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Midlife Fruit and Vegetable Consumption and Risk of Dementia in Later Life in Swedish Twins

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Abstract

Objective: Diet may be associated with risk of dementia and Alzheimer's disease (AD). We examined the association between fruit and vegetable consumption in midlife and risk for all types of dementia and AD.

Methods: Participants were 3,779 members of the Swedish Twin Registry who completed a diet questionnaire approximately 30 years prior to cognitive screening and full clinical evaluation for dementia as part of the HARMONY study. Among the participants, 355 twins were diagnosed with dementia. Among these, 81 twin pairs were discordant for dementia (50 discordant for AD). Data were analyzed with logistic regression for the entire sample using generalized estimating equations to adjust for relatedness of twins, and with conditional logistic regression for the co-twin control design.

Results: In fully-adjusted models, a medium or great proportion of fruits and vegetables in the diet, compared to no or small, was associated with a decreased risk of dementia and AD. This effect was observed among women and those with angina. Similar, but non-significant, odds ratios were found in the co-twin control analyses.

Conclusion: Our findings suggest that higher fruit and vegetable consumption may reduce the risk of dementia, especially among women and those with angina pectoris in midlife.

Keywords

dementia; Alzheimer's disease; diet; fruits and vegetables

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Objective

The potential for adults to alter their risk for dementia through health behaviors is an important area of inquiry. A healthy lifestyle including mental, physical, and social stimulation as well as a healthy diet is thought to increase brain or cognitive reserve and possibly alter the expression of dementia. (1-4) Evidence is building that intake of antioxidants (5-9), either through supplements or from food, may reduce the risk of dementia. Current studies of the relation between sources of antioxidants, including fruits and vegetables, are susceptible to misinterpretation given the relatively short time period between dietary assessment and dementia onset. This is because dementia has a long preclinical phase (10) that is commonly associated with difficulties performing instrumental activities of daily living (11) and weight loss (12,13) that may influence dietary habits. Further, these studies have been unable to account for genetic or early-life influences that may account for any associations between diet and dementia, which is important based on knowledge that dementia is highly heritable (14) and dietary habits may be influenced by genetics (15) or by familial environment and early-life behaviors (16).

We sought to address these limitations by examining the relation between the relative intake of fruits and vegetables at midlife and risk of dementia approximately three decades later in members of a large population-based twin study. Using all available data, we tested whether a medium or great proportion, compared to no or small, of fruits and vegetables in the diet in midlife offered protection against dementia and AD in later life. We also used a co-twin control design to explore whether these results would be affected by accounting for unmeasured factors shared by twins.

Methods

Participants

The Swedish Twin Registry (STR) is the largest twin registry in the world and consists of three population-based cohorts of like-sexed twin pairs. It was initially designed to study the importance of environment on several diseases while controlling for genetic influences. (17) This study draws from the members of the cohort born between 1886 and 1925 who responded to a questionnaire mailed in 1967.

In 1998, the HARMONY study was initiated to examine the relative influences of environmental and genetic factors on the etiology of AD and other dementias, to identify genes that increase the risk for dementia, and to identify specific environmental risk or protective factors for dementia and AD. Members of HARMONY consisted of all twins who were at least 65 years of age at time of assessment in HARMONY. (18) The HARMONY study was reviewed and approved by the institutional review board of the University of Southern California and the regional ethics board at the Karolinska Institute.

In all, 5,692 mono- and like-sexed dizygotic twins eligible for HARMONY had data for fruit/vegetable intake from 1967. Dementia status (see below) was available for 3,779 of these twins (66.4%). Among the others, 1,020 (17.9%) refused to participate, 255 (4.5%) were not reachable, 283 (5.0%) were unable to be interviewed and an informant was not available, 104 (1.8%) died before they could be screened, and 252 (4.4%) were screened but not seen for a clinical evaluation either by design (because their co-twin was deceased and the pair would be uninformative) or due to refusal. A total of 3,424 non-demented participants and 355 dementia cases (240 AD) were used. For the co-twin control analyses, 81 twin pairs discordant for dementia were identified (18 of whom were discordant for diet), including 50 pairs discordant for AD (12 of whom were discordant for diet). Adjustment for

covariates reduced the sample size for dementia (n=3,318, n=59 for co-twin control) and AD (n=3,217, n=38 for co-twin control) analyses.

Measures

Dementia Diagnosis—Individuals were screened and clinically evaluated for prevalent dementia as part of the HARMONY study. A random sample was selected each month for the primary telephone screening phase to identify twins positive for cognitive dysfunction. (19) Those who screened positive and their co-twin, even if they screened negative, were contacted for an follow-up in-person clinical evaluation using the diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (20) for dementia, and the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (21) criteria for AD.

Dietary Assessment—The STR 1967 questionnaire (22) included 23 items pertaining to dietary habits. Fruit and vegetable consumption was assessed by a single item on a 4-point scale with response choices being “great part”, “medium part”, “small part”, or “no part” of the respondent's diet. For the current study, the “no” and “small” part categories and the “medium” and “great” part categories were collapsed due to the small number of participants reporting that fruits and vegetables made up “no part” or a “great part” of their diet.

Covariates—Age at follow-up (continuous), gender, and education (mandatory basic education (≤ 6 years)/more than mandatory (> 6 years)) were included as covariates. Other covariates from the STR 1967 questionnaire included: self-reported current smoking status (yes/no), alcohol consumption (abstain (no drinks)/moderate (1-5 drinks per week)/in excess (> 5 drinks per week)), exercise (hardly any or light/regular or hard), body mass index ($BMI = \text{weight}[\text{kg}] / \text{height squared}[\text{m}^2]$; underweight (< 18.5)/normal (18.5-25)/overweight or obese (≥ 25)), angina pectoris (yes/no), total food intake in comparison to others (less or as much/more or much more), and marital status (married or re-married/unmarried, divorced, or widowed). Unmeasured familial factors were controlled by design in the co-twin control analyses.

Statistical Analyses

The characteristics of the participants by diagnostic status were compared using independent samples *t*-tests for continuous variables and χ^2 tests for categorical variables. In the analysis using the entire sample, where cases were compared to unrelated, non-demented participants, we used generalized estimating equations (GEE) for correlated data with SAS procedure GENMOD with a number unique to each twin pair as the repeated subject variable. We subsequently restricted the sample to those younger than 60 years of age in 1967 to further reduce any influence of preclinical dementia on diet. To test for effect-modification, we entered multiplicative interaction terms of each covariate by fruit and vegetable intake in separate fully adjusted models and, if the interaction reached statistical significance, used stratified analyses by the covariate to aid in interpretation.

Co-twin control analyses, which use disease-discordant twin pairs by comparing exposure in the diagnosed twin to the non-demented co-twin, were conducted using conditional logistic regression in SAS procedure PHREG. Within each twin pair, the twin who reported greater consumption of fruits and vegetables was assigned a value of 1 and the co-twin was assigned a value of 0. When twins reported the same intake level, both twins were assigned a value of 0 and these pairs did not contribute to the calculation of the point estimates. All analyses were conducted in SAS version 9 (23) with *p*-values less than 0.05 (two-tailed) interpreted as being statistically significant.

Results

Comparisons between the 3,779 participants and the 1,914 drop-outs showed that the drop-outs were on average 0.92 years older at follow-up ($t_{[5,691]} = 8.28, p < 0.001$), more likely to be women (70% versus 62%, $\chi^2_{[1]} = 32.56, p < 0.001$), less likely to attain more than a basic education (25% versus 36%, $\chi^2_{[1]} = 60.48, p < 0.001$), more likely to abstain from alcohol than to drink moderately (63% versus 53%, $\chi^2_{[1]} = 32.05, p < 0.001$) or in excess (54% versus 45%, $\chi^2_{[1]} = 31.15, p < 0.001$), and be underweight compared to normal (27% versus 20%, $\chi^2_{[1]} = 31.84, p < 0.001$) or overweight/obese (78% versus 69%, $\chi^2_{[1]} = 16.11, p < 0.001$). For both sets of analyses, we compared participants included in the fully-adjusted models with the participants included in the crude models for differences on the covariates and found no significant differences.

The characteristics of cases ($n = 355$ for dementia, $n = 240$ for AD) and participants without dementia ($n = 3,424$) are shown in Table 1. Independent samples t -test or Chi-square statistic comparing controls and cases revealed that compared to the non-demented, dementia and AD cases were older at baseline and at follow-up, more likely to be women, less educated, less likely to smoke, less likely to drink alcohol in moderation or in excess (compared to abstain), less likely to be married, to be of normal weight (compared to underweight), and less likely to consume more or much more food compared to others.

The association between fruit and vegetable intake and dementia and AD using the entire sample is presented in Table 2. Compared with those reporting no or small proportion of fruits and vegetables, those whose diet consisted of a medium or great part of fruits and vegetables had reduced odds for dementia (by 27%) and AD (by 40%) in fully-adjusted models. The results were strengthened by the addition of covariates, particularly by gender and by the combined effect of lifestyle-related covariates that were related to the consumption of fruits and vegetables but not necessarily to the risk of dementia. Results of analyses restricted to those less than 60 years of age in 1967 (2,938 non-demented, 270 dementia cases, 176 AD cases) showed that a medium or great part remained associated with reduced risks for dementia (OR = 0.71, 95% CI: 0.51 – 0.98, $z = -2.10_{[13]}, p = 0.04$) and AD (OR = 0.57, 95% CI: 0.39 – 0.84, $z = -2.88_{[13]}, p = 0.004$) in fully-adjusted models.

Significant interactions emerged for fruit and vegetable consumption with gender and angina pectoris (Table 3). Separate stratified analyses by these covariates indicated that the inverse association between fruit and vegetable consumption and dementia and AD risk was observed among women but not men, and among those who self-reported angina but not among those who did not.

In the co-twin control analyses, the risk of dementia (OR = 0.50, 95% CI: 0.14-1.84, $\chi^2 = 1.09_{[9]}, p = 0.30$) and AD (OR = 0.47, 95% CI: 0.08-2.71, $\chi^2 = 0.71_{[9]}, p = 0.40$) in fully-adjusted models was in the same direction as in the analyses with the entire sample, but not statistically significant.

Discussion

Using a dietary assessment approximately three decades prior to dementia evaluation, we found that midlife fruit and vegetable consumption was associated with a reduced risk of dementia and AD in case-control analyses. Unlike previous findings based on a relatively short follow-up (5-9), our findings suggest that higher fruit and vegetable intake assessed at midlife (when dementia is unlikely to influence dietary behavior) is associated with a lower risk of dementia and AD later, strengthening the evidence-based support for fruit and vegetable intake as a potential dementia prevention strategy.

The point estimates from the co-twin analyses indicated even stronger effects of fruit and vegetable intake than in the analyses with the entire sample, but were not statistically significant. When an association is observed in a case-control analysis but is not replicated in a co-twin control analysis, then generally there are two possible explanations. First, the association seen in the case-control results was due to genetic or other familial factors, so that the association disappears in a co-twin control analysis. Second, the nonsignificant finding in the co-twin analysis is due to low power (11% for dementia and 10% for AD in this study). Typically, the second explanation is favored when the number of discordant pairs is small and the point estimates are similar in the case-control and co-twin control analyses. Only 22% of the pairs who were discordant for dementia were also discordant for fruit and vegetable consumption and the point estimates in the case-control and co-twin control analyses were similar in the present study. This lends support to attributing the non-significance to low power. Further research is needed to elucidate our findings from the co-twin analyses.

Pathologic processes shown to be involved in dementia and AD include oxidative stress (24) and inflammation (25). Fruits and vegetables contain a number of compounds with antioxidant and anti-inflammatory properties (e.g., vitamins C and E, carotenoids, and polyphenols that are non-vitamin antioxidants more potent than conventional vitamins (6)), which may offer neuroprotection by scavenging free radicals and/or reducing inflammation. Therefore, higher fruit and vegetable intake may reduce the risk of dementia through these mechanisms, hence increasing the brain's ability to withstand more pathology before clinical symptoms are detectable (i.e. brain reserve). (3,4)

We found that the association between fruit and vegetable consumption and AD was modified by gender and angina pectoris. In stratified analyses, the reduction in risk for dementia and AD was significant among women but not among men. This finding is consistent with findings from the Honolulu-Asia Aging Study (HAAS) where midlife antioxidant intake did not predict incident dementia over 30 years of follow-up in an all male sample. (26) Some have shown that women are at greater risk dementia and AD. (27,28) Although this may be a function of greater longevity among women (29), it may also be related to sex-specific differences in antioxidant metabolism in the AD brain where females have more severe oxidative stress (30) that contributes to increased pathology. Higher consumption of fruits and vegetables among women may ameliorate this vulnerability to oxidative stress. Another explanation is that there are gender differences in fruit and vegetable consumption where women have been shown to consume more compared with men. (31)

We also found higher fruit and vegetable consumption was protective for those who reported angina but not among those who did not. The risk of dementia has been shown to be higher with the presence of vascular factors such as angina pectoris. (32) Since vascular health can be improved with a healthier diet, which may include a higher intake of fruits and vegetables (33), the risk of dementia may be reduced in those with angina through a vascular mechanism.

Limitations of this study include the use of a single item to assess fruit and vegetable consumption, which likely does not capture total intake. However, the fact that we found an association with a single item increases our confidence that fruit and vegetable intake plays a role in dementia risk. In addition, these data still have unique value given the current sparseness of data on diet many decades before dementia onset. We also could not assess the stability of responses. However, the question was formulated to measure overall dietary habits and only 14% of the non-demented and 12% of cases reported a past change in diet. The measurement of fruit and vegetable intake was by self-report, making it susceptible to

social desirability bias, although this is unlikely to vary by outcome status many decades later. Finally, we did not examine if other foods interacted with fruits and vegetables to impact dementia risk, which should be considered in future analyses.

Additional limitations include our inability to restrict our co-twin control analyses to monozygotic twins only due to small sample size. Therefore, our findings account for unmeasured early life factors in both groups of twins but only partially account for genetic influences. We also could not adjust for total energy intake since these data were not available. However, we adjusted for self-reported total food consumption compared to others and for BMI. Adjustments for full family history of dementia and APOE-ε4 were not included since only those who participated in the follow-up in-person evaluation had these data available. Control for other cardiovascular risk factors (e.g., diabetes, hypertension), which are now known risk factors for dementia, would have been desirable; however, in 1967 when participants were asked about their health problems, very few suffered from these conditions. There is also the potential for selection bias because we used prevalent cases and because those missing a dementia diagnosis (i.e., the “drop-outs”) were older, more likely to be women, less educated, more likely to abstain from alcohol and be underweight, which have been previously shown to be associated with dementia. However, since lower fruit and vegetable intake would likely increase the risk of mortality (34), and the drop-outs may have been at a greater risk of dementia (but were similar with respect to fruit and vegetable consumption); our results may have underestimated the association with dementia.

In conclusion, this study suggests that greater fruit and vegetable consumption may lower the risk of dementia and AD, especially among women and those with angina pectoris. These findings emphasize the importance of including a greater proportion of fruits and vegetables in the diet for cognitive health.

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Table 1

Characteristics of the Participants by Disease Status

	All	Non-demented	Cases		^a Test statistic (adj) p-value	
			Dementia	Alzheimer's Disease	Dementia	Alzheimer's Disease
n	3,779	3,424	355	240		
Age at diet assessment, Mean (SD, Range)	48.33 (5.14, 42-71)	47.87 (4.85, 42-71)	52.81 (5.71, 42-71)	52.96 (5.63, 42-68)	-17.94 [3,777], <.001	-15.54 [3,662], <.001
Age at cognitive screening, Mean (SD, Range)	79.81 (5.09, 70-103)	79.35 (4.81, 70-102)	84.22 (5.58, 72-103)	84.41 (5.53, 72-99)	-17.89 [3,777], <.001	-15.61 [3,662], <.001
Follow-up years, Mean (SD, Range)	31.47 (0.91 - 28-35)	31.48 (0.91, 28-35)	31.41 (0.95, 30-34)	31.45 (0.93, 30-34)	1.29 [3,777], 0.20	0.42 [3,662], 0.67
Gender, n (%) women	2,346 (62.08)	2,087 (60.95)	259 (72.96)	184 (76.67)	19.69 [1], <0.001	2.50 [1], <0.001
Education, n (%) more than basic	1,342 (35.57)	1,266 (37.03)	76 (21.47)	55 (23.01)	33.89 [1], <0.001	19.02 [1], <0.001
Smoke, n (%) yes	1,059 (29.52)	989 (30.38)	70 (21.02)	222 (20.72)	12.73 [1], <0.001	9.28 [1], 0.002
Drink alcohol, n (%) no drinks/ week	1,229 (32.52)	1,075 (31.25)	159 (44.79)	108 (45.00)	reference	reference
n (%) 1-5 drinks/week	1,074 (28.42)	979 (28.59)	95 (26.76)	68 (28.33)	9.78 [1], 0.002	5.44 [1], 0.02
n (%) > 5 drinks/week	1,476 (39.06)	1,375 (40.16)	101 (28.45)	64 (26.67)	28.67 [1], <0.001	23.51 [1], <0.001
Body mass index, n (%) < 18.5	695 (18.39)	601 (17.55)	94 (26.48)	64 (26.67)	reference	reference
n (%) 18.5 - 25	2,773 (73.38)	2,545 (74.33)	228 (64.23)	159 (66.25)	18.55 [1], <0.001	12.10 [1], <0.001
n (%) > 25	311 (8.23)	278 (8.12)	33 (9.30)	17 (7.08)	1.65 [1], 0.20	3.94 [1], 0.05
Angina pectoris, n (%) yes	887 (25.43)	812 (25.64)	75 (23.36)	48 (22.22)	0.80 [1], 0.37	1.25 [1], 0.26
Total food intake compared to others, n (%) more or much more	344 (9.18)	324 (9.54)	20 (5.68)	11 (4.64)	5.70 [1], 0.02	6.35 [1], 0.01
Exercise, n (%) hardly any or light	3,012 (82.57)	2,724 (82.35)	288 (84.71)	93 (84.65)	1.19 [1], 0.27	0.78 [1], 0.38
Married, n (%) married or remarried	3,117 (83.16)	2,842 (83.69)	275 (78.13)	187 (78.24)	7.05 [1], 0.01	4.76 [1], 0.03
Fruit and vegetable intake, n (%) medium or great	2,998 (79.07)	2,716 (79.32)	272 (76.62)	178 (74.17)	1.42 [1], 0.23	3.59 [1], 0.06

t -test for continuous variables, χ^2 test for categorical variables comparing non-demented to cases.

Table 2

The Association between Medium or Great Fruit and Vegetable Intake and Dementia or Alzheimer's Disease

	Cases/Non-demented	z-score	OR (95% CI)	p-value
Dementia				
Model 1 (Crude)	355/3424	-1.19	0.85 (0.66 - 1.11)	0.23
Model 2 *	354/3419	-1.53	0.80 (0.60 - 1.07)	0.13
Model 3 †	302/3016	-1.94	0.73 (0.53 - 1.00)	0.05
Alzheimer's Disease				
Model 1 (Crude)	240/3424	-1.89	0.75 (0.55 - 1.01)	0.06
Model 2 *	239/3419	-2.35	0.67 (0.48 - 0.94)	0.02
Model 3 †	201/3016	-2.77	0.60 (0.41 - 0.86)	<0.01

Note. df = degrees of freedom; OR = odds ratio; 95% CI = 95% confidence interval. No or small fruit and vegetable intake is the reference group. Crude model df = 1.

* Models adjusted for age at cognitive screening (continuous), gender (men/women), and education (basic/more than basic) with df = 4.

† Models adjusted for variables mentioned above and smoking (yes/no), alcohol drinking (no/1-5 drinks/> 5 drinks), angina pectoris (yes/no), body mass index (<18.5/18.5-25/≥25), total food compared to others (less or more/more or much more), marital status (married or remarried/unmarried, divorced, or widowed), and exercise (hardly any or light/regular or hard) with df = 11.

Table 3

Stratified Analyses of the Association between Medium or Great Fruit and Vegetable Intake and Dementia or Alzheimer's Disease

	Cases/Non-demented	z-score	OR (95% CI)	p-value
Dementia				
Gender × Fruit and Vegetable Intake	302/3,016	-2.12	0.50 (0.27 - 0.95)	0.03
Men	80/1,217	1.06	1.32 (0.79 - 2.20)	0.29
Women	222/1,799	-2.88	0.56 (0.38 - 0.83)	0.004
Angina × Fruit and Vegetable Intake	302/3,016	-2.00	0.51 (0.27 - 0.99)	0.05
Yes	72/770	-2.46	0.47 (0.26 - 0.86)	0.01
No	230/2,246	-0.68	0.88 (0.60 - 1.28)	0.50
Alzheimer's Disease				
Gender × Fruit and Vegetable Intake	201/3,016	-2.02	0.45 (0.21 - 0.98)	0.04
Men	46/1,217	0.42	1.15 (0.60 - 2.20)	0.67
Women	155/1,799	-3.41	0.47 (0.31 - 0.73)	<0.01
Angina × Fruit and Vegetable Intake	201/3,016	-2.09	0.44 (0.21 - 0.95)	0.04
Yes	46/770	-3.12	0.32 (0.16 - 0.65)	<0.01
No	155/2,246	-1.32	0.74 (0.48 - 1.15)	0.19

Note: Degrees of freedom in the interaction model = 12. Degrees of freedom in the stratified analyses = 11.