

ORIGINAL RESEARCH

# High Variability of Body Mass Index Is Independently Associated With Incident Heart Failure

Chang Liu , MPH\*; Yiyun Chiang , MPH\*; Qin Hui , PhD; Jin J. Zhou , PhD; Peter W. F. Wilson , MD; Jacob Joseph , MD; Yan V. Sun , PhD

**BACKGROUND:** Heart failure (HF) is a serious condition with increasing prevalence, high morbidity, and increased mortality. Obesity is an established risk factor for HF. Fluctuation in body mass index (BMI) has shown a higher risk of cardiovascular outcomes. We investigated the association between BMI variability and incident HF.

**METHODS AND RESULTS:** In the UK Biobank, we established a prospective cohort after excluding participants with prevalent HF or cancer at enrollment. A total of 99 368 White participants with  $\geq 3$  BMI measures during  $>2$  years preceding enrollment were included, with a median follow-up of 12.5 years. The within-participant variability of BMI was evaluated using standardized SD and coefficient of variation. The association of BMI variability with incident HF was assessed using Fine and Gray's competing risk model, adjusting for confounding factors and participant-specific rate of BMI change. Higher BMI variability measured in both SD and coefficient of variation was significantly associated with higher risk in HF incidence (SD: hazard ratio [HR], 1.05 [95% CI, 1.03–1.08],  $P < 0.0001$ ; coefficient of variation: HR, 1.07 [95% CI, 1.04–1.10],  $P < 0.0001$ ).

**CONCLUSIONS:** Longitudinal health records capture BMI fluctuation, which independently predicts HF incidence.

**Key Words:** body mass index ■ heart failure ■ heart failure incidence

**H**eat failure (HF) is a disease of high public health burden. It affects an estimated total of 64 million patients with HF worldwide,<sup>1</sup> including 6 million in the United States.<sup>2</sup> The prevalence of HF is projected to exceed 8 million adults by the year 2030.<sup>3</sup> HF prevalence is similar among both men and women; however, a higher incidence has been observed among men, and a longer survival was observed among women.<sup>4</sup> Many factors play critical roles in HF cause, such as obesity,<sup>5</sup> aging,<sup>6,7</sup> diabetes,<sup>8</sup> and hypertension.<sup>9</sup> Their potential causal effects were supported by recent Mendelian randomization studies.<sup>10,11</sup>

Furthermore, as one of the leading risk factors for HF, obesity is associated with a high population-attributable fraction of up to 21% in HF cases.<sup>12,13</sup> Fluctuation in body mass index (BMI) has a negative impact on health,<sup>14–17</sup> such as associations with higher risk in coronary heart disease, coronary heart disease mortality, and all-cause mortality.<sup>14–17</sup> Although the association between BMI variability and HF was identified among patients with type 2 diabetes<sup>18</sup> with possible explanation of metabolic syndrome development, such an association has not been established among the general population. Herein, we assessed the hypothesis that BMI variability is associated with incident HF

Correspondence to: Yan V. Sun, PhD, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd NE, Atlanta, GA 30322. Email: [yan.v.sun@emory.edu](mailto:yan.v.sun@emory.edu)

\*C. Liu and Y. Chiang contributed equally.

This manuscript was sent to Tiffany M. Powell-Wiley, MD, MPH, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.031861>

For Sources of Funding and Disclosures, see page 7.

© 2024 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: [www.ahajournals.org/journal/jaha](http://www.ahajournals.org/journal/jaha)

## RESEARCH PERSPECTIVE

### What Is New?

- Body mass index fluctuation is an independent predictor of heart failure incidence with consistent associations across risk factor subgroups.
- The research underscores the need for exploring the mechanisms driving longitudinal body mass index changes and their specific associations with heart failure subtypes.

### What Question Should Be Addressed Next?

- Future studies focusing on the underlying mechanisms and drivers of longitudinal body mass index change could lead to new insights of weight management strategies for heart failure prevention and intervention.

## Nonstandard Abbreviations and Acronyms

**CV** coefficient of variation

among a large cohort free of prevalent HF and cancer, independent of mean BMI and slope of BMI change.

## METHODS

The following research was conducted using data from the UK Biobank Resource under application number 34031. The UK Biobank will make the data available to all bona fide researchers for all types of health-related research that is in the public interest, without preferential or exclusive access for any people. All researchers will be subject to the same application process and approval criteria as specified by UK Biobank. For more details on the access procedure, see the UK Biobank website: [www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk).

### Study Population

This study was performed using the data from the UK Biobank, a large prospective cohort study with participants aged 40 to 69 years enrolled in 2006 to 2010.<sup>19</sup> The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee. All participants provided written informed consent. Researchers can access data from the UK Biobank by registering at the UK Biobank server. The procedures for data cleaning and coding, which were used to produce the study's findings, can be obtained from the corresponding author on a reasonable request.

Longitudinal measures of BMI were obtained from the baseline measure and linkage to primary care data,<sup>19</sup> which includes ≈42% of the UK Biobank participants having ≥1 BMI records identified from the primary care data. Inclusion criteria for this current study include: White (British, Irish, and any other White background) participants free of HF at enrollment, and with ≥3 BMI measures from primary care records within a time window of >2 years before and at enrollment, to assess the BMI variability. HF onset was ascertained on the basis of linkage to Hospital Episode Statistics data, using *International Classification of Diseases, Tenth Revision (ICD-10)*, codes I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.8, I42.9, I50.0, I50.1, and I50.9, and self-reported medical conditions during enrollment interview.<sup>19</sup> The earliest date of diagnosis was compared with the enrollment date, and the HF prevalent cases before or at enrollment were excluded, whereas the HF incident cases after enrollment were treated as outcomes of interest. To avoid possible weight loss attributable to malignancy, we excluded participants with cancer diagnosed before or at enrollment using the national cancer registries linked with the UK Biobank.<sup>19</sup> A total of 99368 participants with a median follow-up of 12.5 years (interquartile range, 12.0–13.3 years) were included in this study based on aforementioned inclusion and exclusion criteria. Time to incident HF was defined as time of HF onset compared with enrollment date for 1 of the following: HF diagnosis after enrollment for cases of incident HF or loss to follow-up or end of follow-up (November 12, 2021) for non-HF controls. Information on ejection fraction for the HF incident cases was not available.

### Statistical Analysis

For the overall cohort and separately by HF incident cases, characteristics were summarized as mean±SD or median and interquartile range for continuous variables, and count (percentage) for categorical variables. Two-sample *t* test, Mann-Whitney *U* test for continuous variables, and  $\chi^2$  test for categorical variables were used to compare between incident HF versus no incident HF where appropriate. The within-participant variability of BMI was calculated using SD and coefficient of variation (CV; SD divided by within-participant mean BMI) across the multiple measurements. The SD and CV were mean centered and scaled by SD for downstream analyses, for an interpretation based on a standardized scale. To calculate the participant-specific rate of BMI change, a mixed-effect model of longitudinal BMI regressed on the date of BMI measures adjusting for age and sex was adopted. Participant-specific random intercepts representing differences in individual baseline BMI, and random slopes representing differences in individual rate of BMI change, were

incorporated. The random slopes of BMI change were then scaled to kg/m<sup>2</sup> per year for downstream analysis.

The association of BMI variability with incident HF was assessed using Fine and Gray's competing risk model, treating death events as competing risk events.<sup>20</sup> Three models were assessed: model 1 adjusted for age, sex, smoking history (current or previous smoking versus never smoking), frequent alcohol consumption ( $\geq 3$  times per week versus less frequent), self-reported health conditions, including diabetes, hypertension, heart attack history, stroke history, and *ICD-10* (I44.0, I44.1, I44.2, I44.3, I44.5, I46.0, I46.1, I46.9, I47.0, I47.2, I48, I48.1, I48.2, I48.3, I48.4, I48.9, I49.0, and I49.5) defined atrial fibrillation history based on Hospital Episode Statistics data, high-density lipoprotein cholesterol, low-density lipoprotein, total cholesterol, triglycerides, and estimated glomerular filtration rate estimated using the 2021 Chronic Kidney Disease Epidemiology Collaboration equation.<sup>21</sup> In addition to model 1, model 2 adjusted for within-participant mean BMI across longitudinal measures. In addition to model 2, model 3 adjusted for the participant-specific rate of BMI change per year, which was the random slopes derived using the mixed-effect model aforementioned. Cumulative incidence curves were used to visualize the difference in HF incidence between the groups with highest 20%, middle 60%, and lowest 20% quantile of BMI variability measured in both SD and CV, using Fine and Gray's competing risk model adjusting for the covariates in model 3. Using model 3 and excluding risk factor of stratification, we further explored the associations across risk factor strata: sex, age (<60 or  $\geq 60$  years), diabetes, hypertension, BMI at enrollment categorized as underweight (BMI <18.5 kg/m<sup>2</sup>), normal weight (BMI  $\geq 18.5$  and <25 kg/m<sup>2</sup>), overweight (BMI  $\geq 25$  and <30 kg/m<sup>2</sup>), and obese (BMI  $\geq 30$  kg/m<sup>2</sup>), increase and decrease in BMI over time (positive and negative slopes of BMI change). The interaction between BMI variability and these risk factors was also tested using model 3. A forest plot was used to represent the stratified subgroup analysis results with the *P* value of each interaction term between BMI variability and subgroup indicator. In addition, we performed sensitivity analyses by controlling for blood pressure medication use, sleep apnea, sodium in urine, albumin, and sodium from diet.

Analyses were performed using R, version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and SAS statistical software, version 9.4 (SAS Institute Inc, Cary, NC).

## RESULTS

The cohort of 99 368 participants was 57% women, with mean age of 57.5 (SD, 7.8) years. A total of 3406 incident HF cases were observed during the follow-up (Table 1). Participants who experienced incident

HF had a higher level of BMI variability in SD compared with participants who did not (SD: 1.68 versus 1.53;  $P < 0.001$ ); however, this was not the case in CV (0.0562 versus 0.0560;  $P = 0.137$ ). Participants who experienced incident HF also had a lower proportion of women (35.6% versus 57.8%;  $P < 0.001$ ), higher proportions in lifestyle risk factors and prevalence of cardiovascular comorbidities, medication use, higher mean BMI, and BMI at enrollment, and higher BMI increase rate, and higher levels in lipid profile, except for high-density lipoprotein cholesterol and low-density lipoprotein cholesterol (Table 1).

In model 1, the effect per positive SD in BMI variability, measured in both SD and CV, was associated with greater risk in HF incidence (SD: hazard ratio [HR], 1.12 [95% CI, 1.10–1.14],  $P < 0.0001$ ; CV: HR, 1.11 [95% CI, 1.08–1.14],  $P < 0.0001$ ). After additionally adjusting for within-participant mean BMI in model 2, the associations were reduced but remained statistically significant (SD: HR, 1.05 [95% CI, 1.02–1.07],  $P = 0.0002$ ; CV: HR, 1.06 [95% CI, 1.04–1.09],  $P < 0.0001$ ). In model 3 additionally adjusting for participant-specific rate of BMI change, the associations remained unchanged (SD: HR, 1.05 [95% CI, 1.03–1.08],  $P < 0.0001$ ; CV: HR, 1.07 [95% CI, 1.04–1.10],  $P < 0.0001$ ; Table 2 and Figure). In model 3, the within-participant mean BMI across longitudinal measures and the participant-specific random slope of BMI change were both associated with higher risk of incident HF (Table S1). Results from the sensitivity analyses with additional covariates did not meaningfully change the HR estimates in model 3 (Table S2). By comparing the 3 subgroups with highest 20%, middle 60%, and lowest 20% quantile (reference) of BMI variability, based on model 3, participants with highest 20% quantile of BMI variability measured in both SD (HR, 1.35 [95% CI, 1.18–1.54],  $P < 0.0001$ ) and CV (HR, 1.41 [95% CI, 1.24–1.60],  $P < 0.0001$ ) showed highest incidence of HF, followed by the middle 60% (SD: HR, 1.14 [95% CI, 1.02–1.27],  $P = 0.0169$ ; CV: HR, 1.26 [95% CI, 1.14–1.40],  $P < 0.0001$ ) and lowest 20% quantile (Figures S1 and S2).

Stratified analysis results showed a consistent direction of hazardous effect of BMI variability (Table 2 and Figure). In model 3, the within-participant mean BMI and the participant-specific random slope of BMI change was associated with greater risk of incident HF in subgroups stratified by sex, age, diabetes, and hypertension (Table S1). Stratified analysis among the underweight group was not performed because of the small sample size ( $N = 445$ ) and number of events (13 incident HF cases). Although not reaching statistical significance, we identified a suggestive interaction between BMI variability and sex with potentially stronger associations observed among women than men in the fully adjusted models for both SD (women: HR, 1.09 [95% CI, 1.04–1.13],  $P = 0.0001$ ; men: HR, 1.03 [95% CI, 1.00–1.06],  $P = 0.0880$ ) and CV (women: HR, 1.11 [95%

**Table 1. Cohort Characteristics**

Variables	Overall cohort (N=99368)	Incident heart failure (N=3406 [3.4%])	No incident heart failure (N=95962 [96.6%])	P value*
Female sex, n (%)	56655 (57.0)	1213 (35.6)	55442 (57.8)	<0.001†
Age at enrollment, y	57.5±7.8	62.5±5.8	57.4±7.8	<0.001†
Smoking history, n (%)	45430 (45.7)	2053 (60.3)	43377 (45.2)	<0.001†
Frequent alcohol consumption, n (%)	42611 (42.9)	1356 (39.9)	41255 (43.0)	<0.001†
Diabetes, n (%)	7098 (7.1)	728 (21.4)	6370 (6.7)	<0.001†
Hypertension, n (%)	33249 (33.5)	1951 (57.4)	31298 (32.7)	<0.001†
Heart attack history, n (%)	2986 (3.0)	571 (16.8)	2415 (2.5)	<0.001†
Stroke history, n (%)	1859 (1.9)	217 (6.4)	1642 (1.7)	<0.001†
Atrial fibrillation history, n (%)	1689 (1.7)	328 (9.6)	1361 (1.4)	<0.001†
BMI at enrollment, kg/m <sup>2</sup>	28.0±5.1	30.55±6.1	27.88±5.0	<0.001†
Within-participant mean BMI (across longitudinal measures), kg/m <sup>2</sup>	27.0±4.7	29.4±5.6	26.9±4.6	<0.001†
HDL-C, mg/dL	55.8±14.8	49.9±14.1	56.0±14.8	<0.001†
LDL-C, mg/dL	136.0±34.3	122.2±35.7	136.6±34.1	<0.001†
Total cholesterol, mg/dL	218.0±45.2	227.0±43.9	207.1±44.4	<0.001†
Triglycerides, median (IQR), mg/dL	134.3 (95.0–193.4)	151.7 (106.7–214.7)	133.7 (94.6–192.6)	<0.001†
eGFR, mL/min/1.73m <sup>2</sup>	93.9±13.1	87.6±16.4	94.1±13.0	<0.001†
Cholesterol-lowering medication, n (%)	22611 (22.9)	1774 (52.4)	20837 (21.8)	<0.001†
Blood pressure medication, n (%)	12308 (12.5)	541 (16.0)	11767 (12.3)	<0.001†
BMI variability				
SD	1.54±1.26	1.68±1.24	1.53±1.26	<0.001†
Coefficient of variation	0.0560±0.0393	0.0562±0.0396	0.0560±0.0394	0.137
BMI change				
Slope, kg/m <sup>2</sup> per year	0.160±0.140	0.194±0.170	0.159±0.139	<0.001†

Mean±SD shown for continuous variables unless stated otherwise; count (percentage) shown for categorical variables.

BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

\*P value for comparing incident heart failure vs no incident heart failure groups.

†P<0.05 used for defining statistical significance.

CI, 1.06–1.16],  $P<0.0001$ ; men: HR, 1.04 [95% CI, 1.00–1.08],  $P=0.0422$ ). Furthermore, the associations were identified only among participants with increased BMI, in comparison to decreased BMI for both SD (BMI increase: HR, 1.06 [95% CI, 1.01–1.10],  $P=0.0091$ ; BMI decrease: HR, 1.00 [95% CI, 0.79–1.27],  $P=0.9996$ ) and CV (BMI increase: HR, 1.07 [95% CI, 1.02–1.12],  $P=0.0037$ ; BMI decrease: HR, 1.05 [95% CI, 0.87–1.27],  $P=0.6148$ ) (Table 2 and Figure). Interactions with age, diabetes, hypertension, and BMI weight status category at enrollment were not identified.

## DISCUSSION

This is the first large study that reports a positive association between BMI variability and incident HF, independent of known HF risk factors and mean BMI, after excluding prevalent cancer cases that are susceptible to weight fluctuations. The associations of BMI variability with incident HF were consistent across all BMI categories. It has been shown in recent studies that obesity

plays a potential causal role in HF incidence based on single measurement of BMI.<sup>10,22,23</sup> However, longitudinal multiple measures of time-varying BMI contain additional information that can better characterize an individual's underlying metabolic condition. The associations between BMI variability and incidence of cardiovascular diseases, such as coronary heart disease, and mortality outcomes have been established,<sup>14,24</sup> but the relationship between BMI variability and incident HF in the general population remains unclear. Our study addresses an important knowledge gap in HF susceptibility across several risk factor categories. Potential sex differences may indicate that the hazardous effect of major changes in body weight impacts women more than men in HF onset. Furthermore, the effect of BMI variability on HF incidence may be of greater influence among the population with increasing trend of body weight. The associations we identified in the overall cohort are independent from the BMI change rate over time, which indicates that BMI variability may be included as an informative measurement of HF risk to better assess populations susceptible to HF.

**Table 2. Association Between BMI Variability (Measured in SD and CV, per SD) and Incident HF**

Cohort	SD HR (95% CI), <i>P</i> value			CV HR (95% CI), <i>P</i> value		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Overall	1.12 (1.10–1.14), <i>P</i> <0.0001*	1.05 (1.02–1.07), <i>P</i> =0.0002*	1.05 (1.03–1.08), <i>P</i> <0.0001*	1.11 (1.08–1.14), <i>P</i> <0.0001*	1.06 (1.04–1.09), <i>P</i> <0.0001*	1.07 (1.04–1.10), <i>P</i> <0.0001*
Female sex	1.15 (1.11–1.19), <i>P</i> <0.0001*	1.07 (1.03–1.12), <i>P</i> =0.0009*	1.09 (1.04–1.13), <i>P</i> =0.0001*	1.14 (1.09–1.19), <i>P</i> <0.0001*	1.09 (1.04–1.14), <i>P</i> <0.0001*	1.11 (1.06–1.16), <i>P</i> <0.0001*
Male sex	1.10 (1.08–1.13), <i>P</i> <0.0001*	1.03 (1–1.06), <i>P</i> =0.0674	1.03 (1.00–1.06), <i>P</i> =0.0880	1.09 (1.05–1.13), <i>P</i> <0.0001*	1.04 (1.01–1.08), <i>P</i> =0.0178*	1.04 (1.00–1.08), <i>P</i> =0.0422*
Aged <60y	1.15 (1.11–1.19), <i>P</i> <0.0001*	1.07 (1.02–1.12), <i>P</i> =0.0024*	1.07 (1.02–1.12), <i>P</i> =0.0072*	1.14 (1.09–1.2), <i>P</i> <0.0001*	1.09 (1.04–1.15), <i>P</i> =0.0004*	1.09 (1.03–1.15), <i>P</i> =0.0018*
Aged ≥60y	1.11 (1.09–1.14), <i>P</i> <0.0001*	1.04 (1.01–1.07), <i>P</i> =0.0076*	1.05 (1.02–1.08), <i>P</i> =0.0028*	1.1 (1.07–1.14), <i>P</i> <0.0001*	1.05 (1.02–1.09), <i>P</i> =0.0006*	1.06 (1.03–1.09), <i>P</i> =0.0004*
No diabetes	1.11 (1.09–1.14), <i>P</i> <0.0001*	1.04 (1.01–1.07), <i>P</i> =0.0023*	1.05 (1.02–1.08), <i>P</i> =0.0012*	1.11 (1.08–1.14), <i>P</i> <0.0001*	1.06 (1.03–1.09), <i>P</i> <0.0001*	1.06 (1.03–1.10), <i>P</i> <0.0001*
Diabetes	1.17 (1.11–1.23), <i>P</i> <0.0001*	1.08 (1.02–1.16), <i>P</i> =0.0119*	1.09 (1.02–1.16), <i>P</i> =0.0073*	1.15 (1.08–1.22), <i>P</i> <0.0001*	1.10 (1.03–1.18), <i>P</i> =0.0053*	1.10 (1.03–1.18), <i>P</i> =0.0052*
No hypertension	1.11 (1.09–1.14), <i>P</i> <0.0001*	1.05 (1.01–1.08), <i>P</i> =0.0037*	1.05 (1.01–1.08), <i>P</i> =0.0049*	1.11 (1.08–1.15), <i>P</i> <0.0001*	1.06 (1.03–1.10), <i>P</i> =0.0003*	1.06 (1.03–1.10), <i>P</i> =0.0009*
Hypertension	1.13 (1.1–1.17), <i>P</i> <0.0001*	1.05 (1.01–1.09), <i>P</i> =0.0157*	1.06 (1.01–1.10), <i>P</i> =0.0091*	1.11 (1.07–1.16), <i>P</i> <0.0001*	1.06 (1.02–1.11), <i>P</i> =0.0030*	1.07 (1.02–1.12), <i>P</i> =0.0025
Normal weight (enrollment BMI ≥18.5 and <25 kg/m <sup>2</sup> )	1.07 (1.01–1.13), <i>P</i> =0.03*	1.09 (1.02–1.18), <i>P</i> =0.016*	1.06 (0.97–1.17), <i>P</i> =0.1838	1.08 (1.02–1.15), <i>P</i> =0.0078*	1.10 (1.03–1.18), <i>P</i> =0.0068*	1.08 (1.00–1.16), <i>P</i> =0.0627
Overweight (enrollment BMI ≥25 and <30 kg/m <sup>2</sup> )	1.07 (1.03–1.11), <i>P</i> =0.0008*	1.06 (1.01–1.11), <i>P</i> =0.0118*	1.06 (1.01–1.11), <i>P</i> =0.0127*	1.08 (1.03–1.13), <i>P</i> =0.0007*	1.08 (1.02–1.13), <i>P</i> =0.0029*	1.08 (1.03–1.13), <i>P</i> =0.0031*
Obese (enrollment BMI ≥30 kg/m <sup>2</sup> )	1.13 (1.08–1.17), <i>P</i> <0.0001*	1.06 (1.02–1.11), <i>P</i> =0.0039*	1.06 (1.01–1.11), <i>P</i> =0.0142*	1.09 (1.04–1.15), <i>P</i> =0.0004*	1.08 (1.03–1.14), <i>P</i> =0.0011*	1.07 (1.02–1.13), <i>P</i> =0.0063*
BMI increase (positive slope [kg/m <sup>2</sup> per year])	1.18 (1.14–1.21), <i>P</i> <0.0001*	1.09 (1.05–1.13), <i>P</i> <0.0001*	1.06 (1.01–1.10), <i>P</i> =0.0091*	1.15 (1.11–1.20), <i>P</i> <0.0001*	1.10 (1.06–1.15), <i>P</i> <0.0001*	1.07 (1.02–1.12), <i>P</i> =0.0037*
BMI decrease (negative slope [kg/m <sup>2</sup> per year])	0.97 (0.88–1.06), <i>P</i> =0.4973	0.98 (0.87–1.10), <i>P</i> =0.7086	1.00 (0.79–1.27), <i>P</i> =0.9996	0.99 (0.90–1.08), <i>P</i> =0.7851	1.00 (0.90–1.12), <i>P</i> =0.9809	1.05 (0.87–1.27), <i>P</i> =0.6148

Model 1: adjusted for age, sex, smoking history (current or previous smoking vs never smoking), frequent alcohol consumption (≥3 times per week vs less frequent), diabetes, hypertension, heart attack history, stroke history, atrial fibrillation history, high-density lipoprotein cholesterol, low-density lipoprotein, total cholesterol, triglycerides, and estimated glomerular filtration rate.

Model 2: model 1+within-participant mean BMI across longitudinal measures.

Model 3: model 2+participant-specific random slope of BMI change per year.

In stratified analyses, corresponding variable for the stratification was not included (eg, sex was excluded in women or men only analysis).

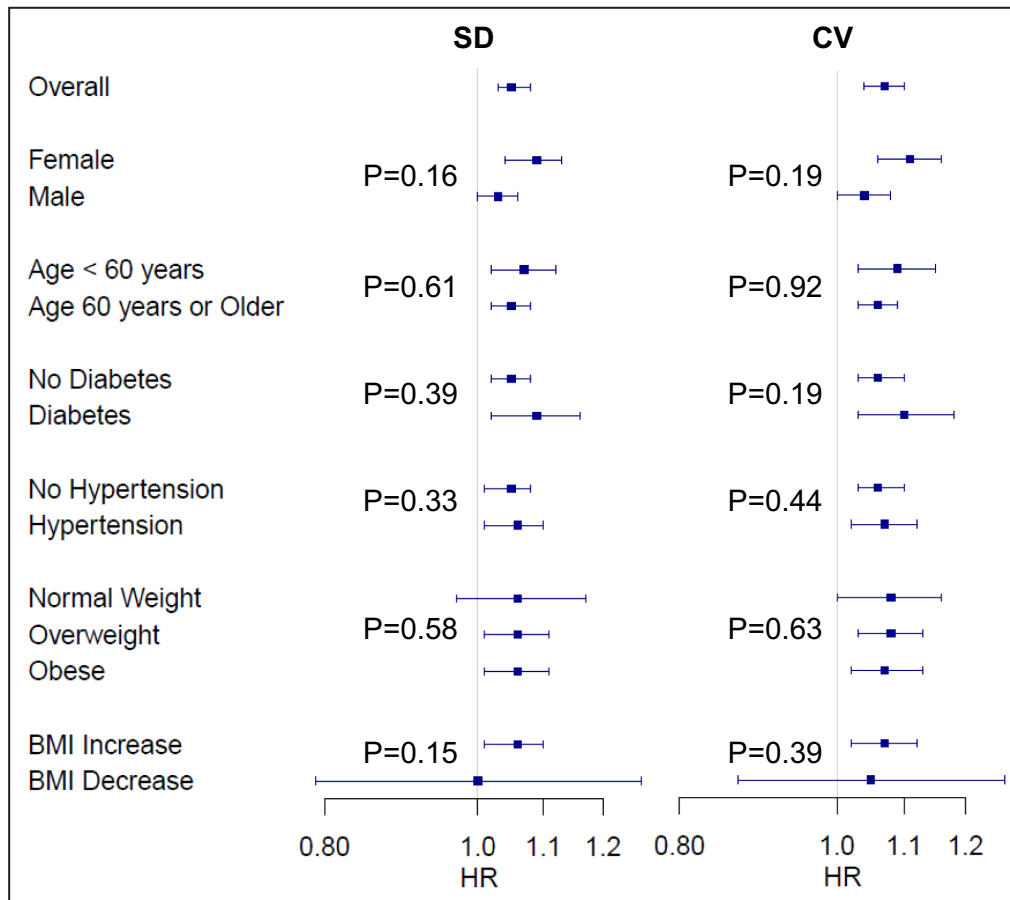
Stratified analysis among underweight group was not performed because of the small sample size and number of events. BMI indicates body mass index; CV, coefficient of variation; and HF, heart failure.

\* *P*<0.05 used for defining statistical significance.

Prior studies have noted an association between body weight change and adverse cardiovascular outcomes, including myocardial infarction, stroke, and mortality, among patients with type 2 diabetes<sup>25</sup> or hypertension.<sup>26</sup> Furthermore, existing evidence has shown that body weight variability is associated with cardiovascular disease risk among patients with type 2 diabetes compared with nondiabetic controls.<sup>27</sup> Although HF shares a similar risk profile with these cardiovascular disease outcomes, no statistically significant difference was observed comparing risk factor categories, including diabetes and hypertension.

This new evidence should not override the well-established benefits of weight loss in obese populations to prevent cardiovascular diseases, including HF.<sup>28</sup> Our definition of BMI variability was solely based on the primary care data, which did not denote intentional or

unintentional weight loss. Intentional weight loss via dieting or exercise is more likely among healthy individuals and might be subject to weight regain, whereas unintentional weight loss might be associated with some chronic medical conditions, such as depression and diabetes, which have been linked with cardiovascular diseases.<sup>29,30</sup> Further studies are needed to separate these 2 mechanisms. Our study has several potential limitations. First, limited by available clinical data, our study did not differentiate between HF subtypes (eg, HF with reduced versus preserved ejection fraction), which might have implications for the interpretation of our findings in specific subgroups within HF. Therefore, our findings in all-cause HF cannot capture potential discrepancy across HF subtypes. Future research endeavors should focus on unraveling these complexities to provide more tailored and nuanced insights into the relationships between



**Figure.** Association between body mass index (BMI) variability (measured in SD and coefficient of variation [CV], per SD) and incident heart failure.

Models adjusted for age, sex, smoking history (current or previous smoking vs never smoking), frequent alcohol consumption ( $\geq 3$  times per week vs less frequent), diabetes, hypertension, heart attack history, stroke history, atrial fibrillation history, high-density lipoprotein cholesterol, low-density lipoprotein, total cholesterol, triglycerides, estimated glomerular filtration rate, within-participant mean BMI across longitudinal measures, and participant-specific random slope of BMI change per year. In stratified analyses, corresponding variable for the stratification was not included (eg, sex was excluded in women or men only analysis). Stratified analysis among underweight group was not performed because of the small sample size and number of events. *P* values indicate the interaction between BMI variability and the variables of stratification. HR indicates hazard ratio.

longitudinal BMI phenotypes and the heterogeneous presentations of HF. Second, we recognize that our study primarily included White European participants. The associations between BMI variability and HF were null in non-European groups in the UK Biobank, likely because of a small sample size and limited number of HF cases. The generalizability of our findings to other racial and ethnic groups requires future investigation in large non-European populations. Third, small sample size of certain subgroups (eg, “negative” slopes in BMI changes) limited statistical power to identify significant association. Furthermore, the stratification of BMI change directions, although initially aimed at understanding weight fluctuation in different trajectories, ignored the group without significant weight gain or loss, and inadvertently constrained the assessment of the full spectrum of BMI

variability over time, prompting a cautious interpretation of our finding in the stratification of BMI change directions. Another potential limitation in our study is not addressing diet as a potential confounding factor. Although our research sought to examine the link between fluctuations in BMI and HF, the influence of diet on both BMI and HF risk cannot be overlooked. Diet plays a pivotal role in shaping an individual’s BMI and is a complex and multifaceted aspect of an individual’s lifestyle. Further studies should explore how dietary factors might interact with BMI fluctuations and subsequently contribute to the development of HF. Finally, this study only used data from participants who had multiple BMI measurements in the primary care data. Multiple primary care visits indicate a propensity to more comorbidities, although we excluded prevalent cancer and HF at enrollment.

## CONCLUSIONS

BMI fluctuation is an independent predictor of HF incidence with consistent associations across risk factor subgroups. Future studies focusing on the underlying mechanisms and drivers of longitudinal BMI change could lead to new insights of weight management strategies for HF prevention and intervention.

## ARTICLE INFORMATION

Received July 20, 2023; accepted March 27, 2024.

### Affiliations

Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA (C.L., Y.C., Q.H., Y.V.S.); Department of Medicine and Biostatistics, University of California, Los Angeles, CA (J.J.Z.); Atlanta VA Health Care System, Decatur, GA (P.W.W., Y.V.S.); Department of Medicine, Emory University School of Medicine, Atlanta, GA (P.W.W.); VA Providence Healthcare System, Providence, RI (J.J.); and Warren Alpert Medical School Brown University, Providence, RI (J.J.).

### Acknowledgments

Author contributions: C. Liu and Dr Sun contributed to the conception and design of the work. C. Liu and Y. Chiang conducted the statistical analysis. C. Liu, Y. Chiang, and Dr Sun contributed to the acquisition and interpretation of data. C. Liu drafted the manuscript. C. Liu, Y. Chiang, Dr Hui, Dr Zhou, Dr Wilson, Dr Joseph, and Dr Sun critically revised the manuscript. Dr Sun was responsible for project funding. All authors gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

### Sources of Funding

This research has been conducted using the UK Biobank resource under application number 34031. This research is supported in part by funding from the National Institute of Health grant P01-HL154996, and Department of Veterans Affairs Office of Research and Development, Million Veteran Program grants I01-BX005831 and I01-BX004821.

### Disclosures

None.

### Supplemental Material

Data S1

## REFERENCES

- Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res*. 2023;118:3272–3287. doi: [10.1093/cvr/cvac013](https://doi.org/10.1093/cvr/cvac013)
- Tsao CW, Aday AW, Almarazgo ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, et al. Heart disease and stroke Statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639. doi: [10.1161/CIR.0000000000001052](https://doi.org/10.1161/CIR.0000000000001052)
- Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomicis JS, Khavjou O, Konstam MA, Maddox TM, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail*. 2013;6:606–619. doi: [10.1161/HHF.0b013e318291329a](https://doi.org/10.1161/HHF.0b013e318291329a)
- Stromberg A, Martensson J. Gender differences in patients with heart failure. *Eur J Cardiovasc Nurs*. 2003;2:7–18. doi: [10.1016/S1474-5151\(03\)00002-1](https://doi.org/10.1016/S1474-5151(03)00002-1)
- Bozkurt B, Aguilar D, Deswal A, Dunbar SB, Francis GS, Horwich T, Jessup M, Kosiborod M, Pritchett AM, Ramasubbu K, et al. Contributory risk and Management of Comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e535–e578. doi: [10.1161/CIR.0000000000000450](https://doi.org/10.1161/CIR.0000000000000450)
- Tromp J, Paniagua SMA, Lau ES, Allen NB, Blaha MJ, Gansevoort RT, Hillege HL, Lee DE, Levy D, Vasani RS, et al. Age dependent associations of risk factors with heart failure: pooled population based cohort study. *BMJ*. 2021;372:n461. doi: [10.1136/bmj.n461](https://doi.org/10.1136/bmj.n461)
- Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin*. 2012;8:143–164. doi: [10.1016/j.hfc.2011.08.011](https://doi.org/10.1016/j.hfc.2011.08.011)
- Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. *Card Fail Rev*. 2017;3:52–55. doi: [10.15420/cfr.2016.20.2](https://doi.org/10.15420/cfr.2016.20.2)
- Levy D, Larson MG, Vasani RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557–1562. doi: [10.1001/jama.1996.03530440037034](https://doi.org/10.1001/jama.1996.03530440037034)
- Shah S, Henry A, Roselli C, Lin H, Sveinbjornsson G, Fatemifar G, Hedman AK, Wilk JB, Morley MP, Chaffin MD, et al. Genome-wide association and mendelian randomisation analysis provide insights into the pathogenesis of heart failure. *Nat Commun*. 2020;11:163. doi: [10.1038/s41467-019-13690-5](https://doi.org/10.1038/s41467-019-13690-5)
- Joseph J, Liu C, Hui Q, Aragam K, Wang Z, Charest B, Huffman JE, Keaton JM, Edwards TL, Demissie S, et al. Genetic architecture of heart failure with preserved versus reduced ejection fraction. *Nat Commun*. 2022;13:7753. doi: [10.1038/s41467-022-35323-0](https://doi.org/10.1038/s41467-022-35323-0)
- Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasani RS. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–313. doi: [10.1056/NEJMoa020245](https://doi.org/10.1056/NEJMoa020245)
- Sinha A, Ning H, Carnethon MR, Allen NB, Wilkins JT, Lloyd-Jones DM, Khan SS. Race- and sex-specific population attributable fractions of incident heart failure: a population-based cohort study from the lifetime risk pooling project. *Circ Heart Fail*. 2021;14:e008113. doi: [10.1161/CIRCHEARTFAILURE.120.008113](https://doi.org/10.1161/CIRCHEARTFAILURE.120.008113)
- Lissner L, Odell PM, D'Agostino RB, Stokes J 3rd, Kreger BE, Belanger AJ, Brownell KD. Variability of body weight and health outcomes in the Framingham population. *N Engl J Med*. 1991;324:1839–1844. doi: [10.1056/NEJM199106273242602](https://doi.org/10.1056/NEJM199106273242602)
- Hamm P, Shekelle RB, Stamler J. Large fluctuations in body weight during young adulthood and twenty-five-year risk of coronary death in men. *Am J Epidemiol*. 1989;129:312–318. doi: [10.1093/oxfordjournals.aje.a115135](https://doi.org/10.1093/oxfordjournals.aje.a115135)
- Choi D, Choi S, Park SM. Impact of weight variability on mortality among Korean men and women: a population based study. *Sci Rep*. 2019;9:9543. doi: [10.1038/s41598-019-46037-7](https://doi.org/10.1038/s41598-019-46037-7)
- Kim MK, Han K, Park YM, Kwon HS, Kang G, Yoon KH, Lee SH. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation*. 2018;138:2627–2637. doi: [10.1161/CIRCULATIONAHA.118.034978](https://doi.org/10.1161/CIRCULATIONAHA.118.034978)
- Kaze AD, Erqou S, Santhanam P, Bertoni AG, Ahima RS, Fonarow GC, Echouffo-Tcheugui JB. Variability of adiposity indices and incident heart failure among adults with type 2 diabetes. *Cardiovasc Diabetol*. 2022;21:16. doi: [10.1186/s12933-021-01440-1](https://doi.org/10.1186/s12933-021-01440-1)
- Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi: [10.1371/journal.pmed.1001779](https://doi.org/10.1371/journal.pmed.1001779)
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509. doi: [10.1080/01621459.1999.10474144](https://doi.org/10.1080/01621459.1999.10474144)
- Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med*. 2021;385:1737–1749. doi: [10.1056/NEJMoa2102953](https://doi.org/10.1056/NEJMoa2102953)
- Benn M, Marott SCW, Tybjaerg-Hansen A, Nordestgaard BG. Obesity increases heart failure incidence and mortality: observational and mendelian randomization studies totalling over 1 million individuals. *Cardiovasc Res*. 2023;118:3576–3585. doi: [10.1093/cvr/cvab368](https://doi.org/10.1093/cvr/cvab368)
- Huang J, Huffman JE, Huang Y, Do Valle I, Assimes TL, Raghavan S, Voight BF, Liu C, Barabasi AL, Huang RDL, et al. Genomics and phenomics of body mass index reveals a complex disease network. *Nat Commun*. 2022;13:7973. doi: [10.1038/s41467-022-35553-2](https://doi.org/10.1038/s41467-022-35553-2)
- Bangalore S, Fayyad R, Laskey R, DeMicco DA, Messerli FH, Waters DD. Body-weight fluctuations and outcomes in coronary disease. *N Engl J Med*. 2017;376:1332–1340. doi: [10.1056/NEJMoa1606148](https://doi.org/10.1056/NEJMoa1606148)

25. Kaze AD, Santhanam P, Erqou S, Ahima RS, Bertoni AG, Echouffo-Tcheugui JB. Body weight variability and risk of cardiovascular outcomes and death in the context of weight loss intervention among patients with type 2 diabetes. *JAMA Netw Open*. 2022;5:e220055. doi: [10.1001/jamanetworkopen.2022.0055](https://doi.org/10.1001/jamanetworkopen.2022.0055)
26. Cai Z, Wu W, Chen Z, Fang W, Li W, Chen G, Chen Z, Wu S, Chen Y. Long-term body mass index variability, weight change slope, and risk of cardiovascular outcomes: 7-year prospective study in Chinese hypertensive subjects. *Obes Facts*. 2021;14:442–449. doi: [10.1159/000512317](https://doi.org/10.1159/000512317)
27. Youk TM, Kang MJ, Song SO, Park EC. Effects of BMI and LDL-cholesterol change pattern on cardiovascular disease in normal adults and diabetics. *BMJ Open Diabetes Res Care*. 2020;8:8. doi: [10.1136/bmjdr-2020-001340](https://doi.org/10.1136/bmjdr-2020-001340)
28. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ*. 2017;359:j4849. doi: [10.1136/bmj.j4849](https://doi.org/10.1136/bmj.j4849)
29. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and anxiety in heart failure: a review. *Harv Rev Psychiatry*. 2018;26:175–184. doi: [10.1097/HRP.0000000000000162](https://doi.org/10.1097/HRP.0000000000000162)
30. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, Deswal A, Dickson VV, Kosiborod MN, Lekavich CL, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation*. 2019;140:e294–e324. doi: [10.1161/CIR.0000000000000691](https://doi.org/10.1161/CIR.0000000000000691)