Dietary Antioxidants and Long-term Risk of Dementia

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**Background:** The Rotterdam Study previously found that higher dietary intakes of vitamins E and C related to lower risk of dementia and Alzheimer disease (AD) over 6 years of follow-up.

**Objective:** To study consumption of major dietary antioxidants relative to long-term risk of dementia.

**Design:** Population-based prospective cohort study.

**Setting:** The Rotterdam Study in the Netherlands.

**Participants:** A total of 5395 participants, 55 years and older, who were free of dementia and provided dietary information at study baseline.

**Main Outcome Measures:** Incidence of dementia and AD, based on internationally accepted criteria, relative to dietary intake of vitamin E, vitamin C, beta carotene, and flavonoids.

**Results:** During a mean follow-up period of 9.6 years, dementia developed in 465 participants, of whom 365 were diagnosed as having AD. In multivariate models adjusted for age, education, apolipoprotein E ε4 genotype, total energy intake, alcohol intake, smoking habits, body mass index, and supplement use, higher intake of vitamin E at study baseline was associated with lower long-term risk of dementia (P = .02 for trend). Compared with participants in the lowest tertile of vitamin E intake, those in the highest tertile were 25% less likely to develop dementia (hazard ratio, 0.75; 95% confidence interval, 0.59-0.95 with adjustment for potential confounders). Dietary intake levels of vitamin C, beta carotene, and flavonoids were not associated with dementia risk after multivariate adjustment (P > .99 for trend for vitamin C and beta carotene and P = .60 for trend for flavonoids). Results were similar when risk for AD was specifically assessed.

**Conclusion:** Higher intake of foods rich in vitamin E may modestly reduce long-term risk of dementia and AD.


Oxidative stress is thought to have an important role in the pathogenesis of Alzheimer disease (AD), a disease that likely begins years, if not decades, before clinical onset of dementia. In line with this hypothesis, experimental data support the notion that antioxidants protect against neurodegeneration. Although clinical trials have shown no benefit of antioxidant supplements for AD, the wider variety of antioxidants in food sources is not well studied relative to dementia risk; a few studies, with varying lengths of follow-up, have yielded inconsistent results. Results of the Rotterdam Study previously found that higher dietary intakes of vitamins E and C were related to lower risk of dementia and AD over 6 years of follow-up. Still, substantial evidence indicates that earlier exposures are important for predicting dementia risk in later life, and specific evidence indicates that antioxidants may affect early stages of dementia development. Therefore, we evaluated the associations of dietary vitamin E, vitamin C, beta carotene, and flavonoid intake with long-term risk of dementia based on 10 years of follow-up, taking advantage of longer follow-up and substantially more dementia cases than were available in the 2002 Rotterdam Study.

**METHODS**

The Rotterdam Study is a population-based cohort study in Ommoord (a district of Rotterdam, the Netherlands) designed to investigate determinants of disease in older populations. In 1990, a total 7983 residents of Ommoord, 55 years and older, agreed to participate in the study (78% response rate). Between 1990 and 1993,
participants underwent a baseline examination consisting of an extensive home interview and 2 clinical examinations to obtain health and lifestyle information. Subsequently, follow-up examinations were performed in 1993-1994, 1997-1999, and 2002-2004. The cohort is also continuously monitored for mortality and major morbidity. The medical ethics committee of Erasmus University Rotterdam approved this study.

**POPULATION FOR ANALYSIS**

Of 7983 individuals who agreed to participate, 7046 (88.3%) underwent cognitive screening and were free of dementia at baseline. One hundred twenty-five individuals were excluded from dietary assessment because of questionable cognitive status (defined as a score of <80 on the Cambridge Examination of Mental Disorders in the Elderly, which might lead to unreliable reporting). An additional 477 individuals were excluded owing to nursing home residence because their institutional diet may not have reflected previous eating habits. Therefore, 6444 participants at risk of incident dementia were eligible for dietary assessment. However, we did not include dietary information from 1049 of these individuals (16.3%): 212 (3.3%) had inconsistencies in their responses, 192 (3.0%) were not present during the examination when dietary interviews were conducted, and 645 (10.0%) were without a dietician at their examination. Hence, we analyzed 5395 noninstitutionalized participants who were free of dementia and provided dietary information at study baseline.

**DIETARY ASSESSMENT**

The diagnosis of dementia was made according to a 3-step protocol at baseline and follow-up examinations. First, a combined Mini-Mental State Examination and Geriatric Mental State Schedule organically used to screen all subjects, those with Mini-Mental State Examination scores lower than 26 or Geriatric Mental State Schedule scores higher than 0 underwent the Cambridge Examination of Mental Disorders in the Elderly. Third, if necessary, participants were evaluated by a neurologist and neuropsychologist; when available, neuroimaging data were used. In addition, the total cohort was continuously monitored for memory problems and dementia via computerized linkage of the study database to digitalized medical records from general practitioners and the regional institute for outpatient mental health care. For this study, dementia was diagnosed by a panel consisting of a neurologist, neuropsychologist, and research physician using all existing information. Diagnoses were made in accord with internationally accepted criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders [Third Edition Revised]). AD (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association), and vascular dementia (National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neuroscience). Follow-up for incident dementia was complete through January 1, 2005.

**COVARIATES**

At the baseline home interview, participants provided information on their highest level of education, smoking habits, and medications (including supplements). Baseline height and weight were measured at the study center, and total energy intake and alcohol consumption were assessed using the semiquantitative food frequency questionnaire. Without knowledge of dementia diagnosis, the apolipoprotein (APOE) genotype was assessed on coded DNA samples using polymerase chain reaction.

**STATISTICAL ANALYSIS**

We used age- and multivariate-adjusted Cox proportional hazards models to evaluate the associations of antioxidant intake with risk of dementia and AD, with censoring at the time of development of dementia or AD, death, or loss to follow-up (including persons who could not be contacted and those who refused to participate further in the study). Dietary intakes of antioxidants (vitamin E, vitamin C, beta carotene, and flavonoids) were derived from food sources only (not supplements) and were evaluated across sex-specific tertiles based on energy-adjusted values. To evaluate possible confounding, we considered adjustment for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking, body mass index, and supplement use (including multivitamins and single supplements for vitamin E, vitamin C, beta carotene, flavonoids, or ω-3s). Because only 19 participants reported use of ω-3 supplements, the covariate “supplement use” essentially reflects use of antioxidant supplements. Level of education was categorized into the following 3 groups: low (primary education only), intermediate (lower vocational or general education), and high (intermediate or higher vocational or general education, college, or university). Smoking habits were categorized as current, former, or never; alcohol intake was divided into the following 5 categories: none, less than 1 drink per week, 1 or more drinks per week but less than 1 drink per day, 1 to 3 drinks per day, and 4 or more drinks per day. Body mass index was analyzed as a continuous variable, supplement use was dichotomized (yes or no), and APOE ε4 genotype was dichotomized based on the presence of at least 1 ε4 allele.

We further evaluated an interaction term for vitamins E and C (assigning median values for tertiles) and interaction terms for each antioxidant (using tertile medians) with education (low, intermediate, or high), smoking status (current, former, or never), and APOE ε4 carrier status (yes or no). To assess whether...
When we examined various health and lifestyle characteristics, we found few meaningful differences across tertiles of dietary intake for vitamin E, vitamin C, beta carotene, and flavonoids (Table 1); however, for all 4 antioxidants, participants in higher tertiles of consumption were less likely to be current smokers. In addition, participants with greater flavonoid intake tended to be slightly older, and those with lower vitamin E consumption and greater intakes of vitamin C and beta carotene, on average, had slightly higher body mass index.

During a mean follow-up period of 9.6 years, dementia developed in 465 participants, of whom 365 were diagnosed as having AD. Higher vitamin E intake at baseline was associated with lower long-term risk of dementia in age- and multivariate-adjusted models (P = .02 for trend for both) (Table 2). For participants in the top tertile of vitamin E intake, we found a 24% lower risk of dementia compared with those in the bottom tertile in age-adjusted models (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.60-0.96); this estimate was similar in models adjusted for age, education, APOE ε4 genotype, total energy intake, alcohol intake, smoking habits, body mass index, and supplement use (0.75; 0.59-0.95). However, participants in the middle tertile of vitamin E intake did not have a lower risk of dementia compared with those in the bottom tertile in age- or multivariate-adjusted models (HR, 1.20; 95% CI, 0.97-1.49 after multivariate adjustment). For vitamin C, beta carotene, and flavonoids, we found no associations in multivariate models between dietary intake level and long-term risk of dementia (P > .99 for trend for vitamin C and beta carotene and P = .60 for trend for flavonoids). When we excluded 644 participants who used supplements at baseline, our results for all 4 antioxidants remained unchanged in age- and multivariate-adjusted models (HR, 0.75; 95% CI, 0.58-0.97; P = .03 for trend comparing extreme tertiles of vitamin E and adjusting for potential confounders).

When assessed for AD specifically, we found a lower risk among participants with greater consumption of vitamin E, which was similar in age- and multivariate-adjusted models (P = .03 for trend after multivariate adjustment) (Table 3). The estimated long-term risk reduction was 26% in the top tertile of vitamin E intake compared with the bottom tertile (HR, 0.74; 95% CI, 0.56-0.97 after multivariate adjustment), although risk was not lower when the middle vs bottom tertiles were compared (1.12; 0.88-1.44). Vitamin C, beta carotene, and flavonoid intakes were unrelated to AD risk (P = .80 for trend for vitamin C and beta carotene and P = .50 for flavonoids after multivariate adjustment). Again, excluding supplement users did not change the observed relations, as higher vitamin E intake remained associated with lower long-
We found that higher dietary intake of vitamin E, but not vitamin C, beta carotene, or flavonoids, was associated with lower long-term risk of dementia over a mean of 9.6 years in the Rotterdam Study. These findings extend results of an earlier study in this cohort, which indicated that higher consumption of vitamins E and C might be related to lower AD risk. Despite their differences, these findings do not include an inverse association between intake of vitamin E and AD risk. The brain is a site of high metabolic activity, and oxidative stress is a sustained contribution of oxidative damage and a continued benefit of vitamin E intake throughout the pathogenesis of AD. Further, antioxidant action was not modified by vitamin C intake. Although we found a borderline significant interaction for vitamin E intake on dementia risk, this should not be overinterpreted. When we divided follow-up time into shorter (years 0-8) vs longer (years 9-14) periods (data not shown), we found no interaction between intake of vitamin E, C, beta carotene, or flavonoids and time relative to dementia risk. All results were similar when AD risk was considered separately.

**Table 2. Adjusted Hazard Ratios of Incident Dementia Across Tertiles of Dietary Vitamin E, Beta Carotene, and Flavonoids**

<table>
<thead>
<tr>
<th>Tertile</th>
<th>No. of Subjects</th>
<th>Total Population (N=5395)</th>
<th>Age Adjusted</th>
<th>Multivariate Adjusted</th>
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<tr>
<td>1</td>
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<td>1.00 [Reference]</td>
<td>1.00 [Reference]</td>
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<tr>
<td>2</td>
<td>27.6</td>
<td>1.14 (0.91-1.43)</td>
<td>1.14 (0.91-1.44)</td>
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<tr>
<td>3</td>
<td>39.3</td>
<td>1.20 (0.97-1.49)</td>
<td>1.20 (0.97-1.44)</td>
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<tr>
<td></td>
<td></td>
<td>Median Intake</td>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin E (mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>154</td>
<td>1.12 (0.87-1.43)</td>
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<tr>
<td></td>
<td></td>
<td>148</td>
<td>1.18 (0.93-1.51)</td>
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<tr>
<td></td>
<td></td>
<td>136</td>
<td>1.00 [Reference]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Median Intake</td>
<td>HR (95% CI)</td>
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<tr>
<td></td>
<td></td>
<td>Beta carotene (µg/d)</td>
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<td></td>
<td></td>
<td>154</td>
<td>1.18 (0.93-1.51)</td>
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<td></td>
<td>148</td>
<td>1.12 (0.87-1.43)</td>
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<td>1.00 [Reference]</td>
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<tr>
<td></td>
<td></td>
<td>Median Intake</td>
<td>HR (95% CI)</td>
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<tr>
<td></td>
<td></td>
<td>Flavonoids (mg/d)</td>
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<td>154</td>
<td>1.12 (0.87-1.43)</td>
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<td></td>
<td></td>
<td>136</td>
<td>1.00 [Reference]</td>
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</tbody>
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**COMMENT**

Studies provide consistent evidence for a modest benefit of vitamin E on dementia risk over the shorter- and longer-term. Although we found that vitamin E makes a contribution to antioxidant effects in rodents and in the brain, an inflammatory response is thought to drive the development of such damage over a lifetime. When antioxidant action was not modified by vitamin C intake, this should not be overinterpreted. When we divided follow-up time into shorter (years 0-8) vs longer (years 9-14) periods (data not shown), we found no interaction between intake of vitamin E, C, beta carotene, or flavonoids and time relative to dementia risk. All results were similar when AD risk was considered separately. Finally, the effect of vitamin E intake on dementia risk was not modified by vitamin C intake and antioxidant effects were not modified by education, smoking, or body mass index.

**Abbreviations:** CI, confidence interval; HR, hazard ratio.
Project found no association of dietary vitamin E, vitamin C, or beta carotene with AD over a mean follow-up of 4 years, although CIs were wide and vitamin E intake seemed low. The much longer-term Honolulu-Asia Aging Study found no association of dietary vitamin E, vitamin C, beta carotene, or flavonoids with dementia risk over a 30-year period (HR, 1.33; 95% CI, 0.90-1.96 for vitamin E after multivariate adjustment comparing extreme quartiles); however, 30% of participants were lost to follow-up, which could have contributed to these null findings. Furthermore, the ascertainment of dietary antioxidants 30 years before diagnosis of incident dementia may be too remote to detect associations. Overall, more research is needed to assess points at which antioxidant intake might be most relevant to dementia risk.

In our study, dietary intakes of antioxidants were comparable to, if not greater than, those of existing studies. For vitamin E, our participants had similar intake (mean, 13.9 mg/d) compared with those participants in the Honolulu-Asia Aging Study (mean, 13.8 mg/d) but considerably higher intake than those participants in the Chicago Health and Aging Project (median, 5.7 mg/d) or the Washington Heights–Inwood Columbia Aging Project (mean, 4.0 mg/d). Vitamin C and beta carotene levels were consistent across cohorts (the exception was low beta carotene levels in participants in the Honolulu-Asia Aging Study), and flavonoid intake was considerably higher in our cohort (mean, 28.5 mg/d) compared with those participants in the PAQUID (mean, 14.1 mg/d) and Honolulu-Asia Aging Study (mean, 4.1 mg/d). Therefore, dietary antioxidant levels seem sufficient
compared with previously studied populations, such that low dietary exposure is unlikely to explain our null findings for 3 of 4 antioxidants.

Several meaningful differences distinguish the implications of our study from those of previous clinical trials involving vitamin E intake and risk of dementia. First, we provide population-based estimates of incident dementia risk over a decade, as opposed to trials that examined short-term risk of dementia progression in clinic-based populations. Second, our study focused on food-based antioxidants in the context of a Western-type diet, with intakes several-fold lower than supplementation levels in clinical trials. Third, we studied various antioxidants and total vitamin E (including all 8 forms), whereas clinical trials evaluated single-form α-tocopherol supplements. Therefore, our study provides additional information, beyond that of clinical trials, on diet-based antioxidants and long-term risk of incident dementia at levels consistent with a Western-type diet.

Several limitations of this study should be considered. This is an observational study, and residual confounding could explain the associations we observed. Although we cannot dismiss this possibility, we adjusted our statistical models for various health and lifestyle factors, which made little difference in our results compared with adjustment for age alone. We were particularly concerned about possible confounding by polyunsaturated fat intake; however, this is unlikely to have occurred because it was previously shown in the Rotterdam Study that polyunsaturated fat was not associated with dementia risk. In addition, any participants who changed dietary or supplement habits with respect to antioxidants over the long-term follow-up period would tend to bias our results toward the null. However, because we would expect such attenuation to affect observed relations for all 4 antioxidants, our consistent findings for vitamin E over shorter- and longer-term follow-up periods suggest that these changes did not affect our results substantially.

In summary, higher consumption of vitamin E from foods was modestly associated with lower long-term risk of dementia and AD in this cohort of older adults in the Netherlands. Future studies should continue to evaluate dietary intake of antioxidants relative to dementia risk, including different points at which antioxidant intake might modulate risk.

Accepted for Publication: December 9, 2009.

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Author Contributions: Dr Devore takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Devore, Hofman, Witteman, and Breteler. Acquisition of data: Devore, van Rooij, Witteman, and Breteler. Analysis and interpretation of data: Devore, van Rooij, Witteman, and Breteler. Drafting of the manuscript: Devore, Grodstein, van Rooij, Hofman, Stampler, Witteman, and Breteler. Critical revision of the manuscript for important intellectual content: Devore, Grodstein, van Rooij, Hofman, Stampler, Witteman, and Breteler.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grant 918-46-615 from the Netherlands Organization for Scientific Research (Dr Breteler) and by training grant AG00158 from the National Institutes of Health and by a US Fulbright Fellowship to the Netherlands (Dr Devore).

Role of the Sponsor: Funding agencies did not participate in design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Additional Contributions: Bernard Rosner, PhD, provided statistical guidance for this study.

References