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Authors
Paganini-Hill, Annlia
Bukhari, Syed
Montine, Thomas J
et al.

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Alzheimer's Disease Neuropathologic Change and Vitamin Supplement Use Decades Earlier

The 90+ Study

Annlia Paganini-Hill, PhD, Syed Bukhari, MA,† Thomas J. Montine, MD, PhD,† Maria M. Corrada, ScD,‡ and Claudia H. Kawas, MD*§*

Background: Alzheimer's disease (AD) is the most common cause of dementia. AD neuropathologic change (ADNC) likely begins decades before clinical manifestations. One mechanism implicated in AD is oxidative stress. We explored the potential association of ADNC with antioxidant vitamin supplements taken about 30 years before death.

Methods: The 264 brain-autopsied participants were part of The 90+ Study, a longitudinal study of aging among people aged 90+ years, and originally members of the Leisure World Cohort Study, a population-based health study established in the 1980s. Intake of supplemental vitamins A, C, and E was collected by the Leisure World Cohort Study about 30 years before ADNC assessment. Odds ratios of ADNC (intermediate/high vs. none/low) for vitamin intake were estimated using logistic regression.

Results: The adjusted odds ratio (95% CI) of ADNC was 0.52 (0.29-0.92) for vitamin E supplements and 0.51 (0.27-0.93) for vitamin C supplements. Supplemental vitamin E intake was the first variable, after education, to enter the stepwise model. Intake of vitamin A or C did not improve the model fit.

Conclusions: The observed association of ADNC and supplemental vitamin E intake decades earlier suggests a beneficial effect and supports further investigation into a nutritional approach to preventing AD with vitamin supplementation.

Key Words: Alzheimer disease, neuropathologic change, vitamin supplements, vitamin A, vitamin C, vitamin E

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From the Departments of *Neurology; ‡Epidemiology; §Neurobiology & Behavior, University of California, Irvine; and †Department of Pathology, Stanford University, Palo Alto, CA.

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Reprints: Annlia Paganini-Hill, PhD, Clinic for Ageing Research and Education, 24361 El Toro Road #150, Laguna Woods, CA 92637 (e-mail: apaganin@uci.edu).

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BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia and its lesions are the most prevalent brain lesion at autopsy. Its histopathologic hallmarks remain amyloid plaques and neurofibrillary tangles (NFTs) as first described by Alois Alzheimer in 1907.[1] An estimated 6.5 million Americans aged 65 years and older are living with AD today. Without medical breakthroughs to prevent AD, this number is expected to more than double by 2060.[2] In addition to sheer numbers, AD is associated with personal, social, and economic burdens.

In the absence of therapeutic options or cure, prevention has been emphasized as a key to counteract the dementia epidemic.[3] AD neuropathologic change (ADNC) likely begins decades before the appearance of clinical manifestations; these brain lesions may be present up to 30 years before the onset of symptoms.[4] Multiple biological mechanisms associated with disease onset and progression have been described.[5] One mechanism implicated in AD is oxidative stress,[6,7] which may be modifiable through diet and/or supplements.[8] Therefore, the risk of AD might be reduced by intake of antioxidants that counteract the detrimental effects of oxidative stress. We explored the potential association of ADNC with antioxidant vitamin supplements taken about 30 years before brain autopsy.

METHODS

Study Population

Participants were part of The 90+ Study, a longitudinal study of aging and dementia among people aged 90 years and older.[9,10] These individuals were originally members of the Leisure World Cohort Study (LWCS), a population-based epidemiological health study established in the early 1980s of a California retirement community (Leisure World Laguna Hills).[11,12] This cohort is composed of moderately affluent, highly educated, and health-conscious individuals; two-thirds are women. Persons alive and aged 90 years and older on January 1, 2003, on January 1, 2008, and on or after January 1, 2009 were invited to participate in The 90+ Study. Of the 2009 eligible cohort members, 1629 joined The 90+ Study but 303 died and were never seen, 216 were "telephone participants", and 151 were "active by informant". Of the remaining 959, 308 have consented to brain autopsy. Brain autopsy data were available for 264. The Institutional Review Boards of the University of California, Irvine and of the University of Southern California approved the studies. Written informed consent was obtained from all participants or their surrogates.

Brain Autopsy and Pathologic Classification

The brain specimens were procured by the University of California, Irvine Alzheimer's Disease Research Center pathology team and sent to the Department of Pathology at Stanford University where neuropathologic assessment was performed blinded to clinical diagnosis. Neuropathologic index scores were assigned as follows: (1) amyloid beta (Aβ) plaque score (none, Thal phase 1 or 2, Thal phase 3, Thal phases 4 or 5)[13–15]; (2) NFT score (none, Braak stage I or II, Braak stage III or IV, Braak stage V or VI)[13,14,16,17]; (3) Consortium to Establish a Registry for AD staging for neuritic plaques (none, sparse, moderate, frequent).[18] ADNC was defined using the National Institute on Aging-Alzheimer's Association (NIA-AA) "ABC" score, which incorporates Thal Phase for Aβ plaques, Braak staging for NFT, and Consortium to Establish a Registry for AD staging for neuritic plaques (none, low, intermediate, high).[13,14]

Dementia Determination

Participants were evaluated in-person every 6 months. Assessments included physical and neurological examination, neuropsychological test battery[19] that included the Mini-Mental State Examination,[20] and medical history and medication reviews. Dementia diagnosis (DSM-IV)[21] was assigned by a group of trained clinicians during a post-mortem consensus case conference using all available information from the longitudinal evaluations, brain imaging when clinically available, and medical records. The clinical evaluations and dementia diagnoses were blinded to results of the pathologic evaluation.

Antioxidant Vitamin Intake

The Leisure World Cohort survey in the 1980s included questions on current use of any vitamin supplements (no/yes), the number of years taken any vitamins on a regular basis (at least once a week), and specific intake (number per week and dose) of vitamins A, C, and E. Number of years of regular vitamin supplement intake was categorized as <10, 10 to 19, 20+ years. For vitamins A, C, and E, the estimated daily intake was calculated. Users were dichotomized into low and high intake groups with the median intake as the cut-point and compared with nonusers. A follow-up survey in 1998, asked frequency of intake of multivitamin supplements and vitamin A, C, and E supplements with the categories several times a day, 5 to 7 times/week, 3 to 4 times/week, 1 to 2 times/week, a few times/month, about monthly, less often or never. We defined use as that of at least 5 to 7 times/week.

Statistical Analyses

Odds ratios (ORs) of ADNC (intermediate/high vs. none/low) for vitamin supplement intake as measured by the LWCS were estimated using logistic regression analysis. Both unadjusted ORs and ORs adjusted for age at LWCS entry, age at death, sex, and education (college graduate yes vs no) are reported. For supplemental vitamin A, C, and E intake, the ORs are reported for both low and high versus no use as well as any versus no use. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

We also performed a forward stepwise regression to identify those variables most strongly associated with odds of ADNC. The potential variables included age at LWCS entry, age at death, sex, education (college graduate no/yes), and the vitamin variables: currently taking vitamins (no/yes), years regularly taken vitamin supplements (< 10, 10 to 19, 20+), vitamin A supplements (no/yes), vitamin C supplements (no/yes), vitamin E supplements (no/yes).

We conducted supplementary analyses to determine whether the ORs of ADNC for vitamin intake was confounded by other lifestyle practices (smoking, alcohol consumption, caffeine intake, active exercise, body mass index, dietary vitamin C, dietary vitamin A) or by vascular risk factors (hypertension, angina), We also classified participants by the presence of vascular neuropathologies (arteriosclerosis, atherosclerosis, microvascular lesions). See Supplement for a description of these variables.

RESULTS

Table 1 shows the characteristics of the 264 participants included in the analyses. The average age at LWCS entry was 69 years (range 53 to 87), the average age at death was 98 (range 90 to 107), and the average number of years from entry to death was 29 (range 18 to 40). Most participants (76%) were female. About half (51%) were classified as having dementia by consensus case conference.

Participants with ADNC (intermediate/high) were similar to those without (none/low) in age at LWCS entry, age at death, interval from LWCS entry to death, post-mortem interval, and brain weight. As expected, they performed more poorly on Mini-Mental State Examination at last visit (17.6 vs. 22.6, $P < 0.0001$) and were more likely to be classified as having dementia (59% vs. 31%, $P = 0.0001$). A smaller proportion was college graduates (42% vs. 63%, $P = 0.003$). Although a greater proportion were female (78% vs. 69%, $P = 0.15$) or had an *APOE* ε4 allele (24% vs. 13%, $P = 0.06$), these differences were not statistically significant.

Table 2 shows the ORs and 95% CI (both unadjusted and adjusted for age at LWCS entry, age at death, sex, and education) of ADNC in relation to supplemental intake of vitamins A, C, and E. Odds of ADNC were about half for intake of each vitamin compared with those not taking that vitamin. The ORs differed little between "low" and "high" dose intake. The adjusted OR (and 95% CI) of ADNC was 0.52 (0.29-0.92) for vitamin E supplements, 0.51 (0.27-0.93) for vitamin C supplements, and 0.58 (0.33-1.00) for vitamin A supplements.

Stepwise regression found that, after education, supplemental vitamin E intake was the first variable to enter the model. Intake of supplemental vitamin A or C did not improve the model fit.

A follow-up survey in 1998 was completed by 137 (52%) of the participants who had a brain autopsy. Of these, the percent agreement on vitamin E supplement use between the original and follow-up questionnaires was 72% (kappa = 0.4). Fifty-nine (43%) took vitamin E at both times, 39 (28%) took it at neither time, 15 (11%) had stopped taking it, and 24 (18%) had started taking it by time 2. Among these 137 participants, the OR (95% CI) of ADNC was 0.67 (0.27-1.65) for those taking vitamin E at both times, 0.58 (0.19-1.72) for who has started taking by time 2, and 2.24 (0.43-11.7) for those who had stopped taking it by time 2 compared with those taking it at neither time.

Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A435 gives the ORs and 95% CI (both unadjusted and adjusted for age at LWCS entry, age at death, sex, and education) of ADNC in relation to other lifestyle practices, dietary intakes of vitamins A and C,

TABLE 1. Characteristics of 90+ Year Olds by ADNC

	ADNC		
	None, low (n = 75)	Intermediate, high (n = 189)	
	Mean+SD (range)		*P t* test
Age at LWCS entry (y)	68.4+4.5 (56-78)	69.3+5.2 (53-87)	0.15
Age at death (y)	97.9+3.8 (90-107)	98.2+3.4 (90-106)	0.59
Interval from LWCS entry to death (y)	29.5+4.2 (21-40)	28.9+4.7 (18-40)	0.28
Postmortem interval (h) (n = 74, 186)	8.4+9.4 (1.0-67.3)	8.4+12.8 (1.5-98.2)	1.00
Brain weight (n = 70, 180)	1138+125 (907-1412)	1117+123 (864-1670)	0.23
Interval from last MMSE to death (mo) (n = 72, 182)	5.4+5.0 (0.2-26.6)	8.2+12.0 (0.2-84.5)	0.009
MMSE (n = 72, 182)	22.6+6.9 (0-29)	17.6+9.8 (0-30)	< 0.0001
	Number (%)		*P* χ^2
Female sex	52 (69)	148 (78)	0.15
Education—college graduate	47 (63)	79 (42)	0.003
APOE ε4 allele (n = 71, 182)	9 (13)	44 (24)	0.06
APOE ε2 allele (n = 71, 182)	8 (11)	28 (15)	0.55
Case conference diagnosis (n = 75, 188)			0.0001
Normal	28 (37)	34 (18)	
CIND	24 (32)	44 (23)	
Dementia	23 (31)	110 (59)	
Aβ plaque score			
0	29 (39)	0 (0)	
1,2	40 (53)	11 (6)	
3	2 (3)	48 (25)	
4,5	4 (5)	130 (69)	
NFT stage score			
0	3 (4)	0 (0)	
I, II	8 (11)	0 (0)	
III, IV	61 (81)	89 (47)	
V, VI	3 (4)	100 (53)	
Neuritic plaque score			
None	57 (76)	3 (2)	
Sparse	16 (21)	21 (11)	
Moderate	2 (3)	26 (14)	
Frequent	0 (0)	139 (73)	

ADNC indicates Alzheimer's disease neuropathologic change; Aβ, amyloid beta; CIND, cognitive impairment no dementia; LWCS, Leisure World Cohort Study; MMSE, Mini-Mental State Examination; NFT, neurofibrillary tangle.

and comorbidities of hypertension and angina. No association was found. In addition, the ORs for vitamin intake were unchanged when additional adjustment was made for these variables (Supplementary Table 2, Supplemental Digital Content 1, http://links.lww.com/WAD/A435). Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/WAD/A435 shows the relationships of ADNC with the neuropathologies of atherosclerosis, arteriosclerosis and microvascular regions. No significant associations were observed.

DISCUSSION

In our neuropathologic study of persons aged 90 years and older, odds of ADNC was reduced by half with vitamin supplement intake, especially vitamin E supplements, taken about 30 years before death. Several studies have examined the relationship between risk of dementia due to AD and intake of supplemental vitamins, but to our knowledge none have investigated the association between ADNC and intake of vitamins collected decades earlier. Previous longitudinal studies of antioxidant vitamin intake and risk of AD have shown mixed results.[22] Some studies found significant associations for supplemental intake[23–25] whereas others have not.[26–28] Similar mixed results have been found for dietary vitamin intake.[26,29,30] An early report of a prospective study of 633 persons 65 years and older followed for a mean 4.3 years found that use of vitamin E and C supplements was associated with a lower incidence of AD; none of the 27 subjects taking vitamin E supplements developed AD compared with 3.9 predicted based on the crude observed incidence among nonusers and none of the 23 vitamin C supplement users had AD compared with 3.3 predicted.[23] The Cache County Study of 4740 residents age 65 years and older followed for a mean 3 years found nonsignificant reduced incidence of AD (adjusted OR (95% CI)) for vitamin E users of 0.53 (0.20-1.12) and for vitamin C users of 0.74 (0.37-1.35), but a significant reduction for vitamin E and C combined (0.36 (0.09-0.99).[24] A community-dwelling subset of the Canadian Study of Health and Aging (CSHA) including 5269 participants aged ≥ 65 years and followed for a mean 5 years reported hazard ratios (HR) (95% CI) for AD of 0.65 (0.46-0.94) for vitamin E and/or C, 0.62 (0.39-0.98) for vitamin E, and 0.60 (0.38-0.94) for vitamin C.[25]

In contrast, several prospective studies have failed to detect associations between either dietary or supplemental vitamin intake and AD. The Washington Heights-Inwood Columbia Aging Project (WHICAP) with 980 participants aged 65 years and older and followed for a mean 4 years reported lower, but not statistically significant, adjusted HR

TABLE 2. OR and 95% CI for Intermediate/High ADNC by Supplemental Vitamin Intake About 30 Years Earlier

	ADNC			
	None/low (n = 75)	Intermediate/high (n = 189)		
	Number (%)		Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Currently taking vitamin supplements				
No	18 (24)	64 (34)	1.00 (reference)	1.00 (reference)
Yes	57 (76)	125 (66)	0.61 (0.33-1.14)	0.60 (0.32-1.11)
Years regularly taken vitamin supplements				
< 10	29 (40)	92 (51)	1.00 (reference)	1.00 (reference)
10-19	17 (23)	37 (20)	0.69 (0.34-1.40)	0.71 (0.34-1.48)
20+	27 (37)	52 (29)	0.61 (0.32-1.13)	0.67 (0.35-1.28)
Supplementary vitamin A				
None	31 (41)	106 (56)	1.00 (reference)	1.00 (reference)
Low	19 (25)	38 (20)	0.59 (0.30-1.16)	0.64 (0.32-1.28)
High	25 (33)	45 (24)	0.53 (0.28-0.99)	0.53 (0.27-1.01)
Yes			0.55 (0.32-0.95)	0.58 (0.33-1.00)
Supplementary vitamin C				
None	19 (25)	75 (40)	1.00 (reference)	1.00 (reference)
Low	37 (49)	63 (33)	0.43 (0.23-0.82)	0.41 (0.21-0.79)
High	19 (25)	51 (27)	0.68 (0.33-1.41)	0.71 (0.34-1.51)
Yes			0.52 (0.28-0.94)	0.51 (0.27-0.93)
Supplementary vitamin E				
None	24 (32)	91(48)	1.00 (reference)	1.00 (reference)
Low	25 (33)	47 (25)	0.50 (0.26-0.96)	0.51 (0.26-1.00)
High	26 (35)	51 (27)	0.52 (0.27-0.99)	0.53 (0.27-1.04)
Yes			0.51 (0.29-0.89)	0.52 (0.29-0.92)

*Adjusted for age at LWCS entry, age at death, sex, and education (college graduate no/yes).
ADNC indicates Alzheimer's disease neuropathologic change; LWCS, Leisure World Cohort Study; OR, odds ratio.

(95% CI) of 0.85 (0.64-1.13) for vitamin C supplements, 0.91 (0.68-1.22) for vitamin E supplements, 0.84 (CI 0.56-1.26) for fourth versus first quartile dietary vitamin C, and 0.98 (95% CI 0.67-1.44) fourth versus first quartile dietary vitamin E.[26] Similarly, a cohort of 2969 participants aged 65 years and older and followed for a mean 5.5 years in the Adult Changes in Thought study found that the use of supplemental vitamin E and C, alone or in combination did not reduce risk of AD.[27] Results from a prospective study in a biracial community (Chicago Health and Aging Project, CHAP) of 815 residents aged 65 years and older and followed for a mean 3.9 years found a decreasing risk of AD with increasing intake of dietary vitamin E with those in the highest quintile having a relative risk (95% CI) of 0.30 (0.10-0.92).[29] About 20% of the participants reported taking vitamin supplements and no results specifically for supplements were reported. The prospective Rotterdam Study of 5395 participants aged at least 55 years followed for a mean 9.6 years found high dietary intake of vitamin E was associated with lower risk of AD (adjusted HR 0.74, 95% CI 0.56-0.97 for the top tertile compared with the bottom).[30] Use of antioxidant supplements was reported by only 12% of the participants and the risk of AD for supplement intake was not reported. The Honolulu-Asia Aging Study of 2369 Japanese-American men aged 71 to 92 years and followed for a mean 5.2 years found that men using both supplemental E and C intake had no reduced risk of AD.[28]

Few clinical trials have investigated supplemental vitamins and cognitive function. A review and meta-analysis of multivitamins on cognitive performance identified 10 randomized, placebo-controlled trials.[31] Multivitamins were related to improved immediate recall but not delayed free recall memory or verbal fluency. Other cognitive abilities sensitive to AD pathology, such as executive function and visuospatial functions, were found to be under studied. A later randomized trial was a substudy of The Physicians' Health Study II, which included 5947 male physicians aged 65+ years randomized to daily multivitamin or placebo with cognitive assessments by telephone interview over an average 8.5 years.[32] No benefit in slowing cognitive decline was observed. A recent randomized trial, the 3-year COSMOS-Mind study, found evidence to support a multivitamin-mineral supplement to improve cognition in older adults.[33] Of 2262 participants (mean age = 73 y), those receiving the vitamin supplement demonstrated significant benefits on global cognition, memory and executive function. compared with the placebo group.

The only primary prevention controlled trial of supplemental antioxidant intake and AD (PREADVISE) included 7540 men aged 60 years and older randomized to vitamin E (400 IU/day), selenium, or placebo.[34] Supplements were given from 2001 to 2008, with case ascertainment to 2015. Although not significant, patients who took vitamin E supplements alone had a HR of 0.88 (95% CI 0.64-1.20) compared with the placebo group. However, as the authors state, the study was underpowered, included only men, and had a short supplement exposure time (mean 5.4 y).

Our study has the advantages of pathologic diagnosis of AD and of data on vitamin supplement use decades earlier, possibly before disease genesis. The large proportion of vitamin users increases the power of the study to detect differences in risk. However, data on vitamin intake were self-reported using a mailed questionnaire and reflects intake at one point in time. To validate information on vitamin supplement use, we previously compared data with that collected by personal interview 15 months later.[35] Current supplement use as ascertained by the two methods was

comparable with 84% agreement. In addition, a follow-up survey more than 10 years after the initial found that nearly half took vitamin E at both times and a quarter took it at neither time. Change (either stopping or starting the vitamin), if unrelated to ADNC, would attenuate the observed risk to the null. Moreover, many participants reported having regularly taken vitamin supplements for many years (over half of the participants for 10 or more). Another strength is our ability to consider and adjust for multiple lifestyle practices and dietary intake in our analyses, which did not change the observed associations between vitamin supplements and ADNC.

One limitation of our study is the lack of dietary vitamin E data. However, the LWCS members were well fed. The median intake of vitamin A from food sources was 17,206 IU, and more than 95% received the 1980 Recommended Dietary Allowance specified by the National Research Council for vitamin A (5000 IU for men, 4000 IU for women) from food sources alone.[36] Another limitation is that our primarily white, moderately affluent, and highly educated cohort may limit the generalization of our results to more diverse groups. In addition, the results may apply to only those who reach age 90 years.

We previously compared the vitamin supplement intake and lifestyle behaviors (smoking, alcohol consumption, caffeine intake, exercise, body mass index) of the 264 participants who had neuropathologic evaluation with the 1365 who did not and found no significant differences (Paganini-Hill et al, personal communication). Similarly, we found no difference in age at LWCS entry or proportion female. However, those with a neuropathologic evaluation were more likely to be college graduates (58% vs. 36%, $P = 0.0005$). In addition, none of the lifestyle behaviors was associated with odds of ADNC.

Vitamin E has a broad range of biological functions that extend beyond its potent antioxidant capabilities. These include other neuro-protective, anti-inflammatory and cholesterol-reducing properties as well as influencing immune function and cellular signaling.[37,38] In studies in a mouse model of AD vitamin E reduced Aβ deposition, but only at an early age, that is, at an early stage of the disease process.[39,40]

A nutritional approach to preventing AD with vitamin supplementation would be an easily administered, safe, cost effective, and acceptable intervention. However, despite years of scientific research, no definitive evidence exists for disease prevention or modification outside of animal and in vitro experiments. Nonetheless, epidemiological and clinical trials in humans are suggestive and nutritional interventions, such as vitamin supplementation, merit further investigation.

REFERENCES

1. Alzheimer A, Stelzmann RA, Schnitzlein HN, et al. An English translation of Alzheimer's 1907 paper, "Uber eine eigenartige Erkankung der Hirnrinde". *Clin Anat*. 1995;8:429–431.
2. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18:700–789.
3. Tariq S, Barber PA. Dementia risk and prevention by targeting modifiable vascular risk factors. *J Neurochem*. 2018;144:565–581.
4. Rabbito A, Dulewicz M, Kulczynska-Przybik A, et al. Biochemical markers in Alzheimer's disease. *Int J Mol Sci*. 2020;21:1989.
5. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25:5789.
6. Tonnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. *J Alzheimers Dis*. 2017;57:1105–1121.
7. Mielech A, Puscion-Jakubik A, Markiewicz-Zukowska R, et al. Vitamins in Alzheimer's Disease-Review of the Latest Reports. *Nutrients*. 2020;12:3458.
8. Arslan J, Jamshed H, Qureshi H. Early detection and prevention of Alzheimer's disease: role of oxidative markers and natural antioxidants. *Front Aging Neurosci*. 2020;12:231.
9. Paganini-Hill A, Kawas CH, Corrada MM. Lifestyle factors and dementia in the oldest-old: the 90+ study. *Alzheimer Dis Assoc Disord*. 2016;30:21–26.
10. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: the 90+ study. *Curr Alzheimer Res*. 2012;9:709–717.
11. Paganini-Hill A, Ross RK, Henderson BE. Prevalence of chronic disease and health practices in a retirement community. *J Chronic Dis*. 1986;39:699–707.
12. Paganini-Hill A, Chao A, Ross RK, et al. Exercise and other factors in the prevention of hip fracture: the Leisure World study. *Epidemiology*. 1991;2:16–25.
13. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012;8:1–13.
14. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123:1–11.
15. Thal DR, Rub U, Orantes M, et al. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002;58:1791–1800.
16. Braak H, Alafuzoff I, Arzberger T, et al. Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathol*. 2006;112:389–404.
17. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239–259.
18. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*. 1991;41:479–486.
19. Whittle C, Corrada MM, Dick M, et al. Neuropsychological data in nondemented oldest old: the 90+ Study. *J Clin Exp Neuropsychol*. 2007;29:290–299.
20. Folstein MF, Folstein SE, McHugh PR. Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
21. American Psychiatric Association. Task Force on DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders : DSM-IV*. American Psychiatric Association; 1994.
22. Zhao R, Han X, Zhang H, et al. Association of vitamin E intake in diet and supplements with risk of dementia: a meta-analysis. *Front Aging Neurosci*. 2022;14:955878.
23. Morris MC, Beckett LA, Scherr PA, et al. Vitamin E and vitamin C supplement use and risk of incident Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1998;12:121–126.
24. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. *Arch Neurol*. 2004;61:82–88.
25. Basambombo LL, Carmichael PH, Cote S, et al. Use of vitamin E and C supplements for the prevention of cognitive decline. *Ann Pharmacother*. 2017;51:118–124.
26. Luchsinger JA, Tang MX, Shea S, et al. Antioxidant vitamin intake and risk of Alzheimer disease. *Arch Neurol*. 2003;60:203–208.
27. Gray SL, Anderson ML, Crane PK, et al. Antioxidant vitamin supplement use and risk of dementia or Alzheimer's disease in older adults. *J Am Geriatr Soc*. 2008;56:291–295.
28. Laurin D, Foley DJ, Masaki KH, et al. Vitamin E and C supplements and risk of dementia. *JAMA*. 2002;288:2266–2268.

29. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA*. 2002;287: 3230–3237.
30. Devore EE, Grodstein F, van Rooij FJ, et al. Dietary antioxidants and long-term risk of dementia. *Arch Neurol*. 2010;67:819–825.
31. Grima NA, Pase MP, Macpherson H, et al. The effects of multivitamins on cognitive performance: a systematic review and meta-analysis. *J Alzheimers Dis*. 2012;29:561–569.
32. Grodstein F, O'Brien J, Kang JH, et al. Long-term multivitamin supplementation and cognitive function in men: a randomized trial. *Ann Intern Med*. 2013;159:806–814.
33. Baker LD, Manson JE, Rapp SR, et al. Effects of cocoa extract and a multivitamin on cognitive function: a randomized clinical trial. *Alzheimers Dement*. 2022. [Epub ahead of print]. doi:10.1002/alz.12767
34. Kryscio RJ, Abner EL, Caban-Holt A, et al. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). *JAMA Neurol*. 2017;74:567–573.
35. Gray GE, Paganini-Hill A, Ross RK, et al. Assessment of three brief methods of estimation of vitamin A and C intakes for a prospective study of cancer: comparison with dietary history. *Am J Epidemiol*. 1984;119:581–590.
36. Paganini-Hill A, Kawas CH, Corrada MM. Antioxidant vitamin intake and mortality: the Leisure World Cohort Study. *Am J Epidemiol*. 2015;181:120–126.
37. Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. *Free Radic Biol Med*. 2014;72:76–90.
38. Browne D, McGuinness B, Woodside JV, et al. Vitamin E and Alzheimer's disease: what do we know so far? *Clin Interv Aging*. 2019;14:1303–1317.
39. Ibrahim NF, Yanagisawa D, Durani LW, et al. Tocotrienol-rich fraction modulates amyloid pathology and improves cognitive function in AbetaPP/PS1 Mice. *J Alzheimers Dis*. 2017;55:597–612.
40. Sung S, Yao Y, Uryu K, et al. Early vitamin E supplementation in young but not aged mice reduces Abeta levels and amyloid deposition in a transgenic model of Alzheimer's disease. *FASEB J*. 2004;18:323–325.