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# Two-week continuous glucose monitoring-derived metrics and degree of hepatic steatosis: a cross-sectional study among Chinese middle-aged and elderly participants

Haili Zhong<sup>1,2,3†</sup>, Ke Zhang<sup>2,3†</sup>, Lishan Lin<sup>1</sup>, Yan Yan<sup>1</sup>, Luqi Shen<sup>2,3</sup>, Hanzu Chen<sup>1</sup>, Xinxiu Liang<sup>2,3</sup>, Jingnan Chen<sup>2,3</sup>, Zelei Miao<sup>2,3</sup>, Ju-Sheng Zheng<sup>2,3,4\*</sup> and Yu-ming Chen<sup>1\*</sup>

## Abstract

**Background** Continuous glucose monitoring (CGM) devices provide detailed information on daily glucose control and glycemic variability. Yet limited population-based studies have explored the association between CGM metrics and fatty liver. We aimed to investigate the associations of CGM metrics with the degree of hepatic steatosis.

**Methods** This cross-sectional study included 1180 participants from the Guangzhou Nutrition and Health Study. CGM metrics, covering mean glucose level, glycemic variability, and in-range measures, were separately processed for all-day, nighttime, and daytime periods. Hepatic steatosis degree (healthy: n = 698; mild steatosis: n = 242; moderate/severe steatosis: n = 240) was determined by magnetic resonance imaging proton density fat fraction. Multivariate ordinal logistic regression models were conducted to estimate the associations between CGM metrics and steatosis degree. Machine learning models were employed to evaluate the predictive performance of CGM metrics for steatosis degree.

**Results** Mean blood glucose, coefficient of variation (CV) of glucose, mean amplitude of glucose excursions (MAGE), and mean of daily differences (MODD) were positively associated with steatosis degree, with corresponding odds ratios (ORs) and 95% confidence intervals (CIs) of 1.35 (1.17, 1.56), 1.21 (1.06, 1.39), 1.37 (1.19, 1.57), and 1.35 (1.17, 1.56) during all-day period. Notably, lower daytime time in range (TIR) and higher nighttime TIR were associated with higher steatosis degree, with ORs (95% CIs) of 0.83 (0.73, 0.95) and 1.16 (1.00, 1.33), respectively. For moderate/severe steatosis (vs. healthy) prediction, the average area under the receiver operating characteristic curves were higher for the nighttime (0.69) and daytime (0.66) metrics than that of all-day metrics (0.63,  $P < 0.001$  for all comparisons). The

<sup>†</sup>Haili Zhong and Ke Zhang have contributed equally to this work and share first authorship.

\*Correspondence:

Ju-Sheng Zheng  
zhengjusheng@westlake.edu.cn

Yu-ming Chen  
chenyum@mail.sysu.edu.cn

Full list of author information is available at the end of the article



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model combining both nighttime and daytime metrics achieved the highest predictive capacity (0.73), with nighttime MODD emerging as the most important predictor.

**Conclusions** Higher CGM-derived mean glucose and glycemic variability were linked with higher steatosis degree. CGM-derived metrics during nighttime and daytime provided distinct and complementary insights into hepatic steatosis.

**Keywords** Hepatic steatosis, Continuous glucose monitoring, Mean glucose level, Glycemic variability, Time in range

## Background

Metabolic dysfunction-associated steatotic liver disease (MASLD), characterized by hepatic lipid accumulation, has become the major cause of chronic hepatic diseases and cardiovascular diseases (CVDs) [1–3]. Given the important role of impaired glucose in the development and progression of MASLD [4], maintaining optimal glycemic control is crucial for its prevention and management. However, traditional blood glucose biomarkers like fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) cannot provide information on daily glucose control and glycemic variability [5].

Continuous glucose monitoring (CGM) could capture dynamic glycemic profiles, addressing the limitations of traditional glucose biomarkers [6]. Clinical practice guidelines have already established specific goals for diabetes management based on CGM-derived measures [7], while their applicability to classify the degree of hepatic steatosis in the general population is still unclear. In addition, given the circadian regulation of glucose and differences in daily activity [8], patterns of glucose characteristics are distinct between the nighttime and daytime periods. The international consensus also recommends reporting CGM glucose data separately for nighttime and daytime periods [9]. So far, there is no study reporting the associations of nighttime and daytime CGM metrics with MASLD progression.

Therefore, in this population-based study of middle-aged and elderly Chinese adults, our primary aim was to examine the cross-sectional associations between CGM-derived metrics and the degree of hepatic steatosis, which was determined with magnetic resonance imaging (MRI)-derived proton density fat fraction (PDFF). Our secondary aim was to evaluate the predictive performance of CGM-derived metrics during different time periods for hepatic steatosis.

## Methods

### Study design and participants

This study was based on the Guangzhou Nutrition and Health Study (GNHS; ClinicalTrials.gov, ID: NCT03179657), a community-based prospective cohort study in South China. Briefly, 4048 participants aged 40–75 years were enrolled between 2008 and 2013 and followed up every 3 years. Participants with previously

confirmed diabetes, CVDs, dyslipidemia, cancers or those using medication known to affect lipid metabolism within the three months prior to enrollment were excluded. Sociodemographic, lifestyle, physical activity, dietary intake, anthropometrics, and blood samples were collected at baseline and each follow-up [10]. The study protocol of the GNHS was approved by the Ethics Committee of the School of Public Health at Sun Yat-sen University, and all participants provided written informed consent.

The present study included GNHS participants who completed the fourth follow-up investigation between 2020 and 2023 ( $n=1952$ ). CGM devices were used to monitor continuous glucose for two weeks. MRI was applied to assess liver fat content with PDFF. Participants were excluded with following criteria: without valid CGM recordings ( $n=553$ ), without abdominal MRI examination ( $n=164$ ), heavy alcohol drinkers ( $>70$  g/week for women and  $140$  g/week for men) ( $n=5$ ), history of liver cirrhosis ( $n=0$ ), or self-reported viral hepatitis ( $n=50$ ). Finally, 1180 participants were included in the statistical analyses of the present study (Fig. S1).

### Continuous glucose monitoring and glycemic metrics extraction

Participants were equipped with a CGM device (FreeStyle Libre H; Abbott, Abbott Park, IL, USA) for two weeks to continuously monitor interstitial glucose, with readings taken every 15 min. Participants were blinded to their CGM measurements throughout the monitoring period. Valid CGM data were determined after excluding: (1) CGM recordings  $<72$  h; (2) the first and last two incomplete days; and (3) days with extreme time spent below the target range  $3.9$  mmol/L ( $>99$ th percentile).

Our present study included nine key CGM-derived measures, which represent different aspects of clinically relevant glycemic characteristics [11, 12]: (1) mean glucose measures, including mean of continuous blood glucose values (MBG), total area under the curve (AUC), and glucose management indicator (GMI); (2) variability measures, including the coefficient of variation (CV) of glucose values, mean amplitude of glucose excursions (MAGE), and mean of daily differences (MODD); and (3) in-range measures, including time in range (TIR), time above range (TAR), and time below range (TBR).

GMI was a linear transformation of the mean glucose value to estimate HbA1C and was calculated using the following formula:  $3.31 + 0.02329 \times (\text{mean glucose in mg/dL})$  [13]. CV was calculated by dividing the standard deviation (SD) by the mean of the corresponding glucose readings [14]. MAGE was calculated as the average amplitude exceeding one SD from the mean within a day period [15] using the *CGMTSA* R package [16]. MODD was calculated as the mean difference between glucose values measured at the same time of the day on two consecutive days under standardized conditions [15]. TIR, TBR, and TAR were defined as the percentage of time within the target glucose range of 3.9–10 mmol/L, below 3.9 mmol/L, and above 10 mmol/L, respectively [17].

CGM-derived measures were calculated separately for all-day, nighttime, and daytime intervals. The starting time for night and day period was predefined at 23:00 and 6:30 [18], respectively, aligned with the median bedtime and wake-up time observed within our study population. To consider random errors, the CGM-derived metrics were processed for each day and averaged across all days for further analysis.

#### Magnetic resonance imaging

Abdominal MRI was performed to measure liver fat content after participants finished the continuous glucose monitoring within a few days. The procedure was conducted by experienced technologists according to the protocol of Siemens LiverLab on 3.0 T MAGNETOM Skyra (Siemens Healthineers, Erlangen, Germany), with participants in the supine position. Medical conditions were not considered, except for those that would exclude the participant from being able to undergo an MRI (e.g., if they had an implanted defibrillator or metal implant). Degree of hepatic steatosis was defined by MRI-PDFF [19, 20] as follows: healthy group (PDFF < 5%), mild steatosis ( $5\% \leq \text{PDFF} < 10\%$ ), and moderate/severe steatosis (PDFF  $\geq 10\%$ ).

#### Statistical analyses

All statistical analyses were performed using R software (version 4.1.2) and Python (version 3.8.5). We presented the characteristics of the study participants according to the degree of hepatic steatosis. Continuous and categorical variables were presented as median (interquartile range 25th and 75th percentiles) and frequencies (%), respectively. Wilcoxon tests were conducted to compare the distributions of CGM-derived metrics between nighttime and daytime.

To normalize the CGM-derived metrics, an arcsine square root transformation was performed for the in-range measures (i.e., TIR, TBR, and TAR), and a log transformation was conducted for the remaining CGM-derived metrics. Normalized CGM-derived metrics were

then transformed into sex-specific standardized z-scores for further statistical analyses.

We used multiple ordinal logistic regression models to estimate the cross-sectional associations of CGM-derived metrics (i.e., MBG, AUC, GMI, CV, MAGE, MODD, TIR, TAR, and TBR) during all-day, nighttime and daytime periods with degree of hepatic steatosis (ordered scale), adjusted for age, sex, marital status, education, household income, smoking status, tea drinking, physical activity, total energy intake, dietary carbohydrate, use of glucose-lowering drugs, lipid-lowering drugs, and antihypertensive drugs in model 1, and further adjusted for body mass index (BMI), waist-to-hip ratio (WHR), triglycerides (TG), and high-density lipoprotein (HDL) in model 2. We controlled the false discovery rate (FDR) using the Benjamini–Hochberg method, considering  $\text{FDR} < 0.05$  as statistically significant for the above analyses.

To further explore whether the associations between CGM metrics and hepatic steatosis degree could be modified by HbA1c or BMI, we further conducted subgroup analyses stratified by HbA1c (normal glucose tolerance:  $\text{HbA1c} < 5.7\%$ ; prediabetes:  $\text{HbA1c} \geq 5.7\%$  and  $< 6.5\%$ ; and diabetes:  $\text{HbA1c} \geq 6.5\%$ ) and BMI (underweight/normal weight:  $\text{BMI} < 24 \text{ kg/m}^2$ ; and overweight/obese:  $\text{BMI} \geq 24 \text{ kg/m}^2$ ), adjusting for covariates in model 2. An interaction term was included in the model to test for the interaction effects.

To test the reliability of our primary findings based on above ordinal logistic regression models, we conducted several sensitivity analyses using multiple ordinal logistic regression models, adjusting for covariates in model 2. First, we excluded participants with diabetes ( $n = 172$ ). Second, we excluded participants with CGM monitoring < ten days ( $n = 36$ ), as it is recommended to obtain 70% of the CGM data for each participant for statistical analysis [9]. Third, we treated the CGM-derived metrics as sex-specific quantiles. To explore whether different targets of glucose levels may influence the associations between in-range measures and degree of hepatic steatosis, we further processed the in-range measures defined with a target range 3.9–7.8 mmol/L [9] and re-ran the main analyses of model 2.

Then, we employed multinomial logistic regression models to examine the associations between aforementioned CGM-derived metrics and different degrees of hepatic steatosis (unordered scale; healthy group as reference), adjusting for covariates in the model 2.  $\text{FDR} < 0.05$  was considered statistically significant.

To evaluate the performance of CGM-derived metrics in the classification of mild and moderate/severe steatosis (healthy group as reference), we built prediction models based on Light Gradient Boosting Machine (lightGBM) [21], which was known for its robust training and low overfitting risk [22]. In the machine learning model, we

investigated the performance of different CGM metrics during all day (all-day model), nighttime (nighttime model) and daytime (daytime model), respectively. To explore whether integrating CGM metrics from nighttime and daytime improve the prediction performance for steatosis, we also developed models incorporating CGM metrics from both periods (combined model). We used the average area under the receiver operating characteristic curves (AUROC) derived from 100 iterations of fivefold cross-validation to assess the predictive performance, and performed Wilcoxon tests to compare the performance of different models. Additionally, Youden index was calculated for the developed machine learning models, and the sensitivity and specificity at the maximum Youden index were determined. We used the average Shapley Additive exPlanations (SHAP) [23] values from the combined models to estimate the contribution of CGM-derived metrics for the overall model.

To further explore the associations between CGM metrics and liver fibrosis, we calculated FIB-4 using age and laboratory results from aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count (PLT) as previously described [24]:  $FIB-4 \text{ score} = \text{Age} [\text{years}] \times \text{AST} [\text{U/L}] / (\text{PLT} [10^9/\text{L}] \times \text{ALT}^{1/2} [\text{U/L}])$ . Participants were categorized into low-risk ( $FIB-4 < 1.45$ ), indeterminate-risk ( $FIB-4 \ 1.45\text{--}2.67$ ), and high-risk ( $FIB-4 > 2.67$ ) fibrosis groups. Then, we conducted multiple ordinal logistic regression models to explore the associations between CGM metrics and liver fibrosis degree, adjusting for covariates in model 2.  $FDR < 0.05$  was considered statistically significant.

## Results

### Population characteristics

A total of 1180 participants were included in the present study (Fig. S1), with a median age of 69.5 years. 698 (59.2%), 242 (20.5%), and 240 (20.3%) participants were categorized as healthy, mild steatosis, and moderate/severe steatosis, respectively. Participant characteristics according to hepatic steatosis degree were summarized in Table 1 and Table S1. Participants with higher degree of hepatic steatosis were more likely to be female, had increased prevalence of diabetes, hypertension and dyslipidemia, higher levels of BMI, waist-to-hip ratio, triglycerides, fasting blood glucose, insulin and HbA1c, and lower levels of high-density lipoprotein cholesterol (Table 1).

The distributions of the CGM-derived metrics during nighttime and daytime periods are presented in Table S2. Overall, daytime period presented higher glucose levels and variability than nighttime period, including lower TBR and higher MBG, AUC, GMI, CV, MAGE, and TAR (all  $P < 0.001$ ). However, no significant difference was

observed in the distribution of MODD and TIR between daytime and nighttime ( $P > 0.05$ ).

### CGM-derived mean glucose and glycemic variability and hepatic steatosis degree

In our analyses with ordinal logistic regression models, after adjusting for potential confounders and multiple testing correction in model 2, higher CGM-derived mean glucose and variability measures were associated with higher degree of hepatic steatosis (Fig. 1A; B). The adjusted ORs (95% CI) of all-day metrics (log-transformed and standardized) for higher steatosis degree were 1.35 (1.17, 1.56) for MBG, 1.35 (1.17, 1.56) for AUC, 1.32 (1.15, 1.52) for GMI, 1.21 (1.06, 1.39) for CV, 1.37 (1.19, 1.57) for MAGE, and 1.35 (1.17, 1.56) for MODD (all  $FDR < 0.05$ ). Similar results were observed for mean glucose and variability metrics during both nighttime and daytime, with association patterns more pronounced for daytime metrics. The ORs (95% CI) of nighttime and daytime metrics (log-transformed and standardized) for higher steatosis degree were as follows: 1.27 (1.10, 1.46) and 1.37 (1.18, 1.58) for MBG, 1.27 (1.10, 1.45) and 1.37 (1.18, 1.58) for AUC, 1.24 (1.08, 1.42) and 1.34 (1.16, 1.55) for GMI, 1.10 (0.96, 1.26) and 1.25 (1.09, 1.43) for CV, 1.13 (0.99, 1.30) and 1.34 (1.16, 1.54) for MAGE, and 1.29 (1.12, 1.49) and 1.44 (1.25, 1.67) for MODD, respectively (all  $FDR < 0.05$ , except for nighttime CV and nighttime MAGE). Consistent results were observed across model 1 (Fig. S2) and model 2. In the subgroup analyses adjusting for covariates in model 2, the association patterns between CGM metrics and hepatic steatosis among subgroups of HbA1c (NGT and prediabetes) (Table S3) and BMI ( $BMI < 24 \text{ kg/m}^2$  and  $BMI \geq 24 \text{ kg/m}^2$ ) (Table S4) were consistent with those observed in the main analysis among all participants. No significant interactions were observed (all  $P$  for interaction  $> 0.05$ ).

In the sensitivity analyses with multiple ordinal regression models after adjusting for covariates in model 2, similar results were observed for the associations of CGM-derived mean glucose and variability metrics with steatosis degree after excluding participants with diabetes (Fig. S3), excluding participants with CGM data of less than ten days (Fig. S4), or treating the CGM-derived metrics as sex-specific quantiles (Fig. S5).

### CGM-derived in-range measures and hepatic steatosis degree

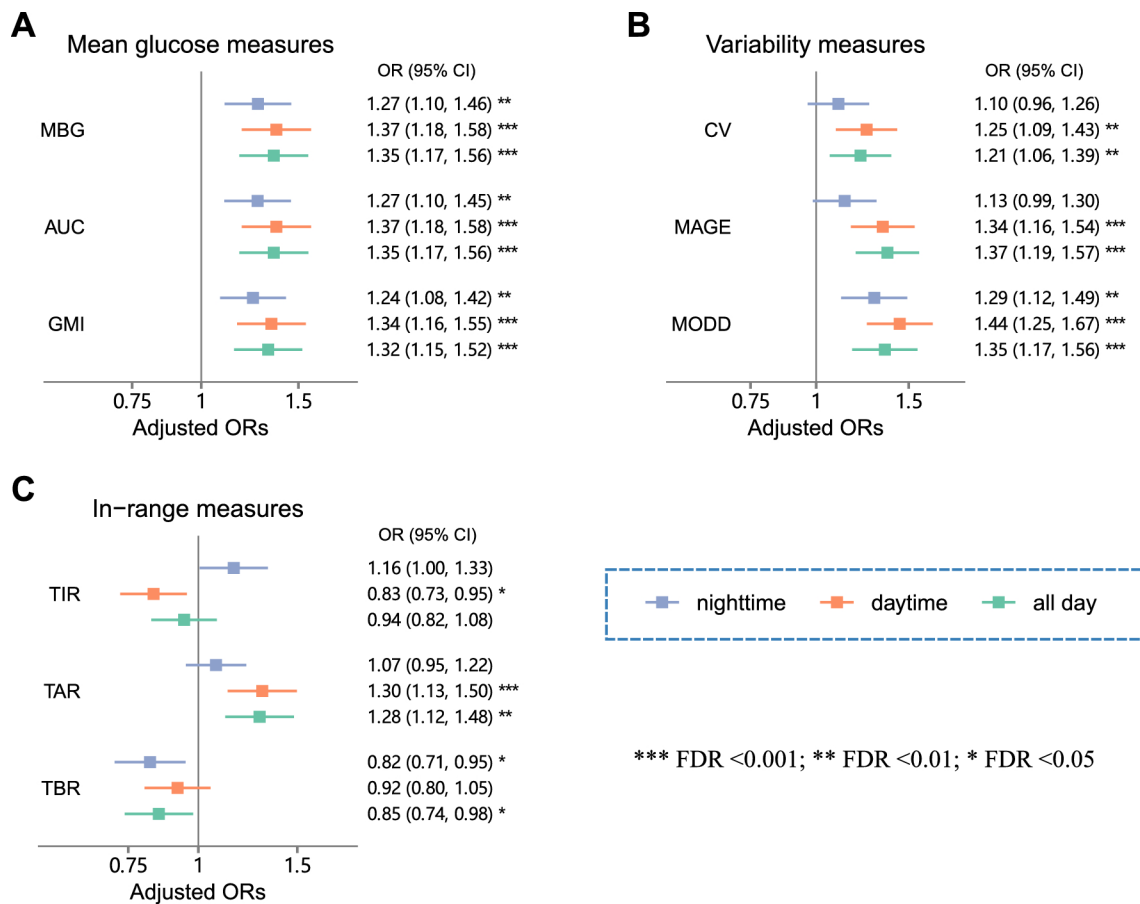
For in-range measures (arcsine square root transformed and standardized) with the target glucose of range 3.9–10.0 mmol/L, TBR exhibited a negative association (OR: 0.85, 95% CI: 0.74–0.98), TAR showed a positive association (OR: 1.28, 95% CI: 1.12–1.48), and TIR exhibited a null association (OR: 0.94, 95% CI: 0.82–1.08) with steatosis degree during all-day period. Notably, the negative

**Table 1** Characteristics of the study population according to different degrees of hepatic steatosis in the Guangzhou Nutrition and Health Study

	Healthy n = 698	Mild hepatic steatosis n = 242	Moderate/Severe hepatic steatosis n = 240	P value
Age, years	69.1 (66.2, 72.7)	69.2 (66.2, 72.6)	69.2 (65.8, 72.4)	0.369
Female	483 (69.2)	160 (66.1)	192 (80.0)	0.001
Married	634 (90.8)	229 (94.6)	220 (91.7)	0.179
Education				0.280
Secondary school or below	160 (22.9)	64 (26.4)	58 (24.2)	
High school	341 (48.9)	98 (40.5)	111 (46.2)	
College or above	197 (28.2)	80 (33.1)	71 (29.6)	
Household income, Yuan/person				0.279
< 1500	308 (45.4)	112 (47.1)	107 (45.1)	
1500–3000	194 (28.6)	55 (23.1)	56 (23.6)	
> 3000	177 (26.1)	71 (29.8)	74 (31.2)	
Current smoking	71 (10.2)	34 (14.0)	11 (4.6)	0.002
Current alcohol drinking	33 (4.7)	21 (8.7)	14 (5.8)	0.076
Current tea drinking	358 (51.3)	142 (58.7)	121 (50.4)	0.104
Diabetes	78 (11.2)	46 (19.0)	48 (20.0)	< 0.001
Hypertension	239 (34.3)	100 (41.3)	126 (52.5)	< 0.001
Dyslipidemia	316 (45.3)	102 (42.1)	140 (58.3)	< 0.001
Antidiabetic medications	66 (9.5)	39 (16.1)	41 (17.1)	0.001
Antihypertensive drugs	215 (30.8)	95 (39.3)	115 (47.9)	< 0.001
Lipid-lowering drugs	202 (29.1)	74 (30.6)	66 (27.5)	0.758
Physical activities, MET-h/d	36.4 (30.9, 52.6)	35.9 (31.0, 53.9)	36.2 (30.7, 47.7)	0.923
Total energy intake, kcal/d	1259 (1047, 1549)	1259 (1023, 1549)	1202 (977, 1488)	0.129
Carbohydrate intake, g/d	170 (149, 192)	168 (150, 192)	166 (148, 188)	0.706
BMI, kg/m <sup>2</sup>	22.4 (20.7, 24.2)	24.4 (22.6, 26.2)	25.3 (23.6, 27.4)	< 0.001
Waist-to-hip ratio	0.92 (0.88, 0.96)	0.94 (0.91, 0.98)	0.95 (0.92, 0.98)	< 0.001
<b>Laboratory tests</b>				
TC, mmol/L	5.43 (4.68, 6.16)	5.26 (4.56, 6.00)	5.38 (4.58, 6.09)	0.469
TG, mmol/L	1.16 (0.91, 1.53)	1.54 (1.13, 2.07)	1.82 (1.33, 2.56)	< 0.001
HDL, mmol/L	1.58 (1.35, 1.84)	1.37 (1.17, 1.55)	1.29 (1.12, 1.46)	< 0.001
LDL, mmol/L	3.38 (2.71, 4.04)	3.28 (2.64, 4.01)	3.37 (2.54, 3.94)	0.716
FBG, mmol/L	5.48 (5.12, 5.93)	5.78 (5.37, 6.56)	5.97 (5.48, 6.75)	< 0.001
Insulin, $\mu$ U/mL	7.50 (5.40, 10.09)	10.9 (7.8, 14.0)	15.2 (10.6, 21.1)	< 0.001
HbA1c, $\mu$ mol/L	5.80 (5.50, 6.00)	5.90 (5.70, 6.30)	6.00 (5.80, 6.40)	< 0.001
<b>CGM metrics, all day</b>				
MBG, mmol/L	5.47 (5.10, 5.91)	5.70 (5.35, 6.33)	5.93 (5.51, 6.59)	< 0.001
AUC, mmol/L	130 (121, 140)	135 (127, 150)	141 (131, 157)	< 0.001
GMI, mmol/L	5.60 (5.45, 5.79)	5.70 (5.55, 5.96)	5.80 (5.62, 6.07)	< 0.001
CV, %	23.7 (20.3, 27.6)	23.8 (20.1, 28.5)	24.0 (21.1, 28.3)	0.604
MAGE, mmol/L	3.17 (2.61, 4.00)	3.32 (2.68, 4.31)	3.61 (2.83, 4.58)	< 0.001
MODD, mmol/L	0.23 (0.18, 0.30)	0.25 (0.19, 0.38)	0.29 (0.21, 0.39)	< 0.001
TAR, %	0.64 (0.11, 2.46)	1.00 (0.24, 4.33)	1.80 (0.39, 6.19)	< 0.001
TBR, %	3.29 (1.12, 8.81)	1.92 (0.58, 5.69)	1.60 (0.40, 4.23)	< 0.001
TIR, %	93.7 (86.1, 97.4)	94.4 (87.7, 97.7)	94.1 (86.3, 97.5)	0.374

Continuous variables were presented as median (interquartile range) and compared by Kruskal–Wallis tests. Categorical variables were presented as n (%) and compared by *chi*-squared tests. Total number of participants = 1180

*MET* metabolic equivalent; *TC* total cholesterol; *TG* triglycerides; *HDL* high-density lipoprotein cholesterol; *LDL* low-density lipoprotein cholesterol; *FBG* fasting blood glucose; *MBG* mean blood glucose; *AUC* total glucose area under the curve; *GMI* glucose management indicator; *CV* coefficient of variation; *MAGE* mean amplitude of glycemic excursions; *MODD* mean of daily differences; *TIR* time in range; *TAR* time above range; *TBR* time below range



**Fig. 1** Associations of CGM-derived metrics with higher degree of hepatic steatosis. Forest plots present the ORs (95% CI) of mean glucose measures (A), variability measures (B), and in-range measures (C) for higher degree of hepatic steatosis. Multiple ordinal logistic regression models were performed to examine the associations of CGM-derived measures (normalized and standardized) with higher degree of hepatic steatosis, adjusting for covariates in model 2. False discovery rate (FDR) was applied to correct for multiple comparisons using the Benjamini–Hochberg method. \*\*\*FDR < 0.001; \*\*FDR < 0.01; \*FDR < 0.05. MBG mean blood glucose; AUC glucose area under the curve; GMI glucose management indicator; CV coefficient of variation; MAGE mean amplitude of glycemic excursions; MODD mean of daily differences; TIR time in range; TAR time above range; TBR time below range

association between nighttime TBR and steatosis degree was observed (OR: 0.82, 95% CI: 0.71–0.95), while the positive association between daytime TAR and steatosis degree was observed (OR: 1.30, 95% CI: 1.13–1.50).

Interestingly, TIR demonstrated a negative association with steatosis degree during daytime (OR: 0.83, 95% CI: 0.73–0.95), while a positive association during nighttime (OR: 1.16, 95% CI: 1.00–1.33) (Fig. 1C). To assess whether the associations between TIR and steatosis degree are independent of TAR and TBR, we included TAR and TBR separately into model 2. The positive association between nighttime TIR and steatosis degree remained significant after further adjustment for nighttime TAR, and the negative association between daytime TIR and steatosis degree remained significant after further adjustment for daytime TBR ( $P < 0.05$ ; Table S5). We obtained similar results with in-range measures when utilizing a target glucose of range 3.9–7.8 mmol/L (Fig. S6; Table S5).

### CGM-derived metrics and different degrees of hepatic steatosis

In our subsequent analyses with the multinomial logistic regression models, we obtained consistent results for the associations between CGM-derived metrics and hepatic steatosis, after adjusting for covariates in model 2 (Table 2). Notably, among all nighttime glucose level (i.e., MBG, AUC, and GMI) and variability (i.e., CV, MAGE, and MODD) metrics, only nighttime MODD (OR: 1.32; 95% CI: 1.10, 1.59) was associated with mild steatosis (FDR < 0.05). In addition, a negative association was observed between daytime TIR and moderate/severe steatosis (OR: 0.76; 95% CI: 0.63, 0.92), while a positive association was observed between nighttime TIR and mild steatosis (OR: 1.21; 95% CI: 1.01, 1.45; FDR = 0.054).

**Table 2** Associations of CGM-derived metrics with different degrees of hepatic steatosis

	Nighttime		Daytime		All day	
	OR (95% CI)	FDR	OR (95% CI)	FDR	OR (95% CI)	FDR
MBG						
Mild	1.18 (0.99, 1.42)	0.090	1.24 (1.02, 1.50)	0.047	1.23 (1.02, 1.49)	0.046
M/S	1.41 (1.17, 1.72)	0.001	1.55 (1.26, 1.90)	<0.001	1.53 (1.25, 1.87)	<0.001
AUC						
Mild	1.18 (0.99, 1.42)	0.092	1.23 (1.02, 1.50)	0.047	1.23 (1.02, 1.49)	0.046
M/S	1.41 (1.16, 1.72)	0.001	1.55 (1.26, 1.90)	<0.001	1.53 (1.25, 1.87)	<0.001
GMI						
Mild	1.17 (0.97, 1.40)	0.118	1.22 (1.00, 1.48)	0.064	1.21 (1.00, 1.47)	0.066
M/S	1.38 (1.14, 1.67)	0.002	1.51 (1.24, 1.84)	<0.001	1.49 (1.22, 1.81)	<0.001
CV						
Mild	1.01 (0.85, 1.20)	0.944	1.24 (1.05, 1.47)	0.023	1.17 (0.98, 1.39)	0.097
M/S	1.17 (0.97, 1.42)	0.118	1.27 (1.05, 1.54)	0.023	1.26 (1.04, 1.53)	0.030
MAGE						
Mild	1.00 (0.84, 1.20)	0.998	1.26 (1.06, 1.51)	0.018	1.26 (1.06, 1.51)	0.019
M/S	1.26 (1.04, 1.54)	0.034	1.44 (1.18, 1.75)	<0.001	1.50 (1.23, 1.83)	<0.001
MODD						
Mild	1.32 (1.10, 1.59)	0.006	1.34 (1.11, 1.61)	0.005	1.21 (1.00, 1.46)	0.063
M/S	1.45 (1.18, 1.78)	<0.001	1.66 (1.34, 2.04)	<0.001	1.55 (1.26, 1.91)	<0.001
TIR						
Mild	1.21 (1.01, 1.45)	0.054	0.92 (0.76, 1.11)	0.419	1.05 (0.88, 1.25)	0.640
M/S	1.12 (0.92, 1.37)	0.285	0.76 (0.63, 0.92)	0.009	0.88 (0.73, 1.06)	0.200
TAR						
Mild	1.03 (0.87, 1.23)	0.771	1.19 (0.98, 1.44)	0.103	1.19 (0.98, 1.44)	0.099
M/S	1.14 (0.97, 1.35)	0.143	1.45 (1.19, 1.76)	<0.001	1.43 (1.18, 1.74)	<0.001
TBR						
Mild	0.81 (0.68, 0.97)	0.038	0.93 (0.79, 1.10)	0.422	0.85 (0.71, 1.01)	0.080
M/S	0.81 (0.66, 1.00)	0.067	0.90 (0.74, 1.09)	0.321	0.83 (0.68, 1.02)	0.097

Multinomial logistic regression models were performed to examine the associations of CGM-derived measures (normalized and standardized) with mild hepatic steatosis and moderate/severe hepatic steatosis (healthy group as reference), adjusting for covariates in model 2

CGM continuous glucose monitoring; M/S moderate/severe; MBG mean blood glucose; AUC total glucose area under the curve; GMI glucose management indicator; CV coefficient of variation; MAGE mean amplitude of glycemic excursions; MODD mean of daily differences; TIR time in range; TAR time above range; TBR time below range

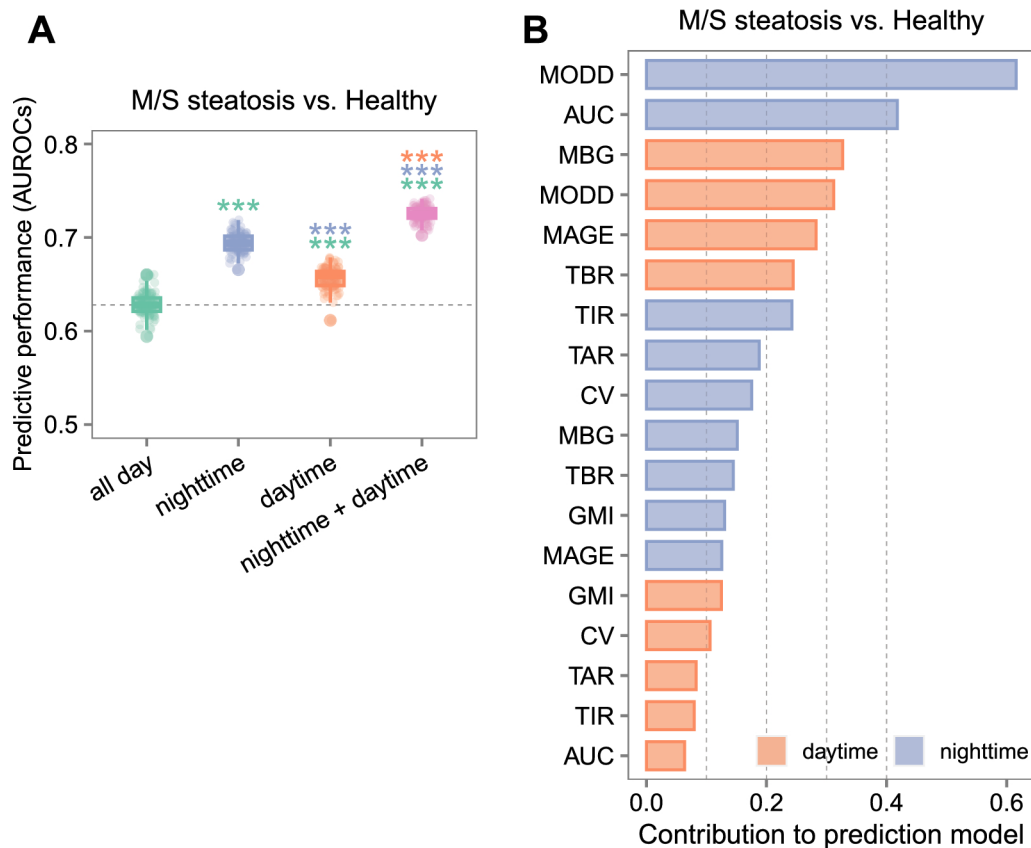
### Predictive performance of CGM-derived metrics during different time periods for hepatic steatosis

In the prediction of moderate/severe steatosis (healthy group as reference), nighttime and daytime models both demonstrated higher AUROCs compared to the all-day model ( $P < 0.001$  for both comparisons). The combined model incorporating both nighttime and daytime metrics achieved the greatest performance, with higher AUROC compared to the all-day, nighttime and daytime models (all  $P < 0.001$ ). The average AUROCs (95% CI) were 0.63 (0.61, 0.65) for the all-day model, 0.69 (0.68, 0.71) for the nighttime model, 0.66 (0.63, 0.68) for the daytime model, and 0.73 (0.71, 0.74) for the combined model, respectively (Fig. 2A). The average sensitivity and specificity (95% CI) were 0.67 (0.50, 0.84) and 0.54 (0.38, 0.71) for the all-day model, 0.70 (0.57, 0.83) and 0.60 (0.47, 0.74) for the nighttime model, 0.65 (0.50, 0.81) and 0.60 (0.44, 0.76) for the daytime model, and 0.73 (0.63, 0.83) and 0.64 (0.54, 0.74) for the combined model (Fig. S7). As ranked by the average SHAP values from the combined model, nighttime

MODD showed the strongest predictive power for the prediction of moderate/severe steatosis (Fig. 2B). Similar results were observed for mild steatosis (Fig. S8).

### CGM-derived metrics and liver fibrosis

Among 1115 participants with FIB-4 score, 538 (48.3%), 523 (46.9%) and 54 (4.8%) participants were categorized into low-risk, indeterminate-risk and high-risk fibrosis groups, respectively. After adjusting for covariates in model 2 and applying multiple testing correction, lower mean glucose (i.e., MBG, AUC, and GMI) and glycemic variability (i.e., MAGE) were associated with higher FIB-4 (Fig. S9) ( $FDR < 0.05$ ). As liver fibrosis is progressed from steatosis, we then performed subgroup analyses among participants with and without hepatic steatosis and examined potential interactions. Notably, the negative associations of mean glucose measures and glycemic variability with liver fibrosis degree were observed among participants without hepatic steatosis, but not among



**Fig. 2** Comparison in the predictive performance of CGM-derived metrics during different time periods for moderate/severe hepatic steatosis. **A** Area under the receiver operating characteristic curves (AUROCs) of CGM-derived metrics for the prediction of moderate/severe steatosis. Models were constructed with CGM-derived metrics during all-day, nighttime and daytime periods separately, as well as nighttime and daytime metrics together. AUROCs were measured by 100 iterations of fivefold cross-validation. Wilcoxon tests were conducted to compare AUROCs of different models. Horizontal dash lines indicate the median AUROCs of the all-day model. Asterisks denote significant differences in AUROCs compared with the model in the same color as the asterisks. \*\*\* $P < 0.001$ ; \*\* $P < 0.01$ ; \* $P < 0.05$ . **B** Contribution of CGM-derived metrics during nighttime and daytime to the prediction of moderate/severe steatosis. Mean SHAP values from the combined model of nighttime and daytime metrics were used to estimate the contribution of CGM-derived metrics to the overall prediction of hepatic steatosis. *AUROC* area under the receiver operating characteristic curves; *M/S* moderate/severe

those with hepatic steatosis (FDR interaction  $< 0.05$ ) (Table S6).

## Discussion

In this study, we investigated the associations of CGM-derived metrics with MRI-diagnosed steatosis degree among 1180 middle-aged and elderly Chinese adults. We demonstrated positive associations of CGM-derived mean glucose and variability measures with hepatic steatosis degree, especially for the daytime measures. We observed opposite associations between TIR and hepatic steatosis degree during the nighttime and daytime periods. In addition, we found that CGM metrics during nighttime and daytime alone had superior performance than that of all-day metrics, and together improved the predictive performance for hepatic steatosis. Notably, nighttime MODD was the most important CGM metric in predicting hepatic steatosis.

Our results confirm and extend prior studies demonstrating positive associations between blood glucose levels and fatty liver disease [25–27]. Previous studies have showed positive associations between visit-to-visit fasting plasma glucose variability, an indicator of long-term glycemic variability, and MASLD [28, 29]. In contrast, CGM-derived variability metrics indicated short-term glycemic variability [30], and were reported to be associated with adverse clinical outcomes such as diabetic macrovascular and microvascular complications [31]. Moreover, a recent population-based study of non-diabetic individuals has found positive correlations between CGM-derived variability metrics and liver-related clinical measures [11]. However, some studies have reported null associations between CGM-derived variability measures (e.g., SD, MAGE, and MODD) and liver enzymes [32], liver fat content [33], or liver fibrosis [34]. The inconsistency may arise from variations in sample size and study population.



In addition, as a parameter of inter-day glycemic variability reflecting irregular habits and lifestyle [35], MODD demonstrated the strongest predictive power for hepatic steatosis in the current study. The potential mechanism underlying the impact of glycemic variability on hepatic steatosis may involve oxidative stress [30, 36]. It has been suggested that increased glycemic variability led to the production of more reactive oxygen species compared to hyperglycemia alone [30], and oxidative stress was known to be involved in the pathogenesis of MASLD [37].

As an essential metric for diabetic management in clinical practice, TIR has been shown to be inversely associated with HbA1c and the risk of diabetic complications in diabetic patients [38]. However, in our population-based study of middle-age and elderly adults, we did not observe a significant association between daily TIR and hepatic steatosis. Interestingly, when assessed separately during nighttime and daytime periods, TIR exhibited a negative association with hepatic steatosis during daytime, while a positive association during nighttime. This finding was also supported by Keshet et al. that TIR was positive correlated with liver-related clinical measures during sleep time but not wake time in a large non-diabetic population [11]. The discrepancy may stem from the differences in glucose distributions during different periods, as a wide range of glucose exists for a given TIR level. Our findings supported the recommendation from an international consensus statement to assess and appropriately define time in range measures during sleep periods and active periods [9].

Our study is novel to reveal different associations patterns between CGM-derived metrics and hepatic steatosis during nighttime and daytime periods. Blood glucose levels during sleep at night are mainly regulated by insulin secretion to maintain basic metabolism, while during the day are largely influenced by behavioral factors such as diet, activity, and medication intake [39]. In the current study, associations of mean glucose level and glycemic variability metrics with hepatic steatosis were more prominent during daytime, highlighting the importance of glycemic control through regulating behavioral factors for the management of hepatic steatosis. In addition, our observation of improved predictive capacity with CGM metrics during both nighttime and daytime indicated that impairment of both physiological and behavior-responsive glucose contributed to the development of hepatic steatosis, providing insights into the role of glycemic dysfunction in the pathophysiology of hepatic steatosis.

Interestingly, the association patterns of CGM metrics with FIB-4 score among participants without hepatic steatosis were opposite to those of CGM metrics with hepatic steatosis. In contrast, previous studies have

demonstrated positive associations between postprandial glucose and liver fibrosis risk in NAFLD patients [40]. However, studies indicated that FIB-4 index is not suitable for primary screening for liver fibrosis in the general population without liver disease [41]. Therefore, the findings we observed between CGM metrics and FIB-4 among participants without hepatic steatosis still need validation in future studies.

The present study has several strengths. First, unlike previous population-based studies that relied on ultrasound or biomarkers for the diagnosis of hepatic steatosis, our utilization of MRI in a large sample size allows the classification of different degree of hepatic steatosis and helps minimize the misclassification bias. Second, CGM-derived metrics were processed separately for nighttime and daytime periods, going beyond the conventional analyses largely focused on metrics of all day. Our study also has several limitations. First, the nature of cross-sectional study restricts the establishment of temporal and causal relationships between the CGM-derived metrics and hepatic steatosis. Second, all participants included in the current study are middle-aged and elderly Chinese individuals, limiting the generalizability of our findings to other age groups or ethnicities. Third, we cannot exclude the potential for selection biases due to the non-probability sampling, although the initial subject selection is unlikely to be differentially related to CGM metrics between participants with and without hepatic steatosis. Lastly, although MRI is recognized as the most accurate non-invasive method to quantify liver fat content, liver biopsy remains the gold standard for assessing histological features of liver diseases.

## Conclusions

In summary, we found that higher CGM-derived mean glucose and variability metrics were associated with higher degree of hepatic steatosis, and CGM-derived metrics during the nighttime and daytime periods offered unique and complementary information for hepatic steatosis. Our findings provide novel insights into the preventive strategy of hepatic steatosis via precision glycemic management.

## Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUROC	Area under the receiver operating characteristic curves
BMI	Body mass index
CGM	Continuous glucose monitoring
CI	Confidence interval
CV	Coefficient of variation
FBG	Fasting blood glucose
FDR	False discovery rate
GMI	Glucose management indicator
GNHS	Guangzhou Nutrition and Health Study
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein

lightGBM	Light Gradient Boosting Machine
MAGE	Mean amplitude of glucose excursions
MBG	Mean of continuous blood glucose values
MODD	Mean of daily differences
MRI	Magnetic resonance imaging
MASLD	Metabolic dysfunction-associated steatotic liver disease
OR	Odds ratio
PDFF	Proton density fat fraction
PLT	Platelet count
SD	Standard deviation
SHAP	Shapley Additive exPlanations
TAR	Time above range
TBR	Time below range
TG	Triglycerides
TIR	Time in range
WHR	Waist-to-hip ratio

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-024-02409-6>.

Additional file 1

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## Author contributions

Y.-m.C. and J.-S.Z. designed and supervised the research; H.Z., K.Z., and X.L. contributed to the development of methodology; H.Z., L.L., Y.Y., and H.C. contributed to data collection; H.Z., K.Z., X.L., L.S., J.C., and Z.M. contributed to data curation; H.Z. performed the data analysis and visualization; H.Z., K.Z., and Z.M. drafted the manuscript. Y.-m.C. and J.-S.Z. critically revised the manuscript. Y.-m.C. and J.-S.Z. contributed to the funding acquisition. All authors have read, revised, and approved the final version of the manuscript.

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## Data availability

The datasets supporting the conclusions of this article are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study protocol of the GNHS was approved by the Ethics Committee of the School of Public Health at Sun Yat-sen University, and all participants provided written informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

## Author details

<sup>1</sup>Department of Epidemiology, Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-Sen University, Guangzhou 510275, China

<sup>2</sup>Westlake Center for Intelligent Proteomics, Westlake Laboratory of Life Sciences and Biomedicine, Hangzhou, China

<sup>3</sup>Zhejiang Key Laboratory of Multi-Omics in Infection and Immunity, Center for Infectious Disease Research, School of Medicine, Westlake University, Hangzhou, China

<sup>4</sup>Research Center for Industries of the Future, School of Life Sciences, Westlake University, Hangzhou, China

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