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Highlights

- The prevailing understanding is that most women gain weight in the postmenopausal period. Many studies on obesity in older adults have relied on a single point exposure and self-report height and weight to assess the relationship between BMI and adverse health outcomes.
- We found limited evidence of BMI change, either gain or loss, over time in this large sample of postmenopausal women.
- Despite the lack of change in BMI, there was a clear relationship between high BMI with higher likelihood of diabetes and cardiovascular disease.
- It is important for researchers and clinicians to understand the lack of change in women's BMI after menopause. However, that does not mean BMI in older women is uninformative. Women with high BMI should be counseled with effective interventions to lower BMI even though they are in an older age group.

Relationship between BMI trajectories and cardiometabolic outcomes in postmenopausal women – a growth mixture modelling approach

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Abstract

Purpose: The objective of this manuscript is to identify longitudinal trajectories of change in body mass index (BMI) after menopause and investigate the association of BMI trajectories with risk of diabetes and cardiovascular disease (CVD) among postmenopausal women.

Methods: Using data from 68,132 participants in the Women's Health Initiative (WHI) clinical trials, we used growth mixture modeling (GMM) to develop BMI trajectories. Cox proportional hazards models were used to examine the relationship between BMI trajectories with incident diabetes and CVD. Further, we stratified by hormone therapy trial arm and time since menopause.

Results: Using GMM, we identified five BMI trajectories. We did not find evidence of substantial change in BMI over time; the trajectories were stable over the study follow-up period in this sample of postmenopausal women. Risk of diabetes and CVD increased by BMI trajectory; risk was greater for women in moderate-high, high, and very high BMI trajectories compared to those in the lowest trajectory group.

Conclusions: Despite minimal change in BMI over the follow-up period, our results demonstrate a strong association of high BMI with diabetes and CVD. These results highlight the importance of further longitudinal research focused on adverse health effects of BMI in older women.

Introduction

Older adults represent the fastest growing segment of the population in the United States. (1) On average, life expectancy is 5 years longer in women than men, thus there is an overrepresentation of women in the oldest age groups. (2) There has been a concomitant rise in the prevalence of obesity over the past four decades, and, as a result, there are an increasing number of older women with obesity in the population (3). Obesity is strongly associated with morbidity and mortality, including cardiovascular disease and diabetes. (4)

Many prior studies on the relationship between body weight and health outcomes in older adults have used body mass index (BMI) measured at one point in time as the primary exposure. Often, participants are asked to self-report their body weight, and this may introduce systematic error (bias) (5, 6). The use of a single, point exposure fails to capture any variation and longitudinal patterns in disease risk that may occur because of changes in exposure. Alternative approaches to study adiposity include using body weight as a time varying exposure with multiple measurement time points, examining weight change (i.e., difference between two measurement time points), and using trajectory modeling approaches to assess change over time.(7) Research using these alternative approaches has demonstrated that sustained overweight and obesity and weight gain over time results in an increased risk of cardiovascular disease (CVD), hypertension, diabetes, and mortality.(8-16) For example, Zheng et al. found different trajectories of body shape from ages 5 years to 55 years were associated with subsequent risk of developing type 2 diabetes and CVD. (17) However, limited research has focused specifically on weight change in postmenopausal women, nor the effects of the changing hormone milieu owing to the use of hormone therapy.

The extant scientific literature on weight change in postmenopausal women is equivocal: some studies report substantial weight gain as women age(18) while others report minimal change during the postmenopausal period (19). Questions about the effect of obesity in old age are particularly salient with respect to older women because the hormone changes that occur during menopause, and the use of hormone replacement therapy, may impact late-life weight change.(18-24) In the present study we will use a data-driven statistical approach, growth mixture modeling, to examine longitudinal change in BMI in postmenopausal women. With this approach, we will develop BMI trajectories using body weight and height measured at multiple in-person clinic visits as part of the WHI. The objectives of this manuscript are to identify latent longitudinal trajectories of BMI after menopause and examine patterns of change in BMI in postmenopausal women. We will further examine whether BMI trajectories are modified by time since menopause or hormone therapy use. Finally, we will investigate the association of the identified BMI trajectories with risk of diabetes, CVD, and stroke among postmenopausal women.

Methods

Study Sample

Between 1993 and 1998, the WHI enrolled 161,808 postmenopausal women aged 50-79 at 40 clinical centers across the United States.(25-27) The WHI is comprised of an observational study and three overlapping clinical trials (CT) examining hormone therapy use, dietary modification, and use of calcium/vitamin D supplements. We used data from the WHI clinical trials in this analysis. The WHI includes comprehensive annual questionnaires on medical history, demographic information, and lifestyle behaviors as well as clinical visits, collection of biological specimens, and in-person interviews. We excluded WHI participants with diabetes, CVD, or cancer at baseline (n=9,526) and those with less than 3 measured BMI values (n=4,533). Our final analytic sample included 54,073 women. After recruitment and randomization, clinic visits were required annually, and consisted of questionnaires, anthropometric measures, and clinical examinations.(28) The study protocol was reviewed by institutional review boards at each of the 40 WHI clinical centers as well as the WHI coordinating center and each participant provided informed consent.(29)

Measures

Exposure

Measured height and weight were used to calculate BMI (kg/m^2). Between 1993-2005, women in the WHI clinical trial had height and weight measured annually by trained WHI examiners. We used measured BMI at WHI clinic visits to create trajectories of BMI change. Participants had between 3 and 11 BMI measurements, with the majority having 7 measures (19%), 8 measures (26%), or 9 measures (20%). We examined time since menopause measured via questionnaire (0-10 years, ≥10 years) as a potential effect modifier. We additionally examined effect modification by hormone therapy use among women enrolled in the WHI hormone therapy (HT) trial. Women in this trial (n=21,603) were randomly assigned to hormone therapy or placebo group.

Outcomes

The primary outcomes of interest in this analysis are: 1) diabetes 2) total CVD, defined as the first occurrence of an acute myocardial infarction (MI) requiring overnight hospitalization, definite silent MI, coronary heart disease (CHD) death, coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), coronary revascularization, congestive heart failure, or ischemic or hemorrhagic stroke; 3) CABG and PCI, and 4) stroke (ischemic and hemorrhagic). CVD outcomes were ascertained in the WHI through self-reported medical questionnaires completed by participants every 6 to 12 months. Medical records for all overnight hospitalizations and outpatient coronary revascularization procedures were reviewed by central physician adjudicators or trained local adjudicators.(30) Incident diabetes is defined from annual questionnaires. Validation studies have demonstrated high validity of self-report diabetes incidence and prevalence in WHI compared to medical records and physician diagnoses of diabetes.(31) Median follow-up time for outcomes of interest was 19.3 years (mean=18.4 years, standard deviation=3.6).

Covariates

We examined relevant baseline covariates in our analyses, including: sociodemographic characteristics (age, race/ethnicity, education, income), physical activity (frequency of moderate exercise per week), diet intake

(healthy eating index diet score), smoking status (never/past/current smoker), alcohol consumption (non-drinker/past drinker/drinker), and family history.

Statistical Analysis

We used a growth mixture modeling (GMM) approach to divide the study population into subgroups (unobserved "latent classes") that each have distinct longitudinal patterns of BMI. GMM is a statistical technique that combines linear mixed models commonly used for longitudinal repeated measures and general mixture modeling.(32, 33) The underlying assumption of GMM is that the individuals in the same latent subgroup share similar longitudinal patterns of BMI change, while participants from different latent subgroups have distinct trajectories. It simultaneously estimates the probabilities of each latent class, probabilities of class membership for each individual, and, using linear mixed modeling, longitudinal patterns of the BMI change within each latent class. Rather than classifying participants into weight-change categories (e.g., stable weight, weight gain, weight loss) based a subjective determinations of weight change (e.g., 5% gain vs. 5% loss), growth mixture modeling assigns each individual a probability of belonging to a specific (latent) BMI trajectory.(24)

BMI trajectory groups were estimated using PROC TRAJ, a SAS procedure for GMM.(34, 35) The procedure identifies clusters of individuals following similar progressions of an outcome over time by fitting a semi-parametric, group-based model(34, 35). The choice of the optimal number of classes was based on the comparison of various class-size models using 3 indicators of model fit: (1) Schwarz's Bayesian Information Criteria (BIC), (2) the sample-size-adjusted BIC, (3) Akaike Information Criteria (AIC). Further, we assessed the entropy of each model as an indicator for class separation and performed likelihood ratio tests (LRT) to test the difference in the likelihoods of two models.(36) Based on these criteria (see Appendix Table s1), we identified five subgroups of participants according to their BMI trajectories. We included cubic functions for time in the BMI trajectory models to flexibly model longitudinal change patterns. WHI participants were classified into latent subgroups based on the maximum posterior probability of class membership.

Next, we examined the relationship between BMI trajectories and incident diabetes and cardiovascular outcomes between baseline and March 2017 using Cox proportional hazards models with days since enrollment

as the underlying time scale. We examined both crude and adjusted models. Models were adjusted for age at baseline, race/ethnicity, education, income, diabetes family history, and hypertension status at baseline, baseline health habit characteristics about physical activity level, diet score, alcohol intake and smoking. The lowest BMI trajectory served as the referent group. We verified the proportional hazards assumptions. To examine potential effect modification by years since menopause and hormone therapy use, we stratified the analyses by years since menopause (0-10 years or >10 years) and HT trial arm.

Results

Using the GMM approach, we identified five distinct BMI trajectories: 1) low (n=12417), 2) moderate (n=18539), 3) moderate-high (n=13635), 4) high (n=7406), and 5) very high (n=2076). Baseline characteristics of the study population overall and by BMI trajectory are presented in Table 1. At baseline, mean BMI values were 21.8 kg/m^2 (SD=1.7) for the low trajectory, 25.6 kg/m^2 for the moderate trajectory, 29.8 kg/m^2 (SD=3.3) for the moderate-high trajectory, 34.7 kg/m^2 (SD=2.8) for the high trajectory, and 43.3 kg/m^2 (3.9) for the very high trajectory. Overall, there was a greater representation of young women in the higher trajectory groups and older women in lower trajectory groups. Moreover, as shown in Table 1, women who were 0-10 years since menopause were more likely to be in the high trajectory groups while women more than 10 years since menopause were more frequently classified in lower trajectory groups.

We found minimal change in BMI over time in this sample of postmenopausal women, as demonstrated in Figure 1. The term 'trajectory' is used herein to reference the latent BMI classes, even though there does not appear to be substantial change in BMI within each trajectory (i.e., each of the trajectories appears to be stable). Comparison of actual values of BMI at baseline and the end of follow-up reveals that most women stayed in the same BMI group across the 9-years of follow up (see Table S2). For example, 68% of women with BMI 25-30kg/m^2, 61% of women with BMI 30 to 35 kg/m^2, 54% of women with BMI 35 to 40 kg/m^2, and 70.1% of women with BMI over 40 kg/m^2 remained in the same BMI group over the follow up period.. Among women who did change categories, most moved up or down by a single BMI category. Table 2 describes the proportion of women in each trajectory group according to baseline BMI category. Although there was high concordance between baseline BMI category and trajectory assignment (Table 2, diagonal), only utilizing baseline BMI

would result in a loss of some information. For example, 71% of women with BMI 25-30 kg/m^2 were classified in the moderate (second) trajectory, but 3.8% were classified in the low trajectory and 25% were classified in the moderate-high trajectory. These results demonstrate that BMI remained consistent (within a 5-unit category) across the follow-up for many women. Additional information about change in BMI values within a trajectory is depicted using boxplots in Figure S2. In the total cohort, BMI change was between -4% and +6% for most women. Average BMI change values were 0.1% (SD=8.9) for women in the lowest trajectory, 1.4% (SD=10.5) for women in the moderate group, 1.7% (SD=11.3) for women in the moderate-high group, 1.9% (SD=11.5)for women in the high group, and 1.8% (SD=10.1) for women in the very high group. Trajectory results were similar when stratified by years since menopause (see Appendix Figure s1).

Using the latent BMI classes developed with the GMM, we examined the association between BMI trajectory with risk of diabetes, total CVD, and CABG+PCI. The time at risk of outcome spanned from the beginning of the WHI up to 19 years post-enrollment. There was a greater absolute risk of diabetes, total CVD, and CABG+PCI with increasing BMI trajectory, but the risk of stroke remained approximately constant at 4% in each of the trajectories (Figure 2). The greatest increase in risk across trajectories was for diabetes; this relationship appears positive, linear, and monotonic. For example the risk of diabetes was 7.9% (95% CI=7.4, 8.4) in the low trajectory and 34.3% (95% CI=31.8, 36.8) for the very high trajectory.

Crude and adjusted Cox proportional hazard models were used to examine time to event (diabetes, CVD, CABG+PCI, and stroke) according to BMI trajectory (see Table 3). The referent group in all analyses was the low BMI trajectory. In this analysis, time since enrolment was used as the timescale. Multivariate adjusted results demonstrate the risk of diabetes increasing markedly with increasing BMI trajectory. Compared to the lowest trajectory, adjusted hazard ratios were 1.50 (1.39, 1.61) in the moderate trajectory, 2.41 (2.24, 2.59) in the moderate-high trajectory, 3.08 (2.84, 3.33) in the high trajectory, and 3.97 (3.58, 4.39) in the very high trajectory. There was also evidence of a consistently increased risk of both total CVD and CABG+PCI associated with being in higher BMI trajectories. Compared to the low BMI group, adjusted HRs for total CVD were: 1.13 (1.06, 1.22), 1.21 (1.12, 1.30), 1.21 (1.11, 1.32), and 1.22 (1.07, 1.40) for moderate, moderate-high,

high, and very high trajectories. Corresponding HRs for CABG+PCI were 1.37 (1.23, 1.53), 1.51 (1.35, 1.70), 1.52 (1.33, 1.74), and 1.49 (1.22, 1.83) for moderate, moderate-high, high, and very high trajectories. HRs for stroke demonstrated a decreasing trend comparing across increasing trajectories, however the confidence intervals are wide and include the null, making it difficult to draw a definitive conclusion. Results are also depicted graphically in Figure 3.

Analyses stratified by years since menopause demonstrate some evidence of effect modification (Table 3). In general, the hazard ratios for high BMI trajectories on diabetes, total CVD, CABG+PCI were greater for women who were 0-10 years from menopause compared to women who were more than 10 years from menopause. For diabetes and total CVD, there was greater heterogeneity across strata defined by years since menopause with increasing BMI trajectory group. For instance, in the moderate BMI trajectory, the adjusted HR for diabetes was 1.52 (1.34, 1.73) in women 0-10 years since menopause and 1.48 (1.34, 1.63) in women who were >10 years after menopause. But in women in the very high trajectory, it was 4.44 (3.77, 5.23) higher in those with 0-10 years since menopause compared to 3.74 (3.24, 4.31) in women >10 years since menopause. Overall, results among the sub-group of women in the HT trials (n=21,603) were similar to the results in the entire WHI clinical trials cohort (n=54,073). Results for the subset of women in the HT trial are presented in Table 4, overall and stratified by treatment arm.

Sensitivity Analyses

We conducted several sensitivity analyses to assess the robustness of the study findings (see Appendix Table S3). In the main analyses, we used time since enrolment as the underlying time scale in time to event analyses. Results were broadly consistent when we used since menopause as the time scale in the analyses. To examine potential concerns related to confounding by pre-existing disease and sudden weight loss before those diseases, also referred to as reverse causation, we assessed whether results changed when we removed BMI values in the two years preceding diagnosis of the study outcomes. Results were robust; there was minimal change in effect estimates in these sensitivity analyses. Finally, we examined the relationship between baseline BMI with the

outcomes of interest. As expected, given the high degree of concordance between baseline BMI and BMI trajectories, results from these models were very similar to the main analyses.

Discussion

In this study, we used a novel exposure modeling approach, growth mixture modeling (GMM), to identify longitudinal trajectories of BMI after menopause and examine the association between BMI trajectories with risk of diabetes, CVD, and stroke among postmenopausal women. We identified five distinct BMI trajectory groups that were stable over time, regardless of time since menopause or HT use. We found a positive association between risk of diabetes, CABG+PCI, and total CVD and increasing BMI. Consistent with prior WHI research, time since menopause had an important impact on effect estimates: women who were 0-10 years from menopause were at greater risk of adverse outcomes compared to those more than 10 years since menopause.

We did not find evidence of substantial change in BMI over time among postmenopausal women during the WHI clinical trials. This was an unexpected finding but contributes to our understanding of weight change in postmenopausal women. Of note, a recent study also showed small changes in body weight over a 10-year period in women 55-74 years old, which is consistent with our findings.(37) Five distinct BMI trajectories were identified in the GMM analysis, low, moderate, moderate-high, high, and very high, but women in each trajectory largely maintained similar BMI throughout the duration of the trials. The use of GMM, rather than standard BMI categories, revealed different latent classes of BMI than would have been examined in a traditional analysis using categories defined by underweight (BMI <18.5), normal weight (18.5-24.9), overweight (25-29.9), and obese (>30).(38) At baseline, the low BMI trajectory had a mean BMI value of 21.8, the moderate BMI trajectory had a mean of 25.6, the moderate-high trajectory had a mean of 29.8, the high trajectory had a mean of 34.7, and the very high trajectory had a mean of 43.3. These differences highlight the utility of using BMI trajectories in longitudinal analyses to accurately describe health risks associated with patterns of BMI change.

Another potential explanation for the lack of change in BMI during the trials is related to BMI itself. Though BMI, a ratio of height (kg) over weight (m^2), did not change substantially within each trajectory, we did not examine change in body composition in this analysis. In the postmenopausal period, body fat is known to shift toward a more centralized distribution pattern, increasing visceral fat (i.e., a shift from more gynoid to android patterns) and women lose height with aging.(19, 23, 39-41) Despite these known changes in body composition, it is plausible that total mass (in kilograms), and the related BMI value, does not change substantially. For example, consider a woman who loses height as she ages, decreasing the value of the denominator of BMI. If she is also losing bone mineral density over time, the numerator (Kg) of BMI will decrease since she has less overall mass.(42, 43) These plausible age-related changes in body composition could result in a consistent BMI value over time, despite changes in body composition. This is a potential limitation of using BMI as an anthropometric measure in older adults and should be considered when interpreting the results of the present analysis. An important strength of the present research is that we leverage the repeat measures of both height and weight collected as part of the routine WHI clinical examination.

The risk of diabetes, CVD, and CABG+PCI increased with increasing BMI trajectory. This finding is consistent with previous studies; high BMI is associated with increased risk of CVD and diabetes.(44-47) It is also consistent with a previous study reporting trajectories of body shape from ages 5 years to 55 years, which found the trajectories with increasing body shape had significantly higher risk of diabetes and CVD than those who remained lean throughout this lifespan.(17) Our results emphasize that, although BMI does not change substantially over time in postmenopausal women, stable high BMI during the postmenopausal period remains to be a strong risk factor for chronic diseases. Our findings extend those of Zheng et al. to an older age group and add to the extant literature; using the GMM approach, we revealed important latent, longitudinal patterns of BMI.(17) Even though the trajectories were all relatively stable over time among postmenopausal women, our results highlight that 16-29% of the participants would have been misclassified into a different risk group based on baseline BMI measure only. Using GMM assigned them into a more accurate risk group using repeated measures of BMI. Recently, there has been increased calls for to individual-level approaches to understand how changing exposure patterns influence chronic disease risk across the life course. Studying BMI trajectories over

time using GMM highlights the added value of this type of person-centered approach in guiding precision medicine, where everyone's risk profile is more accurately predicted using their latent class of longitudinal weight change patterns.

Interestingly, we found greater hazard ratios in women who were in the placebo group than HT groups, albeit with overlapping confidence intervals. These results contribute another important piece to our understanding of hormone therapy use in postmenopausal women, suggesting that women in high BMI trajectories who use HT are at no greater risk of CVD than women in lower BMI trajectories who do not use HT. After the WHI trial results were published, use of HT declined substantially in the United States and globally, and it was recognized that there is unlikely to be any cardioprotective benefit of HT use.(26, 48-51) However, as Manson and Kaunitz highlight, there is evidence that both CEE and E+P can be used by younger women (ages ~ 40s and 50s) with no contraindications who are recently menopausal to manage physical and vasomotor symptoms of menopause.(52) They, along with a number of professional societies, such as the American College of Obstetrics and Gynecologists advise that HT can be an effective therapy that stands to improve the quality of life of postmenopausal women.(52, 53) Our results add another dimension to this complex picture; women with high BMI who take HT appear to have similar CVD risks as those with lower BMI. Stated slightly differently, we did not find evidence that women with high BMI who take HT are worse off than women with low BMI who do not take HT.

An important and novel contribution of the present study are the results pertaining to diabetes risk. The relation between HT use and diabetes has received less attention than the relation of HT with CVD. We found a strong and monotonic effect of increasing BMI category with diabetes risk. The hazard ratio for diabetes appears invariant to the effects of time since menopause and HT use: the risk of diabetes still increases with BMI among women 0-10 and >10 years since menopause as well as those assigned to take HT and those assigned to take placebo. We found the risk of diabetes was lower in women taking HT compared to those taking placebo and the difference in diabetes risk between treatment and placebo groups was greatest with higher BMI. For example, for women in the highest BMI trajectory, the risk of diabetes was 43% higher for

women in the placebo group compared to those in the treatment groups (=3.79-3.36) whereas for women in the moderate BMI trajectory, the risk of diabetes was 15% higher for women in the placebo group compared to those in the treatment groups (=1.45-1.30). This again highlights the nuance associated with HT use in older women; reduction in diabetes risk appears to be a key benefit of using HT.(52, 54)

Conclusion

This study makes an important contribution to the literature on obesity, women's health, and aging. Obesity in older adults is an under-researched topic area. The WHI clinical trials dataset provides a unique opportunity to examine longitudinal changes in BMI in older women using objective measures of height and weight. We were surprised to find minimal evidence of BMI change over time as it is often stated that, in general, women gain weight after menopause. Our findings do not support this conclusion; BMI remained mostly stable over the course of follow-up even though all participants were postmenopausal. Additional research on longitudinal patterns of BMI in older adults is necessary to assess whether these relationships generalize to other populations.

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Table 1. Baseline characteristics of study population overall and by BMI trajectory groups

Characteristics	Overall		Low		Moderate		Moderate-high		High		Very high	
	n	%	n	%	n	%	n	%	n	%	n	%
	54073	100	12417	23.0	18539	34.3	13635	25.2	7406	13.7	2076	3.8
Age at baseline (years)												
<50-59	19768	36.6	4140	33.3	6313	34.1	5134	37.7	3214	43.4	967	46.6
60-69	24978	46.2	5782	46.6	8691	46.9	6341	46.5	3255	44.0	909	43.8
70-79	9327	17.2	2495	20.1	3535	19.1	2160	15.8	937	12.7	200	9.6
Race/Ethnicity												
White	44919	83.1	10905	87.8	15798	85.2	11049	81.0	5703	77.0	1464	70.5
Black	4886	9.0	465	3.7	1300	7.0	1510	11.1	1143	15.4	468	22.5
Hispanic	2125	3.9	320	2.6	734	4.0	631	4.6	347	4.7	93	4.5
Asian/Pacific Islander	1423	2.6	568	4.6	487	2.6	250	1.8	98	1.3	20	1.0
Education												
≤ High school	17962	33.2	3424	27.6	6022	32.5	4859	35.6	2834	38.3	823	39.6
College	21145	39.1	4917	39.6	7242	39.1	5356	39.3	2807	37.9	823	39.6
>College	14619	27.0	4005	32.3	5147	27.8	3334	24.5	1717	23.2	416	20.0
Income												
< $50,000	31792	58.8	6553	52.8	10672	57.6	8314	61.0	4817	65.0	1436	69.2
≥$50,000	19276	35.6	5128	41.3	6852	37.0	4578	33.6	2185	29.5	533	25.7
Hormone therapy												
Never used	19175	35.5	4019	32.4	6197	33.4	4986	36.6	2985	40.3	988	47.6
Past hormone users	13042	24.1	2765	22.3	4422	23.9	3416	25.1	1898	25.6	541	26.1
Current hormone user	19370	35.8	5058	40.7	6998	37.7	4592	33.7	2234	30.2	488	23.5
Physical activity												
No activity	8927	16.5	1332	10.7	2488	13.4	2578	18.9	1871	25.3	658	31.7
Limited activity	21005	38.8	4257	34.3	7061	38.1	5616	41.2	3165	42.7	906	43.6
2 - 4 episodes per week	8357	15.5	2144	17.3	3075	16.6	1987	14.6	895	12.1	256	12.3
>4 episodes per week	10444	19.3	3428	27.6	3939	21.2	2149	15.8	803	10.8	125	6.0
Alcohol intake												
Non-drinker	5426	10.0	1115	9.0	1727	9.3	1485	10.9	816	11.0	283	13.6
Past drinker	8794	16.3	1604	12.9	2703	14.6	2361	17.3	1592	21.5	534	25.7
Drinker	39444	73.0	9610	77.4	13978	75.4	9678	71.0	4929	66.5	1249	60.2
Diet Score												

Poor	5764	10.7	1085	8.7	1793	9.7	1522	11.2	1010	13.6	354	17.1
Needs improvement	44974	83.2	10314	83.1	15572	84.0	11365	83.4	6074	82.0	1649	79.4
Good	3165	5.9	983	7.9	1108	6.0	703	5.2	301	4.1	70	3.4
Smoking												
Non-smoker	27835	51.5	6303	50.8	9556	51.5	7102	52.1	3806	51.4	1068	51.4
Past smoker	21669	40.1	4835	38.9	7401	39.9	5467	40.1	3071	41.5	895	43.1
Current smoker	4025	7.4	1151	9.3	1396	7.5	930	6.8	453	6.1	95	4.6
Time since menopause												
0-10	19754	39.7	4512	39.0	6460	37.8	5012	40.2	2904	43.3	866	46.5
>10 years	29960	60.3	7058	61.0	10636	62.2	7459	59.8	3810	56.7	997	53.5
HRT trial												
Treatment	10991	50.9	2389	51.3	3690	51.2	2850	50.6	1615	51.4	447	46.8
Placebo	10612	49.1	2271	48.7	3521	48.8	2786	49.4	1526	48.6	508	53.2

Table 2. Cross tabulation of baseline BMI (in 5-unit categories) with BMI trajectory group from generalized mixture modeling

			Trajectory group					
			Low	Moderate	Moderate-high	High	Very high	Total
BMI category at start of follow-up	≤ 25	n	11651	4042	91	10	0	15794
		%	**73.8**	**25.6**	**0.6**	**0.1**	**0.0**	
	25 to <30	n	746	13919	4900	102	2	19669
		%	**3.8**	**70.8**	**24.9**	**0.5**	**0.0**	
	30 to <35	n	14	537	8237	2836	11	11635
		%	**0.1**	**4.6**	**70.8**	**24.4**	**0.1**	
	35 to <40	n	5	25	364	4052	401	4847
		%	**0.1**	**0.5**	**7.5**	**83.6**	**8.3**	
	≥ 40	n	1	16	43	406	1662	2128
		%	**0.1**	**0.8**	**2.0**	**19.1**	**78.1**	
	Total		12417	18539	13635	7406	2076	54073

Table 3. Crude and adjusted hazard ratios and 95% confidence intervals for the association between BMI trajectory group and cardiometabolic outcomes for the overall study population and stratified by years since menopause (n=54073)

Outcome[b]		Moderate (n=18539)	Moderate-high (n=13635)	High (n=7406)	Very high (n=2076)	P-value for interaction
Diabetes	Crude	1.61 (1.49, 1.73) *	2.81 (2.62, 3.03)*	3.83 (3.55, 4.13)*	5.36 (4.87, 5.90)*	
	Adjusted[a]	1.50 (1.39, 1.61) *	2.41 (2.24, 2.59)*	3.08 (2.84, 3.33)*	3.97 (3.58, 4.39)*	
	0-10 y	1.52 (1.34, 1.73) *	2.55 (2.25, 2.89)*	3.61 (3.16, 4.12)*	4.44 (3.77, 5.23)*	0.002
	>10 y	1.48 (1.34, 1.63) *	2.27 (2.06, 2.51)*	2.69 (2.41, 3.00)*	3.74 (3.24, 4.31)*	
Total CVD	Crude	1.19 (1.11, 1.27) *	1.29 (1.20, 1.38)*	1.27 (1.17, 1.38)*	1.29 (1.13, 1.48)*	
	Adjusted[a]	1.13 (1.06, 1.22) *	1.21 (1.12, 1.30)*	1.21 (1.11, 1.32)*	1.22 (1.07, 1.40)*	
	0-10 y	1.14 (0.97, 1.34)	1.25 (1.06, 1.48)*	1.35 (1.12, 1.63)*	1.75 (1.35, 2.26)*	0.18
	>10 y	1.15 (1.06, 1.24) *	1.19 (1.09, 1.30)*	1.17 (1.05, 1.30)*	1.24 (1.05, 1.48)*	
CABG+PCI	Crude	1.46 (1.31, 1.63) *	1.67 (1.49, 1.87)*	1.70 (1.49, 1.93)*	1.69 (1.39, 2.05)*	
	Adjusted[a]	1.37 (1.23, 1.53) *	1.51 (1.35, 1.70)*	1.52 (1.33, 1.74)*	1.49 (1.22, 1.83)*	
	0-10 y	1.55 (1.22, 1.98) *	1.71 (1.33, 2.20)*	1.90 (1.44, 2.50)*	1.39 (0.92, 2.08)	0.13
	>10 y	1.35 (1.18, 1.54) *	1.42 (1.24, 1.64)*	1.39 (1.17, 1.64)*	1.49 (1.22, 1.83)*	
Stroke	Crude	1.03 (0.93, 1.15)	1.06 (0.94, 1.19)	0.99 (0.87, 1.14)	0.93 (0.74, 1.17)	
	Adjusted[a]	0.98 (0.88, 1.10)	0.99 (0.88, 1.12)	0.96 (0.83, 1.11)	0.88 (0.70, 1.13)	
	0-10 y	0.90 (0.69, 1.17)	0.94 (0.71, 1.25)	0.92 (0.66, 1.27)	1.10 (0.70, 1.72)	0.55
	>10 y	1.02 (0.90, 1.16)	1.01 (0.88, 1.17)	0.96 (0.81, 1.14)	0.86 (0.63, 1.16)	

[a] Multivariate proportional hazards model included age at baseline, race/ethnicity, education, income, diabetes family history, hormone therapy and hypertension status at baseline, baseline health habit characteristics about physical activity level, diet score, alcohol intake, smoking and trial group. BMI trajectory low group is the referent group.

[b] There were 8814 cases of diabetes, 6519 cases of CVD, 2927 cases of CABG+PCI, and 2379 cases of stroke

* p<0.05

Table 4. Adjusted hazard ratios and 95% confidence intervals for the association between BMI trajectory group and cardiometabolic outcomes for women in the WHI hormone therapy trials overall and stratified by treatment arm (n=21,603)

Outcome[a]		Moderate (n=7211)	Moderate-high (n=5653)	High (n=3141)	Very high (n=955)	P-value for interaction
Diabetes	Overall	1.37 (1.22, 1.55) *	2.84 (2.50, 3.21) *	2.23 (1.99, 2.51) *	3.57 (3.05, 4.16) *	
	Treatment	1.30 (1.11, 1.53) *	2.09 (1.78, 2.45) *	2.94 (2.48, 3.48) *	3.36 (2.69, 4.19) *	0.20
	Placebo	1.45 (1.22, 1.73) *	2.40 (2.03, 2.85) *	2.79 (2.32, 3.35) *	3.79 (3.04, 4.72) *	
Total CVD	Overall	1.14 (1.03, 1.25) *	1.21 (1.07, 1.37) *	1.20 (1.08, 1.33) *	1.15 (0.95, 1.39)	
	Treatment	1.05 (0.92, 1.20)	1.11 (0.96, 1.28)	1.21 (1.03, 1.43) *	1.01 (0.76, 1.33)	0.27
	Placebo	1.25 (1.04, 1.44) *	1.31 (1.13, 1.52) *	1.21 (1.01, 1.45) *	1.29 (0.99, 1.68)	
CABG+PCI	Overall	1.33 (1.13, 1.55) *	1.52 (1.26, 1.84) *	1.48 (1.26, 1.75) *	1.55 (1.17, 2.04) *	
	Treatment	1.21 (0.98, 1.50)	1.30 (1.04, 1.63) *	1.27 (0.98, 1.64)	1.30 (0.88, 1.94)	0.52
	Placebo	1.47 (1.16, 1.86) *	1.71 (1.34, 2.19) *	1.86 (1.40, 2.46) *	1.86 (1.25, 2.76) *	
Stroke	Overall	0.99 (0.85, 1.14)	0.98 (0.80, 1.18)	0.98 (0.83, 1.14)	0.81 (0.58, 1.12)	
	Treatment	0.97 (0.77, 1.15)	0.98 (0.78, 1.22)	1.11 (0.86, 1.44)	0.60 (0.35, 1.01)	0.15
	Placebo	1.02 (0.82, 1.26)	0.98 (0.78, 1.23)	0.82 (0.61, 1.11)	1.00 (0.65, 1.54)	

Note: Multivariate proportional hazards model included age at baseline, race/ethnicity, education, income, diabetes family history, and hypertension status at baseline, baseline health habit characteristics about physical activity level, diet score, alcohol intake, smoking and trial arm. BMI trajectory low group is the referent group.

[a] There were 3637 cases of diabetes, 3380 cases of CVD, 1445 cases of CABG+PCI, and 1336 cases of stroke

Figure 1. Five BMI trajectories identified from the growth mixture modeling approach

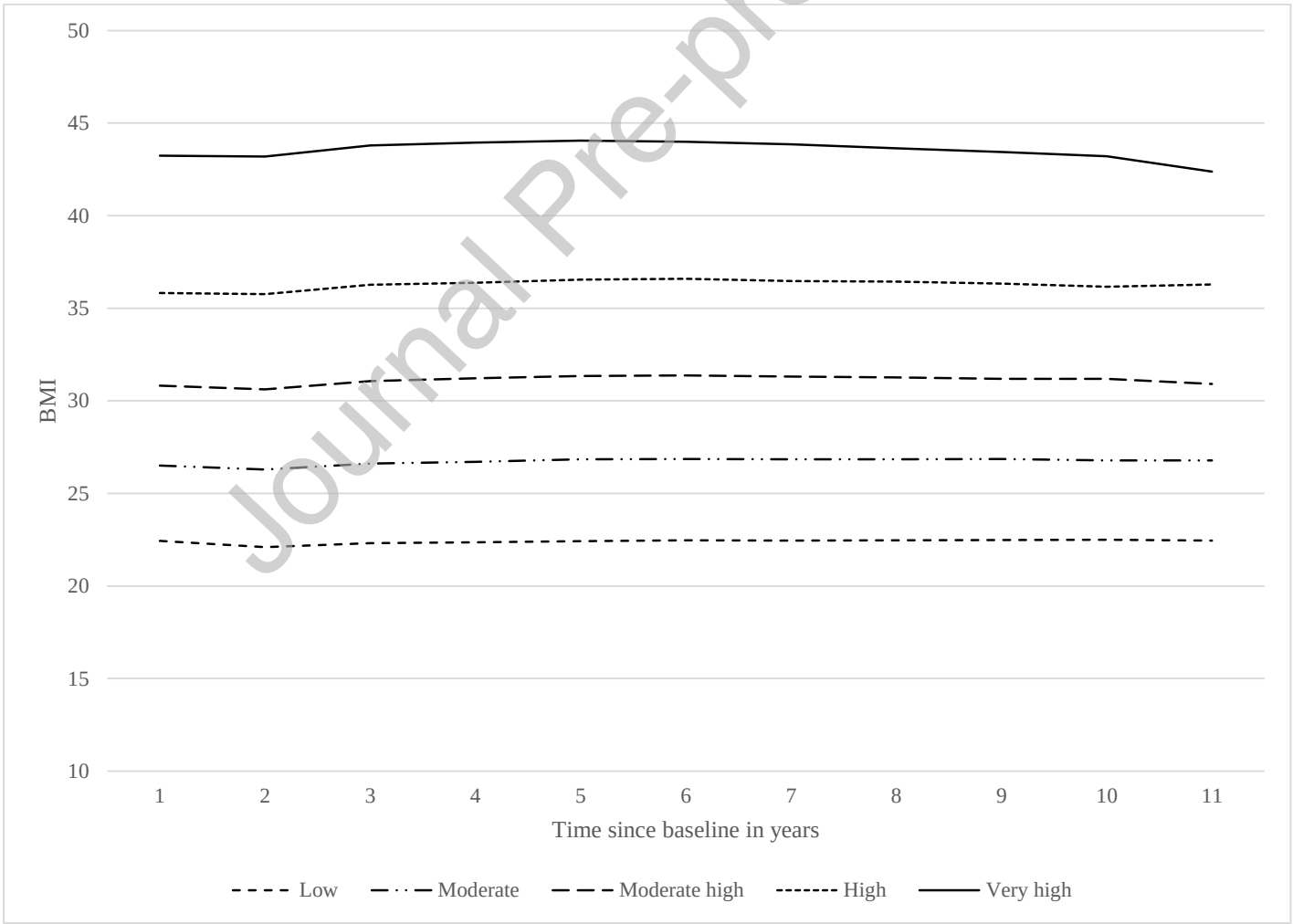
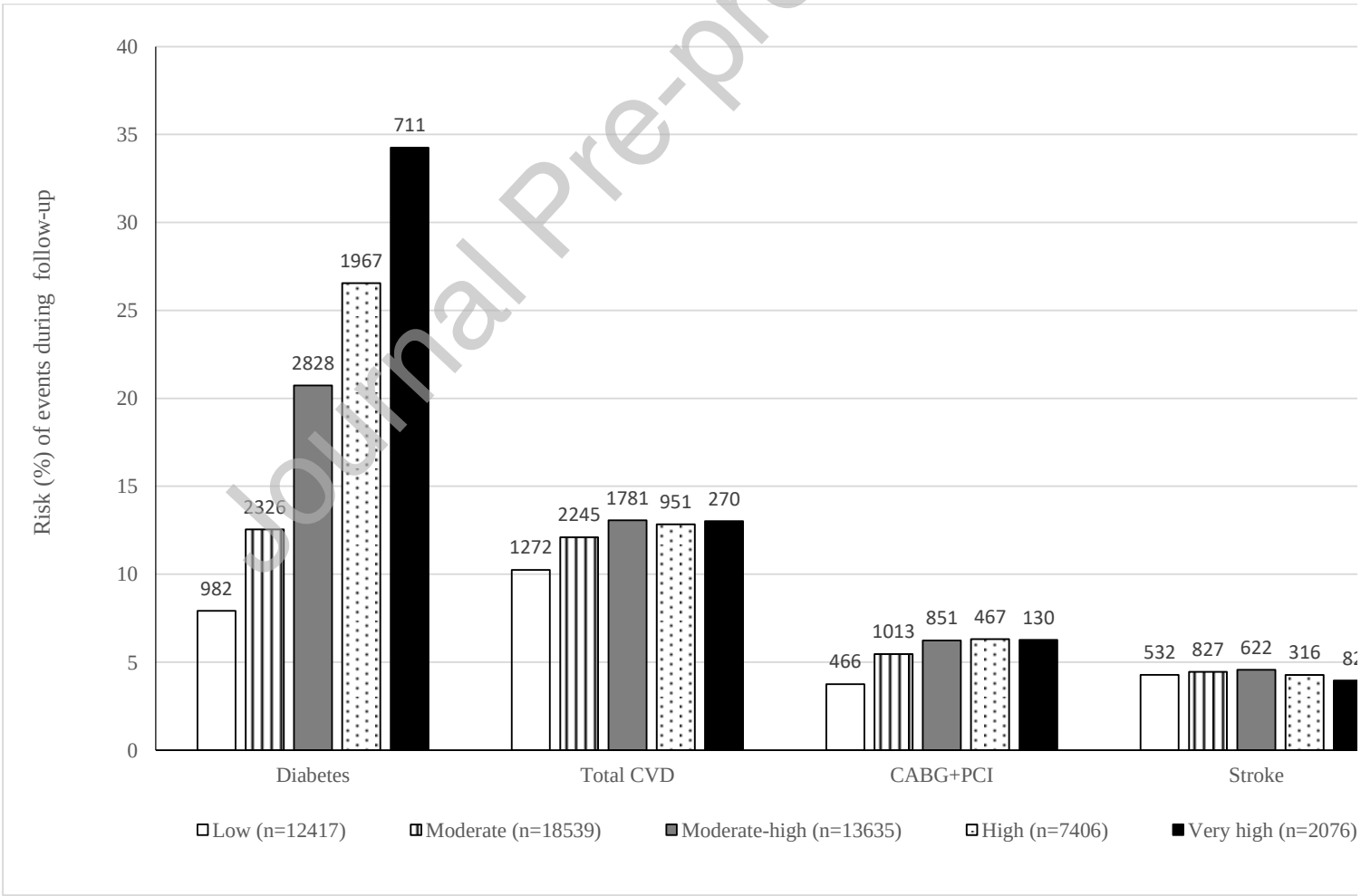


Figure 2. Risk of total CVD, CABG+PCI, Stroke and Diabetes during follow-up by BMI trajectory



Note: The numbers above each of the bars represent the number of outcome events that occurred in that trajectory (e.g., there were 982 incident cases of diabetes in the low trajectory group, 2326 cases in the moderate

group, 2828 cases in the moderate-high group, 1967 cases in the high group, and 711 cases in the very high group).

Figure 3. Hazard ratios of diabetes, total CVD, CABG+PCI, and stroke by BMI trajectory groups