

# Body Weight Variability and the Risk of Cardiovascular Outcomes in Patients with Nonalcoholic Fatty Liver Disease A Nationwide Cohort Study

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## Original investigation

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## Abstract

**Background:** Body weight variability is thought to be an indicator of poor health outcomes, including cardiovascular disease (CVD) and mortality. Given that the vast majority of NAFLD patients have difficulty maintaining weight loss and CVD is closely associated with NAFLD, the investigation of the influence of body weight variability on CVD and mortality in NAFLD patients is crucial to prevent the deleterious consequences of NAFLD. We investigated the association between body weight variability and the risks of CVD and mortality in patients with NAFLD using large-scale, nationwide cohort data.

**Methods:** We included 726,736 individuals with NAFLD who underwent a health examination provided by the Korean National Health Insurance System between 2009 and 2010, with follow-up through the end of 2017. NAFLD was defined as a fatty liver index  $\geq 60$ , after excluding excess alcohol intake, viral hepatitis, and alcoholic cirrhosis. Significant liver fibrosis was defined as a BARD score  $\geq 2$ . Body weight variability was assessed using four indices, including variability independent of the mean (VIM). A multivariate-adjusted Cox proportional hazards regression analysis was performed.

**Results:** During a median 8.1-year follow-up, we documented 11,358, 14,714, and 22,164 cases of myocardial infarction (MI), stroke, and all-cause mortality, respectively. Body weight variability was associated with an increased risk of MI, stroke, and mortality after adjusting for confounding variables. The hazard ratios (HRs) (95% confidence intervals) for the highest quartile, compared with the lowest quartile, of VIM for body weight were 1.15 (1.10–1.20), 1.22 (1.18–1.26), and 1.56 (1.53–1.62) for MI, stroke, and all-cause mortality, respectively. When examined jointly, the risk of outcomes was highest among NAFLD patients with both significant liver fibrosis and the highest VIM for body weight.

**Conclusions:** Body weight variability was associated with increased risks of MI, stroke, and all-cause mortality in NAFLD patients. Appropriate interventions to maintain a stable weight could positively affect health outcomes in NAFLD patients.

## Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease, and its prevalence is increasing worldwide.[1, 2] NAFLD encompasses simple steatosis without fibrosis and nonalcoholic steatohepatitis with varying degrees of fibrosis and cirrhosis.[2, 3] NAFLD is related to the development of hepatocellular carcinoma or liver failure[4–6] and is also associated with the risk of developing extra-hepatic manifestations, such as cardiovascular disease (CVD), chronic kidney disease, and certain extra-hepatic malignancies.[7, 8] Among these, CVD is the leading cause of increased long-term morbidity and mortality in NAFLD patients.[7, 9–12]

Structured programs with lifestyle modifications, targeting a weight loss of 7–10%, are the first approach to treat NAFLD.[9, 13, 14] However, weight loss is rarely sustainable, and a substantial proportion of NAFLD patients who try weight loss experience weight regain.[9] A pooled follow-up analysis of three large weight-loss trials showed that only 23% maintained weight loss during the third year.[15] Weight regain after weight loss results from homeostatic feedback mechanisms, including change in hunger and satiety hormones and altered characteristics of adipocytes to store more energy during periods of weight loss.[16]

Body weight variability, which is also termed weight fluctuation or weight cycling, is defined as repeated weight loss and subsequent regain. In several epidemiologic studies, body weight variations have been associated with increased risks of future cardiovascular events and mortality.[17–19] Given that the vast majority of NAFLD patients have difficulty maintaining weight loss, and because CVD is closely associated with NAFLD, investigating of the influence of body weight variability on CVD and mortality in NAFLD patients is crucial to prevent the deleterious consequences of NAFLD.

Therefore, we investigated the association between body weight variability and the risks of CVD and mortality in patients with NAFLD using large-scale, nationwide cohort data.

## Methods

### Study population

We used a representative sample cohort provided by the Korean National Health Insurance Service (NHIS) of the National Health Insurance Corporation (NHIC). Approximately 97% of the South Korean population is insured by the NHIS (the sole insuring organization). Standardized health examinations are recommended for enrollees in the NHIS. The NHIC releases data containing various types of individual health information.[20]

From this cohort, we enrolled 17,539,992 individuals who underwent health examinations between January 2009 and December 2010. Subjects who met the following criteria were excluded based on our protocol: (1) received a health examination fewer than three times within 5 years of enrollment ( $n = 9,163,132$ ), (2) aged  $< 20$  years ( $n = 106$ ), (3) any missing data ( $n = 319,788$ ), (4) fatty liver index (FLI)  $< 20$  ( $n = 7,008,442$ ), (4) heavy alcohol consumption (defined as alcohol intake  $\geq 30$  g/day for men or  $\geq 20$  g/day for women) ( $n = 198,203$ ), (5) prior hepatocellular carcinoma history ( $n = 576$ ), (6) viral hepatitis or alcoholic cirrhosis ( $n = 113,295$ ) or (7) prior diagnosis of myocardial infarction (MI) or stroke ( $n = 9,714$ ). The remaining 726,736 participants were included in the final analysis (**Supplementary Fig. 1**) and were followed up until death or December 31, 2017. This study protocol was reviewed and approved by the Institutional Review Board of CHA University (IRB no. 2020-07-073).

### Definitions of NAFLD and liver fibrosis

NAFLD was defined using the FLI, which is a previously validated predictive marker of fatty liver.[21] A FLI  $\geq 60$  is indicative of NAFLD. The fibrotic burden of subjects with NAFLD was assessed using the BARD score, a previously validated predictive marker of liver fibrosis. Significant liver fibrosis was defined as a BARD score  $\geq 2$ . [22] **Supplementary table 1** summarizes these prediction models.

## Anthropometric measurements and indices of body weight variability

Body weight (kg), height (m), and waist circumference (cm) were measured at each visit. Body mass index (BMI) was calculated as body weight divided by height squared. Obesity was defined as a BMI  $\geq 25$  kg/m<sup>2</sup> based on the World Health Organization recommendation for Asian populations.[23] Our analysis used a minimum of three body weight measurements taken within 5 years before the index date (including the examination on the index date). Body weight variability was determined using the following four indices: 1) variability independent of the mean (VIM), 2) standard deviation (SD), 3) coefficient of variation (CV), and 4) average real variability (ARV). VIM was calculated as  $100 \times SD / \text{mean}^\beta$ , where  $\beta$  is the regression coefficient, based on the ln of the SD over the ln of the mean.[24] ARV is based on the average absolute difference between consecutive values. The following formula was

used to calculate ARV in this study: 
$$\text{ARV} = \frac{1}{n-1} \sum_{k=1}^{n-1} |\text{Value}_{k+1} - \text{Value}_k|,$$
 where  $n$  denotes the number of anthropometric measurements.[19]

## Study outcomes and follow-up

The primary endpoints of this study were incident MI, stroke, and all-cause mortality. Using our claims database, MI was determined as ICD-10-CM code I21 or I22 during hospitalization, or these codes were recorded at least twice. Stroke was defined as ICD-10-CM code I63 or I64 during hospitalization according to brain magnetic resonance imaging or brain computed tomography. Mortality data were obtained from the Korean National Statistical Office. Follow-up was completed at the occurrence of cardiovascular events (MI or stroke) or all-cause death.

## Definition of covariates

Demographic and lifestyle data were obtained using a self-reported questionnaire. Smoking status was classified as nonsmoker, former smoker, or current smoker. Regular exercise was defined as strenuous physical activity for  $\geq 20$  min at least three times per week or moderate physical activity for  $\geq 30$  min at least five times per week. Income level was dichotomized into  $< 25\%$  or  $\geq 25\%$ . Data from health examinations, such as blood pressure (BP) and laboratory measurements, were provided. Diabetes mellitus (DM) was defined as a fasting plasma glucose level  $\geq 126$  mg/dL or having at least one prescription claim per year for an antidiabetic medication under the ICD-10 codes E11-E14. Systolic BP  $\geq 140$  mmHg, diastolic BP  $\geq 90$  mmHg, or at least one prescription claim per year for antihypertensive medication under ICD-10-CM codes I10-I13 and I15 was defined as having hypertension. Dyslipidemia was defined as a serum total cholesterol level  $\geq 240$  mg/dL or at least one prescription claim per year for a lipid-lowering medication under ICD-10-CM code E78. Chronic kidney disease was defined as an estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>. [25]

## Statistical analysis

The baseline characteristics of the study participants according to the VIM categories of body weight are presented as means  $\pm$  SD for continuous variables and numbers (percentages) for categorical variables. Analysis of variance was used to compare continuous variables, and the chi-square test was used to compare categorical variables. The incidence rate was calculated by dividing the number of events by 1,000 person-years. The association between the quartile of body weight variability and the risk of the study outcome was analyzed using Cox proportional hazards regression, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. In the multivariate-adjusted models, model 1 was adjusted for age and sex, model 2 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, DM, hypertension, dyslipidemia, and chronic kidney disease; and model 3 was further adjusted for baseline BMI on the index date in addition to the variables adjusted in model 2. Subgroup analyses according to age, sex, smoking status, DM, hypertension, dyslipidemia, alcohol consumption, physical activity, and baseline BMI were performed.  $P$ -values for interaction were calculated using Cox regression analyses. All statistical analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

## Results

### Baseline characteristics

Table 1 demonstrates the baseline characteristics of the study population ( $n = 726,736$ ) according to the quartiles of VIM for body weight. The mean waist circumference and BMI was highest in quartile 4, and lower in the lower quartiles of VIM. The mean age, the rates of DM, hypertension, and chronic kidney disease, and the proportion of those who exercised regularly were highest in quartile 1 and decreased with increasing quartile of VIM for body weight. The mean values on liver function tests, such as aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase levels, were lower in the higher quartiles of VIM for body weight. The mean total cholesterol and high-density lipoprotein-cholesterol levels increased from the lowest to highest quartile. The proportion of patients with significant liver fibrosis was lower in the higher quartiles.

### Association between body weight variability and the risks of outcomes

During a median 8.1-year follow-up, we documented 11,358, 14,714, and 22,164 cases of MI, stroke, and all-cause mortality, respectively. **Table 2** shows the risks of MI, stroke, and all-cause mortality according to the quartile of VIM for body weight. After adjusting for age and sex (model 1), the HRs for MI, stroke, and all-cause mortality were significantly greater in the higher quartiles of VIM for body weight (all  $P$  for trend  $< 0.001$ ). These significant and positive associations remained after adjusting for the covariates in model 2, and further adjusting for baseline BMI ( $P$  for trend = 0.0001 for MI and  $< 0.001$  for stroke and mortality). After further adjusting for baseline BMI in model 3, the HRs (95% CI) were 1.09 (1.03–1.14) for MI, 1.22 (1.17–1.28) for

stroke, and 1.53 (1.47–1.58) for all-cause mortality in quartile 4, compared with quartile 1. The risks for MI, stroke, and all-cause mortality were significantly higher in the higher quartiles of other parameters of body weight variability (SD, CV, and ARV) (all *P* for trend < 0.001). (Supplementary table 2)

## Association between body weight variability and the risk outcomes according to significant liver fibrosis

The risks of MI, stroke, and all-cause mortality according to the quartile of VIM for body weight were separately analyzed according to significant liver fibrosis. (Table 3) After adjusting for covariates and baseline BMI (model 3), the risk for MI was significantly higher in the higher quartiles of VIM for body weight only in the group with significant fibrosis (*P* for trend = 0.0002). The risks for stroke and all-cause mortality were significantly higher in the higher quartiles of VIM for body weight, regardless of significant fibrosis (all *P* for trend < 0.05).

Figure 1 presents the risks for MI, stroke, and all-cause mortality according to the joint analysis of significant liver fibrosis and the quartile 4 of VIM. Compared with individuals who did not have either significant liver fibrosis or quartile 4 of VIM for body weight, those with both significant liver fibrosis and quartile 4 of VIM for body weight had the highest HRs for all outcomes (for MI: HR 1.07; 95% CI, 1.00–1.13; for stroke: HR 1.45; 95% CI, 1.27–1.41; and for all-cause mortality: 1.76; 95% CI, 1.68–1.84).

## Subgroup analyses

Supplementary table 3 shows the results of subgroup analyses comparing the risks for the outcomes between quartiles 4 and 1–3 of VIM for body weight. The associations of VIM for body weight with MI and all-cause mortality revealed significant interactions with age (*P* for interaction = 0.0007 and 0.037, respectively). The association between VIM for body weight and stroke was stronger in nonsmokers than in former or current smokers (*P* for interaction = 0.0095). The associations between VIM for body weight and the risks of stroke and all-cause mortality were more prominent in non-obese individuals than in obese individuals (*P* for interaction = 0.0283 and 0.0184, respectively) (Supplementary table 3).

## Sensitivity analyses

Our findings were robust across the sensitivity analyses. The findings were similar after excluding the study outcomes diagnosed within 3 years of follow-up (Supplementary table 4). We also repeated the analyses after excluding subjects with cancer, and this did not affect the main results (Supplementary table 5).

## Discussion

This study investigated the associations between body weight variability and the risks of MI, stroke, and all-cause mortality in NAFLD patients. The associations were independent of traditional CVD and mortality risk factors. The risks of CVD and all-cause mortality among subjects with NAFLD were highest in those with both significant liver fibrosis and the greatest body weight variability.

Weight loss reduces intrahepatic fat content and improves liver enzyme levels.[26–28] Furthermore, greater weight loss is associated with greater improvements in histological steatosis, hepatocyte ballooning, and lobular inflammation.[26–28] Based on these findings, a 7–10% weight loss is the recommended target when managing overweight or obese NAFLD patients.[9, 13] Nevertheless, weight loss achieved intentionally tends to be transient, with subsequent weight gain, even in those motivated enough to participate in a long-term clinical trial.[29, 30] Such weight regain attenuates the improvements in fibrosis in patients with NAFLD.[31] However, the long-term health outcomes of weight variability in patients with NAFLD have not been investigated.

High body weight variability has been associated with increased risks of cardiovascular events and mortality in the general population. A recent meta-analysis showed that weight fluctuations are associated with increased risks of CVD (relative risk, 1.49; 95% CI 1.26–1.76; *P* < 0.001) and mortality (relative risk, 1.41; 95% CI 1.27–1.57; *P* < 0.001).[17] Another meta-analysis demonstrated that the pooled overall HR for all-cause mortality in the group with the greatest weight fluctuations compared with the least was 1.45 (95% CI 1.29–1.63).[32] A similar trend was reported in studies conducted in patients with underlying disease, such as coronary artery disease,[18] DM[19, 33] and cancer.[34, 35] In a post hoc analysis of a randomized controlled trial, patients with coronary artery disease in the greatest quintile of body weight variability had 85% and 124% greater risks of cardiovascular events and mortality, respectively.[18] However, there is little evidence of a similar association between weight variability and long-term health outcomes in NAFLD patients. Our data involved more than 720,000 patients with NAFLD and showed that body weight variability was associated with a significant increase in the risks of cardiovascular events and death. Greater body weight variability was associated with higher CVD and mortality rates.

It is hypothesized that weight regain after weight loss is due to decreased total daily energy expenditure and increased hunger accompanied by a weight-reduced state called metabolic adaptation.[36] Metabolic adaptation manifest as enhanced metabolic efficiency with reduced resting energy expenditure due to weight loss and altered fuel utilization (favoring carbohydrate oxidation).[37] This, combined with an increased drive to eat (hyperphagic response), promotes weight regain, particularly when the motivation for restricting caloric intake is lower.[37]

The mechanism behind the associations of increased body weight variability with cardiovascular events and mortality in NAFLD patients remains unclear. However, there are several plausible hypotheses. First, adipose tissue expands more rapidly with weight variability because of metabolic shifts favoring lipid storage.[38] Lipid accumulation induces excess hepatic lipid accumulation and often causes insulin resistance and chronic inflammation.

In addition, animal and human studies have shown that weight fluctuations per se are related to an increased risk of developing hyperinsulinemia and insulin resistance.[39, 40] Increased insulin resistance plays a crucial role in the progression of NAFLD,[41, 42] which is related to adverse health outcomes. Second, weight fluctuations have been linked to several indicators of cardiometabolic disorders associated with an elevated risk of mortality. For example, weight fluctuations are associated with an increased C-reactive protein level[43] and a lower high-density lipoprotein-cholesterol level.[44] Third, weight fluctuations may be related to a change in immune function,[45] as shown in a study reporting an association between repetitive episodic weight loss and reduced natural killer cell-mediated cytotoxicity.[46] Finally, weight variability can lead to sarcopenia via a loss of lean muscle mass and replacing fat mass for fat-free mass during weight regain. Sarcopenia is an independent risk factor for significant fibrosis in NAFLD,[47] and is also associated with CVD.[48]

We also investigated the impact of coexisting significant liver fibrosis and the highest weight variability on the risk of CVD and mortality. The synergistic unfavorable influence of coexisting significant liver fibrosis and the highest weight variability on CVD and mortality risk was identified in this study. Compared with controls without significant liver fibrosis and the highest weight variability, individuals with both had an approximately 1.06-fold higher risk of MI, 1.34-fold higher risk of stroke, and 1.76-fold higher risk of all-cause mortality, even after adjusting for potential confounders. Advanced fibrosis is important risk factor of CVD and mortality in NAFLD patients.[49, 50] Thus, our data suggest that it is particularly important that patients with NAFLD and significant liver fibrosis is especially needed to maintain normal body weight to prevent CVD and mortality.

Associations of weight variability with stroke and all-cause mortality were stronger in non-obese than obese NAFLD patients in the subgroup analyses. MI development was not associated with high weight variability in non-obese NAFLD patients. Bangalore et al.[18] reported consistent findings of no association between high body weight variability and an increased risk of coronary events among normal-weight subjects. Although non-obese NAFLD patients tend to receive a better prognosis than obese NAFLD patients, they have a comparable CVD risk if they have advanced fibrosis.[51] This explains the associations of weight variability with CVD and mortality in non-obese and obese NAFLD patients. Nonsmokers may be more sensitive than former or current smokers to the effect of weight variability on the development of MI in NAFLD patients. Smoking is a major risk factor for CVD and mortality.[52, 53] Our results indicate that high weight variability is a risk factor for CVD in NAFLD patients, even in nonsmokers, who normally are at lower risk of developing CVD. Further studies are warranted to confirm these findings.

The current study has several notable strengths. First, we demonstrated associations of body weight variability with CVD and mortality in a large sample size of > 720,000 individuals after a long follow-up of > 7 years, using a well-established and validated longitudinal national database. Second, we adjusted for potential confounding factors that potentially influence the associations between weight variability and long-term outcomes, including baseline BMI, to clarify the associations. In addition, various subgroup analyses were performed using nationwide cohort data, which supported the robustness of our main findings and provided interesting results. Third, because the NHIS cohort includes only Koreans, heterogeneity in the results induced by racial differences was avoided.

Despite these strengths, our study also has some limitations. First, although we defined NAFLD and liver fibrosis using well-validated NAFLD and fibrosis markers, misclassification of the true presence of NAFLD may have been unavoidable. Analyses using liver imaging or histological data were not available in the current population-based study. However, these non-invasive markers for diagnosis of NAFLD and liver fibrosis have been validated as reliable noninvasive panels for NAFLD and are independently associated with outcomes related to NAFLD.[54] Second, because of the retrospective nature of this study, reverse causation may have been at play in our results. However, we considered the washout period when assessing study outcomes to address this issue. Our sensitivity analysis results with a 3-year lag time were consistent with our main findings. Third, because the study population was limited to Koreans, future studies in other ethnic groups are needed to generalize our results.

## Conclusions

In conclusion, in this nationwide, population-based study conducted in South Korea, body weight variability was independently associated with increased risks of MI, stroke, and all-cause mortality in patients with NAFLD. Overall, appropriate interventions for maintaining a normal body weight are needed to prevent future adverse health outcomes in NAFLD patients.

## Abbreviations

ARV, average real variability; BMI, Body mass index; CVD, cardiovascular disease; CV, coefficient of variation; CI, confidence interval; FLI, fatty liver index; HR, hazard ratio; NHIC, National Health Insurance Corporation; NHIS, National Health Insurance Service; NAFLD, Nonalcoholic fatty liver disease; SD, standard deviation; VIM, variability independent of the mean.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of CHA University Republic of Korea (no. CHAMC 2020-07-073-001). Anonymous and de-identified information was used for analysis; therefore, informed consent was not obtained.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to the rules of the Korean National Health Insurance System.

### Competing interests

Dr. Chan has consulted for Bayer Pharma AG, Pfizer Inc., and Boehringer Ingelheim for topics unrelated to this work. The authors have no disclosures and no conflicts of interest to disclose.

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### Authors' contributions

MNK: study design, data analysis and interpretation, drafting of the manuscript, review of the manuscript, overall study oversight and guarantor of the manuscript

KH: data analysis and interpretation

JY: data analysis and interpretation

YH: review of the results

YEC: review of the results

JHL: review of the results

TGS: data interpretation, review of the results, review of the manuscript

ATC: data interpretation, review of the results, review of the manuscript

SGH: review of the results, overall study oversight

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## Tables

Table 1. Baseline characteristics of study population according to VIM for body weight category				
	VIM			
	Q1 (n=181907)	Q2 (n=181484)	Q3 (n=181668)	Q4 (n=181677)
<b>Variables</b>				
<b>Demographic variables</b>				
Age, years	49.74±11.72	48.31±11.82	47.17±12.29	44.88±13.63
Male sex	156566(86.07)	157615(86.85)	156428(86.11)	147713(81.31)
Height, cm	167.88±8.08	168.21±8.24	168.44±8.32	168.33±8.95
Weight, kg	77.65±9.39	78.22±10.14	79.01±10.37	80.77±11.67
Waist circumference, cm	91.67±6.15	91.67±6.34	91.95±6.51	92.93±7.12
BMI, kg/m <sup>2</sup>	27.53±2.57	27.61±2.67	27.81±2.79	28.47±3.23
SD of weight	0.82±0.32	1.57±0.26	2.35±0.37	4.44±2.07
CV of weight	1.06±0.4	2.03±0.25	3.02±0.35	5.72±2.68
VIM of weight	0.7±0.26	1.34±0.17	2±0.23	3.79±1.76
ARV of weight	0.96±0.49	1.83±0.58	2.63±0.82	4.72±2.65
Systolic BP, mm Hg	129.31±13.89	129.33±13.82	129.31±13.89	129.41±14.04
Diastolic BP, mm Hg	81.17±9.56	81.34±9.57	81.29±9.59	81.24±9.66
Hypertension	81302(44.69)	78290(43.14)	76016(41.84)	72632(39.98)
DM	31953(17.57)	30375(16.74)	29719(16.36)	28465(15.67)
Dyslipidemia	50961(28.01)	51412(28.33)	50516(27.81)	47841(26.33)
Chronic kidney disease	11499(6.32)	10866(5.99)	10545(5.8)	10471(5.76)
<b>Smoking status</b>				
Current	71104(39.09)	74639(41.13)	75353(41.48)	73085(40.23)
Former	42350(23.28)	41500(22.87)	41097(22.62)	38241(21.05)
Never	68453(37.63)	65345(36.01)	65218(35.9)	70351(38.72)
<b>Alcohol intake, g/day</b>				
None	64203(35.29)	62346(34.35)	63444(34.92)	69785(38.41)
Mild	117704(64.71)	119138(65.65)	118224(65.08)	111892(61.59)
Central obesity <sup>a</sup>	119511(65.7)	118280(65.17)	120807(66.5)	128985(71)
Obesity <sup>b</sup>	155338(85.39)	154046(84.88)	156501(86.15)	159887(88.01)
Regular exerciser	34264(18.84)	33677(18.56)	32592(17.94)	29873(16.44)
Low income	32217(17.71)	32043(17.66)	32825(18.07)	35571(19.58)
<b>Laboratory variables</b>				
Fasting blood glucose, mg/dL	106.04±27.64	105.69±28.5	105.43±29.26	104.91±31.08
Total cholesterol, mg/dL	211.56±37.48	212.09±37.6	212.43±37.92	212.66±38.44
Triglyceride, mg/dL	251.9±126.43	255.44±130.74	253.04±130.77	244.57±129.12
HDL cholesterol, mg/dL	47.72±14.71	47.73±14.42	47.93±14.78	48.41±14.76
LDL cholesterol, mg/dL	114.49±37.63	114.31±37.82	114.93±37.98	116.29±38.03
Serum creatinine, mg/dL	1.08±0.79	1.09±0.81	1.08±0.8	1.06±0.77
eGFR, mL/min/1.73 m <sup>2</sup>	85.43±43.87	85.7±42.27	86.47±44.66	88.03±45.64
Aspartate aminotransferase, IU/L	30.53±15.74	32.41±16.66	33±17.5	34.1±19.68

Alanine aminotransferase, IU/L	41.13±25.34	42.5±26.89	44.1±28.93	46.95±33.41
Gamma-glutamyl transpeptidase, IU/L	79.6±71.07	81.76±74.96	81.72±76.41	80.02±80.49
<b>Liver fibrosis</b>				
BARD scale				
0	42877(23.57)	42351(23.34)	42020(23.13)	37043(20.39)
1	36817(20.24)	40256(22.18)	43801(24.11)	52115(28.69)
2	55303(30.4)	53050(29.23)	49291(27.13)	41993(23.11)
3	39742(21.85)	39136(21.56)	39579(21.79)	42911(23.62)
4	7168(3.94)	6691(3.69)	6977(3.84)	7615(4.19)
Significant liver fibrosis (defined by BARD score ≥2)	102213(56.19)	98877(54.48)	95847(52.76)	92519(50.92)
Data are presented as mean±SD or number (percentage).				
<sup>a</sup> Central obesity was defined as waist circumference ≥90 cm in men and ≥85 cm in women.				
<sup>b</sup> Obesity was defined as BMI ≥25 kg/m <sup>2</sup> .				

Table 2. Risks of outcomes with respect to quartiles of VIM for body weight							
	n	Event	Person-years	Incidence-rate*	HR (95% CI)		
					Model 1†	Model 2‡	Model 3§
<b>Myocardial infarction</b>							
Q1	181907	2959	1426357.7	2.07451	1(Ref.)	1(Ref.)	1(Ref.)
Q2	181484	2830	1435701.79	1.97116	1.02 (0.97,1.08)	1.01 (0.96,1.07)	1.01 (0.96,1.07)
Q3	181668	2901	1432967.52	2.02447	1.11 (1.05,1.16)	1.09 (1.04,1.15)	1.09 (1.04,1.15)
Q4	181677	2668	1423773.15	1.87389	1.11 (1.06,1.17)	1.09 (1.03,1.14)	1.09 (1.03,1.14)
<i>P</i> for trend					<.0001	0.0001	0.0002
<b>Stroke</b>							
Q1	181907	3811	1423641.67	2.67694	1(Ref.)	1(Ref.)	1(Ref.)
Q2	181484	3544	1433205.76	2.47278	1.02 (0.98,1.07)	1.02 (0.97,1.06)	1.01 (0.97,1.06)
Q3	181668	3577	1430396.39	2.50071	1.09 (1.05,1.14)	1.08 (1.03,1.13)	1.08 (1.03,1.13)
Q4	181677	3782	1420030.07	2.66332	1.24 (1.19,1.30)	1.22 (1.17,1.28)	1.22 (1.17,1.28)
<i>P</i> for trend					<.0001	<.0001	<.0001
<b>All-cause mortality</b>							
Q1	181907	5242	1436156.4	3.65002	1(Ref.)	1(Ref.)	1(Ref.)
Q2	181484	5091	1444803.25	3.52366	1.08 (1.04,1.13)	1.08 (1.03,1.12)	1.07 (1.03,1.11)
Q3	181668	5461	1442152.91	3.7867	1.23 (1.19,1.28)	1.22 (1.17,1.26)	1.22 (1.17,1.26)
Q4	181677	6370	1432023.1	4.44825	1.55(1.49,1.61)	1.52 (1.47,1.58)	1.53 (1.47,1.58)
<i>P</i> for trend					<.0001	<.0001	<.0001
*Incidence per 1,000 person-years.							
†Model 1 was adjusted for age and sex.							
‡Model 2 was further adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, chronic kidney disease.							
§Model 3 was further adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, chronic kidney disease, and baseline BMI.							

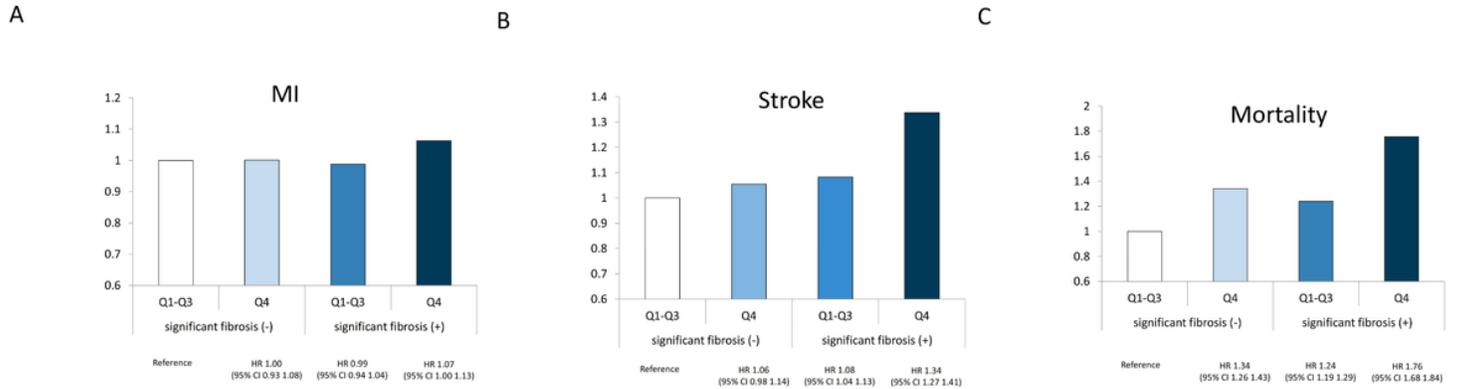
Table 3. Risks of outcomes with respect to quartiles of VIM for body weight according to the presence of significant liver fibrosis								
Significant fibrosis (defined by BARD score $\geq 2$ )	n	Event	Person-years	Incidence-rate*	HR (95% CI)			
					Model 1†	Model 2‡	Model 3§	
<b>Yes</b>	<b>Myocardial infarction</b>							
Q1	102213	1951	797689.77	2.44581	1(Ref.)	1(Ref.)	1(Ref.)	
Q2	98877	1837	778255.33	2.36041	1.024(0.96,1.091)	1.014(0.952,1.081)	1.014(0.951,1.081)	
Q3	95847	1873	750862.74	2.49446	1.112(1.044,1.185)	1.093(1.026,1.165)	1.093(1.026,1.165)	
Q4	92519	1787	718596.99	2.48679	1.145(1.074,1.221)	1.111(1.042,1.185)	1.111(1.042,1.185)	
<i>P</i> for trend					<.0001	0.0002	0.0002	
<b>No</b>	<b>Stroke</b>							
Q1	79694	1008	628667.93	1.60339	1(Ref.)	1(Ref.)	1(Ref.)	
Q2	82607	993	657446.47	1.51039	1.02(0.935,1.114)	1.012(0.927,1.105)	1.012(0.927,1.105)	
Q3	85821	1028	682104.79	1.5071	1.092(1,1.191)	1.081(0.991,1.179)	1.079(0.989,1.178)	
Q4	89158	881	705176.15	1.24933	1.052(0.96,1.152)	1.037(0.947,1.136)	1.034(0.943,1.133)	
<i>P</i> for trend					0.1174	0.2086	0.2361	
<b>Yes</b>	<b>All-cause mortality</b>							
Q1	102213	3978	804159.05	4.94678	1(Ref.)	1(Ref.)	1(Ref.)	
Q2	98877	3831	784097.43	4.88587	1.08(1.033,1.129)	1.07(1.024,1.119)	1.063(1.017,1.111)	
Q3	95847	4148	756699.64	5.4817	1.244(1.191,1.299)	1.222(1.17,1.276)	1.218(1.166,1.272)	
Q4	92519	4993	724054.16	6.89589	1.582(1.517,1.649)	1.541(1.477,1.606)	1.541(1.478,1.607)	
<i>P</i> for trend					<.0001	<.0001	<.0001	
<b>No</b>	<b>All-cause mortality</b>							
Q1	79694	1264	631997.35	2.00001	1(Ref.)	1(Ref.)	1(Ref.)	
Q2	82607	1260	660705.82	1.90705	1.088(1.006,1.176)	1.085(1.004,1.173)	1.085(1.003,1.173)	
Q3	85821	1313	685453.27	1.91552	1.196(1.107,1.292)	1.191(1.102,1.287)	1.193(1.104,1.289)	
Q4	89158	1377	707968.94	1.945	1.45(1.343,1.565)	1.444(1.337,1.558)	1.449(1.342,1.564)	
<i>P</i> for trend					<.0001	<.0001	<.0001	
*Incidence per 1,000 person-years.								
†Model 1 was adjusted for age and								

sex.

‡Model 2 was further adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, chronic kidney disease.

§Model 3 was further adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, chronic kidney disease, and baseline BMI.

## Figures



**Figure 1**  
Risks of MI (A), stroke (B), and all-cause mortality (C) based on the existence of significant liver fibrosis or the highest quartile level (Q4) of VIM for body weight.

## Supplementary Files

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