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# Menopausal Symptoms in Women with Chronic Kidney Disease

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## Abstract

**Objectives—**To determine if menopausal symptoms differed among women with *versus* without chronic kidney disease (CKD) and whether CKD modified associations of late vasomotor symptoms (VMS) with mortality and/or cardiovascular events.

**Methods—**Chronic kidney disease, defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m$^2$ by the CKD-EPI equation, was determined in 17,891 postmenopausal women, aged 50–79 at baseline, in the multiethnic Women's Health Initiative (WHI) cohort. Primary outcomes were presence, severity and timing/duration of VMS (self-reported hot flushes and night sweats) at baseline. We used polytomous logistic regression to test for associations among CKD

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and four VMS categories (none; early- present before menopause but not at enrollment; late- present only at enrollment; persistent- present before menopause and at enrollment) and determined whether CKD modified associations between late VMS and mortality or cardiovascular events, using Cox regression.

**Results—**Women with CKD (1017/17891; mean eGFR, 50.7mL/min/1.73m$^2$) were more likely to have had menopause before age 45 (26% *versus* 23%, P=0.02), but were less likely to experience VMS (38% *versus* 46%, P<0.001) compared to women without CKD. Women with CKD were not more likely than women without CKD to experience late VMS. Late VMS (HR=1.16; 95% CI: 1.04, 1.29) and CKD (HR=1.74; 95% CI: 1.54, 1.97) were each independently associated with increased risk for mortality, but CKD did not modify the association of late VMS with mortality ($P_{interaction}$=0.53), coronary heart disease ($P_{interaction}$=0.12) or stroke ($P_{interaction}$= 0.68).

**Conclusions—**Women with mild CKD experience earlier menopause and fewer VMS than women without CKD.

### Keywords

kidney disease; menopause; vasomotor symptoms; cardiovascular; epidemiology

## Introduction

Vasomotor symptoms (VMS) are common menopausal symptoms, occurring in 30–50% of peri-menopausal and 30–80% of post-menopausal women.[1] While the pathogenesis of VMS remains incompletely understood, VMS are thought to be due to thermoregulatory dysfunction leading to exaggerated activation of heat dissipation including peripheral vasodilation and sweating.[2] Vasomotor symptoms have been associated with a higher prevalence of cardiovascular risk factors and subclinical markers of cardiovascular disease.[3–7] Consequently, VMS may help to identify women at heightened cardiovascular risk. Indeed, participants in the Women's Health Initiative (WHI) who developed VMS after menopause (late VMS) were at increased risk for cardiovascular events and mortality, whereas women with early VMS were at lower risk for both compared to women who never experienced VMS.[8]

Chronic kidney disease (CKD) has been reported to affect 15% of all women in the United States[9] but relatively little is known about the relation between CKD and menopause. Women with end-stage renal disease have characteristics of accelerated aging, with premature menopause, bone fractures, and cardiovascular events.[10–14] Women with earlier stages of CKD experience premature cardiovascular morbidity and may also experience an excess burden of fractures,[15,16] yet studies of menopausal characteristics across the spectrum of kidney function are lacking.

In this study, we sought to explore the associations among CKD, menopausal symptoms (specifically VMS), mortality and cardiovascular events. We hypothesized that women with CKD would have earlier onset and more severe menopausal symptoms. Given that late VMS (i.e. not present at menopause, but appearing later) are associated with increased CV risk,

we hypothesized that the association between late VMS and mortality and CV events would be magnified in women with CKD.

## Methods

### Study population and data source

The WHI is an ongoing longitudinal study funded by the National Heart Lung and Blood Institute that was designed to identify risk factors for cardiovascular disease, cancer and osteoporosis in older women. The WHI consists of two major parts, a set of clinical trials and an observational study, both of which have been previously described.[17,18] In brief, the WHI recruited a predominantly healthy, ethnically and socioeconomically diverse cohort of post-menopausal women, aged 50 and 79 years, between 1993 and 1998 with follow-up planned initially through 2005, but extended, first through 2010, then through 2015. Postmenopause was defined as no menses for at least six months if aged ≥55 or no menses for at least 12 months if aged 50–54 years. Women were excluded if they had any medical condition predicted to have less than a 3 year survival, had a condition that might impair adherence to the study protocol or retention or were participating in a randomized intervention trial. Study protocols and consent forms were approved by the institutional review boards at all participating institutions.

We used data from the WHI biomarker cohort (N = 22,313), comprised of 8,505 self-identified Black and 3,502 self-identified Hispanic participants in the WHI observational study and clinical trials, plus 10,306 White participants from the hormone trial, such that the biomarker cohort reflects the age distribution of the hormone trial population. Characteristics of women in the general WHI cohort and the WHI biomarker cohort are presented in Supplementary Table 1.

### Main predictor variable

Participants in the biomarker cohort had baseline blood samples collected including serum creatinine, lipids and glucose. Serum creatinine was measured at baseline at the University of Minnesota at Fairview using the Roche enzymatic method on the Roche Modular P Analyzer (Roche Diagnostics Corporation) and was calibrated to isotope dilution mass spectroscopy standard. The laboratory coefficient of variation was 2.3%. We computed estimated glomerular filtration rate (eGFR) with the CKD-EPI equation.[19] The presence of CKD was defined by an eGFR below 60 mL/min/1.73m$^2$ at study baseline.

### Main outcomes

The main outcomes of this study were the age at menopause, presence, severity and timing/duration of VMS, defined as the presence of hot flashes or night sweats based on participant self-report at study baseline. Age at menopause was defined according to a WHI algorithm as the age at which a woman first experiences last menstrual bleeding, bilateral oophorectomy or began using hormone replacement therapy (HRT). If a woman had a hysterectomy but not a bilateral oophorectomy, then her age at menopause was defined as the age at which she either began using HRT or first had symptoms of menopause, e.g. VMS. If a woman had a hysterectomy at age ≥50 years without bilateral oophorectomy, *and*

she did not experience VMS *and* she did not take HRT then her age at menopause was defined as age at hysterectomy. If VMS were present, participants were asked to rate the symptoms as mild (symptom did not interfere with usual activities), moderate (symptom interfered somewhat with usual activities), or severe (symptom was so bothersome that usual activities could not be performed). The severity of VMS was determined only among women who reported VMS at study entry.

The timing and duration of VMS were analyzed using categories previously defined by WHI, as follows: (1) no VMS if women reported never experiencing VMS, (2) early VMS if women reported VMS that began before menopause but were not present at study baseline, (3) persistent VMS if women reported VMS that began before menopause and were present at study baseline, and (4) late VMS if women reported not having VMS prior to menopause but reported VMS at study baseline.[8]

We also assessed whether CKD modified the association between late VMS and all-cause mortality, coronary heart disease (CHD) and cerebrovascular accident (CVA).[20] Mortality was ascertained by hospitalization records from time of death and most recent relevant hospitalization before death, if in-hospital death, as well as autopsy records and death certificate diagnoses. To ascertain cause of death for all participants, data were linked to the National Death index of the National Center for Health Statistics throughout the study. Coronary heart disease was defined as hospitalized myocardial infarction (MI), definite silent MI, and coronary death. Myocardial infarction was defined by medical history, electrocardiograms, and results of cardiac enzymes/troponins. Cerebrovascular accident was defined as a rapid onset of persistent (lasting more than 24 hours) neurologic deficit attributed to an obstruction or rupture of the brain arterial system and without evidence of other cause. Events were adjudicated by formally trained adjudicators, after self-report through annual (observational study) or semi-annual (clinical trial) questionnaires.

## Covariates

We considered several baseline factors as covariates in these analyses that might confound the association between CKD and VMS, including age, race/ethnicity (self-reported non-Hispanic white; Hispanic or Latino; Black or African-American), diabetes, hypertension, hyperlipidemia, cardiovascular disease (CVD), body mass index (BMI), smoking history, alcohol intake, physical activity, prior use of hormone therapy (HT), and in longitudinal analyses, active HT arm for HT clinical trial participants. Diabetes mellitus was defined as self-report of taking pills or insulin and/or serum fasting blood glucose >126mg/dL. Hypertension was defined as systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg or taking pills for hypertension. Hyperlipidemia was defined as total cholesterol>240mg/dL or LDL>160 mg/dL or taking cholesterol-lowering medication. Smoking history, alcohol intake, prior cardiovascular disease and prior use and duration of hormones were ascertained by questionnaire. Physical activity was ascertained with a personal habits questionnaire, and categorized into total metabolic equivalent (MET) per week.

### Statistical Analysis

We used descriptive statistics to characterize differences among women with versus without CKD, including Chi-square tests for categorical variables and independent t-tests for continuous variables. We used polytomous logistic regression to determine the unadjusted, demographics-adjusted, and multivariable-adjusted associations among CKD and VMS categories. We determined crude event rates for women with versus without late VMS, and women with versus without CKD using Kaplan-Meier plots. Unadjusted, demographics-adjusted, and multivariable-adjusted proportional hazards regression (Cox) models were fit for each event. We confirmed the validity of the proportionality assumption with graphical methods. The multivariable adjusted model included all aforementioned covariates. To test for differential associations among VMS status, mortality and CVD events for participants with versus without CKD at baseline, we included a CKD x VMS status interaction term in the multivariable model. We stratified analyses by baseline hormone use and hormone therapy randomization arm. We conducted all analyses using SAS V9.3 (Cary, NC) and R V 3.0.1.[21]

## Results

Of the 22,313 participants in the biomarker cohort, 189 were missing serum creatinine, 2,251 were missing baseline information on VMS, and 1,982 were missing other key covariates. Women missing any of these variables were excluded, resulting in a final cohort of 17,891 participants (Supplementary Figure 1).

By design, the cohort was ethnically diverse: 38% Black, 16% Hispanic/Latino and 46% White. Women who were excluded from this analysis were more likely to have CKD (6.7% *vs*. 5.6%), to have experienced menopause prior to 45 years (35% *vs*. 25%) and to have used hormone therapy at baseline (44% *vs*. 38%). They were also more likely to have experienced late VMS (43% *vs*. 15%), and less likely to have had early VMS (13% *vs*. 25%) or no VMS (16% *vs*. 29%). Other characteristics were not meaningfully different.

The analytic cohort included 1,007 women (5.6%) with CKD. Mean eGFR was 50.7 ±9.1 and 89.9 ± 14.1 mL/min/1.73m$^2$ in women with and without CKD, respectively. Compared to women without CKD, women with CKD were older, more likely to be Black, more likely to have hypertension, diabetes, hyperlipidemia, CV disease or obesity, were less physically active, less likely to be current smokers or alcohol drinkers and less likely to have used hormone therapy prior to enrollment (Table 1).

Menopause was more likely to occur before 45 years of age in women with CKD than women without CKD (26% *vs* 23%), but there was no difference in prevalence of hysterectomy (1.2% vs 2.0%, P=0.16) or bilateral oophorectomy (18.8% vs 18.4%, P=0.44) in women with versus without CKD. Women with CKD were less likely to have VMS at baseline (38% *vs* 46%) compared to women without CKD. The frequency of severe VMS was not significantly different in women with compared to without CKD (Table 2). Persistent VMS were more common in women without CKD compared to women with CKD (Figure 1).

In unadjusted analyses, CKD was associated with a lower odds of persistent (odds ratio (OR) 0.60, 95% CI 0.51, 0.71) or late VMS (OR 0.80, 95% CI 0.67, 0.96) compared to women without CKD and with no VMS. After adjustment for demographics and other covariates, only the association between CKD and persistent VMS remained statistically significant (Table 3).

Over a median 10.6 years, 2,366 deaths, 1,091 CHD events and 775 CVA events were recorded. Women with late VMS had a higher risk of all-cause mortality (multivariable-adjusted hazard ratio (HR) 1.16, 95% CI 1.04, 1.29). In this cohort, there was no significant association between late VMS and CHD or CVA before or after adjustment for CKD. As expected, baseline CKD was independently associated with all-cause mortality (multivariable-adjusted HR 1.74, 95% CI 1.54, 1.97), CHD (HR 1.60, 95%CI 1.33, 1.93), and CVA (HR 1.52, 95%CI 1.21, 1.91). CKD did not modify the association of late VMS with any events (Table 4).

## Discussion

In this analysis we characterized the menopausal transition in a diverse cohort of older women with particular focus on CKD. We found that, relative to women with normal or near normal kidney function, women with CKD experienced earlier menopause, fewer VMS and less persistent VMS. CKD was significantly associated with all-cause mortality, CHD and CVA, and late VMS was associated with all-cause mortality, however the presence of CKD did not modify the association of late VMS with mortality or CVD events.

The body of evidence characterizing menopausal symptoms in women with CKD is limited. Women receiving maintenance dialysis have an earlier onset of menopause, occurring between 46 and 48 years,[22,23] compared to the U.S. median age of 51 years.[24] We found that women with primarily mild to moderate CKD also experienced, on average, earlier menopause. Lim and colleagues studied premenopausal women receiving dialysis and found hormone levels consistent with hypothalamic anovulation. She had her colleagues also noted a high prevalence of hyperprolactinemia, which may contribute to infertility by inhibition of gonadotropin secretion.[25] While many women have a resumption of menses post renal transplantation, up to 31% of women with end-stage kidney disease have no return of menses, and others who were menstruating prior to transplantation develop amenorrhea or abnormal menses after transplantation.[26,27] Earlier menopause in women with CKD may also be a due to the effect of CKD on the hypothalamic-pituitary axis but this has not yet been studied in detail. CKD is characterized by accelerated aging, which is thought to be due to uremic toxins, oxidative stress and persistent inflammation.[28] We speculate that earlier menopause may represent a part of the accelerated aging phenotype CKD through these pathways.

Earlier menopause may have a variety of clinical implications including potential adverse effects on bone health, cardiovascular risk and sexual function, which may be affected by CKD via other pathways.[25] For instance, chronic kidney disease is frequently associated with disturbances in bone and mineral metabolism, including demineralization due to secondary hyperparathyroidism. This could be exacerbated by early onset menopause and

further predispose women to fractures. Early onset of menopause may impair sexual function, which is also reported to be decreased in women with CKD.[29–31]

Women with CKD experience premature cardiovascular disease[32] and given that VMS are associated with cardiovascular risk factors, we hypothesized that women with CKD would have a higher prevalence of VMS. To the contrary, we found that CKD was associated with a lower prevalence of VMS in this cohort. We speculate that pre-existing vascular disease among women with CKD including vascular calcification, arterial stiffness and impaired endothelial function[33,34] might interfere with vasodilation required to expel heat in VMS. Alternatively, the lower prevalence of VMS among women with CKD may be related to lower body temperature[35,36] in patients with CKD or alterations in the hypothalamic-pituitary axis.[37] It is conceivable that women with CKD may also be less inclined to report VMS due to competing symptoms or other health concerns.

Using data from the WHI, Szmuilowicz and colleagues showed that early VMS were associated with a decreased risk of CVA, total CVD events and all-cause mortality while late VMS were associated with increased risks of CHD and all-cause mortality.[8] In this sub-cohort of the WHI, we found that after adjusting for CKD, late VMS remained a significant predictor of all-cause mortality, but there was no interaction between CKD and late VMS. In contrast to prior research, late VMS were not associated with CHD or CVA. This finding may be due to the differences between the general WHI cohort and the biomarker cohort, which is smaller and more ethnically and racially diverse. We also had less power to demonstrate a modest association.

Our study has several limitations. VMS were ascertained by self-administered questionnaires, which may be subject to recall bias, and for most participants in our study, menopause occurred several years prior to the measurement of kidney function. In the Study of Women's Health Across the Nation accuracy of recall for VMS using a daily log of VMS was high: sensitivity 78–84% and specificity 85–89%.[38] Of note the biomarker cohort is not a random sample of the WHI. Women in the biomarker cohort were older, more likely to be non-White and were less likely to have used hormone therapy (Supplementary Table 1); these differences may affect the association between CKD and VMS. Timing of menopause may not be accurate in women who have undergone a hysterectomy,[39] however prevalence of hysterectomy was low in this cohort and similar in women with and without CKD. We used a single measurement of serum creatinine as a marker of kidney function and this may misclassify individuals with acute rather than chronic kidney disease. We also lacked urine albumin measurements, which would have improved our assessment of kidney disease and could have identified patients with proteinuria but near normal serum creatinine concentrations, many of whom have heightened cardiovascular risk.

## Conclusions

In summary, women with predominantly mild CKD reported earlier menopause, consistent with other body systems where diseases of aging appear earlier in the life course of CKD. Women with CKD also experienced fewer VMS and less persistent VMS, suggesting that

CKD may interfere with the pathogenesis of this condition. Further studies are needed to fully characterize how CKD influences other aspects of gender-specific health.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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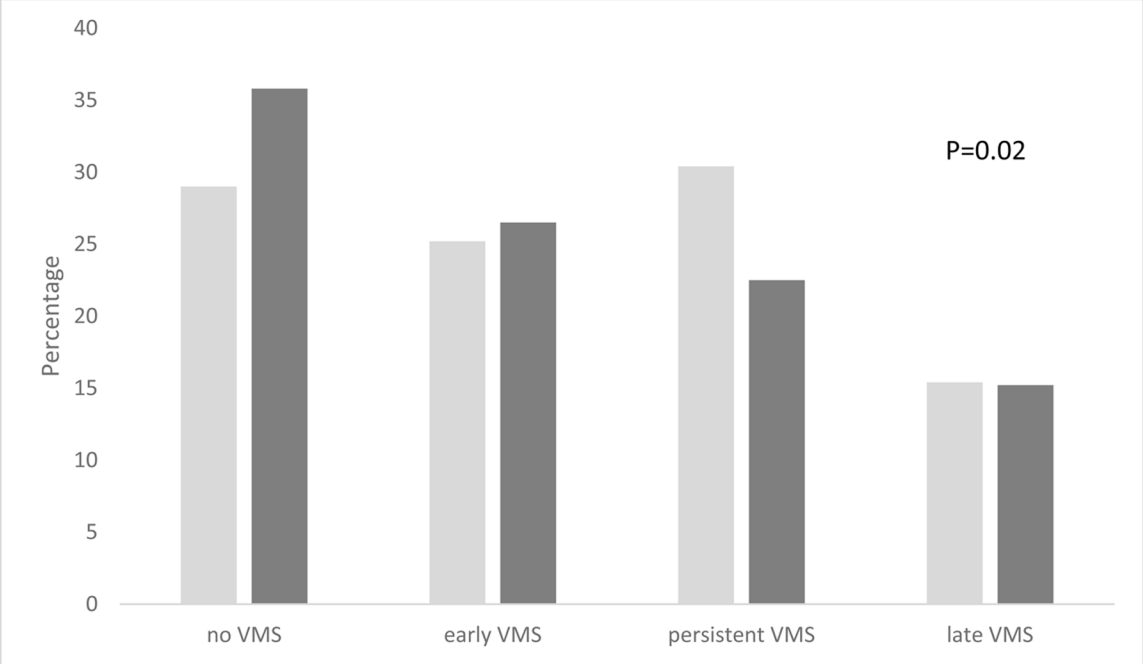


**Figure 1.**
Timing of vasomotor symptoms (VMS) among women with and without chronic kidney disease (CKD)

| | no CKD | CKD |
|---|---|---|
| no VMS | 4,928 | 365 |
| Early VMS | 4,283 | 270 |
| Late VMS | 5,182 | 228 |
| Persistent VMS | 2,614 | 154 |

## Table 1

Baseline characteristics of the Women's Health Initiative biomarker cohort, by chronic kidney disease (CKD) status

| Variable | No CKD (eGFR ≥ 60) n (%) or mean ±SD | CKD (eGFR < 60) n (%) or mean ±SD | P-value |
|---|---|---|---|
| *Total N* | 16884 (94.4) | 1007 (5.6) | |
| Mean eGFR ml/min/1.73m$^2$ | 89.9 ± 14.1 | 50.7 ± 9.1 | |
| *eGFR* ml/min/1.73m$^2$ | | | |
| 45–<60 | 0 | 820 (81.4) | |
| *30–<45* | 0 | 142 (14.1) | |
| *<30* | 0 | 45 (4.5) | |
| Age (years) | 63.5 ± 7.3 | 68.6 ± 6.5 | <0.01 |
| *Age group* | | | <0.01 |
| <50–59 years | 5426 (32.1) | 111 (11.0) | |
| 60–69 years | 7594 (45.0) | 401 (39.8) | |
| 70–79+ years | 3864 (22.9) | 495 (49.2) | |
| *Race/ethnicity* | | | <0.01 |
| Black or African-American | 6486 (38.4) | 395 (39.2) | |
| Hispanic/Latino | 2675 (15.8) | 113 (11.2) | |
| Non-Hispanic white | 7723 (45.7) | 499 (49.6) | |
| *Body mass index (kg/m$^2$)* | | | <0.01 |
| <25 | 3918 (23.2) | 187 (18.6) | |
| 25–<30 | 5891 (34.9) | 354 (35.2) | |
| ≥30 | 7075 (41.9) | 466 (46.3) | |
| *Hypertension* | 8045 (47.7) | 714 (70.9) | <0.01 |
| Systolic blood pressure (mmHg) | 130.0 (17.6) | 135.7 (19.4) | <0.01 |
| Diastolic blood pressure[a] (mmHg) | 76.4 (9.3) | 75.6 (9.8) | 0.01 |
| *Diabetes* | 2061 (12.2) | 214 (21.3) | <0.01 |
| *Hyperlipidemia* | 8038 (47.6) | 623 (61.9) | <0.01 |
| *Cardiovascular disease* | 2727 (16.2) | 305 (30.3) | <0.01 |
| *Hormone therapy use* | 6461 (38.3) | 328 (32.6) | <0.01 |
| *Smoking status* | | | 0.31 |
| Never Smoked | 8688 (51.5) | 543 (53.9) | |
| Past Smoker | 6581 (39.0) | 374 (37.1) | |
| Current Smoker | 1615 (9.6) | 90 (8.9) | |
| *Alcohol use* | | | <0.01 |
| Non drinker | 2,297 (13.6) | 184 (18.3) | |
| Past drinker | 4,059 (24.0) | 298 (29.6) | |
| Current drinker | 10,528 (62.4) | 525 (52.1) | |
| MET-hrs per week | 10.5 ±13.0 | 9.4 ±12.0 | <0.01 |

Abbreviations: eGFR- estimated glomerular filtration rate using CKD-EPI equation; MET- metabolic equivalent of task.

[a] Diastolic blood pressure (missing n=4)

## Table 2

Association of chronic kidney disease (CKD) with menopause characteristics

| | No CKD 16,884 (94.4) | CKD 1,007 (5.6) | P-value |
|---|---|---|---|
| *Age at menopause, years*[a] | 47.8 ±6.8 | 47.2 ±7.2 | 0.02 |
| *Age category at menopause*[a] | | | 0.02 |
| Missing | 1,185 (7.0) | 92 (9.1) | |
| <45 years | 3,876 (23.0) | 264 (26.2) | |
| 45–<50 years | 4,027 (23.9) | 227 (22.5) | |
| 50–<55 years | 5,582 (33.1) | 288 (28.6) | |
| 55+ years | 2,214 (13.1) | 136 (13.5) | |
| *VMS at baseline* | 7,730 (45.8) | 380 (37.7) | <0.01 |
| *Severe VMS at baseline* | 698 (4.1) | 32 (3.2) | 0.13 |

[a] Age at menopause was missing in 1291 women.

VMS- vasomotor symptoms; early VMS refers to VMS that began before menopause but were not present at study baseline, persistent VMS refers to VMS that began before menopause and were present at study baseline, and late VMS refers to no VMS prior to menopause but reported VMS at study baseline

Descriptive statistics in N (%) or mean (±SD) where appropriate.

## Table 3

Association of chronic kidney disease with timing and duration of vasomotor symptoms (VMS)

| | Unadjusted OR (95% CI) | Demographics adjusted OR (95% CI) | Multivariable adjusted OR (95% CI) |
|---|---|---|---|
| | P-value <.0001 | P-value 0.25 | P-value 0.16 |
| No VMS | 1.00 (Ref) | 1.00 (Ref) | 1.00 (Ref) |
| Early | 0.85 (0.72, 1.00) | 0.96 (0.80, 1.14) | 0.94 (0.79, 1.13) |
| Late | 0.80 (0.66, 0.98) | 0.97 (0.78, 1.20) | 0.93 (0.76, 1.14) |
| Persistent | 0.60 (0.51, 0.71) | 0.85 (0.71, 1.01) | 0.80 (0.67, 0.96) |

Abbreviations: OR, odds ratio; CI- confidence interval.

For each model, the OR correspond to the odds of being in the early, late or persistent VMS groups for women with CKD relative to being in the no VMS group for women without CKD.

Demographics-adjusted model is adjusted for age and race/ethnicity. Multivariable adjusted model is additionally adjusted for diabetes, hypertension, hyperlipidemia, history of cardiovascular disease, body mass index, smoking status, alcohol intake, physical activity and prior hormone use.

**Table 4**

Association between CKD, late VMS and all-cause mortality, CHD and CVA in a multiethnic cohort of postmenopausal women

| Outcome | Unadjusted | | Demographics adjusted | | Adjusted | |
|---|---|---|---|---|---|---|
| | *HR (95% CI)* | *p-value* | *HR (95% CI)* | *p-value* | *HR (95% CI)* | *p-value* |
| ***All-cause mortality*** | | | | | | |
| **Late VMS vs. not** | 1.13 (1.02, 1.26) | 0.03 | 1.23 (1.10, 1.37) | <0.01 | 1.16 (1.04, 1.29) | 0.01 |
| **CKD vs. no CKD** | 2.74 (2.43, 3.09) | <0.01 | 2.06 (1.82, 2.33) | <0.01 | 1.74 (1.54, 1.97) | <0.01 |
| | | | | | $P_{interaction}$=0.53 | |
| ***CHD*** | | | | | | |
| **Late VMS vs. not** | 1.08 (0.91, 1.27) | 0.38 | 1.19 (1.01, 1.40) | 0.04 | 1.10 (0.93, 1.30) | 0.25 |
| **CKD vs. no CKD** | 2.56 (2.14, 3.07) | <0.01 | 2.08 (1.73, 2.50) | <0.01 | 1.60 (1.33, 1.93) | <0.01 |
| | | | | | $P_{interaction}$=0.12 | |
| ***CVA*** | | | | | | |
| **Late VMS vs. not** | 1.06 (0.88, 1.29) | 0.53 | 1.18 (0.97, 1.43) | 0.11 | 1.11 (0.91, 1.35) | 0.30 |
| **CKD vs. no CKD** | 2.30 (1.84, 2.88) | <0.01 | 1.83 (1.46, 2.29) | <0.01 | 1.52 (1.21, 1.91) | <0.01 |
| | | | | | $P_{interaction}$=0.68 | |

Abbreviations: VMS- Vasomotor symptoms; CHD- Coronary heart disease; CVA- cerebrovascular accident; CKD- Chronic kidney disease; OR- Odds ratio; CI- Confidence interval. $P_{interaction}$ tests for interaction between late VMS and CKD. Unadjusted is adjusted for CKD only; Demographics adjusted is adjusted for CKD, age group and ethnicity/race. Adjusted is additionally adjusted for physical activity, diabetes, hypertension, high cholesterol, smoking status, alcohol consumption, CVD, BMI, and hormone use at baseline. All models were stratified by hormone use and trial arm.