

## Supplemental Digital Content 1. WHI studies associating symptoms with cardiovascular disease

Symptom (Author, year published)	WHI Cohort	Exposure groups	Exposure assessment <i>(italicized text indicates partial overlap with current report; see footnote for details)</i>
Depression  (Wassertheil-Smoller, 2004)	WHI OS; n = 93,676	Baseline current depressed mood vs none.          History of depression vs none.	Current depressed mood based on 6 questions: (1) You felt depressed (2) Your sleep was restless (3) You enjoyed life (reversed scoring) (4) You had crying spells (5) You felt sad (6) You felt that people disliked you. Questions used corresponding Likert scale: (0) Rarely or none of the time (1) Some or a little of the time (2) Occasionally or moderate amount of time (3) Most or all of the time. Questions were summed and a score $\geq 5$ was considered depressed.  History of depression (Yes to both questions): (1) In the past year, have you had 2 weeks or more during which you felt sad, blue, or depressed or lost pleasure in things that you usually cared about or enjoyed? (2) Have you had 2 years or more in your life when you felt depressed or sad most days, even if you felt okay sometimes?
Panic Attacks  (Smoller, 2007)	WHI OS participants that also enrolled in Myocardial Ischemia and Migraine Study (MIMS); n = 3369	Full-blown panic attack vs none       Limited-symptom panic attack vs none	Participants were asked two screening questions, in the last 6 months: (1) a sudden attack of feeling frightened, anxious, or extremely uncomfortable; (2) <i>a sudden episode of rapid or irregular heartbeats<sup>a</sup></i> .  Then whether they experienced (yes/no) any of the following 13 symptoms: (1) shortness of breath (2) <i>dizziness, unsteady feelings<sup>a</sup>, faintness</i> (3) <i>palpitations or accelerated heart rate<sup>a</sup></i> (4) <i>trembling or shaking<sup>a</sup></i> (5) wheezing (6) choking (7) nausea or abdominal distress (8) numbness or tingling sensation (9) feeling as though you were watching yourself from a distance (10) <i>flushes or flashes or chills<sup>a</sup></i> (11) chest pain or discomfort (12) fear of dying (13) fear of going crazy or doing something uncontrolled.  Affirmative to 1 to 3 symptoms, or 4 or more symptoms constituted limited-symptom and full-blown panic attacks, respectively.
Vasomotor  (Szmuiłowicz, 2011)	WHI OS with no prior history of CVD or cancer, complete VMS data at menopause onset and enrollment; n = 60,027	Late VMS vs persistent VMS vs early VMS vs no VMS	VMS status (late, persistent, early, no VMS) was a construct of symptoms that occurred on or before self-reported age at menopause, and at enrollment. Specifically, participants were asked at enrollment: <i>Have you ever had menopausal symptoms, such as hot flashes or night sweats?<sup>b</sup></i> If affirmative, followed by: <i>How old were you when you first had symptoms such as hot flashes or night sweats?<sup>b</sup></i>  On a separate questionnaire also administered at enrollment, participants completed a checklist of symptoms that occurred in the past 4 weeks and corresponding severity (none, mild, moderate, severe). <i>Night sweats<sup>b</sup></i> and <i>hot flashes<sup>b</sup></i> were included on this checklist.

## Supplemental Digital Content 1. WHI studies associating symptoms with cardiovascular disease (continued)

Symptom (Author, year published)	WHI Cohort	Exposure groups	Exposure assessment <i>(italicized text indicates partial overlap with current report; see footnote for details)</i>
Sleep duration, Insomnia  (Sands-Lincoln, 2013)	WHI OS with no prior history of CHD; n = 86,329	Sleep time $\leq 5$ , 6, 9, $\geq 10$ vs 7-8 hours  WHI Insomnia Rating Scale (WHIIRS): 3-<6, 6-<9, $\geq 9$ vs < 3 WHIIRS	Based on response to “About how many hours of sleep did you get on a typical night during the past 4 weeks?” Respondents chose from six categories, $\leq 5$ , 6, 7, 8, 9, or $\geq 10$ hours.  Participants were asked, ‘During the last 4 weeks, how often have you been bothered by any of the following problems? (1) Trouble falling asleep (2) <i>Waking up several times per night</i> <sup>c</sup> (3) Waking up earlier than you planned to (4) Trouble getting back to sleep after you woke up too early (5) Overall, was your typical night’s sleep during the past 4 weeks.” Question 1–4 responses included frequency options ranging from “No, not in the past 4 weeks” to “Yes, 5 or more times a week.” Response options to question 5 included “very sound or restful,” “sound or restful,” “average quality,” “restless,” and “very restless.” Responses were scored from 0–4 and then summed.
Joint Pain (Mackey, 2015)	All WHI participants (n=161,808)	Mild vs. none, moderate vs. none, and severe vs. none	Joint pain severity during the past 4 weeks was assessed via self-report by questionnaires at WHI enrollment.
Cognitive function  (Leng, 2018)	WHI HT trial participants that also enrolled in the WHI Memory Study (WHIMS); n = 5,596	Global cognitive functioning (linear)	The Modified Mini-Mental State Examination (3MSE) was used to measure global cognitive function. The 3MSE has 15 parts comprised of 46 items that contribute to a total score (0 worst to 100 best); a higher score reflecting better cognitive functioning. The 3MSE is often used to screen for dementia.
Migraine headaches  (Pavlovic, 2019)	WHI OS participants with no prior history of CVD; n = 71,441	History of migraine vs none	Migraine status was determined at baseline by self-reported clinician diagnosis of migraine headaches.
Vasomotor, somatic and cognitive affective menopausal symptoms  (Nudy, 2020)	WHI CaD trials participants that were not randomized into the HT trials (n = 20,050).	Exploratory analysis used same exposure groups considered in this report (mild, moderate/severe vs. none).	<i>MS severity during the past 4 weeks was assessed via self-report by questionnaires at WHI enrollment.</i>  With the exception of joint pain, all menopausal symptoms considered in this report of WHI-OS participants (n = 80,278) were reported for CaD trial participants. Unlike this report, total CVD was not the primary endpoint and associations with the severity of individual symptoms were reported as exploratory analyses (Nudy, 2020).

<sup>a</sup> Unlike current report, Smoller (2007) did not directly associate individual symptoms to CVD, instead symptoms were used to compute panic attack construct. In addition, symptoms were collected using MIMS-specific questionnaire not used in the WHI-OS, so wording is somewhat different.

<sup>b</sup> Unlike current report, Szmulowicz (2011) did not directly associate individual symptoms at enrollment to CVD, instead symptoms were used to compute VMS status (late, persistent, early, no VMS) construct. VMS at menopause onset were computed from a separate form, while VMS at enrollment was computed using the same questionnaire as this report, and VMS status was computed as the cross-product of these variables.

<sup>c</sup> Unlike current report, Sands-Lincoln (2013) did not directly associate individual symptom to CVD, instead symptoms were used to compute insomnia construct.