment.

HGI correlates closely with HbA1c, to the extent that differentiating the two as separate epidemiological risk factors can be difficult. In this study, there was a significant correlation between HbA1c and HGI levels (Figure 1), which may raise a concern about multicollinearity. Actually, relatively high value of CAVI observed in highest HGI quartile group disappeared after adjusting for HbA1c (data not shown). The association of HGI with diabetic complications may be therefore explained largely by HbA1c in the same patient. However, we think that it is invalid to assert that HGI should not be used to evaluate risk of complications or to guide therapy. It has been reported that the individual regression line of MBG versus HbA1c maintains approximately the same distance to the population regression line during consistent tracking. Furthermore, in the present study, high HGI was associated with arterial stiffening independent of the presence of diabetes. These indicate that individual HGI does not fluctuate easily despite changes in HbA1c. Therefore, HGI may be a glycemic parameter that reflects arterial stiffness independent of HbA1c.

Gender difference in HGI has not been studied in detail. In the present study, women showed higher HGI, and female ratio increased with increasing HGI quartile. Additionally, several studies have also suggested a stronger association of female with high HGI. On the contrary, gender difference of HGI was not observed in many studies. The effects of gender, race, and ethnic group on HGI remain controversial. Further investigations on the factors associated with HGI are required.

The limitations of this study include the lack of data on some potential confounders such as proteinuria, heart rate, alcohol consumption, menopause, and smoking status. From these viewpoints, longitudinal cohort studies are needed to clarify the changes in HGI and arterial stiffness during the evolution of cardiovascular risks.

A key strength of the work is the investigation of a large number of individuals and inclusion of a mixed population without and with diabetes. However, there are a number of weaknesses that should be acknowledged. First, this was a cross-sectional study and therefore a causal relationship between HGI and vascular risk cannot be proven. Second, the vast majority of the population studied did not have diabetes and therefore data appear to be limited to individuals with normal glucose metabolism. Third, the mechanistic pathways linking HGI with increased risk of vascular pathology are unclear. Finally, it remains to be established whether HGI can be used in routine clinical practice as a predictor of vascular pathology.

In conclusion, high HGI is associated with systemic arterial stiffening independent of hyperglycemia. This index is therefore expected to be not only a predictor of hypoglycemia, but also as a therapeutic target for atherosclerosis.

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Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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