Published in final edited form as:

Int J Geriatr Psychiatry. 2012 February ; 27(2): 205–214. doi:10.1002/gps.2714.

Ascertaining dementia-related outcomes for deceased or proxy-dependent participants: an overview of the Women's Health Initiative Memory Study supplemental case ascertainment protocol[†]

Sarah A. Gaussoin¹, Mark A. Espeland¹, John Absher⁴, Barbara V. Howard³, Beverley M. Jones², and Stephen R. Rapp^{1,2}

¹Division of Public Health Science, Wake Forest University School of Medicine, Winston-Salem, NC, USA

²Department of Psychiatry, Wake Forest University School of Medicine, Winston-Salem, NC, USA

³MedStar Research Institute, Hyattsville, MD, USA

⁴Absher Neurology, Greenville, SC, USA

Abstract

Objective—The aim of the study was to compare a two-staged clinic-based standardized protocol with a supplemental proxy-based protocol.

Methods—The Women's Health Initiative Memory Study enrolled 7479 women, aged 65–79 years and free of dementia, in a clinical trial of postmenopausal hormone therapy who were followed for up to 13 years with annual two-staged clinic-based standardized protocols to identify incidence of probable dementia. A supplemental proxy-based protocol, involving telephone administration of the dementia questionnaire, was designed to assess the cognitive status of women who could no longer attend clinic visits because they died ($n = 1058$) or became dependent ($n = 228$). Chi-squared tests were used to compare characteristics of women eligible for proxy-based versus clinic-based assessment. Risk factor relationships were described using proportional hazards regression.

Results—Women who were eligible for proxy-based assessments tended to have worse cognitive impairment risk factor profiles and had higher rates of probable dementia (15.2% vs 3.5%) than clinic-assessed participants. Augmenting the clinic-based cases with those identified from proxy interviews reduced undercounting and materially altered observed relationships that years since menopause, smoking status, diabetes, and prior use of hormone therapy had with incidence of probable dementia.

[†]For the Women's Health Initiative Memory Study

Copyright © 2011 John Wiley & Sons, Ltd.

Correspondence to: S. A. Gaussoin, sgausoi@wfubmc.edu.

ClinicalTrials.gov Identifiers: NCT00000611 (WHIMS)

Conflict of interest

None declared.

Conclusions—Although proxy interviews were successful in reducing biases in estimated incidence rates and risk factor relationships, it is unlikely that they will fully eliminate many biases. Proxy-based assessments are necessary in longer term studies to reduce undercounting of dementia cases and to characterize risk factor relationships.

Keywords

attrition; cognitive impairment; dementia; women's health; missing data

Introduction

Conducting clinical research in older individuals has many challenges, including higher rates of missing data (Lebowitz, 2004). Because lost follow-up can be linked to comorbidities or mortality, which are in turn often related to study outcomes, ignoring missing data may bias findings (Ferrucci *et al.*, 2004). A common approach is to use informants to provide information on participants who are compromised or deceased. For trials involving cognitive outcomes, several methods for using proxy respondents have been proposed and implemented (Jorm and Jacomb, 1989; Carr *et al.*, 2000; Bernstein and Remsburg, 2007). Among the more frequently used is the Dementia Questionnaire (DQ) (Silverman *et al.*, 1986).

Although the validity, sensitivity, and specificity of the DQ has been established (Kawas *et al.*, 1994; Gallo and Breitner, 1995; Ellis *et al.*, 1998; Khachaturian *et al.*, 2000; Hayden *et al.*, 2003; Crooks *et al.*, 2005), how its use affects the results of clinical studies is less understood. Capturing additional cases of cognitive impairment and dementia through proxy interviews is expected to reduce undercounting. Participants for whom proxy responses are necessary to determine cognitive status are likely to have different clinical and possibly demographic characteristics than other participants; because of this, the cases of cognitive impairment and dementia detected through proxy interviews may, when pooled with cases identified directly from participant assessments, have also the potential to alter observed associations with risk factors.

To examine whether this may happen, we used data from long-term follow-up of a large cohort of women from the Women's Health Initiative Memory Study (WHIMS) clinical trials. We contrast the characteristics of women for whom cognitive status was directly evaluable based on clinic-based assessment with those of women for whom proxy interviews were necessary. Among these latter women, we further contrast characteristics of individuals for whom proxy responses were successfully obtained with those for whom it was not obtained. We examine the impact of proxy-based data on estimates of incidence and on relationships with risk factors and draw conclusions on the importance of including proxy interviews.

Methods

The WHIMS randomized controlled clinical trials tested the effect of 0.625 mg/day of conjugated equine estrogens (CEE) alone (E-alone) and in combination with 2.5 mg/day of the progestin medroxyprogesterone acetate (CEE + MPA; E + P) on the incidence of

probable dementia and other cognitive outcomes. Their study design, eligibility criteria, and recruitment procedures have been reported previously (Prentice *et al.*, 1998; Shumaker *et al.*, 1998). Volunteers were recruited from the Women's Health Initiative (WHI) hormone trials, in which women were randomly assigned with equal probability to active therapy (E-Alone if prior hysterectomy; E + P if no hysterectomy) or matching placebo. A 3-month washout from any current hormone therapy was required prior to baseline evaluation. Exclusion criteria were based on competing risks (medical conditions with a predicted survival of less than 3 years), safety (e.g. prior breast cancer at any time or breast cancer suspected at baseline screening, other invasive cancer within the past 10 years except non-melanoma skin cancer, low hematocrit, or platelet count), adherence and retention factors (e.g. dementia, unwillingness, or inability to complete study requirements, alcoholism, performance during a pill run-in), and probable dementia according to the WHIMS protocol (in the following text). The National Institutes of Health and Institutional Review Boards for all participating institutions approved protocols and consent forms. Informed written consent was obtained from all participants. The WHI CEE + MPA trial was terminated earlier than planned in July 2002 because of significantly more non-cognitive adverse events associated with hormone therapy compared with placebo (Rossouw *et al.*, 2002). In 2004, the WHI CEE-alone trial was terminated early because the National Institutes of Health believed that the excess risk of stroke in the active hormone group was unacceptable in healthy women in the absence of benefit for coronary heart disease, the primary outcome of the WHI hormone therapy trials (Anderson *et al.*, 2004). At the conclusion of each trial, assigned study medications were terminated, and women were informed of the study findings and encouraged to discontinue the use of postmenopausal hormone therapy. The participants were continued to be followed after the end of each trial with annual assessments.

Results from the clinic-based WHIMS assessment (Shumaker *et al.*, 2003, 2004) indicated that CEE and CEE + MPA therapy increases women's risk for probable dementia in women 65 years or older. The participants who have died or ceased full follow-up without a determination of their cognitive status were censored in the original analyses that these trials reported. These women may represent subpopulations that are at greater risk for cognitive impairment and dementia. Removing them from the study may have resulted in biased (i.e. under) estimates of incidence. The WHIMS supplemental case ascertainment protocol (SCAP) was conducted to identify cases of probable dementia and mild cognitive impairment (MCI), in the deceased and proxy-dependent participant groups, which have been missed by our clinic-based protocols.

Classifications based on clinic assessments

The WHIMS participants were administered annually the Modified Mini-Mental State Examination (3MSE) (Teng and Chui, 1987). Women scoring below preset cut points based on educational level proceeded to a second stage that included the Consortium for the Established Registry of Alzheimer's Disease neuropsychological battery (Morris *et al.*, 1989) and questionnaires for the participants and a knowledgeable friend or family member regarding acquired cognitive and behavioral deficits, functional status, and neuropsychiatric symptoms (Espeland *et al.*, 2004). Experienced local physician specialists at each study site reviewed these and all prior data, completed structured clinical neurological evaluations, and

classified women as having no cognitive impairment, MCI, or probable dementia based on the DSM-IV criteria (American Psychiatric Association, 1994). If probable dementia was suspected, brain computed tomography and laboratory blood tests were used to rule out possible reversible causes of the cognitive impairment. 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 (Shumaker *et al.*, 2004). Regardless of these findings, the annual 3MSE testing continued. The WHIMS cases include all on-trial and post-trial cases adjudicated through October 2009.

Classifications based on proxy interviews

As of October 2009, 902 women were eligible for the proxy-based classification of cognitive impairment. These women had not been previously classified as having probable dementia based on clinic assessments, had died or otherwise terminated follow-up, and had been followed by one of the 38 of 39 clinical sites continuing to participate in the WHIMS. The proxy-based protocol uses information from persons named by the participant to be contacted in the event that the participant has died or ceased full follow-up in the WHIMS study. The proxies were family members or close friends and initially contacted by the clinic to either agree or refuse further contact. Upon agreement, attempts to contact the proxy for completion of the DQ were conducted by the WHIMS coordinating center. The DQ (Silverman *et al.*, 1986) is a standardized, interviewer-administered questionnaire assessing cognitive and behavioral changes and their course, functional status, and dementia-related health events. It is administered to a knowledgeable informant in person or by telephone. The DQ has been previously validated against a clinic-based evaluation (Kawas *et al.*, 1994; Ellis *et al.*, 1998) and, when used with the 3MSE, has high sensitivity and specificity (Gallo and Breitner, 1995; Khachaturian *et al.*, 2000; Hayden *et al.*, 2003; Crooks *et al.*, 2005).

Similar to the WHIMS, 10% of normal cases, 50% of MCI cases, and all probable dementia cases underwent central adjudication by a committee composed of three board certified physicians (two neurologists, one geropsychiatrist) who were experienced in diagnosing dementia. Each case was assigned to two adjudicators and who reviewed all data from prior (including annual cognitive scores and any clinic-based evaluations) and current assessments who assigned a classification of normal, MCI, or probable dementia. In instances of disagreement, discussion between adjudicators occurred until consensus classification was finalized. If the dyadic discussion failed to produce a consensus, the case was referred to the full adjudication committee for final consensus. The cases and adjudicator assignments were randomly selected. As of October 2009, the proxy agreement status of 373 (40%) of the 902 women eligible for proxy-based classifications had not been resolved.

Statistical methods

Chi-squared tests were used to identify differences between the 902 women eligible for proxy-based classifications, comparing them with the remainder of the WHIMS women with respect to the risk factors for cognitive impairment. Comparisons were also made between women who were classified with probable dementia and MCI using clinic-based and proxy-

based assessments. Proportional hazards regression was used to describe bivariate associations that risk factors had with times until incidence of probable dementia when analyses were based solely on clinic-based cases and, separately, when analyses included both clinic-based and proxy-based assessments. For clinic-based cases, the ascribed date of event was the date of the annual cognitive screening examination (3MSE) that triggered the progression to further testing. For proxy-based cases involving women who had died, the ascribed date of the event was the midpoint between the date of the last annual screening and the date of death. The ascribed event date for other proxy-based assessments was the midpoint between the date of the last 3MSE and the date of the proxy interview. Follow-up times for other women were censored at the date of the last 3MSEs, the date of their death, or the date of their proxy interview, whichever was most recent. We also fitted models in which follow-up time was uniformly censored at the date of the last 3MSE; these did not result in any material differences and were not reported.

Results

Figure 1 portrays the disposition of women who were eligible for proxy-based assessments. The participants were eligible during the trial if they were at a clinic participating in SCAP and were post-trial eligible if they were at a SCAP clinic and consented to the WHIMS extension study. Of those eligible participants, 583 arose from deaths during the trial and 223 from deaths that occurred during post-trial follow-up; 50 occurred from women who had relinquished direct participation during the trial and 46 from women who relinquished direct participation during post-trial follow-up.

Table 1 compares the distribution of risk factors for cognitive impairment at the time of the WHI enrollment for women who were eligible for proxy-based assessments compared with others. Those eligible for proxy-based assessments tended to be older, had more postmenopausal years, were Caucasian, had lower socioeconomic status, were current or past smokers, had hypertension, had a history of cardiovascular disease, had diabetes, and had higher baseline 3MSE scores (all $p < 0.05$).

There were 256 women for whom proxy-based interviews were completed and 423 who were eligible but for whom interviews could not be completed, that is the proxy declined ($n = 266$) or could not be contacted after repeated attempts ($n = 157$). All variables examined demonstrated that the women for whom the DQ was not completed were representative of those women for whom interview completion was successful, with the exception of self-reported family income. Women for whom proxy interviews could not be completed tended to have lower family incomes at the WHI enrollment ($p = 0.028$). As portrayed in Figure 2, proxy-based cases of probable dementia tended to occur earlier in follow-up than in clinic-based assessments.

Table 2 compares the risk factor profiles of women whose classification of probable dementia was proxy-based with those for whom it was clinic-based. Proxy-based compared with clinic-based probable dementia tended to occur in women who had longer postmenopausal years, were current or past smokers, had diabetes, or had used hormone therapy before the trial. Table 3 compares the associations these risk factors had with clinic-

based cases of probable dementia to those from the analyses of all cases (i.e. from both clinic-based and proxy-based assessments). This portrays how these risk factor profiles would have been influenced if proxy-based assessments were not performed. Including proxy-based cases reduced the strength of the association between probable dementia and the years since menopause, but it remained strongly significant. Their inclusion also reduced the strength of associations with smoking status and with prior hormone therapy, in both cases moving associations from being within borderline statistical significance ($p < 0.10$) to non-significance ($p > 0.20$). These new cases, however, increased the strength of associations with diabetes into the range of statistical significance.

Discussion

Missed clinic-based assessments accumulate during longer term studies. This issue is of increased importance in studies conducted in older cohorts, for which age-related comorbidities and other barriers to participation may lead to high rates of attrition (Ellenberg, 2004; Ferrucci *et al.*, 2004) and under-counts of events (Desmond *et al.*, 1998; Izmirlian *et al.*, 2000; Harel *et al.*, 2007). Studies with cognitive outcomes present particular challenges in that the outcomes of interest are strongly associated with many reasons for attrition and missed data. This has spurred the development of alternative strategies for data collection that rely, in part, on proxy informants to provide information regarding observed changes, such as the DQ (Kawas *et al.*, 1994), which has been validated for this purpose and used in several prior studies (Ellis *et al.*, 1998; Khachaturian *et al.*, 2000; Hayden *et al.*, 2003; Crooks *et al.*, 2005; Rocca *et al.*, 2007).

In the WHIMS program, telephone-based proxy interviews have been used to determine the status of 24% of the women for whom clinic-based assessments had been terminated. These have identified an additional 17% of dementia cases so far. Their influence on dementia incidence rates emerged after 4–5 years of follow-up and has grown as follow-up continues. The proxy-based interviews identified relatively few additional cases of MCI. This may be due to the more restricted item content on the DQ compared with the WHIMS protocol. The DQ was specifically designed to include items with high specificity for dementia (Ellis *et al.*, 1998; Crooks *et al.*, 2005). Because the WHIMS follow-up is ongoing, we cannot yet project accurately the overall influence of the proxy-based protocol at this time.

Not surprisingly, we found that women for whom clinic-based assessments were no longer possible differed from other women according to many health characteristics, including many risk factors for cognitive impairment. In general, these women had markers for poorer overall health. The proxy-based women were less ethnically distributed than the clinic-based women as were those that agreed to complete the DQ. It is important to increase minority recruitment and participation as it has been shown that minorities access diagnostic services later than Caucasians and, once diagnosed, are less likely to access medications, clinical trials, and 24-h care (Cooper *et al.*, 2010). As others have noted, ignoring these women would be expected to yield biased characteristics of risk factor relationships (Gao and Hui, 2000; Izmirlian *et al.*, 2000). We found, for example, that the dementia cases identified through proxy interviews compared with clinic-based assessments had different relationships with the years since menopause, history of smoking, diabetes, and prior use of

hormone therapy. These cases tended to occur in women who had longer durations of postmenopausal years, had never smoked, who did not have a history of diabetes, and did not indicate prior use of hormone therapy. Not including these cases altered the risk factor relationships with these factors. Their inclusion attenuated associations with smoking and prior use of hormone therapy but strengthened relationships with postmenopausal years and diabetes. Because the proxy interviews yielded relatively few MCI cases, we have limited ability to examine how including these cases alter risk factor relationships; however, it does appear that they may alter relationships with baseline cognitive function.

On the basis of these findings, we expect that although the proxy interviews will be successful in reducing biases in estimated incidence rates and risk factor relationships, it is unlikely that they will fully eliminate many biases. We were unable to complete many interviews, and the characteristics of women differed according to whether interviews were completed or not. Uncompleted interviews were likely to arise from women who were in poorer overall health, who were members of a minority ethnic/race, and who had reported lower family incomes. More sophisticated analytical approaches will be required to reduce biases in incidence rates and relationships further; these must be sensitive to non-ignorable missing data and may incorporate prior sequences of clinic-based measures (Tsiatis and Davidian, 2001, 2004; Song *et al.*, 2002a, 2002b).

Our findings have important implications for the design of future studies. If clinic-based assessments are included, it is important to take measures to make these as complete as possible because subsequent proxy-based assessments may not be sufficient to restore missing data. This may include more frequent screening and more efficient and compressed assessments. It may be important to cultivate stronger relationships with proxies throughout follow-up by corecruiting them during enrollment and regularly engaging their involvement.

Limitations

Our study is not without limitations. Although the validity of proxy-based ascertainment approaches has been established (Kawas *et al.*, 1994; Ellis *et al.*, 1998), it is not interchangeable with clinic-based assessments so that the cases of cognitive impairment arising from the two protocols may differ and have different risk factor relationships. We were unable to obtain proxy responses in many instances for a variety of reasons, including inability to establish contact and refusal. Because our follow-up is ongoing, we are not able to provide complete assessments of the success and impact of proxy-based assessments. Women in the WHIMS, as appropriate candidates and volunteers for a clinical trial of postmenopausal hormone therapy, do not represent the general population, so that it is not clear how our findings might generalize to other cohorts or settings. We report the affects of proxy assessments on only bivariate associations; however, they certainly would expect to also influence multivariate relationships, as well.

Conclusion

Vigorous campaigns to collect information from proxies are necessary to reduce ascertainment biases, especially in longer term studies. These require separate consenting processes and regular updating of information. The WHIMS proxy-based program is a

successful example. Although potentially useful in reducing biases, these campaigns are unlikely to be adequate to eliminate biases fully.

Acknowledgments

The Women's Health Initiative program is funded by the National Heart, Lung, and Blood Institute, U.S. Department of Health and Human Services. Wyeth Pharmaceuticals provided the study drug and the placebo to the WHI trial. The Women's Health Initiative Memory Study was funded by Wyeth Pharmaceuticals, Inc., St. Davids, PA, USA; Wake Forest University; and the National Heart, Lung, and Blood Institute.

Program Office: (National Heart, Lung, and Blood Institute, Bethesda, MD, USA) Elizabeth Nabel, Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller.

Clinical Coordinating Center: (Fred Hutchinson Cancer Research Center, Seattle, WA, USA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Charles L. Kooperberg, Ruth E. Patterson, Anne McTiernan; (Medical Research Labs, Highland Heights, KY, USA) Evan Stein; (University of California at San Francisco, San Francisco, CA, USA) Steven Cummings.

Clinical Centers: (Albert Einstein College of Medicine, Bronx, NY, USA) Sylvia Wassertheil-Smoller; (Baylor College of Medicine, Houston, TX, USA) Aleksandar Rajkovic; (Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA) JoAnn E. Manson; (Brown University, Providence, RI, USA) Charles B. Eaton; (Emory University, Atlanta, GA, USA) Lawrence Phillips; (Fred Hutchinson Cancer Research Center, Seattle, WA, USA) Shirley Beresford; (George Washington University Medical Center, Washington, D.C., USA) Lisa Martin; (Los Angeles Biomedical Research Institute at Harbor—UCLA Medical Center, Torrance, CA, USA) Rowan Chlebowski; (Kaiser Permanente Center for Health Research, Portland, OR, USA) Yvonne Michael; (Kaiser Permanente Division of Research, Oakland, CA, USA) Bette Caan; (Medical College of Wisconsin, Milwaukee, WI, USA) Jane Morley Kotchen; (MedStar Research Institute/Howard University, Washington, D.C., USA) Barbara V. Howard; (Northwestern University, Chicago/Evanston, IL, USA) Linda Van Horn; (Rush Medical Center, Chicago, IL, USA) Henry Black; (Stanford Prevention Research Center, Stanford, CA, USA) Marcia L. Stefanick; (State University of New York at Stony Brook, Stony Brook, NY, USA) Dorothy Lane; (The Ohio State University, Columbus, OH, USA) Rebecca Jackson; (University of Alabama at Birmingham, Birmingham, AL, USA) Cora E. Lewis; (University of Arizona, Tucson/Phoenix, AZ, USA) Cynthia A Thomson; (University at Buffalo, Buffalo, NY, USA) Jean Wactawski-Wende; (University of California at Davis, Sacramento, CA, USA) John Robbins; (University of California at Irvine, CA, USA) F. Allan Hubbell; (University of California at Los Angeles, Los Angeles, CA, USA) Lauren Nathan; (University of California at San Diego, LaJolla/Chula Vista, CA, USA) Robert D. Langer; (University of Cincinnati, Cincinnati, OH, USA) Margery Gass; (University of Florida, Gainesville/Jacksonville, FL, USA) Marian Limacher; (University of Hawaii, Honolulu, HI, USA) J. David Curb; (University of Iowa, Iowa City/Davenport, IA, USA) Robert Wallace; (University of Massachusetts/Fallon Clinic, Worcester, MA, USA) Judith Ockene; (University of Medicine and Dentistry of New Jersey, Newark, NJ, USA) Norman Lasser; (University of Miami, Miami, FL, USA) Mary Jo O'Sullivan; (University of Minnesota, Minneapolis, MN, USA) Karen Margolis; (University of Nevada, Reno, NV, USA) Robert Brunner; (University of North Carolina, Chapel Hill, NC, USA) Gerardo Heiss; (University of Pittsburgh, Pittsburgh, PA, USA) Lewis Kuller; (University of Tennessee Health Science Center, Memphis, TN, USA) Karen C. Johnson; (University of Texas Health Science Center, San Antonio, TX, USA) Robert Brzyski; (University of Wisconsin, Madison, WI, USA) Gloria E. Sarto; (Wake Forest University School of Medicine, Winston-Salem, NC, USA) Mara Vitolins; (Wayne State University School of Medicine/Hutzel Hospital, Detroit, MI, USA) Michael Simon.

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC, USA) Sally Shumaker.

References

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4. American Psychiatric Association; Washington, D.C: 1994.
- Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004; 291:1701–1712. [PubMed: 15082697]
- Bernstein AB, Remsburg RE. Estimated prevalence of people with cognitive impairment: results from nationally representative community and institutional surveys. *Gerontologist*. 2007; 47:350–354. [PubMed: 17565098]

- Carr DB, Gran S, Baty J, Morris JC. The value of informant versus individual's complaints of memory impairment in elderly dementia. *Neurology*. 2000; 55:1724–1726. [PubMed: 11113230]
- Cooper C, Tandy AR, Balamurali TB, Livingston G. A systematic review and meta analysis of ethnic differences in use of dementia treatment, care, and research. *Am J Geriatr Psychiatry*. 2010; 18(3): 193–203. [PubMed: 20224516]
- Crooks VC, Clark L, Petitti DB, Chui H, Chiu V. Validation of multi-stage telephone based identification of cognitive impairment and dementia. *BMC Neurol*. 2005; 5(1):5–8. [PubMed: 15774006]
- Desmond DW, Bagiealla E, Moroney JT, Stern Y. The effect of patient attrition on estimates of the frequency of dementia following stroke. *Arch Neurol*. 1998; 55:390–394. [PubMed: 9520013]
- Ellenberg SS. Analytical, practical and regulatory issues in prevention studies. *Stat Med*. 2004; 23(2): 297–303. [PubMed: 14716730]
- Ellis RJ, Jan K, Kawas C, et al. Diagnostic validity of the dementia questionnaire for Alzheimer disease. *Arch Neurol*. 1998; 55(3):360–365. [PubMed: 9520010]
- Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens on global cognitive function in postmenopausal women. *JAMA*. 2004; 291:2959–2969. [PubMed: 15213207]
- Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc*. 2004; 52(4):625–634. [PubMed: 15066083]
- Gallo JJ, Breitner JC. Alzheimer's disease in the NAS-NRC Registry of aging twin veterans, IV. Performance characteristics of a two-stage telephone screening procedure for Alzheimer's dementia. *Psychol Med*. 1995; 25(6):1211–1219. [PubMed: 8637951]
- Gao S, Hui SL. Estimating the incidence of dementia from two-phase sampling with non-ignorable missing data. *Statist Med*. 2000; 19:1545–1554.
- Harel O, Hofer SM, Hoffman L, Pedersen NL, Johansson B. Population inference with mortality and attrition in longitudinal studies on aging: a two-stage multiple imputation method. *Exp Aging Res*. 2007; 33:187–203. [PubMed: 17364907]
- Hayden KM, Khachaturian AS, Tschanz JT, et al. Characteristics of a two-stage screen for incident dementia. *J Clin Epidemiol*. 2003; 56(11):1038–1045. [PubMed: 14614994]
- Izmirlian G, Brock D, White L. Estimating incidence of dementia subtypes: assessing the impact or missed cases. *Statist Med*. 2000; 19:1577–1591.
- Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity, and some norms. *Psychol Med*. 1989; 19:1015–1022. [PubMed: 2594878]
- Kawas C, Segal J, Stewart WF, Corrada M, Thal LJ. A validation study of the dementia questionnaire. *Arch Neurol*. 1994; 51(9):901–906. [PubMed: 8080390]
- Khachaturian AS, Gallo JJ, Breitner JC. Performance characteristics of a two- stage dementia screen in a population sample. *J Clin Epidemiol*. 2000; 53(5):531–540. [PubMed: 10812327]
- Lebowitz BD. Clinical trials in late life: new science in old paradigms. *Gerontologist*. 2004; 44(4): 452–458. [PubMed: 15331802]
- Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology*. 1989; 39:1159–1165. [PubMed: 2771064]
- Prentice RL, Anderson G, Cummings S, et al. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998; 19:61–109. [PubMed: 9492970]
- Rocca WA, Bower JH, Ahlskog JE, et al. Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. *Arch Neurol*. 2007; 64:1458–1464. [PubMed: 17923629]
- Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002; 288:321–333. [PubMed: 12117397]
- Shumaker SA, Reboussin BA, Espeland MA, et al. The Women's Health Initiative Memory Study (WHIMS): a trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control Clin Trials*. 1998; 19:604–621. [PubMed: 9875839]

- Shumaker S, Legault C, Rapp S, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003; 289:2651–2662. [PubMed: 12771112]
- Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. *JAMA*. 2004; 291:2947–2958. [PubMed: 15213206]
- Silverman JM, Breitner JC, Mohs RC, Davis KL. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatry*. 1986; 143:1279–1282. [PubMed: 3766791]
- Song X, Davidian M, Tsiatis AA. An estimator for the proportional hazards model with multiple longitudinal covariates measured with error. *Biostatistics*. 2002a; 3:511–528. [PubMed: 12933595]
- Song X, Davidian M, Tsiatis AA. A semiparametric likelihood approach to joint modeling of longitudinal and time-to-event data. *Biometrics*. 2002b; 58:742–753. [PubMed: 12495128]
- Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987; 48:314–318. [PubMed: 3611032]
- Tsiatis AA, Davidian M. A semiparametric estimator for the proportional hazards model with longitudinal covariates measured with error. *Biometrika*. 2001; 88:447–458.
- Tsiatis AA, Davidian M. Joint modeling of longitudinal and time-to-event data: an overview. *Stat Sin*. 2004; 14:809–834.

Key points

- Clinic-based assessments to detect cognitive impairment may lead to undercounts and are more likely to miss individuals who have poorer health and greater burdens of risk factors.
- Established protocols for detecting additional cases of cognitive impairment through interviews of proxy respondents are successful in recouping many additional cases and may reduce biases in risk factor relationships.
- Studies should develop programs to augment clinic assessments with proxy interviews; however, even these may not be sufficient to detect all cases of cognitive impairment and eliminate biases in estimates of incidence and characterizations of risk factor relationships.

Figure 1.

Participants were supplemental case ascertainment protocol (SCAP) ineligible on trial if they were at a clinic not participating in SCAP. They were post-trial ineligible if they were at a clinic not participating in SCAP, or they did not consent to the Women's Health Initiative Memory Extension Study. WHIMS, Women's Health Initiative Memory Study.

Figure 2. Incidence of probable dementia in relation to date of the Women's Health Initiative randomization. WHIMS, Women's Health Initiative Memory Study; SCAP, supplemental case ascertainment protocol.

Table 1

Distribution of risk factors for cognitive impairment for the 902 women eligible for proxy-based assessments and for others: frequency and percentage

Risk factor for cognitive impairment	Eligible for proxy-based assessments (n = 902)	Other women (n = 6577)	χ^2 p-value
Age (years)			
64–69	312 (34.59)	3135 (47.67)	<0.0001
70–74	337 (37.36)	2339 (35.56)	
75+	253 (28.05)	1103 (16.77)	
Duration since menopause (years)			
<15	63 (7.56)	708 (11.59)	<0.0001
15–24	400 (48.02)	3345 (54.74)	
25	370 (44.42)	2058 (33.68)	
Educational level			
<High school	75 (8.33)	503 (7.66)	0.2877
High school/general educational development	193 (21.44)	1458 (22.19)	
Some college	383 (42.56)	2623 (39.92)	
4-year college	249 (27.67)	1986 (30.23)	
Ethnicity			
American Indian/Alaskan native	5 (0.55)	21 (0.32)	0.0127
Asian/Pacific Islander	11 (1.22)	116 (1.76)	
African Americans	63 (6.98)	473 (7.20)	
Hispanic/Latino	10 (1.11)	171 (2.60)	
Caucasian	807 (89.47)	5696 (86.64)	
Other	6 (0.67)	97 (1.48)	
Family income (\$)			
19,999	290 (33.96)	1551 (25.14)	<0.0001
20,000–34,999	264 (30.91)	1947 (31.56)	
35,000–49,999	150 (17.56)	1288 (20.88)	
50,000–74,999	110 (12.88)	869 (14.09)	
75,000	40 (4.68)	514 (8.33)	
Smoking status			
Non-smoker	364 (41.08)	3543 (54.68)	<0.0001
Past smoker	385 (43.45)	2545 (39.27)	
Current smoker	137 (15.46)	392 (6.05)	
Body mass index (kg/m ²)			
<25	282 (31.47)	1884 (28.82)	0.3543
25–29	313 (34.93)	2391 (36.58)	
30–34	186 (20.76)	1447 (22.14)	
35	115 (12.83)	815 (12.47)	
Hypertension status			
None	360 (39.91)	3389 (51.54)	<0.0001
Current/controlled ^d	173 (19.18)	1023 (15.56)	

Risk factor for cognitive impairment	Eligible for proxy-based assessments (n = 902)	Other women (n = 6577)	χ^2 p-value
Current/uncontrolled	369 (40.91)	2163 (32.90)	
Alcohol intake			
None	427 (47.60)	3029 (46.15)	0.3002
<1 drink per day	352 (39.24)	2759 (42.04)	
1–2 drinks per day	106 (11.82)	677 (10.32)	
3 drinks per day	12 (1.34)	98 (1.49)	
Prior cardiovascular disease			
No	753 (83.48)	5920 (90.04)	<0.0001
Stroke	27 (2.99)	97 (1.48)	
Other	122 (13.53)	558 (8.49)	
Diabetes			
No	770 (85.37)	6072 (92.48)	<0.0001
Yes	132 (14.63)	494 (7.52)	
Prior use of hormone therapy			
No	640 (70.95)	4504 (68.50)	0.1362
Yes	262 (29.05)	2071 (31.50)	
Baseline Modified Mini-Mental State Examination			
95–100	117 (13.13)	634 (9.74)	0.0009
90–94	222 (24.92)	1485 (22.80)	
<90	552 (61.95)	4393 (67.46)	
Women's Health Initiative treatment assignment			
Placebo	460 (51.00)	3326 (50.57)	0.8096
Active hormone therapy	442 (49.00)	3251 (49.43)	

^a Blood pressure is less than 140/90 mmHg.

Table 2

Characteristics of women classified as having probable dementia from proxy-based assessments compared with women classified from clinic-based assessments: frequency and percentage

Variables	Proxy-based assessments (n = 39)	Clinic-based assessments (n = 232)	p-value ^a
Age (years)			
64–69	12 (30.77)	56 (24.14)	0.6676
70–74	12 (30.77)	79 (34.05)	
75+	15 (38.46)	97 (41.81)	
Duration since menopause (years)			
4–14	6 (15.38)	11 (5.24)	0.0419
15–24	12 (30.77)	95 (45.24)	
25+	21 (53.85)	104 (49.52)	
Educational level			
<High school	4 (10.26)	31 (13.42)	0.6603
High school/general educational development	6 (15.38)	51 (22.08)	
Some college	16 (41.03)	90 (38.96)	
>4-year college	13 (33.33)	59 (25.54)	
Ethnicity			
American Indian/Alaskan native	0 (0.00)	1 (0.43)	0.9282
Asian/Pacific Islander	0 (0.00)	3 (1.29)	
African Americans	3 (7.69)	29 (12.50)	
Hispanic/Latino	1 (2.56)	8 (3.45)	
Caucasian	34 (87.18)	185 (79.74)	
Other	1 (2.56)	6 (2.59)	
Family income (\$)			
<19,999	10 (27.03)	76 (36.71)	0.7667
20,000–34,999	13 (35.14)	64 (30.92)	
35,000–49,999	6 (16.22)	29 (14.01)	
50,000–74,999	5 (13.51)	20 (9.66)	
75,000+	3 (8.11)	18 (8.70)	
Smoking status			
Non-smoker	16 (44.44)	140 (61.95)	0.0302
Past smoker	15 (41.67)	76 (33.63)	
Current smoker	5 (13.89)	10 (4.42)	
Body mass index (kg/m ²)			
<25	13 (34.21)	91 (39.39)	0.9010
25–29	14 (36.84)	73 (31.60)	
30–34	7 (18.42)	39 (16.88)	
35+	4 (10.53)	28 (12.12)	
Hypertension status			
None ^b	12 (30.77)	103 (44.40)	0.1165
Current/controlled	4 (10.26)	35 (15.09)	

Variables	Proxy-based assessments (<i>n</i> = 39)	Clinic-based assessments (<i>n</i> = 232)	<i>p</i> -value ^a
Current/uncontrolled	23 (58.97)	94 (40.52)	0.1878
Alcohol intake			
None	17 (43.59)	129 (55.84)	
<1/day	17 (43.59)	85 (36.80)	
1–2/day	4 (10.26)	16 (6.93)	
3+/day	1 (2.56)	1 (0.43)	0.2386
Prior cardiovascular disease			
No	30 (76.92)	194 (83.62)	
Stroke	2 (5.13)	4 (1.72)	
Other	7 (17.95)	34 (14.66)	
Diabetes			0.0472
No	31 (79.49)	210 (90.91)	
Yes	8 (20.51)	21 (9.09)	0.0336
Prior use of hormone therapy			
No	22 (56.41)	172 (74.14)	
Yes	17 (43.59)	60 (25.86)	0.5386
Baseline 3MSE			
<90	11 (28.21)	85 (37.28)	
90–94	12 (30.77)	62 (27.19)	
95–100	16 (41.03)	81 (35.53)	0.1160
Women's Health Initiative treatment assignment			
Placebo	22 (56.41)	97 (41.81)	
Hormone therapy	17 (43.59)	135 (58.19)	

^aBased on Fisher's exact test.

^bBlood pressure is less than 140/90 mmHg.

Table 3

Comparison of hazard ratios for probable dementia limited to clinic-based assessments with those fitted to all cases

Risk factor for cognitive impairment	Hazard ratio (95% confidence interval)	
	Clinic-based assessments only (232 cases)	All cases (271 cases)
Duration since menopause (years)		
4–14	1.00	1.00
15–24	1.90 (1.02, 3.55)	1.39 (0.83, 2.32)
25+	3.68 (1.98, 6.85)	2.82 (1.70, 4.68)
	$p < 0.0001$	$p < 0.0001$
Smoking status		
Non-smoker	1.58 (0.83, 3.01)	1.18 (0.69, 2.00)
Past smoker	1.18 (0.61, 2.28)	0.94 (0.54, 1.62)
Current	1.00	1.00
	$p = 0.065$	$p = 0.220$
Diabetes		
No	0.76 (0.48, 1.19)	0.64 (0.43, 0.93)
Yes	1.00	1.00
	$p = 0.229$	$p = 0.021$
Prior use of hormone therapy		
No	1.30 (0.97, 1.75)	1.14 (0.87, 1.48)
Yes	1.00	1.00
	$p = 0.078$	$p = 0.346$