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ORIGINAL RESEARCH

Obesity Duration, Severity, and Distribution Trajectories and Cardiovascular Disease Risk in the Atherosclerosis Risk in Communities Study

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BACKGROUND: Research examining the role of obesity in cardiovascular disease (CVD) often fails to adequately consider heterogeneity in obesity severity, distribution, and duration.

METHODS AND RESULTS: We here use multivariate latent class mixed models in the biracial Atherosclerosis Risk in Communities study (N=14 514; mean age=54 years; 55% female) to associate obesity subclasses (derived from body mass index, waist circumference, self-reported weight at age 25, tricep skinfold, and calf circumference across up to four triennial visits) with total mortality, incident CVD, and CVD risk factors. We identified four obesity subclasses, summarized by their body mass index and waist circumference slope as decline (4.1%), stable/slow decline (67.8%), moderate increase (24.6%), and rapid increase (3.6%) subclasses. Compared with participants in the stable/slow decline subclass, the decline subclass was associated with elevated mortality (hazard ratio [HR] 1.45, 95% CI 1.31, 1.60, $P<0.0001$) and with heart failure (HR 1.41, 95% CI 1.22, 1.63, $P<0.0001$), stroke (HR 1.53, 95% CI 1.22, 1.92, $P=0.0002$), and coronary heart disease (HR 1.36, 95% CI 1.14, 1.63, $P=0.0008$), adjusting for baseline body mass index and CVD risk factor profile. The moderate increase latent class was not associated with any significant differences in CVD risk as compared to the stable/slow decline latent class and was associated with a lower overall risk of mortality (HR 0.85, 95% CI 0.80, 0.90, $P<0.0001$), despite higher body mass index at baseline. The rapid increase latent class was associated with a higher risk of heart failure versus the stable/slow decline latent class (HR 1.34, 95% CI 1.10, 1.62, $P=0.004$).

CONCLUSIONS: Consideration of heterogeneity and longitudinal changes in obesity measures is needed in clinical care for a more precision-oriented view of CVD risk.

Key Words: cardiovascular disease ■ latent class models ■ obesity

The prevalence of obesity has more than doubled among adults in the United States over the past 40 years, with a disproportionate impact on women and on Black and Hispanic populations[1,2] Obesity is associated with decreased life expectancy and increased morbidity,[3] particularly from cardiovascular diseases (CVD). However, many studies inaccurately assume that all individuals at a given body mass index (BMI) will be at similar cardiovascular disease risk,[4] ignoring differences between individuals in

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CLINICAL PERSPECTIVE

What Is New?

- Latent class analysis was used to derive data-driven obesity subgroups in the biracial Atherosclerosis Risk in Communities study.
- These latent classes were associated with incident cardiovascular disease and mortality, adjusting for baseline body mass index, as well as with cardiovascular disease risk factors; for example, individuals with rapid declines in adiposity metrics had elevated mortality, coronary heart disease, stroke, and heart failure risk versus the stable/slow decline reference class.
- Rapid increases in adiposity metrics were associated with increased risk of heart failure hospitalization.

What Are the Clinical Implications?

- A single body-mass-index timepoint is not adequate for understanding the relationship between adiposity and cardiovascular risk.
- Obesity is dynamic and requires consideration across the life-course.
- There is value to accounting for multiple measures of obesity distribution and severity and changes in these measures over time.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
CHNS	China Health and Nutrition Survey
SBP	systolic blood pressure
T2D	type 2 diabetes
WC	waist circumference
WHR	waist hip ratio

obesity duration, severity, distribution, weight trajectory, and resulting cardiovascular risk factor profile. Differences in obesity duration,[5–7] obesity severity,[8] and fat distribution[9,10] (as assessed by waist circumference [WC] and waist hip ratio [WHR]) have all been associated with differential risk of cardiometabolic disease.

Adiposity is in part controlled by genetic factors, with hundreds of loci identified for cross-sectional analyses of body mass index, waist circumference adjusted for BMI, and other measures, and different variants influence central and overall adiposity.[11,12] It is less clear how these loci influence changes in adiposity metrics over time. There is a need for more accurate, individualized identification of overweight and obese adults at highest risk for CVD.

We are not aware of any studies jointly examining the influence of overall and abdominal obesity severity and duration on CVD or CVD risk factors. In this study we applied latent class analysis to summarize multiple obesity metrics across timepoints in an unbiased manner. We then assessed associations with incident CVD events, overall mortality, and differential CVD risk factor profiles.

METHODS

Atherosclerosis Risk in Communities Cohort

The ongoing, longitudinal, and population-based ARIC (Atherosclerosis Risk in Communities) study was initiated in 1987 to study the cause and natural history of CVD and its risk factors. Standardized physical examinations and interviewer-administered questionnaires were conducted at baseline (1987–1989), 3 triennial follow-up examinations, and 3 additional examinations beginning 15 years later (2011–present). For our analyses, we excluded participants who reported a race other than Black or White (n=48, self-reported “Asian” or “American or Alaskan Indian” race) and Black participants recruited in Minnesota because of small site-specific numbers (n=55) as well as participants with adiposity measures only at visit 1 (n=1134), leaving n=14 514 ARIC participants. The ARIC study protocols were approved by Institutional Review Boards at each participating study site, and participants provided informed consent at each study visit.[13] Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the ARIC coordinating center at https://sites.cscc.unc.edu/aric/desc_pub. Much of the data used in this project are also available through BioLINCC (HLB00020020c).

We selected 5 previously validated[14–16] anthropometric measures to capture obesity duration, distribution, and severity: BMI, as a measure of overall body mass; waist circumference, as our indicator of abdominal obesity, given its use in clinical care; tricep skinfold as a measure of peripheral fat that is correlated with overall body fat; calf circumference as a measure of limb muscle mass sensitive to aging; and weight at age 25 as a measure of early life-course adiposity. Waist circumference (visits 1–4) was assessed at the level of the umbilicus. Measured weight (visits 1–4) was collected using a scale zeroed daily and calibrated quarterly and was used to calculate BMI. Tricep skinfold measures (visits 1–2) were assessed using a Lange caliper on standardized right-side locations.

Calf circumference (visit 1) was assessed at the maximum circumference over the calf muscle. Data from visit 5 were excluded due to large gap in time between visits 4 and 5; this approach also enabled estimation of associations between obesity latent classes with total mortality, CVD incidence, and CVD risk factors, as described below.

For ascertainment of CVD events, we used the ARIC event adjudication procedures previously described, with follow-up from baseline through December 31, 2018 or loss to follow-up.[17–19] For the Jackson field center only, adjudication is through December 31, 2017. Follow-up for CHD, heart failure, and stroke was accomplished through a combination of active surveillance of local hospital discharge lists, annual participant interviews querying hospitalizations, examination of vital records, and interviews with decedent's next of kin. Median follow-up was ≈27 years from baseline for heart failure, stroke, CHD, and mortality. Incident heart failure was defined by hospitalization or death certificate codes listing 428 or I-50 in any position, shown previously to have high levels of accuracy.[20] Incident CHD was defined as a validated definite or probable hospitalized myocardial infarction (MI), a definite CHD death, or an unrecognized MI identified by electrocardiograph. The criteria for definite or probable hospitalized MI were based on combinations of chest pain symptoms, electrocardiogram changes, and cardiac enzyme levels. Definite or probable physician-adjudicated stroke (including both ischemic and hemorrhagic subtypes) was identified based on the presence of *International Classification of Diseases, Ninthe Revision* (*ICD-9)* codes 430 to 438 and neurological signs and symptoms. Individuals with self-reported baseline history of stroke or transient ischemic attack, CHD, or heart failure were excluded from analyses of that incident measures.

CVD risk factor assessment was conducted as previously described[13] using standardized procedures. Fasting low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation.[21] Three seated resting blood pressure readings were obtained using random zero sphygmomanometers, retaining the mean of the last two measures. Hypertension was defined as blood pressure >140/90 mm Hg or use of hypertension medications. Type 2 diabetes (T2D) was defined as either fasting glucose ≥126 mg/dL, T2D medication use, self-reported physician diagnosis, or non-fasting glucose ≥200 mg/dL (single timepoint). CRP (C-reactive protein) measurement methods have been described previously.[22] eGFR was calculated using the CKD-EPI equation.[23] The small number of individuals taking statins at visit 1 (n=89) were not included in models for LDL, high-density lipoprotein (HDL), and triglycerides. The much larger number of individuals taking statins at visit 5 (n=3394) were included in all lipid models after applying a 0.8 correction factor to total cholesterol to account for statin use.[24] Frailty score was derived as previously described based on five components: exhaustion, slowness, low energy expenditure, weakness, and weight loss between visits 4 and 5 (which was not considered in our latent class derivation).[25] Education was categorized based on years of schooling as basic (<11), intermediate (12–16), or advanced (17–21).

Latent Class Analysis for Derivation of Obesity Subgroups

To derive obesity latent classes we adapted a multivariate latent class mixed model[26,27] that enabled estimation of the latent process that underlies multiple longitudinal obesity trajectories across this age range. Unlike other classification metrics this data-driven method uses longitudinal data to identify and classify individuals into subgroups based on similar trajectory patterns across all obesity measures. Briefly, the full suite of anthropometric measures were modeled using mixed effects models including a component to account for the latent process across all anthropometric measures and an outcome-specific component to account for the differential effect of age on each outcome and includes a random intercept specific to each given participant and each given outcome.

For the purposes of interpretation, we identified latent classes based on the predictions of each outcome by age for each latent process. Specifically, we identified and classified individuals into latent classes depending on their latent patterns of obesity, which were estimated using age-trajectories of the measures of obesity described above (BMI, waist circumference, triceps skinfold, weight at age 25, and calf circumference). Each subject was assigned to a latent class based on the latent class with the highest posterior probability.

Final model selection, including the selection of the number of latent classes, was guided by: (1) the Akaike and Bayesian Information Criteria, (2) interpretability of model solution with assessment of size and uniqueness of each latent class, (3) the number of individuals with uncertain class assignment (probability of assignment <0.5), and (4) the biological plausibility of the modeled latent classes. The minimum percentage of the population which could be assigned to a particular latent class was 2%.

Association of Obesity Latent Classes With Cardiovascular Disease and Its Risk Factors

We assessed associations with events (MI/Fatal CHD, stroke, heart failure hospitalizations) and mortality

using Cox proportional hazards models, with follow-up time beginning at visit 1. In these survival models, we controlled for sex, baseline age (at visit 1), study center, and race (Model 1), as well as baseline T2D, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate (Model 2), with additional adjustment for baseline BMI in Model 3. For our association analyses of CVD events with latent class assignment, we used a Bonferroni corrected *P* value threshold of $P<0.05/4=0.0125$.

We next assessed associations of obesity latent classes with CVD risk factors, at baseline (visit 1) and visit 5 (the first visit after the obesity measures used to derive the latent classes), including eGFR, fasting glucose, triglyceride levels, LDL and HDL cholesterol levels, CRP, and systolic blood pressure using generalized linear models adjusted for sex, baseline age, study center, and race. Fasting plasma glucose was evaluated in participants without T2D, as defined above. We did not feel it was appropriate to include visit 5 due to the long time gap between visits 4 and 5 (≈13 years, as noted above) and the high potential for frailty related weight loss in a large number of aging participants, but analysis of CVD risk factors (which would generally increase continuously in older adults, even with potential frailty related weight loss) at this "incident" timepoint (ie, after the adiposity gains/losses captured by our latent class trajectories) was informative to examine the CVD risk factor impacts of different trajectories. Analyses of visit 5 measures included at most 6434 participants, as 8080 of the participants included in our analyses had died, dropped out, or declined to participate in-person by this visit. Baseline CRP was assessed at visit 2, not visit 1 (as it was not available at visit 1). For our association analyses of CVD risk factors with latent class assignment, we used a Bonferroni corrected *P* value threshold of $P<0.05/7=0.0071$ at each visit.

Exploratory Polygenic Risk Score Analysis

In self-reported White and Black participants separately, we also examined the association of obesity latent classes with a polygenic risk score calculated using LDpred[28] based on previous genome-wide association studies of BMI.[11] LDpred calculates the posterior mean effects from GWAS summary statistics by conditioning on a genetic architecture prior and LD information from a reference panel. The ARIC sample served as the reference LD panel, stratified by self-reported race. The score used in Black participants was based on a combined GIANT and UK Biobank GWAS for BMI[11] (r^2=3.99% for BMI in Black ARIC participants) and the score for White participants was based on GWAS in UK Biobank (round 2 results accessed at http://www.nealelab.is/uk-biobank/) (r^2=7.28% for BMI in ARIC White participants), as the ARIC White participants were included in the GIANT GWAS. We adjusted only for sex, age at baseline, center, and the first 5 ancestry principal components in Model 1 for the genetic risk score analysis. Model 2 was additionally adjusted for HDL, current smoking, total cholesterol, hypertension, T2D, and estimated glomerular filtration rate, with Model 3 also adjusted for baseline BMI. For our association analyses of polygenic risk scores with latent class assignment, we used a *P* value threshold of 0.05.

RESULTS

Of the n=14 514 participants (median age 54, 74% White, 55% female), most (79%) had adiposity data across 4 visits. We initially fit a 3, 4, and 5 latent class model (Table S1). The 4 latent class model had the best fit and was used for further analyses. For example, both BIC and AIC statistics suggested noticeable model improvement for the 4 class in comparison to the 3 latent class model, likely in part due to better differentiation of moderate versus rapid adiposity increase latent classes. The 5 latent class model had wide CIs around the mean trajectories, and the mean trajectories had substantial overlap, as reflected by the large number of individuals with a probability of class latent assignment <0.5. For the selected 4 class model, only 189 people had a probability of latent class assignment <0.5; these individuals were less likely to have 3 (20.1% low probability individuals, versus 87.9% overall) or 4 visits (4.8% low probability individuals, versus 79.4% overall) of adiposity data.

While each latent class represents a complex combined phenotype, we summarize the latent classes (as seen in Figure) as decline (4.09%, n=594), moderate increase (24.58%, n=3568), rapid increase (3.55%, n=515), and stable/slow decline (67.78%, n=9837) classes. As seen in Figure, the trajectory patterns were relatively similar across all obesity measures, not including self-reported weight at 25 which was only measured at one time point. One small exception was the stable/slow decline class (the largest of our 4 classes) where we see on average a slow decline for BMI, tricep, and calf measures across the life course but a slight increase in waist circumference over this period, though all of these changes are very modest. For simplicity however, we refer to this class as stable/slow decline due to 3 of the 4 obesity measure trajectories suggesting this pattern; in general, this latent class includes individuals with relatively stable adiposity metrics over time. The largest latent class (stable/slow decline) was used as the reference for all analyses. As reflected in Figure and Table S2, there are significant differences in adiposity metrics by latent class. Descriptively, the decline subclass had a higher median baseline BMI

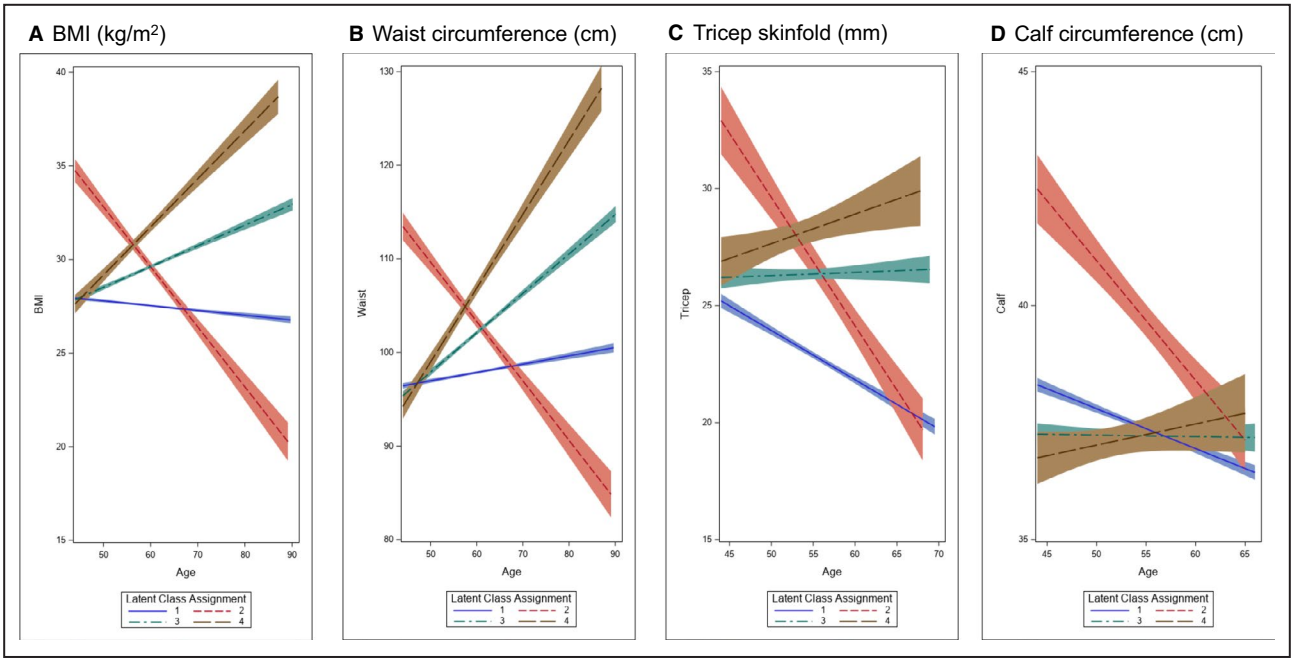

Figure 1. Latent class specific mean predicted BMI (A), waist circumference (B), tricep skinfold (C), and calf circumference (D) trajectories by age.

Class 1—Stable/slow decline, Class 2—Decline, Class 3—Moderate Increase, Class 4—Rapid Increase. Mean values with confidence limits are displayed by participant age, with a maximum of 4 measurements for each participant across ARIC (Atherosclerosis Risk in Communities) visits 1 through 4 (tricep skinfold has at most only 2 measures and calf circumference has only one measurement per participant). Weight at 25 is by definition all at the same age, so trajectories are not displayed; median values are displayed in Table S2.

than the other 3 classes, with an approximate median BMI of 30 in contrast to the overall median of 27, and was the only latent class with a lower median BMI at last visit (≈26) compared to baseline. Patterns in tricep skinfold and waist circumference measures were similar to those for BMI (Table S2). There were also differences in demographic variables across the obesity sub-classes (Table 1).

In models adjusting for age, sex, race, and study center, baseline BMI was significantly higher in the latent class that declined over follow-up (Table S3), as well as in the moderate increase latent class, in comparison to the reference stable/slow decline latent class. At visit 5, which was not included in latent class derivation, we observed higher waist circumference and BMI for all classes versus the stable/slow decline (referent) latent class, with an estimated effect size of 1.60 kg/m^2 for the decline latent class, 2.87 kg/m^2 for the moderate increase latent class, and 5.23 kg/m^2 for the rapid increase latent class for BMI, adjusting for age, sex, race, and study center.

In minimally adjusted models, we observed a higher polygenic risk score in both White and Black participants for the decline latent class and, especially, the rapid increase latent class (Table S4). This association with higher polygenic risk in the rapid increase latent class was robust to adjustment for baseline CVD risk factors and for baseline BMI, suggesting that polygenic risk score may associate with both increased BMI in cross-sectional analyses (as used to derive the polygenic risk score) and a more rapid age-related increase in BMI (Table S4).

We next examined the association of latent classes with incident CVD and mortality. Adjusting for CVD risk factors at baseline (T2D, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate) and baseline BMI (Table 2), the decline latent class had elevated risk of overall mortality as compared with the reference stable/slow decline latent class. Similarly, this subclass had elevated risk of stroke, MI/fatal CHD, and heart failure relative to the stable/slow decline subclass. The moderate increase class was not associated with any significant differences in CVD risk compared with the stable/slow decline subclass but was associated with a lower overall risk of mortality. The rapid increase class was associated with increased risk of heart failure relative to the stable/slow decline subclass but not with other outcomes.

Given the association of the decline latent class with heart failure relative to the stable/slow decline subclass, and the known complication of unintentional weight loss in heart failure patients,[29] we performed a sensitivity analysis removing all individuals with incident heart failure from our analyses of stroke, MI/fatal CHD, and mortality (Table S5). The association of the decline latent class with increased MI/fatal CHD

Table 1. Demographic Characteristics of ARIC Study Participants Included in Latent Class Analysis, Overall and Stratified by Latent Class Assignment

Variable	Overall (N=14 514)	Stable/ slow decline (N=9837)	Decline (N=594)	Moderate increase (N=3568)	Rapid increase (N=515)	*P* value
Median (Q1, Q3) age at baseline	54 (49, 59)	54 (49, 59)	55 (50, 60)	53 (48, 58)	51 (47, 56)	<0.0001
% Female	55.49%	48.91%	47.81%	70.38%	86.99%	<0.0001
% Black (remaining participants self-reported White)	25.73%	25.02%	35.52%	26.04%	25.83%	<0.0001
Basic education or 0 y of education	22.28%	22.29%	28.11%	21.41%	21.36%	0.0042
Intermediate education	41.1%	40.51%	38.22%	42.57%	45.44%	0.0042
Advanced education	36.46%	37%	33.5%	35.96%	33.01%	0.0042
Current smoker	24.87%	23.99%	32.49%	24.36%	36.5%	<0.0001
Field Center (Forsyth County, NC)	25.41%	26.58%	22.56%	23.23%	21.36%	<0.0001
Field Center (Jackson, MS)	22.68%	21.89%	31.82%	23.26%	23.3%	<0.0001
Field Center (Minneapolis, MN)	26.26%	25.94%	21.72%	26.82%	33.79%	<0.0001
Field Center (Washington County, MD)	25.64%	25.59%	23.91%	26.68%	21.55%	<0.0001
Two visits with adiposity data	9.2%	11.25%	8.08%	4.54%	3.69%	<0.0001
Three visits with adiposity data	11.33%	11.58%	16.84%	9.47%	13.2%	<0.0001
Four visits with adiposity data	79.46%	77.17%	75.08%	85.99%	83.11%	<0.0001
Median (Q1, Q3) BMI at baseline (Visit 1)	26.85 (24.02, 30.39)	26.58 (23.87, 29.96)	30.58 (27.29, 34.98)	26.99 (24.15, 30.69)	26.89 (23.55, 30.34)	<0.0001
Median (Q1, Q3) BMI at last visit	27.92 (24.83, 31.65)	26.99 (24.16, 30.37)	26.42 (23.39, 30.24)	30.27 (27.15, 34.12)	33.75 (30.09, 38.43)	<0.0001

P value is for a chi-square based test of differences between latent classes for categorical traits and a type III test for differences between classes in a generalized linear model for a continuous trait (age). Q1 indicates quartile 1; and Q3, quartile 3. ARIC indicates Atherosclerosis Risk in Communities.

risk was attenuated, likely in part due to reduced sample size, but associations of the decline latent class with increased stroke and mortality risk were robust, as was the association of moderate increase class with decreased mortality risk. We also performed a sensitivity analysis excluding individuals with incident cancer cases between ARIC visits 1 and 4 (or their last visit), adjudicated as previously described,[30] as new cancer diagnoses and chemotherapy treatment could be another cause of unintentional weight loss (Table S6). Results were essentially unchanged. Finally, we sought to ensure that individuals with a low probability of class assignment (certainty <50%) were not playing a major role in the observed associations of latent class assignment with incident CVD and mortality (Table S7). Again, results were essentially unchanged. Exclusion of individuals with diabetes at baseline, who might be affected by unintentional weight-loss in later stages of the disease, also did not change the results (Table S8). We hypothesized that the presence of frailty, of which unintentional weight loss is one defining factor, may explain the increased risk of mortality in those with declining adiposity metrics between visits 1 and 4. Excluding the small number of overtly frail individuals at visit 5 (n=396) did not substantially alter results (Table S9), but "prefrail" versus "robust" individuals showed clearer evidence of association ($P<0.05$) of the decline latent class with increased mortality risk and the moderate increase latent class with decreased mortality risk, versus robust individuals ($P>0.05$) (the overtly frail latent class was too small to perform stratified Cox models) (Table S10).

We next tested the association of latent class assignment with cardiovascular disease risk factors at baseline (Table 3). Correcting for multiple testing ($P<0.05/7$ or $P<0.0071$) and with the stable/slow decline latent class as reference, we found that the moderate and rapid increase latent classes were associated with a generally favorable baseline CVD risk profile, with lower triglyceride levels and SBP, and lower fasting glucose and LDL for the rapid increase latent class. By contrast, the decline latent class was associated with a higher cardiometabolic risk profile at baseline, including reduced baseline kidney function, higher fasting glucose, higher triglycerides, lower HDL, and higher SBP relative to the stable/slow decline subclass. All latent classes were all associated with elevated baseline inflammation (as assessed by CRP) versus the stable/slow decline latent class.

We also examined the association of latent class assignment with CVD risk factors at visit 5 (Table 4), which was not included in latent class derivation. Sample size was reduced due to loss to follow-up/mortality by visit 5 (14.8 years on average after visit 4). The decline latent class was associated with lower LDL relative to the stable/slow decline subclass; this association with lower LDL was not robust to adjustment of LDL values for statin

Table 2. Association of Latent Class Assignment With Incident Cardiovascular Disease and Mortality

Outcome (N events/N)	Class	N events (by class)	N controls (by class)	Model 1				Model 2				Model 3			
				Hazard ratio	95% confidence limits		*P* value	Hazard ratio	95% confidence limits		*P* value	Hazard ratio	95% confidence limits		*P* value
Heart failure (3188/13 393)	Stable/slow decline	2136	6995	Reference				Reference				Reference			
	Decline	209	318	2.25	1.95	2.60	<0.0001*	1.65	1.43	1.90	<0.0001*	1.41	1.22	1.63	<0.0001*
	Moderate increase	732	2538	1.02	0.94	1.11	0.62	1.03	0.95	1.12	0.47	1.00	0.92	1.09	0.94
	Rapid increase	111	354	1.40	1.16	1.71	0.0006*	1.38	1.13	1.67	0.001*	1.34	1.10	1.62	0.004*
Stroke (1362/13 945)	Stable/slow decline	910	8553	Reference				Reference				Reference			
	Decline	87	472	2.00	1.60	2.49	<0.0001*	1.55	1.24	1.93	0.0001*	1.53	1.22	1.92	0.0002*
	Moderate increase	314	3114	0.99	0.87	1.13	0.84	1.01	0.88	1.15	0.94	1.00	0.88	1.14	0.97
	Rapid increase	51	444	1.34	1.01	1.78	0.05	1.33	1.00	1.77	0.05	1.33	1.00	1.77	0.05
MI/fatal CHD (2096/13 275)	Stable/slow decline	1443	7542	Reference				Reference				Reference			
	Decline	139	383	2.07	1.74	2.47	<0.0001*	1.42	1.19	1.69	0.0001*	1.36	1.14	1.63	0.0008*
	Moderate increase	452	2844	0.96	0.86	1.06	0.41	0.98	0.88	1.09	0.71	0.97	0.87	1.08	0.61
	Rapid increase	62	410	1.14	0.88	1.48	0.32	1.15	0.89	1.49	0.29	1.14	0.88	1.48	0.32
Mortality (7129/14 185)	Stable/slow decline	5011	4611	Reference				Reference				Reference			
	Decline	432	146	1.93	1.75	2.13	<0.0001*	1.55	1.40	1.71	<0.0001*	1.45	1.31	1.60	<0.0001*
	Moderate increase	1462	2021	0.88	0.82	0.93	<0.0001*	0.86	0.82	0.92	<0.0001*	0.85	0.80	0.90	<0.0001*
	Rapid increase	224	279	1.20	1.05	1.38	0.01*	1.08	0.94	1.24	0.27	1.06	0.92	1.21	0.41

All models are limited to those with complete covariate data for all three models. Model 1: Adjusted age, sex, race, center. Model 2: Additional adjustment diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate (all at baseline). Model 3: Additional adjustment baseline body mass index. CHD indicates coronary heart disease; and MI, myocardial infarction.

*Significant by Bonferroni corrected P-value threshold

Table 3. Association of Latent Class Assignment With CVD Risk Factors at Baseline, Adjusting for Age at Measurement, Sex, Race, and Recruitment Center

Trait	Class	Estimate	Standard error	*P* value
eGFR (n=14 391)	Stable/slow decline	Reference		
	Decline	−2.14	0.56	0.0001*
	Moderate increase	0.17	0.27	0.53
	Rapid increase	1.18	0.61	0.05
Fasting glucose (n=12 796)	Stable/slow decline	Reference		
	Decline	1.65	0.48	0.0005*
	Moderate increase	−0.55	0.19	0.005*
	Rapid increase	−1.99	0.44	<0.0001*
C-reactive protein (n=13 362)	Stable/slow decline	Reference		
	Decline	0.28	0.03	<0.0001*
	Moderate increase	0.12	0.02	<0.0001*
	Rapid increase	0.20	0.04	<0.0001*
Triglycerides (n=14 305)	Stable/slow decline	Reference		
	Decline	0.20	0.02	<0.0001*
	Moderate increase	−0.04	0.01	<0.0001*
	Rapid increase	−0.10	0.02	<0.0001*
LDL (n=14 102)	Stable/slow decline	Reference		
	Decline	2.27	1.68	0.18
	Moderate increase	−0.58	0.78	0.46
	Rapid increase	−5.17	1.79	0.004*
HDL (n=14 304)	Stable/slow decline	Reference		
	Decline	−4.63	0.66	<0.0001*
	Moderate increase	−0.38	0.31	0.22
	Rapid increase	1.25	0.72	0.08
SBP (n=14 507)	Stable/slow decline	Reference		
	Decline	5.42	0.73	<0.0001*
	Moderate increase	−1.21	0.34	0.0005*
	Rapid increase	−3.89	0.79	<0.0001*

C-reactive protein and triglycerides were natural log transformed. Individuals with diabetes at visit 1 were excluded from assessment of fasting glucose. All risk factors are at visit 1 except for C-reactive protein, which is at visit 2. eGFR indicates estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*Significant by Bonferroni corrected P-value threshold

use at visit 5 (*P*=0.20). However, for the moderate and rapid increase latent classes, we observed a generally unfavorable CVD risk factor profile (higher CRP and triglyceride levels, lower HDL, higher fasting glucose for the moderate increase latent class) relative to the stable/slow decline subclass, likely in part due to increased average BMI/waist circumference trajectory versus the stable/slow decline latent class (Table S4). LDL was lower for the rapid increase latent class relative to the stable/slow decline subclass, and this association was robust to adjustment for statin treatment (β=−6.08, *P*=0.008).

DISCUSSION

Middle to older aged adults today are heavier than previous generations and have often carried this excess weight since earlier in the lifecycle. Approximately 72% of US adults ≥60 years are either overweight or obese.[1] While obesity, particularly severe obesity, is consistently associated with CVD risk, not all people with obesity have metabolic complications.[31] Identifying which obese people are at greatest risk of CVD is therefore an urgent clinical and public health priority. Our analysis of the large, longitudinal, and biracial ARIC cohort provides one possible approach to better understand the heterogeneous consequences of obesity across the lifecycle relative to future CVD risk. Combining measures of obesity duration, severity, and distribution, we derived obesity subclass variables which we found were associated with differential mortality and future CVD risk, even when adjusting for baseline BMI. Previous attempts to characterize the impact of obesity duration and severity on CVD risk have relied on

Table 4. Association of Latent Class Assignment With CVD Risk Factors at Visit 5 (After Any Visits Used for Latent Class Assignment), Adjusting for Age, Sex, Race, and Recruitment Center

Trait	Class	Estimate	Standard error	*P* value
eGFR (n=6342)	Stable/slow decline	Reference		
	Decline	−1.71	1.46	0.24
	Moderate increase	0.21	0.48	0.67
	Rapid increase	−0.59	1.12	0.60
Fasting glucose (n=4093)	Stable/slow decline	Reference		
	Decline	0.53	1.24	0.67
	Moderate increase	1.56	0.36	<0.0001*
	Rapid increase	1.45	0.84	0.08
C-reactive protein (n=6320)	Stable/slow decline	Reference		
	Decline	0.11	0.07	0.10
	Moderate increase	0.17	0.02	<0.0001*
	Rapid increase	0.35	0.05	<0.0001*
Triglycerides (n=6323)	Stable/slow decline	Reference		
	Decline	0.05	0.04	0.21
	Moderate increase	0.06	0.01	<0.0001*
	Rapid increase	0.12	0.03	<0.0001*
LDL (n=6284)	Stable/slow decline	Reference		
	Decline	−8.81	2.99	0.003*
	Moderate increase	−1.66	0.98	0.09
	Rapid increase	−8.75	2.28	0.0001*
HDL (n=6323)	Stable/slow decline	Reference		
	Decline	−2.35	1.13	0.04
	Moderate increase	−3.06	0.37	<0.0001*
	Rapid increase	−4.13	0.86	<0.0001*
SBP (n=6397)	Stable/slow decline	Reference		
	Decline	−2.91	1.57	0.06
	Moderate increase	0.27	0.52	0.60
	Rapid increase	1.11	1.20	0.36

C-reactive protein and triglycerides were natural log transformed. Individuals with diabetes at visit 5 were excluded from assessment of fasting glucose. CVD indicates cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*Significant by Bonferroni corrected P-value threshold

fairly simple measures, such as "obese years" or BMI trajectory measures. Our previous work on latent class modeling of weight change trajectories for adults in the China Health and Nutrition Survey (CHNS), while focused on BMI measures only, showed significant heterogeneity in weight trajectories, prompting our interest in further examining this trajectory heterogeneity in the context of CVD risk.[32] Change in BMI or weight has been assessed as a health risk factor in ARIC and other cohorts, for example the recent associations with late-life gait speed[33] and atrial fibrillation risk[34] in ARIC, but simple analysis of change in BMI does not fully capture heterogeneity in obesity and its effects on elevated CVD risk (versus changes in BMI alone). The commonly used "obese-years" metric has been calculated several ways including summation of the years a participant was classified as obese.[5–7,35–37] Thus, "obese-years," constructed most often using body mass, an indicator of overall adiposity, considers risk via a single threshold as a participant reaches 30 kg/m^2 and excludes obese participants at study baseline[38]; increased disease risks associated with overweight or with increases in body mass that do not pass threshold are not considered, nor does this approach consider increases above the obese threshold. Still, even this simple measure of obesity duration has been shown to influence risk of T2D,[6] subclinical CVD,[7] and overall mortality risk.[36] Other investigators have characterized obesity duration using an approach akin to smoking pack-years, calculated as obesity duration multiplied by severity.[38–41] Although this second approach accommodates increased risk from increased BMI, the relative combinations of intensity and duration cannot be disentangled (ie, a given obese-years value could represent different combinations of duration and severity). Previous studies examining smoking

pack-years have demonstrated that disentangling duration and severity may be necessary to fully understand smoking associated risk.[42,43] Other approaches to examine the influence of obesity duration, including specifying BMI as a time-varying exposure in proportional hazards models,[44] requires extrapolation of time-dependent covariate values, which can bias results. Finally, of the handful of studies that avoided the above limitations,[45] none jointly examined the influence of body composition, obesity duration and severity on CVD risk or CVD risk factors. Some previous analyses have also attempted to cluster obese individuals by clinical and demographic factors (such as smoking, sleep disorders, high alcohol consumption, etc.[46]), but few have instead derived clusters based on different obesity measures and trajectories.

Associations with mortality and CVD risk were robust to adjustment for baseline BMI and basic CVD risk factors. Perhaps the most surprising associations were for increased risk of heart failure, stroke, MI/fatal CHD, and mortality with the decline latent class, which may reflect declining health. Yet, this association was robust to exclusion of incident cancer cases, which we hypothesized could be one explanation for weight loss (due to chemotherapy treatment, for example) which would be expected to associate with health declines. This association was also robust to exclusion of individuals with diabetes at baseline, again a potential cause of unintentional weight-loss in late stages of disease, including potential interactions with frailty.[47] The mortality and stroke associations were also robust to exclusion of all incident heart failure cases (heart failure is also well known to lead to unintentional weight loss in some patients,[29] and is associated with both CVD events and overall mortality). Declines in muscle mass and increased frailty could also lead to unintentional weight loss and should be explored in future studies. Our supplementary analyses assessing latent class associations with CVD stratified by frailty status found several of the associations from the full data set in those with a "prefrail" phenotype at visit 5, but not those categorized as "robust." This suggests the interaction of adiposity trajectories with late life frailty is a contributor to our results. Inability to distinguish intentional from unintentional weight loss (which we hypothesize is the main cause for the negative health associations of the decline group) is a major limitation of our results. A previous analysis of weight change in ARIC also found an elevated risk of atrial fibrillation in those with declines in weight between visit 1 and visit 4,[34] consistent with our results for other CVD end points. Along with general age-related frailty, other disorders (such as digestive disorders, psychological health issues, auto-immunity, etc) not well-captured in ARIC could also lead to unintentional weight loss and explain these negative associations with weight decline.[48] Of note, the moderate increase latent class had a lower overall risk of mortality than the reference stable/slow decline latent class, and our sensitivity analyses again suggested early signs of aging-related frailty may play a role (with this association attenuated in "robust" individuals). These results are concordant with the "obesity paradox" (lower overall mortality risk in those with moderately elevated BMI versus a healthy BMI) observed in some large analyses,[49] particularly in participants with existing baseline CVD (who were excluded in our analyses). Our analyses were adjusted for current smoking, one of the factors which may lead to confounding in observational studies of the association of BMI and mortality,[50] but other unknown confounders could also play a role in this reduced risk for the moderate versus stable/slow decline latent classes. We present results for CVD event and mortality associations with the moderate increase group set as reference in Table S11, to better contextualize this lower risk of mortality in baseline BMI adjusted models versus all other latent class groupings. The rapid increase latent class had more expected associations with higher heart failure risk than the stable/slow decline class, given the strong links between overall and central adiposity and incident heart failure.[51] Our polygenic risk score analyses suggest that adiposity trajectories over time are in part driven by genetic variants associated in previous studies with cross-sectional BMI measures, as risk scores associated with latent class even when adjusted for baseline BMI. We also identified differences in many demographic factors, including sex, across latent classes; differing patterns of adiposity between males and females[52] may help drive latent class assignment, along with many other complex individual and societal factors. These relationships should be further explored in additional cohort studies.

Our analysis has several important limitations. First, the latent classes derived are not designed to be directly applied to other cohort studies or clinical populations, although the approach could be used in other studies. In addition, our approach of classifying individuals and then treating class membership as a known exposure variable does not account for the uncertainty in class assignment, which can often lead to an attenuation of the estimates of associations between latent classes and outcomes.[53,54] That we found significant differences between classes using this complex model with this classification error speaks to the potential strength of these associations. In addition, this is more of a concern when there is substantial uncertainty with regards to class assignment and with median posterior probabilities for each class ranging from 0.70 to 0.86 across the four classes (Table S1) we feel we have adequate certainty of assignment for most individuals. Additionally, in our sensitivity analysis excluding the 1.3% of individuals with <50%

certainty of class assignment (all of whom were well above 25% certainty [ie, random chance with 4 class model]) we found extremely similar results (Table S5). It is also important to note that those methods that can account for classification error currently are not incorporated into the multivariate latent class mixed model software and to our knowledge most packages and software that can incorporate these are unable to do so due to the complexity of our models, specifically accounting for multiple longitudinal measures.[53–56] As our primary research question was to identify subpopulations based not just on one single cross-sectional outcome, the multivariate latent class mixed model models not only multiple anthropometric measures but accounts for the changes over this age range and accounts for the correlation within an individual both across outcomes and across the age range. We did not have data on whether weight loss was intentional or unintentional, though past ARIC analyses defining frailty have assumed that late life weight loss of >10% of body weight is usually unintentional. Whereas we used triennial examinations of the ARIC cohort, large biobanks with frequently yearly physical information might provide more detailed information on obesity trajectories, particularly if those biobanks have well measured, detailed body composition measures across large portions of the lifecycle. Differential patterns of missing data/visits across latent classes, as observed in our analyses (Table 1), might be ameliorated by more frequent adiposity assessment. We also note that inclusion of events between visits 1 and 4 may introduce some bias, since events do occur during the exposure period. Specifically, anthropometric measures during visits 1 to 4 but after a non-fatal CVD event are used to derive the latent classes and therefore could play a role in determining the latent class. Therefore, for incident CVD analyses we present, in Table S12, the results from a survival analysis excluding events during visits 1 and 4 and, in Table S13, the results from a survival analysis starting at visit 4, post the exposure period for all individuals. We note that sample size for both cases and controls is smaller in Table S13 due to individuals who were not lost to event follow-up but did not attend visit 4. Individuals with events that occurred during the time period where adiposity measures were assessed for building latent class models were more likely to be older ($P \leq 0.0003$), male ($P \leq 0.0002$), current smokers ($P < 0.0001$), be affected by diabetes and hypertension ($P \leq 0.0004$), and in the decline latent class ($P \leq 0.02$, versus the reference stable/slow decline class). Broadly similar results were observed for heart failure, stroke and MI/Fatal CHD in both supplementary analyses, with consistent directions of effect and differences only in statistical significance. Structural and societal factors which may influence adiposity trajectories (such as differential access to healthy food and resources which support physical activity) are also not considered in our current analyses. One minor limitation for the CVD baseline risk factor association analysis is that CRP was measured at visit 2, not visit 1. Despite these, there are important implications to the work we present here. Our study highlights the importance of jointly considering the duration, severity, and distribution of obesity for our understanding of CVD risk, subsequent CVD events, and mortality. Having such detailed measures and long-term follow up provides an outstanding opportunity to investigate the heterogeneity of obesity in middle to late adulthood in relation to CVD risk and events later in life.

In summary, risk of incident CVD and mortality is different across subclasses of obesity over time, with significant relationships robust to adjustment for baseline BMI. Individuals with rapid declines in adiposity metrics may be at particularly elevated risk of CVD, an observation which requires further study to elucidate potential mechanisms of risk elevation, such as declines in muscle mass or increased frailty. Approaches to disentangle the heterogeneity of obesity hold promise for precision CVD care and preventive strategies.

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Supplemental Material

Tables S1–S13

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SUPPLEMENTAL MATERIAL

Table S1: Fit statistics for different latent class models. We chose the four latent class model for all subsequent analyses in the Atherosclerosis Risk in Communities Study. NA, not applicable. Labels used for the four latent class model throughout the rest of the paper are bolded. Q1, quartile 1, Q3, quartile 3.

	Three Class Model	**Four Class Model**	**Five Class Model**
Bayesian information criterion (BIC)	992,526	992,174	991,534
Akaike information criterion (AIC)	992,313	991,939	991,792
Smallest Class Size	6.48%	3.55%	3.56%
Class 1 Description	Low/Moderate Baseline, Stable	Low/Moderate Baseline, **Stable/Slow Decline**	Low/Moderate Baseline, Slow Increase
Class 2 Description	Moderate/High Baseline, Decline	Moderate/High Baseline, **Decline**	Moderate Baseline, No/Slow Increase
Class 3 Description	Low/Moderate Baseline, Moderate/Rapid Increase	Moderate Baseline, **Moderate Increase**	Low/Moderate Baseline, Moderate Increase
Class 4 Description	NA	Moderate Baseline, **Rapid Increase**	Moderate/High Baseline, Moderate Increase
Class 5 Description	NA	NA	Low/Moderate Baseline, Moderate/Rapid Increase
Class 1 N (% membership)	12,122 (83.52%)	9,837 (67.78%)	9775 (67.35%)
Class 2 N (% membership)	941 (6.48%)	594 (4.09%)	638 (4.40%)
Class 3 N (% membership)	1,451 (10.00%)	3,568 (24.58%)	2973 (20.48%)
Class 4 N (% membership)	NA	515 (3.55%)	612 (4.22%)
Class 5 N (% membership)	NA	NA	516 (3.56%)
Class 1, Median (Q1, Q3) Posterior Probability	0.967 (0.881,0.992)	0.823 (0.694, 0.925)	0.835 (0.696,0.931)
Class 2, Median (Q1, Q3) Posterior Probability	0.856 (0.683,0.972)	0.864 (0.682, 0.975)	0.861 (0.682,0.977)

Class 3, Median (Q1, Q3) Posterior Probability	0.881 (0.691,0.983)	0.703 (0.585, 0.812)	0.668 (0.56,0.788)
Class 4, Median (Q1, Q3) Posterior Probability	NA	0.830 (0.656, 0.958)	0.712 (0.546,0.885)
Class 5, Median (Q1, Q3) Posterior Probability	NA	NA	0.842 (0.668,0.958)
Class 1, Number (%) of Individuals with Probability Class Assignment <0.5	0 (0.00%)	57 (0.58%)	252 (2.58%)
Class 2, Number (%) of Individuals with Probability Class Assignment <0.5	1 (0.11%)	1 (0.17%)	23 (3.61%)
Class 3, Number (%) of Individuals with Probability Class Assignment <0.5	1 (0.07%)	118 (3.31%)	272 (9.15%)
Class 4, Number (%) of Individuals with Probability Class Assignment <0.5	NA	13 (2.52%)	119 (19.44%)
Class 5, Number (%) of Individuals with Probability Class Assignment <0.5	NA	NA	22 (4.26%)
Class 1, Number (%) of Individuals with Probability Class Assignment <0.75	1230 (10.15%)	3375 (34.31%)	3256 (33.31%)
Class 2, Number (%) of Individuals with Probability Class Assignment <0.75	324 (34.43%)	192 (32.32%)	221 (34.64%)
Class 3, Number (%) of Individuals with Probability Class Assignment <0.75	470 (32.39%)	2163 (60.62%)	1988 (66.87%)

Class 4, Number (%) of Individuals with Probability Class Assignment <0.75	NA	194 (37.67%)	340 (55.56%)
Class 5, Number (%) of Individuals with Probability Class Assignment <0.75	NA	NA	200 (38.76%)

Table S2: Adiposity metrics in Atherosclerosis Risk in Communities (ARIC) study participants included in latent class analysis, overall and stratified by latent class assignment. P-value is for a chi-square based test of differences between latent classes for categorical traits and a type III test for differences between classes in a generalized linear model for continuous traits. Q1, quartile 1, Q3, quartile 3.

Variable	**Overall (N = 14,514)**	**Males (N=6,460)**	**Females (N=8,054)**	**Stable/Slow Decline (N = 9,837)**	**Decline, (N = 594)**	**Moderate Increase (N = 3,568)**	**Rapid Increase (N = 515)**	**P-value**
Median (Q1, Q3) Weight at Age 25 (lbs)	138 (124,165)	165 (145, 180)	125 (115,135)	140 (125,167)	160 (135,190)	130 (120,150)	127 (118,140)	<0.0001
Median (Q1, Q3) BMI at baseline (Visit 1) (kg/m^2)	26.85 (24.02,30.39)	27.02 (24.76, 29.79)	26.58 (23.37, 31.07)	26.58 (23.87,29.96)	30.58 (27.29,34.98)	26.99 (24.15,30.69)	26.89 (23.55,30.34)	<0.0001
% Obese (BMI≥30) at Baseline (Visit 1)	27.17% (N = 3941)	23.49% (N=1516)	30.12% (N=2425)	24.81% (N = 2438)	55.14% (N = 327)	28.98% (N = 1034)	27.57% (N = 142)	<0.0001
Median (Q1, Q3) BMI at last visit (kg/m^2)	27.92 (24.83,31.65)	27.76 (25.22, 30.85)	28.14 (24.45, 32.72)	26.99 (24.16,30.37)	26.42 (23.39,30.24)	30.27 (27.15,34.12)	33.75 (30.09,38.43)	<0.0001
Median (Q1, Q3) Waist at Baseline (Visit 1) (cm)	96 (88,105)	98 (92, 105)	93 (84,104)	96 (88,104)	106 (97,116)	95 (86,105)	93 (83,104)	<0.0001
Median (Q1, Q3) Tricep Skinfold at Baseline (Visit 1) (mm)	24.5 (17.5,31.5)	18.0 (14.0, 23.5)	29.5 (24.0, 35.0)	23 (16.5,30.5)	28 (20.5,36)	27 (20,33)	27.5 (22,33.5)	<0.0001
Median (Q1, Q3) Calf Circumference at Baseline (Visit 1) (cm)	37 (35,40)	38 (36,40)	36 (34,39)	37 (35,40)	39 (37,42)	37 (35,39)	37 (35,40)	<0.0001

Table S3: Differences in both baseline and visit 5 adiposity measures by latent class, adjusting for age, sex, race, and recruitment center.

Trait	Class	Estimate	Standard Error	P-value
Baseline BMI (kg/m^2) (n=14504)	Stable/Slow Decline	reference		
	Decline	3.92	0.22	**<0.0001**
	Moderate Increase	0.39	0.10	**0.0001**
	Rapid Increase	-0.06	0.23	0.81
Baseline waist circumference (cm) (n=11532)	Stable/Slow Decline	reference		
	Decline	-0.99	0.66	0.13
	Moderate Increase	8.67	0.30	**<0.0001**
	Rapid Increase	17.60	0.68	**<0.0001**
Visit 5 BMI (kg/m^2) (n=6177)	Stable/Slow Decline	reference		
	Decline	1.60	0.48	**0.0009**
	Moderate Increase	2.87	0.16	**<0.0001**
	Rapid Increase	5.23	0.37	**<0.0001**
Visit 5 waist circumference (cm) (n=6104)	Stable/Slow Decline	reference		
	Decline	3.55	1.18	**0.003**
	Moderate Increase	6.70	0.39	**<0.0001**
	Rapid Increase	11.80	0.90	**<0.0001**

Table S4: Association of latent class assignment with BMI polygenic risk score. BMI polygenic risk scores were calculated separately in self-identified White and Black participants, using methods described further below. Each latent class is analyzed in reference to class 1.

		White participants (n=8828)			**Black participants (n=2531)**		
Model	**Class**	**Estimate**	**Standard Error**	**P-value**	**Estimate**	**Standard Error**	**P-value**
Model 1	Stable/Slow Decline	reference			reference		
	Decline	0.06	0.02	**0.0002**	0.09	0.04	**0.04**
	Moderate Increase	0.03	0.01	**<0.0001**	0.03	0.02	0.20
	Rapid Increase	0.09	0.02	**<0.0001**	0.12	0.06	**0.03**
Model 2	Stable/Slow Decline	reference			reference		
	Decline	0.03	0.02	**0.04**	0.06	0.04	0.16
	Moderate Increase	0.03	0.01	**<0.0001**	0.04	0.02	0.12
	Rapid Increase	0.09	0.02	**<0.0001**	0.15	0.06	**0.007**
Model 3	Stable/Slow Decline	reference			reference		
	Decline	-0.01	0.02	0.38	0.01	0.04	0.79
	Moderate Increase	0.02	0.01	**0.0005**	0.03	0.02	0.18
	Rapid Increase	0.07	0.02	**<0.0001**	0.16	0.05	**0.005**

Model 1: Adjusted age, sex, center, five ancestry principal components
Model 2: Additional adjustment HDL, current smoking, total cholesterol, hypertension, diabetes, estimated glomerular filtration rate (all at baseline visit)
Model 3: Additional adjustment baseline BMI

Risk scores are calculated using LDpred [28]. Scores in self-identified Black participants are based on a combined BMI genome-wide association study (GWAS) analysis of the GIANT consortium+UK Biobank GWAS [11]. Scores in self-identified White participants are based on UK Biobank GWAS alone, as these participants were included in the GIANT consortium. Both scores are calculated using an infinitesimal LDmatrix, with SNPs left in the score regardless of frequency differences with GWAS summary statistics for the score in self-identified Black participants and SNPs with frequency differences >10% removed for the score in self-identified White participants.

Table S5: Association of latent class assignment with incident cardiovascular disease and mortality, with and without excluding all incident heart failure cases.

Outcome	Class	Model 3						Model 3 (no incident heart failure)					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Stroke	Stable/Slow Decline	1362/13945	910/8553	**reference**				854/10848	570/6814	**reference**			
	Decline		87/472	1.53	1.22	1.92	**0.0002**		46/312	1.55	1.14	2.11	**0.005**
	Moderate Increase		314/3114	1.00	0.88	1.14	0.97		203/2517	1.02	0.87	1.21	0.77
	Rapid Increase		51/444	1.33	1.00	1.77	0.05		35/351	1.49	1.06	2.12	0.02
MI/Fatal CHD	Stable/Slow Decline	2096/13275	1443/7542	**reference**				1013/10406	729/6347	**reference**			
	Decline		139/383	1.36	1.14	1.63	**0.0008**		48/290	1.18	0.87	1.59	0.28
	Moderate Increase		452/2844	0.97	0.87	1.08	0.61		208/2412	0.91	0.77	1.06	0.22
	Rapid Increase		62/410	1.14	0.88	1.48	0.32		28/344	1.09	0.74	1.60	0.66
Mortality	Stable/Slow Decline	7129/14185	5011/4611	**reference**				4675/10998	3334/4152	**reference**			
	Decline		432/146	1.45	1.31	1.60	**<0.0001**		250/119	1.41	1.24	1.61	**<0.0001**
	Moderate Increase		1462/2021	0.85	0.80	0.90	**<0.0001**		950/1801	0.84	0.78	0.90	**<0.0001**
	Rapid Increase		224/279	1.06	0.92	1.21	0.41		141/251	1.03	0.87	1.23	0.71

MI, myocardial infarction, CHD, coronary heart disease.
All models are limited to those with complete covariate data.
Model 3: Adjusted age, sex, race, center, diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)

Table S6: Association of latent class assignment with incident cardiovascular disease and mortality, with and without any incident cancer cases between visit 1 and 4.

Outcome	Class	Model 3						Model 3 (without incident cancer cases between visit 1 and 4)					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Heart failure	Stable/Slow Decline	3188/13393	2136/6995	reference				3029/12715	2032/6633	reference			
	Decline		209/318	1.41	1.22	1.63	**<0.0001**		194/298	1.37	1.18	1.60	**<0.0001**
	Moderate Increase		732/2538	1.00	0.92	1.09	0.94		700/2413	1.01	0.92	1.10	0.84
	Rapid Increase		111/354	1.34	1.10	1.62	**0.004**		103/342	1.31	1.07	1.60	**0.008**
Stroke	Stable/Slow Decline	1362/13945	910/8553	reference				1309/13244	877/8108	reference			
	Decline		87/472	1.53	1.22	1.92	**0.0002**		80/441	1.47	1.16	1.86	**0.001**
	Moderate Increase		314/3114	1.00	0.88	1.14	0.97		304/2959	1.01	0.89	1.16	0.83
	Rapid Increase		51/444	1.33	1.00	1.77	0.05		48/427	1.30	0.97	1.75	0.08
MI/Fatal CHD	Stable/Slow Decline	2096/13275	1443/7542	reference				1996/12603	1374/7154	reference			
	Decline		139/383	1.36	1.14	1.63	**0.0008**		129/356	1.31	1.09	1.58	**0.005**
	Moderate Increase		452/2844	0.97	0.87	1.08	0.61		433/2706	0.98	0.88	1.09	0.69
	Rapid Increase		62/410	1.14	0.88	1.48	0.32		60/391	1.15	0.89	1.50	0.29
Mortality	Stable/Slow Decline	7129/14185	5011/4611	reference				6639/13466	4654/4475	reference			
	Decline		432/146	1.45	1.31	1.60	**<0.0001**		395/142	1.42	1.28	1.58	**<0.0001**
	Moderate Increase		1462/2021	0.85	0.80	0.90	**<0.0001**		1378/1940	0.87	0.82	0.92	**<0.0001**
	Rapid Increase		224/279	1.06	0.92	1.21	0.41		212/270	1.09	0.94	1.25	0.25

MI, myocardial infarction, CHD, coronary heart disease.
Model 3: Adjusted age, sex, race, center, diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)
All models are limited to those with complete covariate data.

Table S7: Association of latent class assignment with incident cardiovascular disease and mortality, with and without any individuals with certainty of class assignment <0.5.

Outcome	Class	Model 3, all						Model 3, without any individuals with certainty of class assignment <0.5					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Heart failure	Stable/Slow Decline	3188/13393	2136/6995	reference				3138/13235	2120/6961	reference			
	Decline		209/318	1.41	1.22	1.63	**<0.0001**		209/317	1.42	1.23	1.65	**<0.0001**
	Moderate Increase		732/2538	1.00	0.92	1.09	0.94		703/2472	0.97	0.89	1.06	0.55
	Rapid Increase		111/354	1.34	1.10	1.62	**0.004**		106/347	1.34	1.09	1.63	**0.004**
Stroke	Stable/Slow Decline	1362/13945	910/8553	reference				1338/13772	902/8506	reference			
	Decline		87/472	1.53	1.22	1.92	**0.0002**		87/471	1.53	1.22	1.92	**0.0002**
	Moderate Increase		314/3114	1.00	0.88	1.14	0.97		300/3024	0.98	0.86	1.12	0.79
	Rapid Increase		51/444	1.33	1.00	1.77	0.05		49/433	1.33	0.99	1.78	0.06
MI/Fatal CHD	Stable/Slow Decline	2096/13275	1443/7542	reference				2066/13114	1433/7504	reference			
	Decline		139/383	1.36	1.14	1.63	**0.0008**		139/382	1.37	1.15	1.65	**0.0005**
	Moderate Increase		452/2844	0.97	0.87	1.08	0.61		435/2761	0.96	0.86	1.07	0.44
	Rapid Increase		62/410	1.14	0.88	1.48	0.32		59/401	1.11	0.85	1.45	0.43
Mortality	Stable/Slow Decline	7129/14185	5011/4611	reference				7014/14007	4973/4594	reference			
	Decline		432/146	1.45	1.31	1.60	**<0.0001**		432/145	1.47	1.33	1.62	**<0.0001**
	Moderate Increase		1462/2021	0.85	0.80	0.90	**<0.0001**		1395/1978	0.83	0.78	0.88	**<0.0001**
	Rapid Increase		224/279	1.06	0.92	1.21	0.41		214/276	1.05	0.91	1.21	0.51

MI, myocardial infarction, CHD, coronary heart disease.
Model 3: Adjusted age, sex, race, center, diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)
All models are limited to those with complete covariate data.

Table S8: Association of latent class assignment with incident cardiovascular disease and mortality, with and without any individuals with diabetes at visit 1.

Outcome	Class	Model 3, all						Model 3, without any individuals with diabetes					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Heart failure	Stable/Slow Decline	3188/13393	2136/6995	**reference**				2562/12015	1713/6460	**reference**			
	Decline		209/318	1.41	1.22	1.63	**<0.0001**		125/236	1.56	1.30	1.88	**<0.0001**
	Moderate Increase		732/2538	1.00	0.92	1.09	0.94		625/2417	1.02	0.93	1.12	0.69
	Rapid Increase		111/354	1.34	1.10	1.62	**0.004**		99/340	1.35	1.10	1.66	**0.004**
Stroke	Stable/Slow Decline	1362/13945	910/8553	**reference**				1101/12459	747/7691	**reference**			
	Decline		87/472	1.53	1.22	1.92	**0.0002**		48/328	1.52	1.13	2.05	**0.005**
	Moderate Increase		314/3114	1.00	0.88	1.14	0.97		259/2921	0.96	0.83	1.11	0.55
	Rapid Increase		51/444	1.33	1.00	1.77	0.05		47/418	1.40	1.03	1.89	0.03
MI/Fatal CHD	Stable/Slow Decline	2096/13275	1443/7542	**reference**				1654/11896	1143/6894	**reference**			
	Decline		139/383	1.36	1.14	1.63	**0.0008**		79/274	1.53	1.22	1.93	**0.0003**
	Moderate Increase		452/2844	0.97	0.87	1.08	0.61		376/2685	0.96	0.85	1.08	0.49
	Rapid Increase		62/410	1.14	0.88	1.48	0.32		56/389	1.18	0.90	1.55	0.24
Mortality	Stable/Slow Decline	7129/14185	5011/4611	**reference**				5948/12636	4197/4355	**reference**			
	Decline		432/146	1.45	1.31	1.60	**<0.0001**		277/112	1.56	1.38	1.77	**<0.0001**
	Moderate Increase		1462/2021	0.85	0.80	0.90	**<0.0001**		1273/1950	0.85	0.80	0.91	**<0.0001**
	Rapid Increase		224/279	1.06	0.92	1.21	0.41		201/271	1.05	0.91	1.21	0.54

MI, myocardial infarction, CHD, coronary heart disease.
Model 3: Adjusted age, sex, race, center, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)
All models are limited to those with complete covariate data.

Table S9: Association of latent class assignment with incident cardiovascular disease and mortality, with and without any individuals with overt frailty at visit 5 (n=396). Individuals who do not have data on frailty are included in these analyses.

Outcome	Class	Model 3, all						Model 3, without any individuals listed as frail at visit 5					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Heart failure	Stable/Slow Decline	3188/13393	2136/6995	**reference**				3070/13028	2071/6841	**reference**			
	Decline		209/318	1.41	1.22	1.63	**<0.0001**		206/310	1.42	1.23	1.65	**<0.0001**
	Moderate Increase		732/2538	1.00	0.92	1.09	0.94		688/2466	0.98	0.89	1.07	0.58
	Rapid Increase		111/354	1.34	1.10	1.62	**0.004**		105/341	1.33	1.09	1.62	**0.005**
Stroke	Stable/Slow Decline	1362/13945	910/8553	**reference**				1322/13566	896/8338	**reference**			
	Decline		87/472	1.53	1.22	1.92	**0.0002**		86/462	1.52	1.21	1.90	**0.0004**
	Moderate Increase		314/3114	1.00	0.88	1.14	0.97		292/3016	0.95	0.83	1.09	0.48
	Rapid Increase		51/444	1.33	1.00	1.77	0.05		48/428	1.29	0.96	1.73	0.10
MI/Fatal CHD	Stable/Slow Decline	2096/13275	1443/7542	**reference**				2025/12909	1398/7363	**reference**			
	Decline		139/383	1.36	1.14	1.63	**0.0008**		137/376	1.37	1.14	1.64	**0.0007**
	Moderate Increase		452/2844	0.97	0.87	1.08	0.61		432/2750	0.97	0.87	1.09	0.61
	Rapid Increase		62/410	1.14	0.88	1.48	0.32		58/395	1.11	0.85	1.46	0.43
Mortality	Stable/Slow Decline	7129/14185	5011/4611	**reference**				6980/13798	4915/9387	**reference**			
	Decline		432/146	1.45	1.31	1.60	**<0.0001**		428/567	1.44	1.30	1.60	**<0.0001**
	Moderate Increase		1462/2021	0.85	0.80	0.90	**<0.0001**		1420/3361	0.85	0.80	0.91	**<0.0001**
	Rapid Increase		224/279	1.06	0.92	1.21	0.41		217/483	1.06	0.93	1.22	0.38

MI, myocardial infarction, CHD, coronary heart disease.
Model 3: Adjusted age, sex, race, center, diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)
All models are limited to those with complete covariate data.

Table S10: Association of latent class assignment with incident cardiovascular disease and mortality, limited to individuals with frailty assessed at visit 5. Models are stratified into those in the "robust" and "prefrail" classifications. Those characterized as overtly frail are excluded.

Outcome	Class	Model 3, robust only						Model 3, prefrail only					
		N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value	N events/N	N events/N controls (by Class)	Hazard Ratio	95% Confidence Limits		p-value
Heart failure	Stable/Slow Decline	244/2497	174/1556	**reference**				467/2580	311/1305	**reference**			
	Decline		7/34	1.15	0.53	2.47	0.73		22/43	1.57	1.00	2.46	0.05
	Moderate Increase		57/590	0.93	0.68	1.28	0.66		116/670	0.87	0.70	1.09	0.22
	Rapid Increase		6/73	0.93	0.40	2.13	0.86		18/95	1.24	0.76	2.03	0.39
Stroke	Stable/Slow Decline	127/2550	98/1670	**reference**				202/2666	134/1530	**reference**			
	Decline		3/38	1.01	0.32	3.25	0.98		7/58	1.45	0.67	3.16	0.35
	Moderate Increase		25/634	0.77	0.49	1.21	0.26		51/767	0.84	0.60	1.18	0.32
	Rapid Increase		1/81	0.30	0.04	2.17	0.23		10/109	1.34	0.69	2.61	0.39
MI/Fatal CHD	Stable/Slow Decline	210/2492	165/1561	**reference**				363/2577	250/1357	**reference**			
	Decline		7/34	1.22	0.57	2.64	0.61		12/51	1.36	0.76	2.46	0.30
	Moderate Increase		34/611	0.66	0.45	0.97	0.03		85/708	0.87	0.68	1.13	0.30
	Rapid Increase		4/76	0.65	0.24	1.79	0.41		16/98	1.50	0.89	2.54	0.13
Mortality	Stable/Slow Decline	252/2563	185/1592	**reference**				573/2686	408/1268	**reference**			
	Decline		7/34	1.22	0.57	2.62	0.62		21/45	1.74	1.11	2.74	0.02
	Moderate Increase		52/611	0.96	0.70	1.33	0.82		122/703	0.70	0.57	0.86	**0.001**
	Rapid Increase		8/74	1.31	0.63	2.71	0.47		22/97	1.09	0.70	1.70	0.70

MI, myocardial infarction, CHD, coronary heart disease.
Model 3: Adjusted age, sex, race, center, diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate and BMI (all at baseline)
All models are limited to those with complete covariate data.

Table S11: Association of latent class assignment with incident cardiovascular disease and mortality, with moderate increase latent class set to reference.

Outcome (N events/N)	Class	N events (by Class)	N controls (by Class)	Model 1				Model 2				Model 3			
				Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value
Heart failure (3188/13393)	Stable/Slow Decline	2136	6995	0.98	0.90	1.07	0.62	0.97	0.89	1.06	0.47	1.00	0.92	1.09	0.94
	Decline	209	318	2.21	1.89	2.58	**<0.0001**	1.60	1.36	1.87	**<.0001**	1.41	1.21	1.66	**<0.0001**
	Moderate Increase	732	2538	**reference**				**reference**				**reference**			
	Rapid Increase	111	354	1.37	1.13	1.68	**0.002**	1.34	1.09	1.63	**0.005**	1.34	1.10	1.64	**0.004**
Stroke (1362/13945)	Stable/Slow Decline	910	8553	1.01	0.89	1.16	0.84	1.00	0.87	1.13	0.94	1.00	0.88	1.14	0.97
	Decline	87	472	2.02	1.59	2.57	**<0.0001**	1.54	1.21	1.96	**0.0005**	1.52	1.19	1.95	**0.0007**
	Moderate Increase	314	3114	**reference**				**reference**				**reference**			
	Rapid Increase	51	444	1.36	1.01	1.83	**0.04**	1.32	0.98	1.78	0.06	1.32	0.98	1.78	0.06
MI/Fatal CHD (2096/13275)	Stable/Slow Decline	1443	7542	1.05	0.94	1.17	0.41	1.02	0.92	1.14	0.71	1.03	0.92	1.15	0.61
	Decline	139	383	2.17	1.79	2.63	**<0.0001**	1.45	1.19	1.76	**0.0002**	1.40	1.15	1.70	**0.0009**
	Moderate Increase	452	2844	**reference**				**reference**				**reference**			
	Rapid Increase	62	410	1.19	0.91	1.56	0.19	1.17	0.90	1.53	0.24	1.17	0.90	1.53	0.24
Mortality (7129/14185)	Stable/Slow Decline	5011	4611	1.14	1.08	1.21	**<0.0001**	1.16	1.09	1.23	**<0.0001**	1.17	1.11	1.25	**<0.0001**
	Decline	432	146	2.21	1.98	2.46	**<0.0001**	1.79	1.60	2.00	**<0.0001**	1.70	1.52	1.90	**<0.0001**
	Moderate Increase	1462	2021	**reference**				**reference**				**reference**			
	Rapid Increase	224	279	1.37	1.19	1.58	**<0.0001**	1.25	1.09	1.44	**0.002**	1.24	1.08	1.43	**0.003**

MI, myocardial infarction, CHD, coronary heart disease.
All models are limited to those with complete covariate data for all three models.
Model 1: Adjusted age, sex, race, center
Model 2: Additional adjustment diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate (all at baseline)
Model 3: Additional adjustment baseline BMI

Table S12: Association of latent class assignment with incident cardiovascular disease and mortality, with exclusion of events which occurred between visits 1-4 (these events are included in the main analysis).

Outcome (N events/N)	Class	N events (by Class)	N controls (by Class)	Model 1				Model 2				Model 3			
				Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value
Heart failure (2882/13087)	Stable/Slow Decline	1941	6995	**reference**				**reference**				**reference**			
	Decline	155	318	1.93	1.63	2.27	**<0.0001**	1.42	1.20	1.68	**<0.0001**	1.21	1.02	1.43	0.03
	Moderate Increase	680	2538	1.03	0.94	1.13	0.48	1.04	0.95	1.14	0.39	1.00	0.92	1.10	0.95
	Rapid Increase	106	354	1.46	1.20	1.79	**0.0002**	1.42	1.17	1.74	**0.001**	1.38	1.13	1.68	**0.002**
Stroke (1175/13760)	Stable/Slow Decline	787	8531	**reference**				**reference**				**reference**			
	Decline	60	468	1.68	1.29	2.18	**0.0001**	1.33	1.02	1.73	0.04	1.30	0.99	1.70	0.06
	Moderate Increase	281	3114	0.99	0.86	1.14	0.91	1.01	0.88	1.16	0.91	1.00	0.87	1.15	0.96
	Rapid Increase	47	445	1.37	1.01	1.84	0.04	1.35	1.00	1.82	0.05	1.34	1.00	1.81	0.05
MI/Fatal CHD (1649/12930)	Stable/Slow Decline	1152	7542	**reference**				**reference**				**reference**			
	Decline	93	383	1.88	1.52	2.32	**<0.0001**	1.29	1.04	1.60	0.02	1.22	0.98	1.52	0.07
	Moderate Increase	354	2844	0.90	0.80	1.02	0.10	0.92	0.82	1.04	0.21	0.92	0.81	1.03	0.15
	Rapid Increase	50	410	1.09	0.82	1.46	0.55	1.11	0.84	1.49	0.46	1.10	0.83	1.47	0.50

MI, myocardial infarction, CHD, coronary heart disease.
All models are limited to those with complete covariate data for all three models. Incident events between visits 1-4 (the time period used to derive obesity latent classes) are excluded.
Model 1: Adjusted age, sex, race, center
Model 2: Additional adjustment diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate (all at baseline)
Model 3: Additional adjustment baseline BMI

Table S13: Association of latent class assignment with incident cardiovascular disease, with visit 4 treated as the baseline visit. Sample size is limited to those who attended visit 4.

Outcome (N events/N)	Class	N events (by Class)	N controls (by Class)	Model 1				Model 2				Model 3			
				Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value	Hazard Ratio	95% Confidence Limits		p-value
Heart failure (2189/ 10357)	Stable/Slow Decline	1434	5414	**reference**				**reference**				**reference**			
	Decline	123	245	2.05	1.71	2.47	**<0.0001**	1.69	1.40	2.03	**<0.0001**	1.77	1.47	2.14	**<0.0001**
	Moderate Increase	545	2209	1.06	0.96	1.17	0.27	1.06	0.96	1.17	0.26	0.91	0.82	1.01	0.09
	Rapid Increase	87	300	1.54	1.23	1.92	**0.0001**	1.53	1.22	1.90	**0.0002**	1.13	0.90	1.42	0.29
Stroke (888/10842)	Stable/Slow Decline	583	6566	**reference**				**reference**				**reference**			
	Decline	47	355	1.76	1.31	2.37	**0.0002**	1.52	1.12	2.05	**0.007**	1.52	1.13	2.06	**0.006**
	Moderate Increase	223	2663	1.02	0.87	1.20	0.77	1.02	0.87	1.20	0.81	1.01	0.85	1.19	0.94
	Rapid Increase	35	370	1.36	0.96	1.92	0.08	1.32	0.94	1.87	0.11	1.29	0.90	1.84	0.17
MI/Fatal CHD (1268/ 10163)	Stable/Slow Decline	861	5819	**reference**				**reference**				**reference**			
	Decline	77	292	2.09	1.65	2.64	**<0.0001**	1.77	1.39	2.24	**<0.0001**	1.78	1.41	2.26	**<0.0001**
	Moderate Increase	288	2442	0.93	0.81	1.07	0.30	0.91	0.79	1.04	0.16	0.88	0.76	1.01	0.08
	Rapid Increase	42	342	1.19	0.87	1.63	0.28	1.13	0.82	1.54	0.46	1.06	0.77	1.47	0.73

MI, myocardial infarction, CHD, coronary heart disease.
All models are limited to those with complete covariate data for all three models.
Model 1: Adjusted age at visit 4, sex, race, center
Model 2: Additional adjustment diabetes, current smoking, HDL, total cholesterol, hypertension, estimated glomerular filtration rate (all at visit 4)
Model 3: Additional adjustment visit 4 BMI