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Dementia Outcomes after Addition of Proxy-based Assessments for Deceased or Proxy-dependent Participants

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Abstract

OBJECTIVES: As people age and the incidence of dementia increases, studies of cognitive function continue to be of importance. Ascertaining cognitive data through different mechanisms is necessary to address missing data concerns.

METHODS: The Dementia Questionnaire (DQ), which utilizes proxy-based assessments, is a potential tool to determine cognitive status in participants no longer being followed per traditional study protocol. The DQ is currently being used in the Supplemental Case Ascertainment Protocol (SCAP) which is being conducted in an ongoing study of post-menopausal women as part of the Women's Health Initiative Memory Study (WHIMS).

RESULTS: 94% of the 1260 SCAP participants were eligible due to being deceased. Those who are SCAP eligible were older, less likely to be a minority, were more likely to have hypertension, diabetes and prior history of CVD as well as being a past or current smoker. SCAP added 109 cases of probable dementia to WHIMS. Risk factor relationships were modified upon inclusion of the SCAP cases including an attenuation of a hormone therapy effect and discovery of a hypertension effect.

CONCLUSIONS: Augmenting clinic-based cases with proxy-based assessments is feasible and lead to increased incident cases of dementia. When planning future clinical trials, it may be of study benefit to include a protocol of proxy-based assessments, develop strong relationships with

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proxies early on in the study, and attempt to maintain this relationship throughout the lifespan of the trial.

Keywords

Cognitive aging; clinical trials; missing data

INTRODUCTION

The incidence of dementia worldwide is on the rise with the number of people affected projected to be 115 million in 2050 [(1)], therefore cognitive function and impairment continue to be important areas of research particularly in older adults [(2, 3)]. In research contexts, evaluating participants' cognitive status is challenging due to the high cost of a comprehensive evaluation that includes neurocognitive testing, a clinical evaluation, interviewing knowledgeable family members, and optional ancillary laboratory tests or brain scans. Some modifications to this methodology have been successfully used in research contexts. While face to face cognitive evaluations are still commonly used [(4, 5, 6)], alternative methods have been introduced including phone-based cognitive assessments [(7)] and structured proxy interviews [(8)].

Clinical trials and observational studies involving older adults often have higher rates of missing data [(9)] due to, in part, more comorbidities, functional impairments (vision, hearing, mobility), and higher mortality which may bias study findings [(10)]. Surrogate ascertainment protocols, including the use of proxy informants, represent an innovative approach which may mitigate the effect of missing data.

Using informants or proxies, who are familiar with the study participant and can provide essential information on observed cognitive and behavioral changes of deceased participants or those otherwise lost to follow-up, for example, is one approach to this problem. Standardized questionnaires [(11, 12, 13)] and semi-structured interviews [(14, 15, 16, 17)] have been developed for this purpose.

The Dementia Questionnaire (DQ) is a standardized and validated semi-structured interview administered to a proxy who is familiar with the individual [(18)]. It assesses observed cognitive problems and functional limitations plus specific medical information needed to diagnose dementia. The validity, sensitivity, and specificity of the DQ has been well documented [(17, 19, 20, 21, 22, 23)]. When administered to proxies, the DQ has shown excellent diagnostic properties for dementia compared to clinical evaluations. Kawas et al [(17)] reported the sensitivity and specificity for dementia among community dwelling older adults aged 68-97 years were 100% and 90%, respectively and in a study of older adults with and without dementia, the DQ sensitivity was 93% and specificity was 90% [(20)]. One use of the DQ that has not been studied is whether it might be useful in capturing additional cases of dementia in situations where a study participant is no longer available such as following their death or when active participation is interrupted despite remaining in the study. Missing cases in such situations would lead to undercounting the prevalence. One way to examine the validity of this supplemental case ascertainment approach is to compare these cases' clinical and/or demographic characteristics and observed risk factor associations to cases

ascertained using more conventional procedures. The Women's Health Initiative Memory Study (WHIMS) [4] provides an excellent opportunity to make this comparison.

We previously reported on the value of including SCAP participants to augment clinic-based cognitive assessments [8]. The report extends this to include telephone-based cognitive assessments, roughly doubling the length of follow-up of the WHIMS cohort as women transition to older ages. In this manuscript, we will explore differences between women who qualified for supplemental case ascertainment via SCAP as well as investigate whether the addition of SCAP modifies results of time-to-event outcomes of probable dementia.

METHODS

The Women's Health Initiative Hormone Therapy trials assessed two postmenopausal hormone therapy regimens, conjugated equine estrogens (CEE) with or without medroxyprogesterone acetate (MPA), among women who were appropriate candidates for these therapies [24]. The Women's Health Initiative Memory Study (WHIMS) was an ancillary study to the WHI Hormone Therapy trials with the overall objective to assess the effect of postmenopausal hormone therapy on the incidence of all-cause dementia and global cognitive functioning over time, through annual in-person cognitive assessments, in 7,479 women between 65 and 79 years of age at enrollment into WHI. Following the early termination of the WHI CEE+MPA trial (July, 2002) and WHI CEE-Alone trial (March 2004), WHIMS participants continued their annual assessments during the WHIMS-Extension Study which lasted until June 2008. Following the trial terminations, participants were informed of their treatment assignment but adjudicators remained blinded throughout the course of the studies and interviewers did not have access to treatment assignment.

In September 2008, WHIMS methodology transitioned to a phone-based annual cognitive assessment protocol which continues through today as the Women's Health Initiative Memory Study – Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO). The aim of WHIMS-ECHO is to investigate the long-term effects of hormone therapy treatment assignment on incident cognitive impairment (all-cause dementia, mild cognitive impairment) and global cognitive function. All women provided written informed consent and all protocols were approved by local Institutional Review Boards.

Cognitive and functional assessments

In WHIMS and WHIMS-Extension, a validated cognitive screener, the Modified Mini Mental State Exam (3MSE; [25]), was administered annually to all participants. Women scoring below a pre-set cut-point were administered additional cognitive tests, a neuropsychiatric evaluation by a physician specialist, and optional CT and lab tests. The pre-set cut-points were initially a score of 72 or lower for women with 8 years of education or less and a score of 76 or lower for women with a least 9 years of education. After 16 months of the original WHIMS study, the protocol was altered to increase these cut-points to a score of 80 or lower and 88 or lower, respectively. A knowledgeable proxy designated by the participant was interviewed regarding observed changes in cognitive and behavioral functioning as described previously [4]. In WHIMS-ECHO, face-to-face evaluations were no longer possible due to closure of clinic sites. Instead, participants were administered a

validated battery of telephone-based cognitive tests and questionnaires [7] by trained and certified staff. If a participant scored below 31 on the cognitive screener, the modified Telephone Interview for Cognitive Status (TICSm) [26], the DQ was administered to the designated proxy.

Supplemental Case Ascertainment Protocol

In 2005, the WHIMS Supplemental Case Ascertainment Protocol (SCAP) was developed to capture cases of cognitive impairment (mild cognitive impairment or dementia) that could be otherwise missed because a participant died or was not actively participating even though they remained in the study and had given permission to obtain information from their pre-designated proxy, referred to in WHI as 'Proxy Contact Only.' The SCAP protocol involved the administration of the DQ to a participant-identified proxy. In SCAP, the DQ data were used together with all prior WHIMS/WHIMS-ECHO data for adjudication of dementia and MCI.

Adjudication

During the WHIMS and WHIMS-Extension phases of the trial, a central committee of dementia experts adjudicated all locally identified probable dementia cases, a 50% random sample of MCI cases, and a 10% random sample of no impairment cases to make final study classifications [27]. When the trial transitioned to telephone-based cognitive assessments during the WHIMS-ECHO study, the same committee adjudicated all cases provisionally flagged as possible dementia or MCI based on an algorithm using selected DQ items related to functional status and observed cognitive problems. Due to an initial trial of sending half of the cases classified as No Dementia (ND) to adjudication, all of which were returned with a confirmatory ND classification, the study determined cases classified as ND according to the algorithm would no longer be sent to adjudication. If this pre-adjudication algorithm produced a missing classification due to missing data on the DQ, the case was sent to adjudication. Despite some differences in the specific data available for classification of dementia and MCI across phases of WHIMS, WHIMS-Extension and WHIMS-ECHO, the criteria for adjudication of cases remained the same and all available data from prior assessments was available to adjudicators including face-to-face cognitive assessments from WHIMS and WHIMS-Extension, phone based assessments from WHIMS-ECHO, prior adjudicated outcome, the Geriatric Depression Scale, as well as the entire Dementia Questionnaire.

The adjudication committee consisted of two physician specialists (neurologist, geriatrician) and a clinical geropsychologist all experienced in diagnosing dementia. Each prospective case was randomly assigned to two adjudicators who independently reviewed all available data including cognitive test scores, questionnaire scores, lab results, and proxy interview data. They used standardized diagnostic criteria [28, 29] to classify a case into one of the following categories: probable dementia, mild cognitive impairment, no impairment, or cannot classify. A web-based interface was used to display available data and to record classifications. If the two adjudicators agreed on the classification of the case, their decision was final while disagreements were referred to a monthly telephone consensus conference

with all adjudicators present at which time cases were discussed until consensus was reached.

Variables of interest

The WHI collected baseline demographic, lifestyle, and clinical data via standardized self-report assessments [24]. These included age, education, race/ethnicity, body mass index, hypertension, treatment assignment, prior hormone therapy use, history of stroke, history of cardiovascular disease (myocardial infarction, angina, percutaneous transluminal coronary angioplasty, revascularization, coronary artery bypass graft surgery, or stroke), diabetes and smoking. Apolipoprotein epsilon 4 (APOE-e4) genotype, a risk factor for Alzheimer's disease, was imputed from blood specimens taken at WHI baseline in a subgroup of participants. Time between WHI randomization and cognitive testing was calculated.

Statistical methods

Demographic variables of SCAP participants were compared to conventionally assessed WHIMS participants using chi-square tests. Bivariate risk factor relationships and cumulative hazard plots were examined using proportional hazards regression both with and without inclusion of the proxy-dependent cases. Participants continuing to receive annual cognitive assessments were censored at the first assessment when dementia was classified or their most recent cognitive interview. Those participants who had transitioned to WHIMS-SCAP and were classified as dementia were censored to the midpoint of their last cognitive assessment and date of DQ if they were alive and the midpoint of their last cognitive assessment and date of death if they were deceased. If they were not previously classified as dementia, they were censored back to their date of death if deceased and the maximum of their date of last cognitive assessment and date of DQ if they were alive.

Two distinct protocols were compared: (1) the WHIMS/WHIMS-Extension/WHIMS-ECHO (WHIMS-Main protocol) and (2) the WHIMS-SCAP protocol. Table 1 details the history of the WHIMS trial including what compromised the assessments for each phase. We describe data collected through July 2018.

RESULTS

1181 of the 1260 (94%) SCAP participants were eligible for SCAP due to being deceased compared to 79 (6%) eligible due to being proxy-dependent. The completion rate of the DQ in WHIMS-SCAP was 45.5% which is lower than the rate of 69.0% in WHIMS-Main. In SCAP, those who are missing the DQ, were more likely to be non-white, had lower education, and had lower baseline 3MSE scores (data not shown). As seen in Table 2, those included in WHIMS-Main (N=6,219) and WHIMS-SCAP (N=1,260) cohorts differed with respect to many risk factors for cognitive decline, including age, race/ethnicity, APOE e4 carrier status, smoking, and history of hypertension, cardiovascular disease, and diabetes (all $p<0.05$). The WHIMS-SCAP cohort participants tended to be older, less likely to be a minority, were more likely to have hypertension, diabetes and prior history of CVD as well as being a past or current smoker.

The pattern of associations between risk factors and probable dementia cases ascertained using the WHIMS-Main protocol and those ascertained in WHIMS-Main plus WHIMS-SCAP (Table 3) was comparable except with regards to the WHI hormone trial treatment assignment and hypertension. Adding the WHIMS-SCAP cases attenuates the HT treatment effect (p=0.1161) and unmasks a potential effect with hypertension in that those with no history of hypertension are less likely to be classified as dementia than those who have uncontrolled hypertension (Hazard Ratio, (95% Confidence Interval), 0.77 (0.66, 0.90)). All 1,260 participants were included in this analysis. When looking at the plot of the cumulative hazards (Figure 1) we see that the shape remains consistent after addition of the 109 WHIMS-SCAP cases and only increases the number found.

DISCUSSION

Missing data in clinical trials is a common problem with the data usually not missing completely at random leading to biased results [30]. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) poor cognitive performance was associated with missing data in the Mild Cognitive Impairment (MCI) and Normal Cognition (NC) groups [31]. The former group is of particular concern given the high rate of progression of MCI to dementia particularly as age increases [32]. The SCAP protocol identified 109 additional cases of dementia (an increase of 15%) for analyses, increasing statistical power and decreasing missing data.

Importantly, the cohort evaluated how the SCAP protocol differed from other women with respect to many important risk factors for dementia. Their inclusion likely adds to the generalizability of research findings and curbs some differential attrition. The increase in the number of cases adjudicated through the full 22 years of WHIMS follow-up in our report is similar to what we reported prior to WHIMS-ECHO (i.e. 16%) suggesting that the SCAP protocol continues to provide value even as the cohort ages.

We found the statistical significance of two relationships changed with the inclusion of SCAP cases. For hypertension, the risk factor relationship increased in strength. The prevalence of hypertension was markedly higher for women in the SCAP cohort compared with other women, similar to our earlier report prior to WHIMS-ECHO [8]. This suggests women with hypertension were differentially missed by the main protocol and the observed relationship between hypertension and dementia would have been nonsignificant.

The attenuation of the relationship between intervention assignment and dementia incidence over time with the inclusion of the additional SCAP cases has been reported earlier [33]. During the first six years of follow-up, which captures the treatment phase of the clinical trial, both regimens of hormone therapy were associated with increased risk for dementia in analyses including SCAP cases. With longer follow-up after therapies were terminated, the increased risks associated with assignment to both regimens were attenuated and remained statistically evident only for the CEE+MPA regimen. During long-term follow-up of the full WHI cohort, including the post-treatment observational phase, all-cause mortality rates were similar between the original treatment groups, but deaths among women who had been assigned to hormone therapy tended to be attributed to causes other than Alzheimer's

disease [34]. Thus, capturing additional dementia cases with the SCAP protocol that would otherwise been lost due to mortality may also have attenuated estimates of long-term risks.

Alternative strategies for data collection have been developed in an attempt to reduce the potential bias associated with missing data including phone based [7] and proxy based assessments [8]. A potential limitation is these protocols are not interchangeable with clinic-based assessments and may lead to differing risk factor relationships within the cohorts. Sophisticated modeling approaches may be necessary to reduce any lingering biases.

CONCLUSION

Our findings indicate that augmenting clinic-based cases with proxy-based assessments is feasible and lead to increased incident cases of dementia. When planning future clinical trials, it may be of study benefit to include a protocol of proxy-based assessments, develop strong relationships with proxies early on in the study, and attempt to maintain this relationship throughout the lifespan of the trial.

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KEY POINTS:

Ascertaining cognitive data through different mechanisms is necessary to address missing data concerns. Augmenting clinic-based cases with proxy-based assessments is feasible and lead to increased incident cases of dementia.

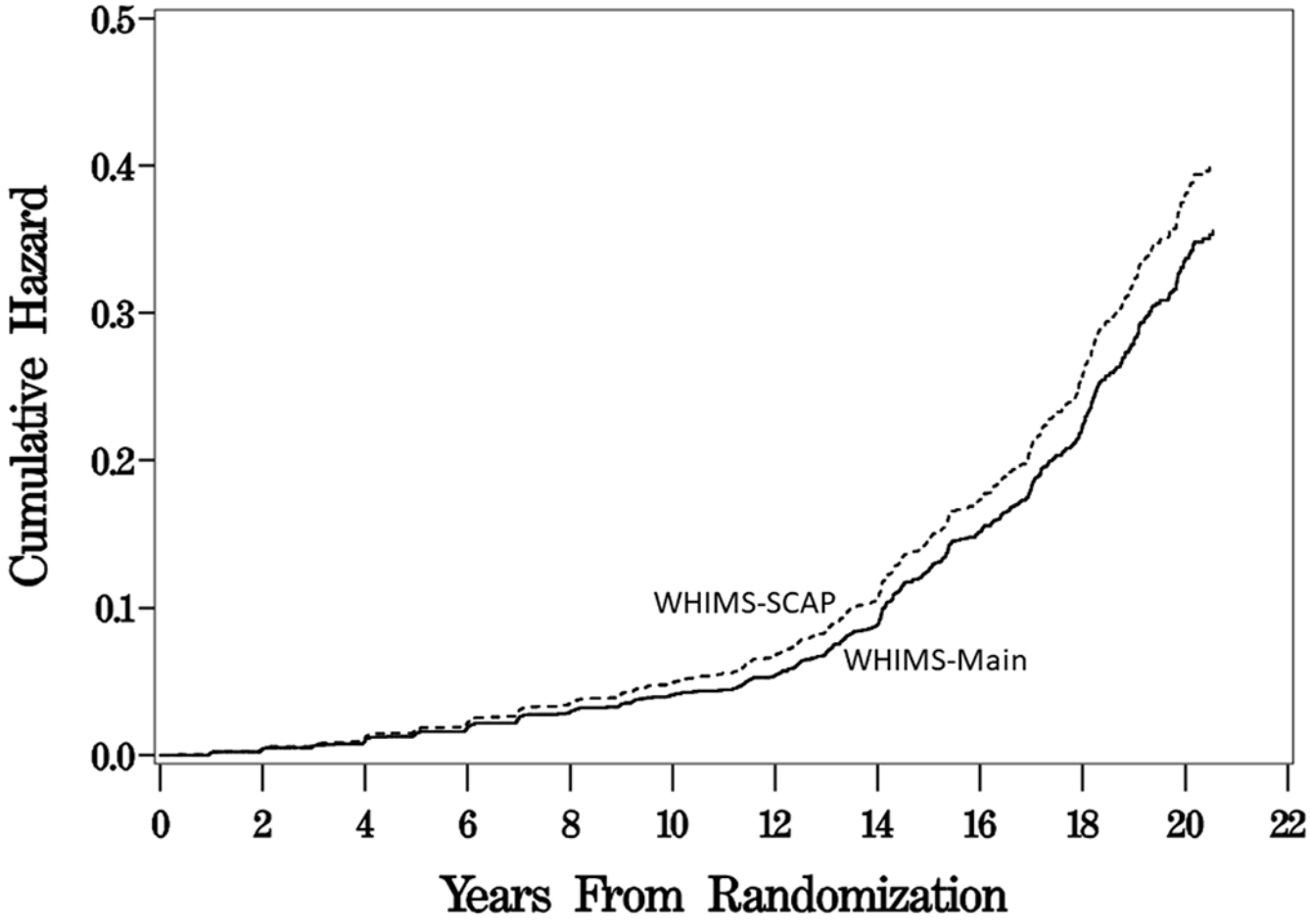

Figure 1:
Incident Adjudicated Dementia by Study Protocol.

Table 1.

Phases of WHIMS

Study Phase	WHIMS (including extension)	WHIMS-ECHO	SCAP
Years in Effect	1996-2007	2007-present	
Assessments			
Cognitive	• Annual face-to-face administered 3MSE (25); cutpoint triggered cases that received additional assessments • CERAD neuropsychological battery (35)	• Annual telephone-administered cognitive battery (7); TICSm (26) triggered cases that also collected Dementia Questionnaire from proxy	
Clinical	• CERAD clinical evaluation (35) • Prime MD psychiatric interview (36) • Geriatric Depression Scale-Short Form (37)	• Geriatric Depression Scale-Short Form (37) • WHI Insomnia Rating Scale (38)	
Proxy	CERAD cognitive and behavioral changes assessment (35)	Dementia Questionnaire (17) administered to knowledgeable proxy	Dementia Questionnaire (17) administered to knowledgeable proxy
Adjudication	Central Adjudication Committee using all prior data; applying standardized diagnostic criteria (28, 29)	Central Adjudication Committee using all prior data; applying standardized diagnostic criteria (28, 29)	Central Adjudication Committee using all prior data; applying standardized diagnostic criteria (28, 29)
Cases identified	Probable dementia: Mild Cognitive Impairment:	Probable dementia: Mild Cognitive Impairment:	Probable dementia: Mild Cognitive Impairment:

Notes: CERAD=Consortium to Establish a Registry for Alzheimer's Disease; TICSm=Telephone Interview for Cognitive Status-modified; 3MSE=Modified Mini Mental State Exam; WHI=Women's Health Initiative; WHIMS=Women's Health Initiative Memory Study; ECHO=Epidemiology of Cognitive Health Outcomes; SCAP=Supplemental Case Ascertainment Protocol

Table 2.

Comparison of Variables of Interest for Two Different Adjudication Ascertainment Protocols

	N (%)		
Variable	**WHIMS-Main (n=6219)**	**WHIMS-SCAP (n=1260)**	**P-Value**
Age at start of study			<.0001
64-69	2972 (47.8%)	475 (37.7%)	
70-74	2187 (35.2%)	489 (38.8%)	
75+	1060 (17.0%)	296 (23.5%)	
Race/Ethnicity			0.0002
Black/African American	449 (7.24%)	86 (6.84%)	
Hispanic/Latino	164 (2.64%)	15 (1.19%)	
Other	231 (3.72%)	25 (1.99%)	
White	5361 (86.4%)	1132 (90.0%)	
Education			0.5249
< High school	486 (7.84%)	89 (7.09%)	
High school/GED	1384 (22.3%)	264 (21.0%)	
Some college	2481 (40.0%)	521 (41.5%)	
College +	1851 (29.8%)	382 (30.4%)	
APOE e4 positive			<.0001
No	3556 (57.2%)	827 (65.6%)	
Yes	1227 (19.7%)	253 (20.1%)	
Missing	1436 (23.1%)	180 (14.3%)	
Treatment Assignment			0.1523
HT	3094 (49.8%)	599 (47.5%)	
Placebo	3125 (50.2%)	661 (52.5%)	
Prior HT			0.2262
No	4259 (68.5%)	885 (70.2%)	
Yes	1958 (31.5%)	375 (29.8%)	
BMI			0.5079
< 25	1805 (29.2%)	361 (28.8%)	
25-29	2258 (36.5%)	446 (35.5%)	
30-34	1358 (22.0%)	275 (21.9%)	
35+	757 (12.3%)	173 (13.8%)	
Hypertension			<.0001
None	3235 (52.0%)	514 (40.8%)	
Current/controlled	967 (15.6%)	229 (18.2%)	
Current/uncontrolled	2015 (32.4%)	517 (41.0%)	
Prior CVD			<.0001
No	5594 (90.0%)	1079 (85.6%)	
Yes	623 (10.0%)	181 (14.4%)	

	N (%)		
Variable	**WHIMS-Main (n=6219)**	**WHIMS-SCAP (n=1260)**	**P-Value**
Diabetes			<.0001
No	5744 (92.5%)	1098 (87.2%)	
Yes	465 (7.49%)	161 (12.8%)	
Smoking			<.0001
Never Smoked	3377 (55.1%)	530 (42.8%)	
Past Smoker	2383 (38.9%)	547 (44.2%)	
Current Smoker	368 (6.01%)	161 (13.0%)	
Baseline 3MS			0.5187
< 90	636 (10.3%)	115 (9.27%)	
90-94	1415 (23.0%)	292 (23.5%)	
95-100	4111 (66.7%)	834 (67.2%)	

Abbreviations: WHIMS=Women's Health Initiative Memory Study; SCAP=Supplemental Case Ascertainment Protocol; HT=hormone therapy; BMI=body mass index; CVD=cardiovascular disease; 3MS= Modified Mini Mental State Exam.

Table 3.

Bivariate Comparison of Dementia HR's with and without inclusion of SCAP cases

	HR (95% CI)	
Variable	**WHIMS-Main (709 cases)**	**WHIMS Main plus SCAP (818 cases)**
Age at start of study		
64-69	0.28 (0.23, 0.34)	0.29 (0.24, 0.35)
70-74	0.55 (0.45, 0.66)	0.54 (0.45, 0.65)
75+	1.00	1.00
	p<0.0001	p<0.0001
Race/Ethnicity		
Black/African American	1.49 (1.15, 1.93)	1.38 (1.07, 1.77)
Hispanic/Latino	1.66 (1.05, 2.62)	1.49 (0.96, 2.33)
Other	0.88 (0.55, 1.41)	0.84 (0.54, 1.31)
White	1.00	1.00
	p=0.0034	p=0.0190
Education		
< High school	1.83 (1.36, 2.46)	1.79 (1.36, 2.36)
High school/GED	1.12 (0.92, 1.37)	1.06 (0.88, 1.28)
Some college	0.98 (0.82, 1.17)	0.97 (0.82, 1.14)
College +	1.00	1.00
	p=0.0003	p=0.0001
APOE e4 positive		
No	1.00	1.00
Yes	2.31 (1.95, 2.73)	2.22 (1.90, 2.60)
Missing	1.67 (1.36, 2.04)	1.51 (1.24, 1.82)
	p<0.0001	p<0.0001
Treatment Assignment		
HT	1.22 (1.05, 1.41)	1.12 (0.97, 1.28)
Placebo	1.00	1.00
	p=0.0092	p=0.1161
Prior HT		
No	1.06 (0.90, 1.25)	1.03 (0.89, 1.20)
Yes	1.00	1.00
	p=0.4710	p=0.6843
BMI		
< 25	1.15 (0.90, 1.48)	1.16 (0.92, 1.47)
25-29	0.98 (0.77, 1.26)	0.98 (0.77, 1.23)
30-34	0.96 (0.73, 1.25)	0.98 (0.76, 1.26)
35+	1.00	1.00
	p=0.2459	p=0.1642

	HR (95% CI)	
Variable	**WHIMS-Main (709 cases)**	**WHIMS Main plus SCAP (818 cases)**
Hypertension		
None	0.86 (0.73, 1.02)	0.77 (0.66, 0.90)
Current/controlled	0.92 (0.73, 1.16)	0.88 (0.71, 1.09)
Current/uncontrolled	1.00	1.00
	p=0.2108	p=0.0039
Prior CVD		
No	0.74 (0.58, 0.94)	0.71 (0.57, 0.89)
Yes	1.00	1.00
	p=0.0153	p=0.0030
Diabetes		
No	1.00	1.00
Yes	1.44 (1.09, 1.89)	1.64 (1.28, 2.09)
	p=0.0103	p<0.0001
Smoking		
Never Smoked	1.29 (0.89, 1.87)	1.02 (0.74, 1.40)
Past Smoker	1.14 (0.78, 1.66)	0.95 (0.69, 1.32)
Current Smoker	1.00	1.00
	p=0.1625	p=0.6632
Baseline 3MS		
< 90	3.90 (3.19, 4.77)	3.69 (3.05, 4.46)
90-94	1.42 (1.18, 1.72)	1.42 (1.19, 1.69)
95-100	1.00	1.00
	p<0.0001	p<0.0001

Abbreviations: WHIMS=Women's Health Initiative Memory Study; SCAP=Supplemental Case Ascertainment Protocol; HT=hormone therapy; BMI=body mass index; CVD=cardiovascular disease; 3MS= Modified Mini Mental State Exam.