Association of variability in body mass index and metabolic health with cardiometabolic disease risk

ORIGINAL RESEARCH

Association of Variability in Body Mass Index and Metabolic Health With Cardiometabolic Disease Risk

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***Background*—**Metabolic syndrome is associated with high risk of cardiovascular disease, although risk may differ according to the specific conditions present and variability in those conditions.

***Methods and Results*—**We defined obesity (body mass index [BMI] ≥30 kg/m^2) and metabolic health (<2 nonobesity National Cholesterol Education Program Adult Treatment Panel III conditions) among 3632 Framingham Heart Study offspring cohort participants (mean age, 50.8 years; 53.8% women) who were followed up from 1987 to 2014. We defined participants whose variance independent of the mean for a metabolic syndrome–associated measure was in the top quintile as being "variable" for that measure. Variable metabolic health was defined as ≥2 variable nonobesity metabolic syndrome components. We investigated the interaction between obesity and metabolic health in their associations with cardiometabolic disease and cardiovascular disease using Cox proportional hazards regression. In addition, we estimated the associations of BMI variability and variable metabolic health with study outcomes within categories of obesity and metabolic health status, respectively. We observed 567 incident obesity (41 439 person-years), 771 incident metabolically unhealthy state (25 765 person-years), 272 incident diabetes mellitus (56 233 person-years), 503 incident hypertension (12 957 person-years), 589 cardiovascular disease (60 300 person-years), and 195 chronic kidney disease (47 370 person-years) events on follow-up. Obesity and being metabolically unhealthy were independently and positively associated with all outcomes. BMI variability, compared with stable BMI, was associated with 163%, 67%, 58%, and 74% higher risks of having obesity, becoming metabolically unhealthy, having diabetes mellitus, and having hypertension, respectively, among nonobese participants. Variable metabolic health, compared with stable metabolic health, was associated with a 28% higher risk of cardiovascular disease, among metabolically healthy participants.

***Conclusions*—**We did not observe evidence for a positive interaction between obesity and metabolic health status with regard to study outcomes. BMI and metabolic health variability are associated with adverse health outcomes. **(*J Am Heart Assoc*. 2019;8: e010793. DOI: 10.1161/JAHA.118.010793.)**

Key Words: cardiovascular disease • chronic kidney disease • metabolic syndrome • obesity • variation

The observation that obesity and metabolic risk factors tend to co-occur resulted in the concept of the metabolic syndrome (MetS).[1] MetS is defined by the presence of ≥3 of the following conditions: obesity, high blood triglycerides, low high-density lipoprotein (HDL) level, high blood pressure (BP), and high blood glucose.[2] MetS is associated with high risk of cardiovascular disease (CVD). Although its utility as a diagnostic condition would seem to be greatest if risk were higher in individuals with MetS than would be expected given its component conditions, it is not clear that this is the case.[3,4] In addition, these conditions do not necessarily co-occur, and different combinations of obesity and metabolic health may have different implications for CVD risk. Several researchers have noted the presence of subpopulations of metabolically unhealthy individuals without obesity

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Clinical Perspective

What Is New?

- Among participants in the community-based Framingham Heart Study offspring cohort, there was little evidence of an interaction between obesity and metabolic health status in their associations with incident diabetes mellitus, hypertension, cardiovascular disease, or chronic kidney disease.
- In examinations of the health consequences of variability in body mass index and metabolic health with study outcomes, body mass index variability was associated with higher risk of incident obesity, metabolically unhealthy state, diabetes mellitus, and hypertension among participants without obesity.
- In contrast, metabolic health variability was associated with cardiovascular disease among metabolically unhealthy patients, but not with risk of other outcomes.

What Are the Clinical Implications?

- Our results suggest that obesity and metabolic health status represent separate axes with independent associations with the outcomes under study.
- Long-term variability in body mass index may serve as a marker for increased risk of future cardiometabolic disease among nonobese individuals.
- In contrast, variability in metabolic health–related measures may signal increased risk of cardiovascular disease among those who have poor metabolic health.

(metabolically unhealthy nonobese [MUNO]) and individuals with obesity but with few metabolic risk factors (metabolically healthy obese [MHO]).[5,6] CVD risk among MUNO individuals has been reported to be intermediate between metabolically healthy nonobese (MHNO) and metabolically unhealthy obese (MUO; roughly equivalent to MetS) individuals. However, studies disagree as to whether risk in MHO individuals is most similar to the MHNO, MUNO, or MUO groups.[7,8] Differences between studies may be caused, in part, by length of follow-up, because several studies have concluded that MHO tends to be a transient state, with most individuals becoming MUO.[9,10]

The tendency for MHO to become MUO highlights the fact that, although it is often modeled as a permanent state, MetS is made up of multiple conditions that vary dynamically over time. Several reports have underscored frequent reversal of both MetS and its components during short-term follow-up of 5 to 8 years.[11–13] Some studies also suggest that long-term variability in individual MetS components such as weight,[14] blood lipids,[15] and BP[16] may influence cardiometabolic disease risk, at least among high-risk populations. Although there is evidence to suggest that MetS component conditions and variability in those conditions may be interrelated,[17–19] little is known about the extent to which observed associations of variability with CVD may be attributable to associations with obesity or metabolic health, and whether variability of body mass index (BMI) or MetS components poses adverse risk above and beyond obesity and MetS by themselves.

The present study has 2 aims. First, we evaluated the potential interaction, on both additive and multiplicative scales,[20,21] between obesity and metabolic health in their associations with incident cardiometabolic outcomes, chronic kidney disease (CKD), and CVD over 30 years in a community-based sample. In addition, we explored whether associations of variability in BMI and metabolic health–related measures with these outcomes differed according to obesity status and metabolic health status, respectively.

Methods

Details of the FHS (Framingham Heart Study) offspring cohort recruitment and data collection have been previously described.[22] All participants provided written informed consent and the institutional review board of the Boston Medical Center approved the study protocol. Our study population consists of participants who attended at least 2 consecutive examination cycles at any time between examination cycles 4 (1987–1991) and 9 (2011–2014). The data, analytic methods, and study materials are not available to other researchers for purposes of reproducing the results or replicating the procedure. Researchers wishing to request data from the FHS may find the procedure to do so at https://www.framinghamheartstudy.org/.

Study Measurements

At each examination, participants completed a questionnaire on demographics, lifestyle, and history of medication use. Weight and height were measured at each examination according to a standardized protocol. BMI was calculated as weight (kg) divided by height $(m)^2$. BP was measured 2 times in the right arm, at least 5 minutes apart, using a mercury column sphygmomanometer and a cuff of appropriate size. The average of the 2 measurements was used in the analysis. A blood sample was drawn, and standard methods were used to assay fasting blood triglycerides, HDL, and glucose. At examination 2, participants were asked for the number of years of education they had completed. Smoking habits were assessed at all examinations. We calculated a physical activity index based on self-reported number of hours per day usually spent sleeping, sedentary, or in light, moderate, or vigorous physical activity.[23]

Definitions of Obesity, Metabolic Health, and Obesity Subphenotypes

At each examination, we defined obesity as BMI $\geq$30 kg/m^2. High triglycerides, low HDL, and elevated blood glucose were

defined according to a previously published definition[24] as follows: triglycerides ≥1.69 mmol/L (150 mg/dL) or currently taking lipid-lowering medication; HDL <1.03 mmol/L (<40 mg/dL) for men and <1.29 mmol/L (<50 mg/dL) for women; and fasting blood glucose ≥5.6 mmol/L (100 mg/dL) or taking antidiabetic medication. High BP was defined as systolic BP (SBP) ≥130 mm Hg or diastolic BP (DBP) ≥80 mm Hg or taking antihypertensive medication.[25,26] To account for the effects of antihypertensive medication, 10 mm Hg was added to SBP and 5 mm Hg was added to DBP measurements of current medication users.[27] Triglyceride and HDL measurements were not adjusted for lipid-lowering medication use. Participants who had ≥2 conditions among high triglycerides, low HDL, high BP, and high blood glucose were defined as being metabolically unhealthy. We defined MHNO as individuals without obesity who were classified as metabolically healthy according to the definitions above. MUNO, MHO, and MUO were defined, respectively, as metabolically unhealthy individuals without obesity, metabolically healthy individuals with obesity, and metabolically unhealthy individuals with obesity (Table S1).

Definition of Variability of Obesity and Metabolic Health

Variability was measured using the variability independent of the mean (VIM).[28] This measure is equal to the (population mean×individual SD/individual mean)^a, where a is estimated by regressing ln(SD) on ln(k×individual mean)×a, k is a constant.[28] The VIM has a lower correlation with the mean value than either the SD or the coefficient of variation.[29] At each examination cycle, VIM was calculated for each MetS component based on all of the participant's measurements. Because we lacked data to define MetS at examination cycle 1, we used data from examination cycles 2 (1979–1983) through 8 (2005–2008) in calculating antecedent variability of MetS components. As noted above, participants were followed up from examination cycle 4 through 9. BMI variability was defined as having VIM in the top quintile among observations pooled across all examinations included in the study. We defined variability of metabolic health as having VIM in the top quintile of ≥2 non-BMI MetS components. Being classified as having both variable SBP and variable DBP was not considered sufficient to be classified as metabolically unhealthy.

Cross-Classified Exposure Variables

To evaluate whether BMI and metabolic health variability modified the associations of obesity and metabolic health status, respectively, with study outcomes, we created cross-classified variables at each FHS examination. For obesity, person-time was classified as follows: if the participant was not classified as having obesity and had not met the definition of variability for BMI, they were classified as having stable BMI, without obesity; if the participant was classified as having met the definition of variability for BMI, they were classified as having variable BMI, without obesity; and if the participant was classified as having obesity and met the definition of variability for BMI, they were classified as having variable BMI, with obesity; otherwise, they were classified as having stable BMI, with obesity. Metabolic health was similarly classified according to metabolic health status and variability as follows: (1) stable metabolic health, metabolically healthy; (2) variable metabolic health, metabolically healthy; (3) variable metabolic health, metabolically unhealthy; and (4) stable metabolic health, metabolically unhealthy (Table S1).

Outcomes

Outcomes of interest for this study included becoming metabolically unhealthy as well as incident obesity, diabetes mellitus, hypertension, CVD, and CKD. Obesity and metabolic health were defined as described above. Incident hypertension was defined as SBP ≥130 mm Hg, DBP ≥80 mm Hg, or current use of antihypertensive medication.[25] Incident diabetes mellitus was defined as blood glucose ≥200 mg/dL, fasting blood glucose ≥126 mg/dL, or current use of antidiabetic medication. Incident CVD was defined as the first occurrence of any of the following conditions: fatal or nonfatal coronary heart disease, fatal or nonfatal cerebrovascular disease, peripheral arterial disease, or heart failure.[30] Serum creatinine was measured in collected blood samples at examination cycle 2 (1979–1983) and from examination cycle 5 (1991–1995) to examination cycle 9 (2011–2014). We calculated estimated glomerular filtration rate using the equation by Levey et al.[31] CKD was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Statistical Analysis

The primary outcomes of interest were incident CVD and CKD. To more fully characterize the pathways by which variability of BMI and metabolic health may influence risk of these outcomes, we included becoming metabolically unhealthy as well as incident obesity, diabetes mellitus, and hypertension as separate secondary outcomes. Of 5124 enrolled FHS offspring cohort participants, we excluded those who died before examination cycle 4 (n=239), those with prevalent CVD at examination cycle 4 (n=375), those who did not attend at least 2 consecutive examinations after the start of follow-up at examination cycle 4 (n=831), and those who lacked exposure-sufficient data to define exposure for at least 1 study period between examination cycle 4 and examination cycle 9 (n=47). Individuals with prevalent CVD were excluded

from all analyses because of the potential for CVD to increase variability in exposure measures, resulting in reverse causation. Additional exclusions of participants with prevalent disease who were not at risk for developing the outcome under study were specific to analyses for each individual outcome. Thus, we excluded 907 participants with a history of obesity, 1816 with a history of being classified as metabolically unhealthy, 174 with a history of diabetes mellitus, 2726 with a history of hypertension at examination cycle 4, and 370 with a history of CKD at examination cycle 5 from the "at risk" samples for analyses of the corresponding outcomes. Our analytic samples included 2725 unique participants (9434 observations) for the obesity analysis, 1816 (5772 observations) for the analysis of becoming metabolically unhealthy, 3458 (12 673 observations) for the analysis of incident diabetes mellitus, 906 (2971 observations) for the analysis of incident hypertension, 3632 (13 792 observations) for the analysis of CVD, and 3262 (10 057 observations) for the analysis of CKD.

We conducted *t* tests (continuous variables) and chi-square tests (categorical variables) to compare baseline (examination cycle 4) characteristics between participants cross-classified by obesity status and BMI variability, and, separately, by metabolic health status and metabolic health variability. Comparisons were made for demographic and behavioral characteristics, MetS-associated measures, and variability measures.

Because VIM may be sensitive to small numbers of observations, we began follow-up at examination cycle 4 (1987–1991) for most outcomes. Analysis of CKD began at examination cycle 5 (1991–1995) because of the lack of available outcome data before that examination. Follow-up continued through examination cycle 9 (2011–2014). We estimated hazard ratios and 95% CIs using Cox proportional hazards regression with age as the underlying time scale. Reference categories for obesity, being metabolically unhealthy, individual MetS-associated conditions, and variability in MetS-associated measures were the absence of those conditions. For the cross-classified variability variables, reference categories were stable BMI, without obesity (for the analysis of BMI variability) or metabolically healthy and lacking the condition associated with the measure whose variability is being analyzed (for all other nonobesity measures, eg, SBP). The Anderson-Gill data structure was used to accommodate time-varying exposures and covariates. Person-time was calculated from the beginning of an examination cycle to the event of interest, censoring event, loss to follow-up, death, or end of the examination cycle. Censoring events included the outcomes of interest and CVD (for analysis of obesity, becoming metabolically unhealthy, diabetes mellitus, hypertension, and CKD). Since exact date of diagnosis of obesity, becoming metabolically unhealthy, diabetes mellitus, hypertension, and CKD were not known, we used Cox models for interval-censored data for these outcomes.

We estimated the associations of being classified as obese, metabolically unhealthy, and both obese and metabolically unhealthy to evaluate the interaction on the multiplicative scale. We calculated the relative excess risk due to interaction[32] to evaluate interaction on the additive scale. The obesity status/BMI variability and metabolic health status/metabolic health variability variables were modeled together, adjusted for age, sex, examination cycle, years of education, smoking status (never/former/current), and physical activity index (quartiles). As a result of the exclusion of participants with obesity, models for incident obesity were additionally adjusted for BMI (continuous). Similarly, models for becoming metabolically unhealthy were also adjusted for SBP, DBP, serum HDL, triglycerides, and blood glucose (all continuous), as well as use of antihypertensive and antidiabetic medication. Wald χ^2 tests were used to make pairwise comparisons to investigate the associations of BMI variability within categories of obesity status and metabolic health variability within categories of metabolic health status, respectively. We checked the proportionality of hazards assumption using interaction terms between main exposure variables and time. No violations were detected.

Sensitivity Analyses

To test the sensitivity of our analysis to different definitions of variability, we defined variability as being in the highest quintile of the coefficient of variation, equal to the individual SD/individual mean for each component, as with VIM. A comparison of the characteristics of excluded and censored observations with included observations indicated the possibility of informative censoring (Table S2). We repeated all analyses using inverse probability of censoring weighting with stabilized weights[33] to investigate its potential impact on our results. We created a logistic model with an indicator variable equal to 1 if the participant was censored and 0 if otherwise. The indicator variable becomes equal to 1 at an examination when the response is missing either by death, lost to follow-up, or any other reason. Therefore, we used baseline data in the calculation of weight to ensure that all excluded participants were included in the inverse probability of censoring weighted analysis. The models included the variables examination cycle, age, sex, years of education, physical activity index, and prevalent obesity, hypertension, high serum triglycerides, low serum HDL, and high blood glucose as predictors. For each observation, we calculated weight as the inverse of the predicted probability of censoring multiplied by the overall probability of not being censored. Weights were trimmed at the 5th and 95th percentiles. All analyses were conducted using SAS software version 9.4 (SAS Institute).

Results

Participant Characteristics

We observed 567 incident obesity cases in 9434 person-periods (41 439 person-years), 771 instances of becoming metabolically unhealthy in 5772 person-periods (25 765 person-years), 272 cases of diabetes mellitus in 12 673 person-periods (56 233 person-years), 503 cases of incident hypertension in 2971 person-periods (12 957 person-years), 589 incident CVD cases in 60 300 person-years, and 195 incident CKD cases in 10 057 person-periods (47 370 person-years) of follow-up. Compared with participants who were nonobese and metabolically healthy, respectively, participants with obesity and those who were metabolically unhealthy had less favorable measures of BMI, triglycerides, HDL, BP, and glucose (all $P<0.0001$; Table 1). Individual variable on 1 axis (ie, BMI or metabolic health) were more likely to be variable on the other axis ($P<0.0001$). Compared with participants included in the study, those excluded were older, more likely to be men, and more likely to be current smokers at baseline (all $P<0.0001$; Table S2). Excluded participants had less favorable measures of triglycerides, BP, and blood glucose (all $P<0.0001$).

Associations of Obesity Subphenotypes With Risk of Study Outcomes

MUNO was associated with increased risk of incident obesity (Table 2). MHO was associated with becoming metabolically unhealthy. MUNO and MHO were both associated with increases in risk of incident diabetes mellitus and hypertension. These associations were of similar magnitude in each case. There was a modest, positive association of obesity with CVD, but this association was weaker than the association between being metabolically unhealthy and having CVD. We only observed strong evidence of a multiplicative interaction between obesity and the metabolically unhealthy state in the analysis of incident diabetes mellitus. The association of MUO was lower than would be expected given the observed associations of MUNO and MHO with incident diabetes mellitus. We did not observe strong evidence of an interaction on the additive scale for any of the associations investigated. We, therefore, modeled obesity and metabolic health status as separate variables.

Association of Variability of BMI and Metabolic Health With Risk of Incident Obesity and Metabolically Unhealthy Status

We observed no evidence that metabolic health variability was associated with incident obesity among metabolically healthy or unhealthy individuals (Table 3). However, BMI variability was associated with higher risk of both incident obesity and incident metabolically unhealthy state among participants without obesity. We did not observe evidence that risk of becoming metabolically unhealthy differed according to variability of metabolic health or according to BMI variability among participants with obesity.

Association of Variability of BMI and Metabolic Health With Risk of Diabetes Mellitus and Hypertension

Incident diabetes mellitus was associated with variable BMI, compared with stable BMI, among participants without obesity (Table 4). However, we did not observe evidence of a difference in risk according to BMI variability among participants with obesity. We observed no evidence for an association of variable metabolic health with diabetes mellitus risk among metabolically healthy or metabolically unhealthy participants. Participants without obesity and with variable BMI had a higher hypertension risk compared with those without obesity and with stable BMI. We did not observe evidence of a similar association among participants with obesity. We observed no evidence that metabolic health variability was associated with hypertension among metabolically healthy or metabolically unhealthy individuals.

Association of Variability of BMI and Metabolic Health With Risk of CVD and CKD

We did not observe evidence that BMI variability was associated with CVD risk among individuals with or without obesity (Table 5). Our data were consistent with an association of variable metabolic health with higher CVD risk, compared with stable metabolic health, among metabolically unhealthy individuals, but not among those who were metabolically healthy. The strength of the associations of obesity and being metabolically unhealthy with incident CKD were similar. We did not observe evidence that either BMI variability or metabolic health variability was associated with CKD among individuals with or without obesity.

Sensitivity Analyses

When we redefined variability of BMI and metabolic health using the top quintile of the coefficient of variation of BMI and of $\geq$2 metabolic health measures, respectively, point estimates tended to be slightly stronger, compared with the original analysis. However, the observed associations were largely similar (Tables S3 through S5). When we reanalyzed the data to account for exclusions and informative censoring, associations of obesity, metabolic health, and variability of BMI and metabolic health with incident obesity and

Table 1. Characteristics of Offspring Cohort Participants* Classified According to Obesity, Metabolic Health, and Variability of BMI and Metabolic Health at Examination Cycle 4

	SNO	VNO	VO	SO	SMH	VMH	VMU	SMU
No.	2343	308	156	531	1602	441	272	899
Men†	1095 (46.7)	88 (28.6)	36 (23.1)	323 (60.8)	685 (42.8)	155 (35.2)	129 (47.4)	536 (59.6)
Age, y‡	51.2 (9.8)	44.9 (9.9)	48.3 (9.2)	53.0 (9.1)	49.6 (9.8)	48.1 (10.1)	51.3 (9.7)	54.0 (9.3)
BMI, kg/m^2‡	24.8 (2.8)	25.2 (2.9)	34.8 (4.6)	33.8 (4.0)	25.5 (4.1)	25.2 (4.2)	29.2 (5.4)	28.9 (4.9)
With obesity†	0 (.0)	0 (0.0)	156 (100.0)	531 (100.0)	204 (12.7)	50 (11.3)	98 (36.0)	303 (33.7)
Serum Triglycerides, mg/dL‡	111.3 (84.4)	102.4 (58.6)	147.4 (79.1)	170.1 (162.3)	82.3 (35.3)	80.1 (32.2)	219.7 (210.5)	184.3 (103.4)
High triglycerides†	464 (19.8)	54 (17.5)	59 (37.8)	232 (43.7)	31 (1.9)	9 (2.0)	192 (70.6)	577 (64.2)
HDL, mg/dL‡	51.8 (15.1)	52.8 (14.7)	46.7 (12.5)	42.6 (11.1)	56.2 (13.4)	56.7 (15.0)	40.0 (10.3)	39.4 (9.2)
Low HDL†	753 (32.1)	108 (35.1)	84 (53.9)	293 (55.2)	220 (13.7)	81 (18.4)	212 (77.9)	717 (79.8)
SBP, mm Hg‡	124.1 (18.2)	120.9 (16.8)	129.4 (16.4)	135.2 (17.3)	120.8 (16.6)	120.2 (19.1)	135.5 (17.6)	134.8 (16.3)
DBP, mm Hg‡	77.7 (9.7)	77.3 (9.8)	82.8 (9.8)	84.4 (9.4)	76.3 (9.0)	75.5 (10.6)	83.5 (10.2)	84.1 (8.5)
High BP†	1227 (52.4)	146 (47.4)	114 (73.1)	435 (81.9)	642 (40.1)	170 (38.6)	243 (89.3)	788 (87.7)
Blood glucose, mg/dL‡	92.7 (19.9)	91.4 (21.8)	94.8 (19.6)	105.0 (36.8)	90.3 (8.9)	86.5 (9.0)	109.0 (50.7)	102.3 (30.4)
High glucose†	68 (2.9)	6 (2.0)	3 (1.9)	52 (9.8)	3 (0.2)	0 (0.0)	47 (17.3)	79 (8.8)
Education, y‡	14.2 (2.7)	13.8 (2.4)	13.6 (2.1)	13.6 (2.6)	14.3 (2.6)	14.0 (2.7)	13.6 (2.5)	13.7 (2.6)
Smoking†								
Never	808 (34.5)	94 (30.5)	55 (35.3)	184 (34.7)	597 (37.3)	141 (32.0)	82 (30.2)	283 (31.5)
Former	999 (42.6)	123 (39.9)	63 (40.4)	233 (43.9)	670 (41.8)	184 (41.7)	110 (40.4)	403 (44.8)
Current	533 (22.8)	91 (29.6)	38 (24.4)	113 (21.3)	334 (20.9)	115 (26.1)	80 (29.4)	211 (23.5)
Physical activity index‡	37.3 (6.9)	36.2 (6.4)	36.0 (6.5)	36.8 (7.5)	37.4 (7.0)	36.9 (6.9)	36.0 (6.9)	36.8 (6.7)
VIM‡								
BMI	1.2 (0.6)	3.4 (1.0)	3.6 (1.0)	1.3 (0.6)	1.5 (1.0)	1.8 (1.2)	1.9 (1.2)	1.4 (0.9)
Triglycerides	41.7 (20.0)	47.2 (23.2)	54.7 (24.0)	41.5 (19.9)	39.1 (17.9)	53.1 (23.7)	59.3 (24.1)	39.5 (18.2)
HDL	6.3 (3.6)	6.8 (3.8)	7.5 (3.7)	6.5 (3.7)	5.6 (3.0)	8.7 (4.3)	9.2 (4.3)	6.0 (3.2)
SBP	9.4 (4.7)	10.7 (5.3)	10.8 (5.2)	9.0 (4.6)	8.7 (4.2)	12.0 (5.4)	12.0 (5.7)	9.0 (4.3)
DBP	5.5 (2.8)	6.3 (3.2)	6.6 (3.4)	5.8 (2.9)	5.1 (2.4)	7.2 (3.4)	7.6 (3.5)	5.4 (2.7)
Blood glucose	8.8 (4.7)	9.2 (5.2)	8.2 (5.4)	8.2 (4.4)	8.1 (3.9)	12.4 (5.0)	10.9 (6.2)	7.5 (4.0)
Variable BMI†	0 (0.0)	308 (100.0)	156 (100.0)	0 (0.0)	192 (12.0)	86 (19.5)	71 (26.1)	94 (10.5)
Variable metabolic health†	474 (20.2)	103 (33.4)	57 (36.5)	100 (18.8)	0 (0.0)	441 (100.0)	272 (100.0)	0 (0.0)

BP indicates blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable body mass index, without obesity; SO, stable body mass index, with obesity; VIM, variance independent of the mean; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable body mass index, without obesity; VO, variable body mass index, with obesity.

*All participants were classified according to both obesity/body mass index (BMI) variability status and metabolic health/metabolic health variability status and are therefore included in the table twice.

†Presented as number (percentage).

‡Presented as mean (SD).

metabolically unhealthy state tended to be weaker compared with the primary analysis (Tables S6 through S9). In addition, we did not observe associations between the metabolically unhealthy state and incident obesity. Estimates of associations of exposures of interest with incident diabetes mellitus, hypertension, CVD, and CKD were similar to those observed in the primary analysis (Tables S7 through S9).

Discussion

In this investigation, both obesity and being metabolically unhealthy were associated with higher risk of cardiometabolic outcomes, CKD, and CVD on follow-up. We did not observe evidence for positive interaction in the associations of these factors with any outcome on the additive or multiplicative

Table 2. Associations of Obesity Subphenotypes With Risk of Obesity and Becoming Metabolically Unhealthy: Framingham Offspring Examination Cycle 4–Examination Cycle 9

Obesity Subphenotype	Cases	Rate*	HR†	95% CI	$P_{interaction}$‡	Cases	Rate*	HR†	95% CI	$P_{interaction}$§
	Incident obesity					Incident metabolically unhealthy state				
MHNO	316	519.5	1.00	Reference		605	1378.8	1.00	Reference	
MUNO	241	911.5	1.88	1.54, 2.30						
MHO						166	2707.9	1.79	1.43, 2.23	
MUO										
	Incident diabetes mellitus					Incident hypertension				
MHNO	49	73.7	1.00	Reference		358	1737.0	1.00	Reference	
MUNO	88	320.2	4.01	2.77, 5.81		45	3125.0	1.74	1.16, 2.62	
MHO	32	253.2	3.59	2.30, 5.61		67	4012.0	2.11	1.42, 3.14	
MUO	100	664.9	8.39	5.86, 12.00		25	5102.0	3.00	1.76, 5.11	
Obesity×MU‖			0.58	0.34, 0.99	0.04			0.82	0.39, 1.72	0.59
RERI¶			1.76	−0.49, 4.02	0.12			0.14	−1.10, 1.38	0.82
	Incident CVD					Incident CKD				
MHNO	170	57.2	1.00	Reference		53	110.2	1.00	Reference	
MUNO	207	146.2	1.86	1.52, 2.29		69	297.8	1.72	1.16, 2.55	
MHO	50	81.8	1.28	0.94, 1.76		18	169.0	1.77	1.02, 3.07	
MUO	157	168.7	2.40	1.93, 2.99		54	343.9	2.43	1.59, 3.70	
Obesity×MU‖			1.01	0.69, 1.47	0.98			0.80	0.39, 1.61	0.52
RERI¶			0.26	−0.33, 0.85	0.39			−0.11	−1.28, 1.06	0.85

CKD indicates chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; MHNO, metabolically healthy, without obesity; MHO, metabolically healthy with obesity; MUNO, metabolically unhealthy without obesity; MUO, metabolically unhealthy with obesity.

*Crude rate per 10 000 person-periods.

†Adjusted for age, sex, examination cycle, education, smoking status, physical activity index, and body mass index.

‡*P* value for the multiplicative interaction between obesity and the metabolically unhealthy state (MU).

§Adjusted for age, sex, examination cycle, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, high-density lipoprotein, triglycerides, blood glucose, and current use of antidiabetic medication.

‖Results of an interaction term from a model including obesity, metabolic health status, and their interaction with the covariates listed above.

¶Relative excess risk due to interaction (RERI; additive scale).

scale. We are unaware of prior studies that have explored this question for both scales and for multiple outcomes. In addition, we simultaneously investigated the associations of variability in BMI and metabolic health–related measures, stratified by obesity status and metabolic health status, respectively, on cardiometabolic and CVD outcomes. Further, our results suggest that associations of weight and metabolic health status with these outcomes differed according to the extent to which MetS-associated factors varied over time. BMI variability, compared with stability, was associated with higher risk of obesity, diabetes mellitus, and hypertension, but not CVD or CKD, among participants without obesity. Among metabolically healthy individuals, we did not observe evidence that risk differed for participants with variable metabolic health, compared with stable metabolic health, for any outcome we investigated. Among metabolically unhealthy people, metabolic health variability was associated with a higher risk of CVD, but our data did not provide evidence to support associations with cardiometabolic outcomes.

Our results are consistent with the independent effects of obesity and metabolic health on cardiometabolic and CVD outcomes. This notion is supported by studies reporting different risks for CHD,[34] CKD,[35–38] and atrial fibrillation,[39] according to the 4 obesity subphenotypes (MHNO, MUNO, MHO, MUO). Our results for obesity after adjustment for metabolic health are consistent with previous reports of positive associations of MHO with incident diabetes mellitus,[40] hypertension,[41–43] CKD,[36–38] and CVD.[44] MUNO has also been reported to be associated with increased risk of becoming obese,[9] consistent with our observations. Similar to the results of our study, Rhee et al[45] observed a higher risk of diabetes mellitus among participants classified as MUNO, compared with MHO.[45] Studies of the association of obesity subphenotypes with incident hypertension differ with regard to whether the association with MUNO is stronger than or

Table 3. Associations of Obesity, Metabolic Health Status, and Variability of BMI and Metabolic Health With Risk of Incident Obesity and Metabolically Unhealthy State: Framingham Offspring Examination Cycle 4–Examination Cycle 9

	Incident Obesity					Incident Metabolically Unhealthy State				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR§	95% CI	$P_{difference}$§
Obesity										
SNO	390	510.3	1.00	Reference	<0.0001	483	1291.4	1.00	Reference	<0.0001
VNO	177	1444.9	2.63	2.07–3.35		122	1882.7	1.67	1.30–2.15	
SO						97	2607.5	1.93	1.46–2.54	0.34
VO						69	2863.1	2.35	1.69–3.26	
Metabolic health										
SMH	247	501.9	1.00	Reference	0.53	629	1534.9	1.00	Reference	0.90
VMH	69	593.8	1.10	0.83–1.46		142	1572.5	1.01	0.82–1.25	
SMU	160	808.5	1.66	1.32–2.08	0.10	. . .				
VMU	81	1218.0	2.23	1.58–3.14						

HR indicates hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable body mass index, without obesity; SO, stable body mass index, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable body mass index, without obesity; VO, variable body mass index, with obesity.

*Crude rate per 10 000 person-periods.

†Adjusted for age, sex, examination cycle, education, smoking status, physical activity index, and body mass index (BMI).

‡*P* value comparing the association of stability with diabetes mellitus with that of variability within a given obesity/metabolic health status.

§Adjusted for age, sex, examination cycle, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, high-density lipoprotein, triglycerides, blood glucose, and current use of antidiabetic medication.

similar to the association with MHO.[43,46] Results may vary according to the metabolic health criteria used.[46] Consistent with prior results using Third Report of the Adult Treatment Panel or Wildman criteria, we observed that associations with obesity and a metabolically unhealthy state were similarly strong.[46,47] Additionally, our data support previous studies which indicate that MHO and MUNO are associated with higher CKD[36–38] and CVD[7] risk compared with MHNO. We observed no evidence to support a positive, additive, or multiplicative interaction between obesity and the

Table 4. Associations of Obesity, Metabolic Health Status, and Variability of BMI and Metabolic Health With Risk of Incident Diabetes Mellitus and Hypertension: Framingham Offspring Examination Cycle 4–Examination Cycle 9

	Incident Diabetes Mellitus					Incident Hypertension				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$‡
Obesity										
SNO	109	135.1	1.00	Reference	0.03	301	1659.3	1.00	Reference	0.0003
VNO	29	195.3	1.58	1.04–2.40		108	2529.3	1.74	1.29–2.34	
SO	103	548.5	2.92	2.19–3.88	0.17	41	3831.8	2.34	1.43–3.83	0.97
VO	31	329.8	2.16	1.41–3.33		53	4690.3	2.31	1.45–3.68	
Metabolic health										
SMH	70	109.9	1.00	Reference	0.16	338	1860.2	1.00	Reference	0.39
VMH	11	70.8	0.63	0.33–1.19		87	2096.4	1.09	0.81–1.46	
SMU	152	476.3	3.24	2.38–4.40	0.13	50	3448.3	1.61	1.11, 2.34	0.72
VMU	36	334.9	2.44	1.60–3.73		21	4285.7	1.88	0.84–4.21	

BMI, body mass index; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable body mass index, without obesity; SO, stable body mass index, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable body mass index, without obesity; VO, variable body mass index, with obesity.

*Crude rate per 10 000 person-periods.

†Adjusted for age, sex, examination cycle, education, smoking status, and physical activity index.

‡*P* value comparing the association of stability with diabetes mellitus with that of variability within a given obesity/metabolic health status.

Table 5. Associations of Obesity, Metabolic Health Status, and Variability of BMI and Metabolic Health With Risk of Incident CVD and CKD: Framingham Offspring Examination Cycle 4–Examination Cycle 9

	Incident CVD					Incident CKD				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate§	HR†	95% CI	$P_{difference}$‡
Obesity										
SNO	344	92.2	1.00	Reference	0.45	113	190.1	1.00	Reference	0.71
VNO	37	51.2	0.87	0.61–1.24		10	80.5	0.87	0.42–1.80	
SO	157	149.3	1.24	1.02–1.50	0.66	61	350.2	1.55	1.08–2.23	0.32
VO	50	97.4	1.33	0.97–1.83		11	63.1	1.08	0.55–2.13	
Metabolic health										
SMH	179	61.9	1.00	Reference	0.83	60	125.5	1.00	Reference	0.88
VMH	41	58.8	1.04	0.74–1.46		11	99.7	0.95	0.50–1.82	
SMU	252	149.4	1.74	1.43–2.12	0.03	80	288.9	1.50	1.03–2.17	0.16
VMU	113	169.8	2.24	1.76–2.87		43	380.9	2.06	1.28–3.34	

BMI indicates body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable body mass index, without obesity; SO, stable body mass index, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable body mass index, without obesity; VO, variable body mass index, with obesity.

*Crude rate per 10 000 person-years.

†Adjusted for age, sex, examination cycle, education, smoking status, and physical activity index.

‡*P* value comparing the association of stability with diabetes mellitus with that of variability within a given obesity/metabolic health status.

§Crude rate per 10 000 person-periods.

metabolically unhealthy state in their associations with any study outcome. Therefore, while the MUO phenotype (which is similar to definitions of MetS) identified individuals at high risk of study outcomes, our evidence suggested that this risk was not higher than would be expected from the individual associations of obesity and metabolic health status for the outcomes we evaluated.[3,4]

The health significance of variability in MetS-associated conditions in the general population has received little attention. A few investigators have observed an association of weight cycling with obesity, cardiometabolic disease, and CVD, although this is controversial.[14,17] It has been suggested that repeated dieting followed by weight gain may cause a progressive increase in weight, loss of lean tissue and/or redistribution of lipids to the visceral depot, and renal damage.[48] It is also possible that associations could be influenced by weight loss experienced before diagnosis of serious conditions. To our knowledge, the question of whether cardiometabolic disease mediates any potential association of BMI variability with CVD or CKD has not been explored. Because the concept of weight cycling often includes the element of intent to lose weight and we lack data on dieting intent, it is unclear how our definition of BMI variability may relate to definitions of weight cycling in prior studies. Nevertheless, consistent with prior literature,[14,17] we observed positive associations of BMI variability with obesity, diabetes mellitus, hypertension, and becoming metabolically unhealthy. We did not observe evidence that BMI variability was associated with increased risk of CVD or CKD. This is consistent with a model where BMI variability was associated with CVD only through its associations with overall adiposity and metabolic health.

It has been suggested that BP variability is a marker for age-related changes in vasculature, stress, behavioral factors, and hypertension treatment, as well as a potential cause of organ damage.[49] Long-term variability in BP has been associated with atherosclerosis,[50] renal damage,[51,52] subclinical cerebrovascular disease,[53,54] CKD,[55–57] CVD,[49,58,59] and CVD-specific and all-cause mortality.[16,60] Most of these studies were conducted in high-risk populations such as older adults,[50,53] patients with cardiometabolic disease,[51,52,54,57] and US military veterans.[49]

Variability in blood lipid levels may lead to destabilized plaques or be markers of other conditions that increase CVD risk,[61] such as diabetes mellitus among patients with heart disease.[15] A study of total cholesterol variability in the FHS original cohort observed a positive association with CVD mortality, but not incidence, after adjustment for common risk factors.[62] Three studies have reported associations of LDL, HDL, and triglyceride variability with cardiovascular events among patients with heart disease.[15,61,63] Both BP variability[56] and blood lipid variability[61] have been linked to medication adherence but remain associated with adverse outcomes after controlling for this variable.

Studies of glucose variability and diabetes mellitus–associated microvascular damage have suggested that generation of reactive oxygen species during periods of hyperglycemia may worsen upon repetition.[64] Associations of blood glucose

variability with complications of diabetes mellitus and intensive care mortality have also been reported,[65,66] although these studies have largely focused on short-term (eg, diurnal) variability and/or included only people with diabetes mellitus.[67]

Consistent with prior literature investigating variability in individual metabolic health–related conditions,* metabolic health variability was associated with increased risk of CVD among metabolically unhealthy individuals. Also consistent with previous studies, our results suggested a higher risk of CKD associated with metabolic health variability among metabolically unhealthy individuals. However, our estimates were not sufficiently precise to clearly differentiate risk according to metabolic health variability among these participants. There was little evidence of an association between metabolic health variability and cardiometabolic conditions among metabolically healthy or unhealthy participants. Therefore, the health consequences of metabolic health variability appear to be confined to metabolically unhealthy individuals.

Strengths and Limitations

Our study has several strengths. We have investigated the associations of obesity subphenotypes on cardiometabolic disease, CVD, and CKD, and found little evidence of positive interaction between obesity and metabolic health on either the additive or multiplicative scales for any outcome. Further, we add to the literature on the associations of variability in MetS-associated measures by the simultaneous estimation of associations with study outcomes and by extending the results to healthy populations. We used data on study-measured BMI, blood triglycerides, HDL, glucose, and BP over 8 examination cycles spanning nearly 30 years. The standardized study protocols minimize the contribution of measurement error to overall variability in MetS-associated measures. In addition, each CVD outcome at FHS is thoroughly reviewed by a panel of 3 experienced physicians using standardized and consistent criteria. However, our results must be interpreted in light of several limitations. Although our definition of variability (ie, VIM) has construct validity, the cutoff value was empirically chosen based on the distribution of the metric. While the point estimates of associations with outcomes were insensitive to the definition used, our relatively small sample size may have limited our ability to distinguish risk of cardiometabolic and CVD outcomes between variability and stability within a given weight or metabolic health status. Variability was defined based on a limited number of observations, which may be expected to result in misclassification of exposure. If nondifferential, the effect of misclassification on variables with >2 categories is not predictable. Although sensitivity analysis using inverse probability of censoring weighting largely supported our findings, we cannot discount the possibility that participants excluded from the study differed from those who were included in ways that may have affected the results. If variability of certain MetS-related factors, such as BP, were associated with specific outcomes while other factors were not, combining 4 factors into a single measure of metabolic health variability would be expected to bias us towards the null hypothesis. We did not perform sensitivity analyses using alternative measures of obesity, such as waist circumference, or metabolic factors, such as glucose tolerance. We have investigated interactions in the associations of obesity and metabolic health with 6 outcomes, as well as associations of BMI and metabolic health variability with those outcomes, within categories of obesity and metabolic health, respectively. This may have increased the chance of observing spurious associations. Our study population was comprised of white Americans living primarily in the Northeastern United States from 1979 to 2014. As such, our results may have limited generalizability to other races, geographic areas, or time periods.

Conclusions

In our study, we did not observe evidence that metabolically unhealthy individuals with obesity were at higher risk of cardiometabolic disease or CVD than would be expected given the individual associations of those 2 risk factors with disease states. Compared with obesity, being metabolically unhealthy appeared to be more strongly associated with CVD risk, but the strength of associations with CKD were similar. Obesity was associated with an increased risk of becoming metabolically unhealthy. However, we observed evidence that BMI variability was associated with higher risk of cardiometabolic conditions only among individuals without obesity. While being metabolically unhealthy increased the risk of obesity, we found little evidence that metabolic health variability was associated with cardiometabolic risk. Metabolic health variability further increased the risk of CVD among metabolically unhealthy individuals, while BMI variability did not appear to be associated with CVD or CKD. BMI variability is detrimental to the metabolic health of community-dwelling adults without obesity. Metabolic health variability appears primarily to be associated with CVD risk among metabolically unhealthy individuals.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Cross-Tabulation of Obesity with BMI Variability and Metabolic Health with Metabolic Health Variability.

	Stable BMI (BMI VIM in quintile 1-4)	Variable BMI (BMI VIM in quintile 5)
Non-obese (BMI<30 kg/m^2)	Stable BMI, non-obese (**SNO**)	Variable BMI, non-obese (**VNO**)
Obese (BMI≥30 kg/m^2)	Stable BMI, obese (**SO**)	Variable BMI, obese (**VO**)
	Stable Metabolic Health (<2 metabolic health conditions with VIM in quintile 5)	Variable Metabolic Health (≥2 metabolic health conditions with VIM in quintile 5)
Metabolically healthy (<2 metabolic health conditions)	Stable metabolic health, metabolically healthy (**SMH**)	Variable metabolic health, metabolically healthy (**VMH**)
Metabolically unhealthy (≥2 metabolic health conditions)	Stable metabolic health, metabolically unhealthy (**SMU**)	Variable metabolic health, metabolically unhealthy (**VMU**)

Table S2. Baseline Characteristics of Offspring Cohort Participants Included In and Excluded From the Analysis.

	Included	Excluded
n	3,632	1,492
Men*	1,669 (46.0)	814 (54.6)
Age, years†	34.8 (9.9)	40.0 (10.9)
BMI, kg/m^2†	25.1 (4.3)	26.1 (4.7)
With obesity*	428 (11.8)	258 (17.3)
Serum triglycerides, mg/dL†	91.9 (62.8)	119.0 (117.9)
High triglycerides*	430 (12.0)	306 (21.0)
Serum HDL, mg/dL†	51.3 (14.6)	48.5 (14.7)
Low HDL*	1,196 (33.6)	597 (41.0)
Systolic blood pressure, mm Hg†	120.0 (14.7)	126.6 (19.4)
Diastolic blood pressure, mm Hg†	77.6 (10.1)	81.1 (12.2)
High blood pressure*	1,782 (49.2)	929 (62.6)
Blood glucose, mg/dL†	100.8 (10.6)	105.9 (23.7)
High glucose*	50 (1.4)	97 (6.8)
Education, years†	14.1 (2.6)	13.2 (2.6)
Smoking*		
Never	1,236 (35.2)	344 (23.4)
Former	749 (21.3)	220 (15.0)
Current	1,527 (43.5)	904 (61.7)
Death prior to examination 4†	0 (0.0)	239 (16.0)

*Presented as n (%)

†Presented as mean (S.D)

Table S3. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Obesity and Metabolically Unhealthy State, Framingham Offspring Examination 4-Examination 9.

	Incident Obesity					Incident Metabolically Unhealthy State				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$§
Obesity										
SNO	397	498.5	1.00	Reference	<0.0001	505	1,290.6	1.00	Reference	<0.0001
VNO	170	1,882.6	3.47	2.67, 4.53		95	2,004.2	1.75	1.32, 2.32	
SO						80	2,564.1	1.84	1.37, 2.48	0.30
VO						79	2,668.9	2.27	1.69, 3.05	
Metabolic health										
SMH	247	511.1	1.00	Reference	0.45	599	1,484.9	1.00	Reference	0.60
VMH	69	552.0	1.12	0.84, 1.48		160	1664.9	1.06	0.86, 1.29	
SMU	152	883.7	1.64	1.27, 2.13	0.21					
VMU	89	963.2	2.00	1.53, 2.60						

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, examination, education, smoking status, physical activity index, and BMI.

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Adjusted for age, sex, examination, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

Table S4. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Diabetes and Hypertension, Framingham Offspring Examination 4-Examination 9.

	Incident Diabetes					Incident Hypertension				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$‡
Obesity										
SNO	113	135.0	1.00	Reference	0.009	324	1,682.2	1.00	Reference	0.002
VNO	25	211.1	1.92	1.18, 3.14		85	2,698.4	1.67	1.21, 2.31	
SO	92	555.6	3.05	2.24, 4.15	0.87	33	4,177.2	2.46	1.39, 4.37	0.70
VO	42	361.4	2.94	1.94, 4.46		61	4,326.2	2.15	1.41, 3.28	
Metabolic health										
SMH	68	101.9	1.00	Reference	0.93	350	1,909.4	1.00	Reference	0.35
VMH	13	104.0	0.97	0.53, 1.79		75	1,879.7	0.87	0.65, 1.17	
SMU	147	477.7	3.33	2.41, 4.60	0.21	50	3,546.1	1.74	1.19, 2.54	0.46
VMU	41	344.8	2.62	1.71, 4.01		21	3,962.3	1.30	0.64, 2.65	

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

Table S5. Associations of Obesity, Metabolic Health Status, and Coefficient of Variability-Defined Variability of Body Mass Index and Metabolic Health with Risk of Incident Cardiovascular Disease and Chronic Kidney Disease, Framingham Offspring Examination 4-Examination 9.

	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$‡
Obesity										
SNO	351	90.7	1.00	Reference	0.38	114	184.3	1.00	Reference	0.87
VNO	30	51.3	0.84	0.57, 1.34		9	90.0	0.94	0.44, 2.00	
SO	143	156.0	1.25	1.03, 1.53	0.98	52	344.8	1.47	1.00, 2.15	0.95
VO	64	98.8	1.25	0.94, 1.65		20	174.1	1.44	0.84, 2.47	
Metabolic health										
SMH	180	59.6	1.00	Reference	0.44	55	122.6	1.00	Reference	0.57
VMH	40	70.3	1.14	0.81, 1.61		16	114.4	0.85	0.48, 1.50	
SMU	220	138.3	1.68	1.37, 2.06	0.0006	58	256.0	1.26	0.84, 1.91	0.01
VMU	145	190.4	2.44	1.94, 3.06		65	398.3	2.11	1.39, 3.21	

CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-years

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Crude rate per 10,000 person-periods

Table S6. Inverse Probability of Censoring-Weighted Associations of Obesity Sub-phenotypes with Risk of Obesity and Becoming Metabolically Unhealthy, Framingham Offspring Examination 4- Examination 9.

Obesity Subphenotypes	Cases	Rate*	HR†	95% CI	$P_{interaction}$‡	Cases	Rate*	HR†	95% CI	$P_{interaction}$§
	Incident Obesity					Incident Metabolically Unhealthy State				
MHNO	316	519.5	1.00	Reference		605	1,378.8	1.00	Reference	
MUNO	241	911.5	1.98	1.63, 2.39						
MHO						166	2,707.9	2.02	1.64, 2.50	
MUO										
	Incident Diabetes					Incident Hypertension				
MHNO	49	73.7	1.00	Reference		358	1,737.0	1.00	Reference	
MUNO	88	320.2	4.94	3.27, 7.45		45	2,125.0	1.89	1.35, 2.65	
MHO	32	253.2	4.45	2.71, 7.29		67	4,012.0	2.19	1.66, 2.89	
MUO	100	664.9	10.49	7.07, 15.55		25	5,102.0	2.31	1.47, 3.62	
Obesity x MU			0.48	0.27, 0.86	0.01			0.56	0.31, 1.01	0.05
Obesity+MU			1.73	-0.80, 4.27	0.18			-0.77	-1.77, 0.22	0.13

	Cases	Rate*	HR†	95% CI	$P_{interaction}$‡	Cases	Rate*	HR†	95% CI	$P_{interaction}$§
	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
MHNO	170	29,717	1.00	Reference		53	4811	1.00	Reference	
MUNO	207	14,158	1.74	1.38, 2.20		69	2317	1.75	1.18, 2.59	
MHO	50	6,113	1.33	0.93, 1.91		18	1065	1.60	0.87, 2.93	
MUO	157	9,304	2.45	1.90, 3.16		54	1570	2.97	1.94, 4.56	
Obesity x MU			1.06	0.79, 1.42	0.71			1.06	0.51, 2.21	0.87
Obeisty+MU			0.06	-0.35, 0.47	0.79			0.62	0.10, 1.15	0.02

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; RERI, relative excess risk due to interaction; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, exam, education, smoking status, physical activity index, and BMI.

‡P-value for the multiplicative interaction between obesity and the metabolically unhealthy state

§Adjusted for age, sex, exam, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

Table S7. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Obesity and Metabolically Unhealthy State, Framingham Offspring Examination 4- Examination 9.

	Incident Obesity					Incident Metabolically Unhealthy State				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR§	95% CI	$P_{difference}$§
Obesity										
SNO	390	510.3	1.00	Reference	0.04	483	1,291.4	1.00	Reference	<0.0001
VNO	177	1,444.9	1.26	1.01, 1.59		122	1,882.7	1.65	1.29, 2.11	
SO						97	2,607.5	1.15	0.87, 1.51	0.02
VO						69	2,863.1	1.89	1.35, 2.65	
Metabolic health										
SMH	247	501.9	1.00	Reference	0.12	629	1534.9	1.00	Reference	0.71
VMH	69	593.8	1.25	0.94, 1.67		142	1572.5	1.08	0.83, 1.31	
SMU	160	808.5	0.92	0.74, 1.13	0.49					
VMU	81	1,218.0	1.02	0.77, 1.33						

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health,

metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods.

†Adjusted for age, sex, examination, education, smoking status, physical activity index, and BMI.

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Adjusted for age, sex, examination, education, smoking status, physical activity index, systolic blood pressure, diastolic blood pressure, current antihypertensive medication use, HDL, triglycerides, blood glucose, current use of antidiabetic medication.

Table S8. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Diabetes and Hypertension, Framingham Offspring Examination 4-Examination 9.

	Incident Diabetes					Incident Hypertension				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$§
Obesity										
SNO	109	121.1	1.00	Reference	0.004	301	1,659.3	1.00	Reference	<0.0001
VNO	29	171.3	2.00	1.24, 3.21		108	2,529.3	1.67	1.31, 2.13	
SO	103	482.2	3.30	2.39, 4.55	0.62	41	3,831.8	1.86	1.29, 2.68	0.15
VO	31	282.1	2.86	1.76, 4.67		53	4,690.3	2.60	1.88, 3.59	
Metabolic health										
SMH	70	109.9	1.00	Reference	0.09	338	1,860.2	1.00	Reference	0.28
VMH	11	70.8	0.55	0.28, 1.10		87	2,096.4	1.16	0.90, 1.50	
SMU	152	476.3	3.47	2.46, 4.90	0.49	50	3,448.3	1.50	1.04, 2.19	0.46
VMU	36	334.9	3.01	1.91, 4.75		21	4,285.7	1.84	1.21, 2.80	

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

Table S9. Inverse Probability of Censoring-Weighted Associations of Obesity, Metabolic Health Status, and Variability of Body Mass Index and Metabolic Health with Risk of Incident Cardiovascular Disease and Chronic Kidney Disease, Framingham Offspring Examination 4-Examination 9.

	Incident Cardiovascular Disease					Incident Chronic Kidney Disease				
	Cases	Rate*	HR†	95% CI	$P_{difference}$‡	Cases	Rate*	HR†	95% CI	$P_{difference}$‡
Obesity										
SNO	344	92.2	1.00	Reference	0.41	113	190.1	1.00	Reference	0.75
VNO	37	51.2	0.84	0.57, 1.25		10	80.5	0.88	0.41, 1.88	
SO	157	149.3	1.31	1.04, 1.63	0.55	61	350.2	1.71	1.20, 2.45	0.70
VO	50	97.4	1.47	1.03, 2.12		11	63.1	1.47	0.71, 3.04	
Metabolic health										
SMH	179	61.9	1.00	Reference	0.69	60	125.5	1.00	Reference	0.84
VMH	41	58.8	1.08	0.73, 1.59		11	99.7	0.93	0.44, 1.97	
SMU	252	149.4	1.72	1.37, 2.15	0.24	80	288.9	1.66	1.14, 2.42	0.31
VMU	113	169.8	2.01	1.53, 2.65		43	380.9	2.07	1.31, 3.28	

CI, confidence interval; HR, hazard ratio; SMH, stable metabolic health, metabolically healthy; SMU, stable metabolic health, metabolically unhealthy; SNO, stable BMI, without obesity; SO, stable BMI, with obesity; VMH, variable metabolic health, metabolically healthy; VMU, variable metabolic health, metabolically unhealthy; VNO, variable BMI, without obesity; VO, variable BMI, with obesity.

*Crude rate per 10,000 person-periods

†Adjusted for age, sex, examination, education, smoking status, and physical activity index

‡P-value comparing association of stability with diabetes to that of variability within a given obesity/metabolic health status

§Crude rate per 10,000 person-periods