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DEMOGRAPHIC AND HEALTH FACTORS ASSOCIATED WITH ENROLLMENT IN POST-TRIAL STUDIES: THE WOMEN'S HEALTH INITIATIVE HORMONE THERAPY TRIALS

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Abstract

Background—After clinical trials end, continued follow-up of the assembled cohort often is desirable for additional research. Factors influencing participants' decisions to consent to additional follow-up and how these shape post-trial cohorts have not been broadly studied.

Purpose—We examined how two re-enrollment campaigns and the passage of time altered features of the post-trial cohorts compared with the original Women's Health Initiative Hormone Therapy clinical trials.

Methods—We examined associations that markers of socio-demography, health, lifestyle and on-trial experiences had with re-enrollment and contrasted the characteristics of successive post-trial cohorts with those of the original enrollees.

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Results—The post-trial enrollment campaigns re-enrolled 81.1% and 82.5% of available women, respectively. Women who re-enrolled tended to have better health characteristics than those not re-enrolled. Compared to women of comparable age in the original cohort, women retained for the second post-trial follow-up less often had a history of cardiovascular disease [odds ratio OR=0.36], hypertension [OR=0.57], diabetes [OR=0.59], or measured cognitive deficit [OR=0.40]. These women more often had graduated from high school [OR=1.72] and had participated in other WHI trials [OR=1.76].

Limitations—We have examined experience with creating follow-up cohorts from participants in a single study. Thus, our findings may not apply to other cohorts and protocols.

Conclusions—Post-trial enrollment in follow-up studies can be successful; however the characteristics of the resulting cohort may differ substantially from the originally assembled group of trial participants. Collection during the original trial of potential predictors of differential re-enrollment may facilitate re-enrollment.

Keywords

Post-trial follow-up; Retention; Missing data

INTRODUCTION

Post-trial follow-up of clinical trial cohorts is conducted for many reasons. These include describing post-trial trajectories of outcomes to see whether they diminish with time [1], remain constant [2-4], or expand [5]; detecting new effects [6,7]; examining longer-term safety issues [2]; examining the downstream consequences of on-trial events [8]; examining post-trial treatment in the control group [9]; assessing the impact of withdrawal of therapy [10]; and establishing surrogate outcomes [11,12]. Post-trial follow-up also provides well-characterized cohorts for epidemiologic studies and for recruitment into new ancillary studies and clinical trials.

Much has been written about general correlates of participation in clinical research studies [13,14]. Participation is thought to be influenced by personal demographics, health status, risk factors, and socio-cultural dimensions. The cohorts that are enrolled in clinical trials, due to eligibility criteria, recruitment approaches, and volunteerism, generally do not reflect the general population and are often healthier with respect to many characteristics, as has been observed in the Women's Health Initiative (WHI) [15]. Much less has been written about correlates of participation in post-trial follow-up studies, and re-enrollment rates may vary markedly. The Physicians' Health Study, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Trial, and the Diabetes Control and Complication Trial enrolled >99%, 97% and 96% of eligible participants in a post-trial follow-up studies after five, three, and six years of on-trial follow-up, respectively [10,16,17]. Other trials have had much less success. For example, the Polyp Prevention Trial enrolled 63% of its available participants into a post-trial study after a 4-year trial [18].

The WHI has organized post-trial follow-up of its clinical trial cohorts for such reasons and provides a rich basis for examining factors that re-shape study cohorts through re-consenting

processes. We have examined how the two WHI re-enrollment campaigns, occurring in 2004-2005 and 2009-2010, and the passage of time altered broad features of the post-trial cohorts compared with the original WHI cohort, which was recruited in 1993-1998. Of the three intersecting clinical trial programs conducted by the WHI, we focus on the hormone therapy trials to have a uniform set of eligibility criteria that defined the baseline cohort. We study measures of socio-economic status, medical history, overall measures of health, and cognitive function based on the rich literature that describes how each of these factors is related to enrollment at the start of clinical trials. We also examine whether participation in other WHI trials or an ancillary study affected re-enrollment to assess the potential role of overall study burden/commitments among the subsets of women eligible for these other studies.

METHODS

The WHI Hormone Therapy (WHI HT) trials were designed to assess the impact of two regimens of postmenopausal hormone therapies compared to placebo on major clinical events, including cardiovascular disease, cancer, bone health, and stroke. Eligibility criteria and recruitment procedures for these trials have been published [19]. Postmenopausal women, 50 through 79 years of age at initial screening, were eligible for participation. A 3-month washout period was required for women who were using postmenopausal hormones when screened. Major exclusions related competing risks for major trial outcomes (invasive cancer in the past 10 years; breast cancer at any time or suspicion of breast cancer at baseline screening; acute myocardial infarction, stroke, or transient ischemic attack in the previous 6 months; known chronic active hepatitis or severe cirrhosis); safety (blood cell counts indicative of disease, severe hypertension, hypertriglyceridemia, current use of oral corticosteroids); and adherence or retention concerns (unwillingness or inability to complete baseline study requirements). Following the completion of three screening visits and a run-in, women who met all inclusion criteria and had no exclusion criteria, who remained interested in participating, and who gave written informed consent were assigned randomly with equal probability to active therapy or placebo. For women with an intact uterus, this therapy was one daily tablet that contained 0.625 mg conjugated equine estrogen and 2.5 mg medroxyprogesterone acetate (PremPro, Wyeth Pharmaceuticals, Philadelphia, Pa) or matching placebo (E+P Trial). For women who had a previous hysterectomy, therapy was one daily tablet that contained either 0.625 mg conjugated equine estrogen (Premarin, Wyeth Pharmaceuticals, Philadelphia, Pa) or matching placebo (E-Alone Trial).

Some women enrolled in the WHI HT trials were also eligible for recruitment into two other intersecting randomized controlled trials that were conducted in parallel to assess the impact of supplementation with vitamin D and calcium [20] or dietary counseling to reduce fat intake [21] on health outcomes. Women over the age of 65 and free of dementia were also eligible for recruitment into a large ancillary study – the WHI Memory Study (WHIMS) [22].

Termination of WHI hormone therapy trials

Both of the WHI HT trials were terminated prior to their planned 8.5-year durations. After a mean follow-up of 5.2 years, the E+P Trial was stopped because the overall risks exceeded benefits. The incidence of cardiovascular outcomes (cardiovascular death, myocardial infarction, stroke, and venous thromboembolic disease) and breast cancer were increased in women assigned to active treatment; however, colorectal cancers, hip fractures, and other fractures were reduced [23]. In February 2004, the E-Alone Trial also was stopped because assignment to conjugated equine estrogen increased risk for stroke and did not affect the risk for coronary heart disease over an average of 6.8 years [24]. Follow-up of women from both trials continued until 2004-2005, when the first post-trial extension study began.

Extensions 1 and 2

The WHI Extension 1 enrolled consenting participants from each of the original WHI study components for an additional five years of follow-up, from 2005 to 2010. Its purpose was to describe the longer term effects of the original interventions, to document changes in hormone use in participants from the WHI HT trials, to expand the range of scientific questions that could be addressed reliably in the WHI, and to provide an infrastructure to support additional investigations requiring some of the unique features of a very large longitudinal study of postmenopausal women. All surviving women who were not lost to follow-up or who had not withdrawn were eligible for the post-trial Extension 1. The WHI Extension 2 enrolled women for five additional years of follow-up from 2010–2015. Extension 2 was designed to extend the goals of Extension 1 in an aging cohort for an additional five years. All surviving women from Extension 1 who were not lost to follow-up or who had not withdrawn were eligible for Extension 2.

Potential predictors of re-enrollment

At WHI enrollment, socio-demographic measures and medical history were collected by self-report. Physical measures such as blood pressure, weight and height were collected at clinic visits by a standard protocol. Body mass index (BMI) in kg/m² was calculated from the measured weights and heights. Hypertension was defined as a self-report of prior diagnosis, current pharmacological treatment, or a measured blood pressure exceeding 140/90 mmHg. The modified Charlson Index [25] was used as a general measure of adverse health history and was collected at baseline and grouped according to scores of 0, 1, and >2. Participants also were asked to rate their general health according to a Likert-type scale. The Modified Mini-Mental State Exam (3MSE) [26] was collected on women aged 65 years or older at WHI enrollment and annually thereafter among the subset of 7,479 women also enrolled in the WHIMS ancillary study. Because the significance of lower 3MSE scores in these measures is dependent on education level [27], scores <88 for women with 9 or more years of formal education or <80 for women with 8 or fewer years of education were used to identify low performers. Moderate performers had scores above these cutpoints (80 and 88) through 94. High performers scored between 95 and 100. During the trial, self-report of health diagnoses, medications and hospitalizations were collected at least annually [13]. Medical histories were updated annually after the end of the trials. Medication use was recorded 3 years after the end of the trials. Health status reports were updated from their

most recent annual assessment to compare the most current status of cohorts in the analysis at different enrollment phases.

Statistical analyses

We computed the percentages of women from the WHI HT trials who re-enrolled in the WHI Extension 1 and Extension 2 and compared those percentages among important subgroups defined by socio-economic factors, health indicators, and on-trial experiences using chi-squared tests for unadjusted comparisons and logistic regression for comparison with adjustment for geographic region and markers of socio-economic status. Because our large sample size affords substantial power, to provide some control for Type 1 error among the multiple inferences we required $P < 0.001$ for the findings from univariable analyses that we chose to highlight. We compared the characteristics of the cohorts of women at the time they enrolled in Extensions 1 and 2 with the characteristics of women in a similar age range at the time when they enrolled in the WHI. To do this, we chose cohorts of women who were in the age range of 64-79 years at three points of time: original WHI enrollment, at Extension 1 re-enrollment, and at Extension 2 re-enrollment. We estimated the odds ratios that women randomly chosen from each of the post-trial cohorts, compared to a randomly selected woman at WHI enrollment, would have selected characteristics. These univariable analyses were supported with forward stepwise logistic regression to identify sets of characteristics that discriminated between randomly selected women from the cohorts at the three time points.

RESULTS

Figure 1 describes the enrollment and re-enrollment campaigns of the WHI HT trials including overall re-enrollment yields. Of the 27,247 women originally enrolled in the WHI HT trials, 25,194 (92.1%) were targeted for re-enrollment in the first WHI extension. Of these, 20,433 (81.1%) consented to re-enrollment. At the end of Extension 1, 18,794 women remained who were targeted for enrollment in Extension 2 (68.7% of the original cohort and 92.0% of those who had enrolled in Extension 1). Of these women, 15,511 (82.5%) agreed to participate in Extension 2 (56.7% of the original cohort).

Table 1 describes cohorts of women at each stage during the follow-up and re-enrollment process grouped according to their characteristics at the time of the original WHI enrollment. We assessed whether women who transitioned to the each stage differed with respect to baseline characteristics from women who did not transition to that stage from the prior stage. Each of the characteristics was associated ($P < 0.001$) with being eligible for Extension 1 (i.e. completing follow-up during the WHI trials) and/or for re-enrollment in Extension 1, except smoking and history of cancer. Each was significantly associated with being eligible and/or re-enrolling in Extension 2.

We also examined re-enrollment percentages into the Extension 1 from the trial and into Extension 2 from Extension 1 with respect to WHI treatment assignment, participation in other WHI studies, and updated markers of health that reflected both events that happened prior to and during the WHI trial follow-up (Table 2). Covariate adjustment was used to control for differences in markers of socio-economic status (age, race/ethnicity, and

education) and geographic region that were found to be related strongly to re-enrollment (see Table 1) and focused on other factors that were associated with decisions women made about re-enrollment. Re-enrollment percentages for Extension 1 were lower among women who had participated in the E-Alone trial (i.e. who had a prior hysterectomy), but did not differ between active and placebo assignment. Women who had also participated in other WHI trials more often re-enrolled in Extension 1; however participation in the WHIMS ancillary study had little influence on re-enrollment. In general, women who reported prior health conditions (cardiovascular disease, diabetes, or cancer) re-enrolled slightly less often. The factors associated with the lowest percentages of re-enrollment into Extension 1 were lower cognitive function, self-report of poor health, and history of cardiovascular disease. The factors associated with the lowest percentages of re-enrollment into Extension 2 were self-report of poor health, history of cardiovascular disease, and current smoking.

We also compared the cohort of women available for study at three phases of WHI: during their hormone therapy trial and during post-trial Extensions 1 and 2 (Table 3). These comparisons aggregate losses to follow-up and to re-enrollment. To limit the influence of age, we described women who were at a common age range of 64-79 years at the beginning of each study phase. The descriptors of these women are the most recent that were available concurrent with or prior to when they entered the stage (e.g. medical histories for women in Extension 1 and 2 were updated to include events that occurred after WHI enrollment). The mean (SD) ages of the cohorts were fairly similar: 69.6 (4.0), 71.5 (4.5), and 73.0 (3.9) respectively. Through the progressive study stages, other characteristics of the cohorts changed. In a graded fashion over time and compared to the original cohort, the typical participant in this age range was more likely to have a high school education [at Extension 2 OR=1.72], but less likely to be of a racial/ethnic minority [at Extension 2, OR=0.72], to smoke [at Extension 2, OR=0.66], or to be obese [at Extension 2, OR=0.81]. Over time, the typical participant had fewer comorbid diseases and better self-reported general health. Women who had participated in other WHI clinical trials were more likely to be represented. The most pronounced differences over time were related to history of cardiovascular disease [less likely to have cardiovascular disease at Extension 2, OR=0.36] and deficits in cognitive function [less likely to have impaired cognitive function at Extension 2, OR=0.40].

To support the univariable analyses, we applied forward stepwise logistic regression to identify a pool of important discriminators between the retained cohorts. Because baseline cognitive function measures were available for only subsets of women, we conducted parallel analyses without and with cognitive function available for selection. In order of odds ratios from the final model, the characteristics selected as being more influential among Extension 1 women compared to the WHI cohort at baseline were no history of cardiovascular disease, participation in other WHI trials, higher education, not currently smoking, majority race, no hypertension, obesity, no diabetes, good general health, and low Charlson Index. When analyses were restricted to women with baseline cognitive function assessment, the ordered factors were participation in other WHI trials, good general health, obesity, no prior cardiovascular disease, higher cognitive function, and no hypertension. The factors selected as being more influential among Extension 2 women compared to the WHI cohort at baseline were no history of cardiovascular disease, higher education, no hypertension, participation in other WHI trials, majority race, not current;y smoking, no

diabetes, obesity, and low Charlson Index. When these analyses were restricted to women with baseline cognitive function assessment, the ordered factors were low Charlson Index, higher cognitive function, and participation in other WHI trials.

DISCUSSION

Our analyses yielded three principal findings, which we discuss in turn. First, experience from the WHI demonstrated that many individuals are very willing to agree to long-term participation in studies and to transition from clinical trials to epidemiologic surveillance studies. Second, while re-enrollment levels may not be as high as retention levels during the trial, similar factors are related to each. Of the factors we studied, the most important are levels of general health and cognitive function. Third, because rates of re-enrollment and retention may vary among subgroups, analyses of post-trial data should address missing data. Minimizing the number of times women are asked to re-enroll may improve overall re-enrollment and follow-up rates.

Post-trial studies provide an opportunity to leverage the considerable effort and expense of recruiting and characterizing cohorts of volunteers for the cost-effective study of new research questions. They permit research goals to be addressed that require longer-term follow-up and may be prohibitively expensive without the upfront investment provided by the original trial. Some draw from the original randomization of the parent trial to compare the longer term consequences of its interventions. Within the WHI HT cohort, these have produced major findings on the long-term impact of conjugated equine therapies and stopping these therapies on individual components of its primary composite outcomes, such as cancers [28,29], cardiovascular disease [28], and mortality [29]; on secondary outcomes such as menopausal symptoms [30]; and on outcomes from ancillary studies such as brain volumes and cognitive function [31,32]. However, the value of a well characterized and sustained cohort of volunteers extends far beyond these aims, as noted in the introduction.

Overall, re-enrollment percentages in observational extensions of the WHI Hormone Therapy trials exceeded 80% at each extension, signaling the commitment women had towards volunteerism and the ability of the study staff and investigators to engender and facilitate this commitment. Re-enrollment percentages were lower than retention percentages (based on refusals) both on-trial and within the time frames of the extensions (which exceeded 90%), indicating that the decision to re-enroll is different from a decision about continued involvement in an ongoing study. Re-enrollment percentages within the WHI trials were fostered through individual contact and repeated attempts to engage all women to participate in the extension studies. The WHIMSY ancillary study was able to achieve high levels of re-enrollment despite its primary negative findings for conjugated equine estrogen therapies [33].

The WHI experience demonstrates that some of the same features that affect initial enrollment in clinical trials and participant retention also affect post-trial re-enrollment. These include socio-demographic markers and medical history. Among the strongest of these factors that we considered in the WHI were markers of health, perceived health, and cognitive function, both in univariable and multivariable analyses. This finding underscores

the importance of tailoring re-enrollment practices to accommodate the needs of women with increasing health-related barriers and cognitive deficits. These findings also signal the importance to expanding data collection modes to include, as may be necessary, home visits, telephone or mail-based assessments, and information from proxies. The higher rates of attrition among less educated women and those from traditionally underrepresented minorities underscore the importance of additional research on better ways to continue to engage these volunteers in post-trial follow-up studies. Importantly, we found that participation in an ancillary study was not associated with poorer retention and participation in other WHI trials was associated with greater re-enrollment. These additional engagements did not appear to lead to participant burn out and may mark women with higher levels of commitment.

The WHI post-trial cohorts grew increasingly healthier and more cognitively intact from baseline through the two extensions, as evidenced by our comparisons of comparably aged cohorts, likely reflecting the successive winnowing of less healthy women through attrition and refusal to re-consent to longer follow up. At each stage, the women who ceased being followed had poorer health and were at higher risk for disease related events. This finding has many consequences for post-trial studies. The age-specific event rates observed on-trial for health outcomes may be higher than those that are encountered post-trial because women who continue to be followed are healthier. This tendency may also alter any projections of long-term (i.e. post-trial) cost benefit and, perhaps, estimates of post-trial safety. If post-trial cohorts over-represent participants who are less likely to have events or to require larger health care expenditures, projections of cost benefit may be under-estimated. If the range of health is compressed during re-enrollment, risk factor relationships may be altered. In post-trial studies in which the control group is offered active therapy, its benefits may differ from those observed on-trial because the post-trial cohort may not be similar to the participants who were assigned to active therapy at baseline during the trial.

Our findings have other important implications for the conduct of studies with planned post-trial follow-up. First, aggressive and targeted re-enrollment may be valuable to preserve as representative a cohort as possible. Ideally, preparations should begin well before the cessation of trials, to prepare trial participants for the prospect of post-trial studies and to underscore their importance. During the trial, data should be collected to identify those at greatest risk for loss to follow-up and for use in analyses to address missing data. Our analyses indicate that it may be critically important to collect markers of self-perceived health, medical history, and cognitive function. Additionally, lower event rates because of the winnowing of participants who have poorer health and who are increased risk for disease outcomes may sap power from post-trial studies. We observed that substantial numbers of WHI participants were lost during each re-consenting campaign; thus, it may be important to maximize the time span for which consent for post-trial studies is obtained, rather than mounting a series of shorter-term extensions that require re-consent. The differential follow-up that we observed has important implications for statistical analyses. Ignoring lost and missing follow-up data is likely to bias estimates and introduce discontinuities in longer term trends. Analytical approaches must assess factors predictive of missing data. For example, we found little difference in the retention rates among women assigned to active versus placebo therapies, so that post-trial comparisons comparing treatment arms may not

be biased. However, we found differential re-enrollment between the E-Alone versus E+P trial cohorts so that comparisons between the relative post-trial effects of these active therapies may be biased if potential missing data mechanisms were ignored. Fortunately, great progress has been made in statistical approaches to dealing with missing data. With the rich resource of having sequences of data available on individuals prior to the time when they are lost to follow-up, the breadth of available approaches and the strength of their performance are increased [34].

Limitations

We have examined a single study whose conduct and results have received considerable media attention. Our findings may not apply to other trial cohorts and protocols.

Conclusions

Post-trial enrollment in follow-up studies can be successful and greatly expand the breadth of scientific findings. However, the characteristics of the resulting cohort may differ substantially from the originally assembled group of trial participants. Collection during the original trial of potential predictors of differential re-enrollment may facilitate re-enrollment.

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Figure 1.
Enrollment and re-enrollment campaigns of the WHI HT clinical trials

Table 1

Percentages of Women Who Re-enrolled at Extension 1 and Extension 2, overall and by baseline characteristics.

	Enrolled in WHI N	Eligible for Extension 1 N	Enrolled in Extension 1 N	Eligible for Extension 2 N	Enrolled in Extension 2 N
	(% of total)	(% of enrolled) P-value ¹	(% of eligible) P-value ²	(% of enrolled in Extension 1) P-value ³	(% of eligible) P-value ⁴
Total	27347	25194 (92.1)	20433 (81.1)	18794 (92.0)	15511 (82.5)
Age					
50-54	3420 (12.5)	3242 (94.8)	2638 (81.4)	2557 (96.9)	2172 (84.9)
55-59	5413 (19.8)	5115 (94.5)	4211 (82.3)	4037 (95.9)	3487 (86.4)
60-64	6268 (22.9)	5863 (93.5)	4829 (82.4)	4529 (93.8)	3841 (84.8)
65-69	6092 (22.3)	5578 (91.6)	4616 (82.8)	4191 (90.8)	3435 (82.0)
70-74	4293 (15.6)	3845 (89.6)	3039 (79.0)	2613 (86.0)	1984 (75.9)
75-79	1861 (6.8)	1551 (83.3)	1100 (70.9)	867 (78.8)	592 (68.3)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
Education					
0-8 years	710 (2.6)	641 (90.3)	350 (54.6)	319 (91.1)	188 (58.9)
Some high school	1459 (5.4)	1289 (88.3)	882 (68.4)	793 (89.9)	552 (69.6)
High school diploma/GED	5645 (20.8)	5186 (91.9)	4203 (81.1)	3827 (91.1)	3089 (80.7)
School after high school	11039 (40.7)	10140 (91.9)	8232 (81.20)	7557 (91.8)	6223 (82.4)
College degree or higher	8298 (30.6)	7757 (93.4)	6623 (85.4)	6168 (93.1)	5364 (87.0)
		P<0.0001	P<0.0001	P=0.0002	P<0.0001
Race/ethnicity					
White	22030 (80.6)	20311 (92.2)	16919 (83.3)	15525 (91.8)	13150 (84.7)
Black	2738 (10.0)	2487 (90.8)	1886 (75.8)	1754 (93.0)	1274 (72.6)
Hispanic	1537 (5.6)	1448 (94.2)	922 (63.7)	864 (93.7)	586 (67.8)
American Indian	130 (0.5)	114 (87.7)	79 (69.3)	75 (94.9)	64 (85.3)
Asian/Pacific Islander	527 (1.9)	478 (90.7)	363 (75.9)	328 (90.4)	239 (72.9)
Unknown	385 (1.4)	356 (92.5)	264 (74.2)	248 (93.9)	198 (79.8)
		P=0.0009	P<0.0001	P=0.05	P<0.0001
U.S. Region					
Northeast	5952 (21.7)	5536 (93.0)	4789 (86.5)	4386 (91.6)	3628 (82.7)
South	7186 (26.3)	6586 (91.7)	5190 (78.8)	4818 (92.8)	3710 (77.0)
Midwest	6721 (24.6)	6219 (92.5)	5114 (82.2)	4715 (91.7)	4042 (85.7)
West	7488 (27.4)	6853 (91.5)	5340 (77.9)	4875 (91.3)	4131 (84.7)
		P=0.0029	P<0.0001	P=0.02	P<0.0001
Smoking					

	Enrolled in WHI N	Eligible for Extension 1 N	Enrolled in Extension 1 N	Eligible for Extension 2 N	Enrolled in Extension 2 N
Never	7264 (26.7)	6695 (92.2)	5503 (82.8)	5062 (92.0)	4240 (83.8)
Former	9540 (35.1)	8817 (92.4)	7173 (81.4)	6611 (92.2)	5495 (83.1)
Current	10396 (38.2)	9548 (91.8)	7648 (80.1)	7025 (91.5)	5695 (81.1)
		P=0.33	P=0.003	P=0.78	P=0.0002
Body mass index, kg/m ²					
< 25	13605 (50.3)	12750 (93.7)	10387 (81.5)	9688 (93.3)	8000 (82.6)
25 -< 30	10595 (39.2)	9704 (91.6)	7955 (82.0)	7287 (91.6)	6100 (83.7)
30	2831 (10.5)	2465 (87.1)	1833 (76.4)	1631 (89.0)	1275 (78.2)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
History of cardiovascular disease					
No	25208 (92.2)	23370 (92.7)	19067 (81.6)	17637 (92.5)	14633 (83.0)
Yes	2139 (7.8)	1824 (85.3)	1366 (74.9)	1157 (84.7)	878 (75.9)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
History of hypertension					
Never	16730 (66.5)	15300 (91.5)	12623 (82.5)	11783 (93.3)	9850 (83.6)
Untreated	2259 (9.0)	2072 (91.7)	1641 (79.2)	1489 (90.7)	1187 (79.7)
Treated	6174 (24.5)	5544 (89.8)	4363 (78.7)	3854 (88.3)	3083 (80.0)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
History of treated diabetes					
No	25770 (94.3)	23858 (92.6)	19461 (81.6)	17974 (92.4)	14932 (83.1)
Yes	1556 (5.7)	1315 (84.5)	959 (72.9)	810 (84.5)	571 (70.5)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
History of cancer					
No	26233 (96.8)	24199 (92.2)	19650 (80.8)	18101 (92.1)	14941 (82.5)
Yes	874 (3.2)	789 (90.2)	622 (78.8)	550 (88.4)	459 (83.5)
		P=0.03	P=0.09	P=0.0008	P=0.58
Charlson co-morbidity index					
0	19153 (72.2)	17882 (93.4)	14757 (82.5)	13771 (94.5)	11521 (83.7)
1	5329 (20.1)	4810 (90.3)	3805 (79.1)	3372 (88.6)	2704 (80.2)
2	2056 (7.7)	1767 (85.9)	1321 (74.8)	1150 (87.1)	901 (78.4)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001
Cognitive function (3MSE) ⁵					
95-100	5811 (64.9)	5368 (92.4)	4519 (84.2)	4057 (89.8)	3346 (82.5)
> lower cut-point - 94	2354 (26.3)	2108 (89.5)	1611 (76.4)	1395 (86.6)	1035 (74.2)
lower cut-point	786 (8.8)	658 (83.7)	452 (68.7)	371 (82.1)	240 (64.7)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001

	Enrolled in WHI N	Eligible for Extension 1 N	Enrolled in Extension 1 N	Eligible for Extension 2 N	Enrolled in Extension 2 N
Self-report of general health					
Excellent	4314 (15.9)	4107 (95.2)	3556 (86.6)	3365 (94.6)	2960 (88.0)
Very good	11196 (41.2)	10473 (93.5)	8805 (84.1)	8185 (93.0)	6920 (84.5)
Good	9234 (34.0)	8361 (90.5)	6568 (78.6)	5936 (90.4)	4707 (79.3)
Fair	2259 (8.3)	1950 (86.3)	1308 (67.1)	1127 (86.2)	785 (69.7)
Poor	155 (0.6)	128 (82.6)	76 (59.4)	69 (90.8)	50 (72.5)
		P<0.0001	P<0.0001	P<0.0001	P<0.0001

¹ Comparison of percentages eligible for Extension 1 among subgroups

² Comparison of Extension 1 re-enrollment percentages among subgroups

³ Comparison of percentages eligible for Extension 2 among subgroups

⁴ Comparison of Extension 2 re-enrollment percentages among subgroups

⁵ Modified MiniMental State Examination--Only collected on women 65 years or older at screening

Table 2

Re-enrollment rates for Extensions 1 and 2 by current health measures, treatment arm, and participation in the WHI Diet Modification trial, the WHI Calcium/Vitamin D trial, or the WHI Memory Study, with adjustment for SES and clinical center.

	Covariate-Adjusted¹ Enrollment Rate (%)	
	Into Extension 1 From Trial	Into Extension 2 From Extension 1
WHI treatment assignment		
E-alone	78.9	82.6
E-alone placebo	79.2	82.2
E+P	82.6	82.1
E+P placebo	82.3	83.4
	P<0.0001	P=0.28
In WHIMS ²		
No	81.2	82.4
Yes	80.8	83.1
	P=0.42	P=0.24
In Dietary Modification or Calcium/Vitamin D trials		
No	75.1	80.5
Yes	83.6	83.4
	P<0.0001	P<0.0001
Prior cardiovascular disease		
No	82.3	83.6
Yes	75.3	77.5
	P<0.0001	P<0.0001
Prior treated hypertension		
No	81.5	82.7
Yes	80.9	82.4
	P=0.29	P=0.69
Prior treated diabetes		
No	81.5	83.3
Yes	78.6	79.5
	P<0.0001	P<0.0001
Prior cancer		
No	81.3	83.0
Yes	79.1	80.5
	P=0.004	P=0.001
Cognitive function (3MSE) ³		

	Covariate-Adjusted¹ Enrollment Rate (%)	
	Into Extension 1 From Trial	Into Extension 2 From Extension 1
95-100	89.5	84.1
> lower cut-point - 94	84.1	80.0
lower cut-point	68.1	89.1
	P<0.0001	P=0.03
Self-report of general health		
Excellent	92.7	85.9
Very good	91.8	87.2
Good	90.0	82.7
Fair	86.2	73.7
Poor	74.5	51.2
	P<0.0001	P<0.0001
Smoking		
Never/past	84.1	83.3
Current	81.1	77.6
	P=0.001	P<0.0001
Body mass index (BMI), kg/m ²		
<25	82.4	82.3
25-29	82.9	83.7
30	82.1	82.2
	P=0.36	P=0.03

¹ Adjusted for measures of socio-economic status (linear age at screening, education, race/ethnicity) and clinical center

² Limited to women 65 years or older

³ Only collected on women ages 65 at screening.

Table 3

Odds that a randomly selected woman from the post-trial cohorts will exhibit selected characteristics compared to a randomly selected woman from the on-trial cohort.

Characteristic	Extension 1 Cohort Compared to On-Trial Cohort	Extension 2 Cohort Compared to On-Trial Cohort
	Odds Ratio	Odds Ratio
High school graduate	1.37	1.72
Racial/ethnic minority	0.80	0.72
Current smoker	0.74	0.66
Obese (BMI ≥ 30 kg/m ²)	0.82	0.81
History of		
Cardiovascular disease	0.56	0.36
Hypertension	0.73	0.57
Diabetes	0.77	0.59
Cancer	0.83	0.78
General health		
Charlson index ≥ 2	0.71	0.60
Self-report “fair” or “poor”	0.75	0.70
Cognitive deficit ¹	0.72	0.40
Assignment to WHI active therapy	1.02	1.04
Participation in		
Other WHI trials	1.50	1.76
WHIMS ancillary study ²	0.97	0.96

¹ 3MSE score below WHIMS dementia screening cutpoint

² Of those 65 years and older at WHI enrollment (i.e. age-eligible for WHIMS)