Prevalence of Dementia in Users of Hormone Replacement Therapy as Defined by Prescription Data

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Background. Studies of hormone replacement therapy (HRT) and dementia and cognitive impairment show mixed results. This study assessed the prevalence of dementia and cognitive impairment in users and nonusers of HRT defined using computer-stored prescription information.

Methods. The study involved 3924 women 75 years of age and older who were members of the Southern California Kaiser Permanente Medical Care Program in 1998. HRT use was determined based on prescription data for 1992–1998. Cognitive function and dementia were assessed using the Telephone Interview of Cognitive Status supplemented by the Telephone Dementia Questionnaire and medical record review.

Results. Odds ratios (ORs) for cognitive impairment/dementia showed expected associations with age, education, ethnicity, and a history of stroke or Parkinson’s disease. After adjustment, the OR for cognitive impairment or dementia in HRT users compared with nonusers was 0.91 (95% confidence interval 0.75–1.10). The adjusted ORs for all dementia and dementia without cause in HRT users compared with nonusers were 0.77 (95% confidence interval 0.59–1.00) and 0.78 (0.58–1.05), respectively. Twenty percent of women with cognitive impairment or dementia who had been classified as HRT users by prescription (one prescription each year from 1992–1998) denied hormone use compared with 8.8% of women without impairment. Medical record review validated prescription information for the impaired women.

Conclusions. The study identified an important methodologic problem in studies of HRT and cognitive impairment and dementia that depend on recalled information about drug exposure. A protective effect of HRT for cognitive impairment and dementia was neither established nor ruled out based on the prescription data.

ESTROGEN affects neuronal functioning, with both neuroprotective and neurotrophic effects. The mechanisms are unclear, but interactions with nerve growth factor (1), brain-derived neurotrophic factor (2), insulin-like growth factor-I (3), and fibroblast growth factor (4) have been implicated. Estrogen acts as an antioxidant, reducing neuronal death after exposure to prooxidant and beta amyloid (5), and it enhances expression of the neuroprotective proto-oncogene bcl-2 family (6).

Because of the positive neuronal effects of estrogen, interest in its effects on cognition is keen. Some studies show that estrogen, given alone or with a progestin as hormone replacement therapy (HRT), may benefit verbal memory among nondemented postmenopausal women (7–9), although other studies report no association (10–12). Epidemiologic studies of HRT and the risk of dementia and Alzheimer’s disease (AD) are mixed (13–27). Randomized trials have failed to find an effect among women with AD (28–30), although the relevance of HRT administration in women with AD to prevention of cognitive decline is not clear.

We are conducting a prospective cohort study of HRT use and cognitive impairment and dementia. This is a report on the prevalence of cognitive impairment and dementia at baseline in women recruited to the cohort.

METHODS

Study Population and Classification of HRT Use by Prescription

This cross-sectional study was done in the defined population comprising female members 75 years of age and older of the Kaiser Permanente Southern California (KPSC) Medical Care Program.

Computer-stored prescription data from the KPSC Pharmacy Information Management System, available since 1992, were used to identify subjects for the study.

Eligible as current HRT users were the 3058 women aged 75 years or older on July 1, 1998 living outside of San Diego who had at least one prescription for oral estrogen filled in a KPSC pharmacy in every calendar year from 1992–1998 and had been continuously enrolled in the health plan from 1992–1998. San Diego was excluded because the study involved obtaining blood specimens for genetic testing, and we could not arrange these in San Diego.

Eligible as non-HRT users were the 24,476 women aged 75 years or older on July 1, 1998 living outside San Diego who did not have any prescriptions for estrogen during the period 1992–1998 and had been continuously enrolled in the health plan from 1992–1998. From these 24,476 non-HRT users, 3058 women, frequency matched by age and zip
code with the current HRT users, were initially selected for the study. Some women classified as non-HRT users based on prescription data reported past HRT use on a baseline interview. To ensure approximately equal numbers of HRT users and nonusers, we subsequently added 900 women, frequency matched by age and zip code to the current HRT users, to the sample of non-HRT users eligible for the baseline interview.

Figure 1 depicts the overall flow of subject recruitment for the study. Of the 6542 women eligible for enrollment (2930 HRT users; 3612 HRT nonusers), after exclusion of women without a phone number and non-English speakers, baseline interviews were completed for 3924 (60.0%; 1944 HRT users and 1980 HRT nonusers). Of these, 3681 were direct interviews, and 243 were interviews with a proxy respondent.

Baseline Interview

The baseline interviews, done in 1999, gathered information on personal habits, medical history, and self-reported hormone use and conducted the first stage of cognitive assessment using the Telephone Interview of Cognitive Status modified (TICSm) (31). For women reached by phone who agreed to be in the study but were unable to complete the TICSm, information on personal habits and medical history was collected from a baseline proxy respondent with an order of preference of spouse, adult child, sibling, and friend. Information about hormone use was not collected from proxies because prior studies show that proxies underreport hormone use (16).

First-Stage Cognitive Assessment Using the TICSm

The first step in classification of cognitive status was based on the results of TICSm done at the time of the baseline interview. Women who could not complete the TICSm and whose proxy respondent indicated a physician diagnosis of dementia were classified as having dementia after a review of the medical records for 130 of these women showed that 126 (97%) had a confirmed diagnosis of dementia and the remaining four women had “memory problems.”

Prior studies have shown the TICSm to be highly correlated with the Mini-Mental State Examination (31). Because the TICSm has a high sensitivity in the detection of dementia but a low positive predictive value (31), it was used to classify women as having no cognitive impairment (TICSm score >27) or possible cognitive impairment (TICSm score ≤27).

For women who were possibly impaired, there was an attempt to do a second-stage cognitive assessment using the Telephone Dementia Questionnaire (TDQ) (32).

Second-Stage Cognitive Assessment Using the TDQ

The second-stage assessment administered the TDQ (32) to a proxy. The TDQ asks a proxy for information about the subject’s cognitive function in several domains (memory, fluency, comprehension, orientation).

Three investigators (V. Crooks, G. Buckholter, D. Petitti) independently reviewed the TDQs, blinded to hormone use status, and used the TDQ information to classify women in one of three categories: (i) definite dementia, (ii) no or minimal cognitive impairment, and (iii) cannot be classified as having definite dementia or having no or minimal cognitive impairment. Classification as having dementia required memory deficits and impairment in at least three other cognitive domains. The reviewers then made a consensus TDQ classification in the same three categories after discussion of the independent assessments.

The test–retest reliability of the consensus TDQ was measured by having the three reviewers reassess 40 TDQs selected at random and blinded to the initial assessment. The kappa coefficient was 0.85 for the consensus assessments.

Medical Record Review

When TDQ information was not available because women declined permission to contact a proxy, the proxy could not be located, or the proxy declined, medical records were reviewed. Medical records were also reviewed, blinded to hormone status and to the TICSm and TDQ, when the TDQ consensus assessment did not permit classification as definite dementia or no or minimal impairment.

Final Classification of Cognitive Status

No or minimal cognitive impairment.—Women were classified as having no or minimal cognitive impairment if they had a score on the TICSm more than 27 (n = 2355) or if their score on the TICSm was 27 or less and the consensus TDQ was no or minimal impairment (n = 457). They were also classified as having no or minimal cognitive impairment if no TDQ could be done and the medical record did not indicate dementia or cognitive impairment (n = 488).
Dementia.—Women who were reached by phone but could not complete the baseline TICSm interview were classified as having dementia if the baseline proxy stated that the woman had a physician diagnosis of dementia (n = 130). Women were also classified as having dementia if the consensus TDQ was definite dementia (n = 88). Finally, women were classified as having dementia if there was a diagnosis of dementia recorded in the medical record (n = 82).

Cognitive impairment without definite evidence of dementia.—Women were classified as having cognitive impairment without definite evidence of dementia (n = 285) if (i) the TDQ consensus did not conclude that there was no or minimal cognitive impairment or dementia and the medical record did not mention dementia or (ii) the medical record mentioned cognitive impairment.

Subclassification of Dementia Type

Information from medical records and the baseline interviews was used to subclassify dementia as being with or without known cause. The latter category corresponds closely to probable AD using the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria (33). Dementia with known cause was the classification if the medical record showed a physician diagnosis of stroke, vascular or multiinfarct dementia, dementia due to Parkinson’s disease (PD), Pick’s disease, frontotemporal dementia, dementia with Lewy bodies, Korsakoff’s dementia, Huntington’s disease, or Creutzfeld-Jacob disease; if magnetic resonance imaging (MRI) or computed tomography (CT) scan showed a cerebral infarction or small vessel disease; or if the woman or her proxy reported a history of stroke or PD.

Analysis

The exposure odds ratio (OR) was used to estimate relative risk. Exact 95% confidence intervals (CIs) were calculated using StatXact (Cytel Software Corporation, Cambridge, MA). The multivariate analyses used unconditional logistic regression to estimate ORs after adjustment for variables associated with the risk of dementia in prior studies.

Separate estimates of ORs were made for the combined group of women with cognitive impairment or dementia, all dementia, and dementia without known cause. The reference group in all analyses was women with no or minimal cognitive impairment.

RESULTS

The mean age of the 3924 women with baseline data was 79.0 (± 3.5 SD) years. Figure 2 shows the final classification of these 3924 women.

Table 1 shows the characteristics of study subjects, the prevalence of cognitive impairment or dementia and of all dementia for each characteristic, and crude ORs, and 95% CIs for each characteristic. For both the combined category of cognitive impairment or dementia and all dementia, crude ORs were elevated in relation to age, lower educational attainment, Hispanic, African-American, or Asian/Pacific Islander ethnicity, and a history of stroke or PD.

The crude OR for cognitive impairment or dementia in HRT users by prescription compared with nonusers of HRT by prescription was 0.87 (95% CI 0.72–1.04). The crude

![Diagram](https://academic.oup.com/biomedgerontology/article-abstract/57/8/M532/556757)
OR for all dementia in HRT users by prescription compared with nonusers of HRT by prescription was 0.77 (95% CI 0.60–0.99).

After adjustment for age and education, the ORs for cognitive impairment or dementia and all dementia in HRT users by prescription compared with nonusers of HRT by prescription (Table 2) were 0.90 (95% CI 0.75–1.09) and 0.79 (95% CI 0.62–1.01). After further adjustment for ethnicity and a history of myocardial infarction (MI), stroke, diabetes, hypertension, and PD, the OR for cognitive impairment or dementia in HRT users compared with HRT nonusers was 0.91 (95% CI 0.75–1.10) and for all dementia 0.77 (95% CI 0.59–1.00).

Table 3 shows the characteristics of women with dementia without known cause and the crude ORs for each characteristic. The associations of each variable with dementia are virtually the same as those with the combined category of cognitive impairment or dementia and all dementia with the exception of stroke and PD, which were exclusions from this category. The crude OR for dementia without known cause in HRT users compared with nonusers was 0.75 (95% CI 0.56–1.01). After adjustment for all of these variables, Table 4 shows that the OR for dementia without known cause in hormone users was 0.78 (95% CI 0.58–1.05).

Table 5 compares HRT by prescription with self-reported HRT use by cognitive status for the 3681 women who provided this information at the baseline interview. Among women with no or minimal cognitive impairment, 91.2% of those classified as HRT users by prescription reported themselves to be current HRT users, and 93.8% of them reported ever HRT use. Among women with cognitive impairment, 82.1% classified as HRT users by prescription reported themselves to be current HRT users, and 85.8% reported ever HRT use. Among women with dementia, only 72.1% classified as HRT users by prescription reported themselves to be current HRT users, and only 80.9% reported ever HRT use. Of the 17 women with dementia who were classified as HRT users by prescription and who denied current HRT use, 16 had a mention of current HRT in their medical record, and the remaining woman had a mention of prior HRT use with recent discontinuation.
Table 2. Adjusted Odds Ratios for Cognitive Impairment or Dementia and for All Dementia in Users of Hormone Replacement Therapy by Prescription

<table>
<thead>
<tr>
<th>Adjustment Variables</th>
<th>Cognitive Impairment or Dementia</th>
<th>All Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age only</td>
<td>0.86 (0.71–1.02)</td>
<td>0.75 (0.59–0.96)</td>
</tr>
<tr>
<td>Age, education</td>
<td>0.90 (0.75–1.09)</td>
<td>0.79 (0.62–1.01)</td>
</tr>
<tr>
<td>Age, education, ethnicity</td>
<td>0.92 (0.76–1.10)</td>
<td>0.80 (0.62–1.03)</td>
</tr>
<tr>
<td>Age, education, stroke</td>
<td>0.91 (0.75–1.09)</td>
<td>0.78 (0.61–1.00)</td>
</tr>
<tr>
<td>Age, education, MI</td>
<td>0.91 (0.76–1.09)</td>
<td>0.79 (0.61–1.01)</td>
</tr>
<tr>
<td>Age, education, HBP</td>
<td>0.91 (0.76–1.10)</td>
<td>0.79 (0.61–1.01)</td>
</tr>
<tr>
<td>Age, education, DM</td>
<td>0.91 (0.76–1.09)</td>
<td>0.78 (0.61–1.00)</td>
</tr>
<tr>
<td>Age, education, PD</td>
<td>0.88 (0.73–1.06)</td>
<td>0.75 (0.58–0.96)</td>
</tr>
<tr>
<td>Age, education, stroke, MI, HBP, DM, PD</td>
<td>0.89 (0.74–1.08)</td>
<td>0.76 (0.58–0.98)</td>
</tr>
</tbody>
</table>

Note: HRT = hormone replacement therapy; MI = myocardial infarction; HBP = high blood pressure; DM = diabetes mellitus; PD = Parkinson’s disease.

Table 3. Characteristics of Subjects With Dementia Without Known Cause and Prevalence and Univariate Odds Ratios for Dementia Without Known Cause

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (Prevalence as %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;75</td>
<td>95 (3.7)</td>
</tr>
<tr>
<td>70–79</td>
<td>70 (6.8)</td>
</tr>
<tr>
<td>85+</td>
<td>42 (13.2)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>&lt;High school</td>
<td>44 (8.1)</td>
</tr>
<tr>
<td>High school</td>
<td>64 (5.8)</td>
</tr>
<tr>
<td>Some college/trade school</td>
<td>58 (4.1)</td>
</tr>
<tr>
<td>College+</td>
<td>36 (4.2)</td>
</tr>
<tr>
<td>Refused/Don’t know</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White, Non-Hispanic</td>
<td>169 (4.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>12 (7.6)</td>
</tr>
<tr>
<td>African American</td>
<td>12 (6.8)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>9 (10.0)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>19 (5.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.15 (0.67–1.89)</td>
</tr>
<tr>
<td>No</td>
<td>185 (5.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>74 (3.6)</td>
</tr>
<tr>
<td>No</td>
<td>126 (6.8)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>15 (4.5)</td>
</tr>
<tr>
<td>No</td>
<td>190 (5.3)</td>
</tr>
<tr>
<td>HRT User by Prescription</td>
<td>89 (4.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.75 (0.56–1.01)</td>
</tr>
<tr>
<td>No</td>
<td>118 (6.0)</td>
</tr>
</tbody>
</table>

Note: HRT = hormone replacement therapy.
*ns may not sum to 207 because of missing data.

Table 4. Adjusted Odds Ratios for Dementia Without Known Cause in Users of Hormone Replacement Therapy by Prescription

<table>
<thead>
<tr>
<th>Adjustment Variables</th>
<th>Odds Ratio in HRT Users (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age only</td>
<td>0.73 (0.54–0.97)</td>
</tr>
<tr>
<td>Age, education</td>
<td>0.79 (0.59–1.06)</td>
</tr>
<tr>
<td>Age, education, ethnicity</td>
<td>0.77 (0.57–1.03)</td>
</tr>
<tr>
<td>Age, education, MI</td>
<td>0.76 (0.57–1.03)</td>
</tr>
<tr>
<td>Age, education, HBP</td>
<td>0.76 (0.57–1.03)</td>
</tr>
<tr>
<td>Age, education, DM</td>
<td>0.75 (0.56–1.01)</td>
</tr>
<tr>
<td>Age, education, MI, HBP, DM</td>
<td>0.77 (0.57–1.04)</td>
</tr>
<tr>
<td>Age, education, ethnicity, MI, HBP, DM</td>
<td>0.78 (0.58–1.05)</td>
</tr>
</tbody>
</table>

Note: HRT = hormone replacement therapy; MI = myocardial infarction; HBP = high blood pressure; DM = diabetes mellitus.

Discussion

The age-specific prevalence of the combined category of cognitive impairment or dementia is similar to AD prevalence reported by Ott and colleagues (34). The lower prevalence of dementia alone may reflect our conservative classification approach. Increased risk of cognitive impairment and dementia showed expected associations with older age, lower education, and a history of stroke and PD.

Table 6 summarizes the results of prior epidemiologic studies of AD and estrogen replacement therapy. Relative risk estimates range from 0.18 (25) to 2.38 (13). Many studies relied on proxy respondents for cases and direct report for controls. Risk estimates from such studies are highly suspect, because proxies are not accurate sources of data on HRT use (16). The basis for AD designation also varied, and some studies relied on death certificates.

Our study highlights a serious problem with the use of self-reported information in observational studies of HRT use and cognitive impairment and dementia. Study subjects with cognitive impairment or dementia underreported HRT use more than women without cognitive impairment. In women with dementia, HRT use by prescription was correct, and self-report was incorrect. The ORs based on self-reported current HRT use were much lower than when based on prescription data (for cognitive impairment or dementia, the adjusted OR based on self-reported current hormone use was 0.80 [95% CI 0.64–0.99]; for all dementia, the adjusted OR was 0.68 [95% CI 0.47–0.97]; for dementia without known cause, the adjusted OR was 0.59 [95% CI 0.39–0.90]). Use of self-reported information on HRT use would have led to an erroneous conclusion about the association of HRT use with dementia.

Our study tried to overcome a number of limitations of prior studies of dementia and HRT use. First, we identified a relatively large number of elderly women who had a very long average duration of hormone use (mean 25.0 years ± 13.6 SD among the HRT users by prescription women who provided self-reports). Second, we classified HRT exposure-based computer-stored information, which is independent of patient or proxy recall. Use of computer data on HRT use allowed us to include women who could not themselves be interviewed without resorting to proxy respondents for information on HRT use. Third, we classified cognitive status systematically and documented our approach carefully. Notwithstanding its methodologic strengths, our study neither establishes nor rules out an association of HRT use with prevention of cognitive decline or dementia.
Our study has potential limitations. First, computer-stored prescription data might underestimate HRT use if women obtain prescriptions outside Kaiser Permanente. However, prescription drugs are a covered benefit for 95% of Kaiser Permanente Southern California Medicare members, who pay only a small copayment if they fill their prescriptions at a KPSC pharmacy and who pay full price elsewhere. Second, our study classifies women who used HRT

Table 5. Hormone Replacement Therapy (HRT) by Prescription and Self-Reported Hormone Replacement Therapy by Cognitive Status

<table>
<thead>
<tr>
<th>HRT by Self-Report</th>
<th>HRT By Prescription</th>
<th>Cognitive Impairment</th>
<th>Dementia</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRT User</td>
<td>Nonuser</td>
<td>HRT User</td>
<td>Nonuser</td>
</tr>
<tr>
<td>Current HRT User</td>
<td>1511 (91.2)</td>
<td>77 (4.8)</td>
<td>110 (82.1)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Not Current User</td>
<td>146 (8.8)</td>
<td>1525 (94.1)</td>
<td>23 (17.2)</td>
<td>124 (95.4)</td>
</tr>
<tr>
<td>Ever HRT User</td>
<td>1555 (93.8)</td>
<td>564 (34.8)</td>
<td>115 (85.8)</td>
<td>38 (29.2)</td>
</tr>
<tr>
<td>Never HRT User</td>
<td>102 (6.2)</td>
<td>1040 (64.2)</td>
<td>18 (13.4)</td>
<td>91 (70.0)</td>
</tr>
<tr>
<td>Unknown/Not Sure</td>
<td>0 (0.0)</td>
<td>19 (1.2)</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Note: All values are n (%). Some percentages may not total 100.0 because of rounding. HRT = hormone replacement therapy.

Table 6. Summary of Prior Epidemiologic Studies of Hormone Replacement Therapy and the Risk of Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects</th>
<th>User Definition</th>
<th>Source of HRT Information</th>
<th>Estimated RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heyman and colleagues, 1984 (13)</td>
<td>Case-Control</td>
<td>40 AD cases, 80 controls</td>
<td>n/a</td>
<td>Proxy interview for all</td>
<td>2.38 (n/a)</td>
</tr>
<tr>
<td>Amaducci and colleagues, 1986 (14)</td>
<td>Case-Control</td>
<td>116 AD cases, 97 controls</td>
<td>Ever use</td>
<td>Proxy interview for all</td>
<td>1.67 (n/a)</td>
</tr>
<tr>
<td>Broe and colleagues, 1990 (15)</td>
<td>Case-Control</td>
<td>170 AD cases, 170 controls</td>
<td>Ever use</td>
<td>Proxy interview for all</td>
<td>.78 (0.39 – 1.56)</td>
</tr>
<tr>
<td>Graves and colleagues, 1990 (16)</td>
<td>Case-Control</td>
<td>130 AD cases, 130 controls</td>
<td>Ever use</td>
<td>Proxy interview for all</td>
<td>1.15 (0.50 – 2.64)</td>
</tr>
<tr>
<td>Brenner and colleagues, 1994 (17)</td>
<td>Case-Control</td>
<td>107 AD cases, 120 controls</td>
<td>Current use at time of enrollment</td>
<td>Proxy interview for cases, self-report for controls</td>
<td>.30 (0.10 – 0.70)</td>
</tr>
<tr>
<td>Henderson and colleagues, 1994 (18)</td>
<td>Case-Control</td>
<td>143 AD cases, 92 controls</td>
<td>Current use</td>
<td>Chart review if available else proxy interview for cases, self-report for controls</td>
<td>.55 (0.3 – 1.2)†</td>
</tr>
<tr>
<td>Mort &amp; Meyer, 1995 (19)</td>
<td>Case-Control</td>
<td>93 AD cases, 65 vascular dementia cases, 148 controls</td>
<td>n/a</td>
<td>Proxy interview for cases, self-report for controls</td>
<td>.50 (0.2 – 1.2)†</td>
</tr>
<tr>
<td>Paganini-Hill &amp; Henderson, 1996 (20)</td>
<td>Case-Control nested in a cohort</td>
<td>248 AD cases, 1198 controls</td>
<td>Ever use</td>
<td>Self-report at intake</td>
<td>.65 (0.49 – 0.88)</td>
</tr>
<tr>
<td>Tang and colleagues, 1996 (21)</td>
<td>Case-Cohort</td>
<td>167 AD cases in a cohort of 1124</td>
<td>Ever use</td>
<td>Self-report at intake</td>
<td>.40 (0.22 – 0.85)</td>
</tr>
<tr>
<td>Kawas and colleagues, 1997 (22)</td>
<td>Case-Cohort</td>
<td>34 AD cases in a cohort of 472</td>
<td>Ever use</td>
<td>Self-report at intake, confirmed every 2 years</td>
<td>.46 (0.21 – 0.997)</td>
</tr>
<tr>
<td>Lerner and colleagues, 1997 (23)</td>
<td>Case-Control</td>
<td>88 AD cases, 176 controls</td>
<td>Ever use</td>
<td>Proxy interview for cases, self-report for controls</td>
<td>.41 (0.12 – 0.69)</td>
</tr>
<tr>
<td>Baldreschi and colleagues, 1998 (24)</td>
<td>Population-based cross-sectional</td>
<td>92 AD cases in 1568 participants</td>
<td>Ever use</td>
<td>Proxy interview for cases, self-report for controls</td>
<td>.24 (0.07 – 0.77)</td>
</tr>
<tr>
<td>Marder and colleagues, 1998 (25)</td>
<td>Population-based cross-sectional</td>
<td>80 Parkinson’s disease cases, 87 Parkinson’s controls, 989 controls</td>
<td>Ever use</td>
<td>Proxy interview for cases, self-report for controls</td>
<td>.18 (0.05 – 0.66)‡</td>
</tr>
<tr>
<td>Sloop and colleagues, 1999 (26)</td>
<td>Case-Control</td>
<td>109 early onset AD cases, 119 controls</td>
<td>Current use</td>
<td>Proxy interview for all</td>
<td>.29 (0.11 – 0.94)</td>
</tr>
<tr>
<td>Waring and colleagues, 1999 (27)</td>
<td>Case-Control</td>
<td>222 AD cases, 222 controls</td>
<td>Ever use lasting ≥6 months</td>
<td>Chart review</td>
<td>.42 (0.18 – 0.96)</td>
</tr>
</tbody>
</table>

Note: HRT = hormone replacement therapy; CI = confidence interval; RR = relative risk; AD = Alzheimer’s disease.

*Crude relative risk reported.
†AD versus controls.
‡Vascular dementia versus controls.
§Previous study using the same sample with a shorter follow-up period is not included.
¶Parkinson’s disease with dementia versus non-demented Parkinson’s disease.
prior to availability of computer-stored data as HRT nonusers. Almost one third of women in the study classified as HRT nonusers by prescription reported HRT use at some time in the past, and about 5% reported current HRT use. Importantly, the overall mean duration of self-reported HRT use in all women classified as HRT nonusers by prescription was only 2.3 (± 6.3 SD) years. Third, the response rate was only 60.0%, and it differed in HRT users and nonusers by prescription. To assess the possibility of bias due to non-response, we reviewed the medical records of a random sample of 565 nonrespondents. The prevalence of a physician diagnosis of dementia was 11% in 165 nonrespondent HRT users and 10% in 400 nonusers.

Long-term follow-up of women in this cohort will help to elucidate the relationship between HRT use and cognitive decline and dementia. Randomized trials will also provide important information on this topic, although maintaining compliance with assigned HRT treatment through the ages when dementia and cognitive impairment become common will be challenging.

Acknowledgments

Rohina Furmuly, Sean Robins, and Joseph Jadav all made important contributions to data collection.

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