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FRUIT, VEGETABLES AND PREVENTION OF COGNITIVE DECLINE OR DEMENTIA: A SYSTEMATIC REVIEW OF COHORT STUDIES

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Abstract: *Background:* Regular consumption of fruit and vegetables has been considered to be associated with a reduced risk of dementia and age-associated cognitive decline, although the association is currently unsupported by a systematic review of the literature. *Methods:* We searched Medline, Embase, Biosis, ALOIS, the Cochrane library, different publisher databases as well as bibliographies of retrieved articles. All cohort studies with a follow-up of 6 months or longer were included if they reported an association of Alzheimer's disease or cognitive decline in regard to the frequency of fruit and vegetables consumption. *Findings:* Nine studies with a total of 44 004 participants met the inclusion criteria. Six studies analyzed fruit and vegetables separately and five of them found that higher consumption of vegetables, but not fruit is associated with a decreased risk of dementia or cognitive decline. The same association was found by three further studies for fruit and vegetable consumption analytically combined. *Conclusion:* Increased intake of vegetables is associated with a lower risk of dementia and slower rates of cognitive decline in older age. Yet, evidence that this association is also valid for high fruit consumption is lacking.

Key words: Fruit, vegetables, dementia, Alzheimer's disease, systematic review.

Introduction

"Five a day" is a public health slogan promoted by WHO since 1990 (1), which promotes eating five portions of fruit and vegetables a day (ca. 400g) in order to prevent chronic diseases.

While the underlying evidence is more (2, 3) or less (4) conclusive for coronary heart disease and stroke or cancer respectively, there is need to clarify the benefits of fruit and vegetable consumption in cognitive decline and dementia.

From an etiologic perspective, fruit and vegetable consumption may influence the pathology of AD in several different ways. Both contain high quantities of a variety of nutrients including vitamin C, vitamin E, trace elements, dietary fiber, flavonoids, ß-carotenes and other classes of phytochemicals.

These compounds exert their action by a plenitude of different mechanisms; for instance, they can modulate detoxifying enzymes, stimulate the immune system, modulate cholesterol synthesis and act as antibacterial, antioxidant or neuroprotective agents (5).

In comparison to single nutrients, the complex mixture of chemicals in whole foods may lead to synergistic health effects (6). Also, nutritional advice is often easier to grasp and thus more likely to be put into practice when related to whole food rather than to nutritional components (7).

In light of the increasing incidence of dementia (8), we need a better understanding on whether the 'Five a day' also covers the prevention of dementia or needs respective modification. We have therefore undertaken a systematic review of cohort studies to better assess whether consumption of fruit and vegetables, which kind and how much, lowers the risk of developing dementia.

Methods

Search Strategy and Selection Criteria

We searched, with no language restriction, the databases Alois, Biosis, Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and publisher data bases of Karger and Thieme from their beginning to March 2011. We searched for studies reporting an association between fruit and vegetable consumption and Alzheimer's disease. In detail, we sought to cover all studies in the intersection of three thematic areas: Alzheimer's disease, cohort studies and fruit and vegetable consumption.

We used terms related to Alzheimer's disease (Alzheimer*, dementia*, cognit*, neurodegen*), prospective studies (cohort*, prospective*, follow up) and fruit and vegetables (fruit*, vegetabl*, vitamin*, flavono*, carotenoid*, antioxidant*).

To assure covering all relevant data we also included related terms (e.g. flavonoids or Mediterranean diet) that could have contained alternative analyses of the original data we are looking for. We supplemented the search by screening the bibliographies of the retrieved articles.

Two investigators independently assessed the studies for eligibility. One of them (ML) iteratively modified the search strategies and terms to assure covering of all relevant studies.

Inclusion criteria were (1) use of tests to measure cognitive changes, for instance, Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) or the mini-mental-state examination (MMSE); (2) number of events or reported risk estimates for Alzheimer's disease (AD), dementia, mild

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cognitive impairment (MCI) or cognitive decline based on measures of fruit and vegetable consumption; (3) cohort studies with 6 months or longer of follow up. Studies on micronutrients or on certain food preparations were excluded.

Data Extraction and Quality Assessment

Two researchers independently performed the study selection and assessed the quality of the manuscripts as recommended elsewhere (9). Disagreement was solved by consensus.

The major criteria of quality assessment were (1) description of baseline scores of cognitive function; (2) description of the assessment of dietary intake; (3) comparibility of the study groups with respect to factors such as age, sex, education, apolipoprotein E ε4 genotype and supplement usage; (4) adjustment for the effects of these confounding variables in the statistical analysis.

The data were extracted by a standardized list, including name and place of the study, study design, mean age of participants, duration of the study and mean duration of follow-up, and clinical outcomes on different cognitive rating scales.

Statistical Analysis

We did not conduct a meta-analysis for the association between the intake of fruits and vegetables and Alzheimer's disease because of the studies' heterogeneity in terms of outcome parameters and their statistical analyses.

Results

Of the 1,764 publications that had been retrieved, we identified nine studies that met the inclusion criteria. Figure 1 shows details of the study selection. The methods and results of the studies are summarized in table 1 (10-18).

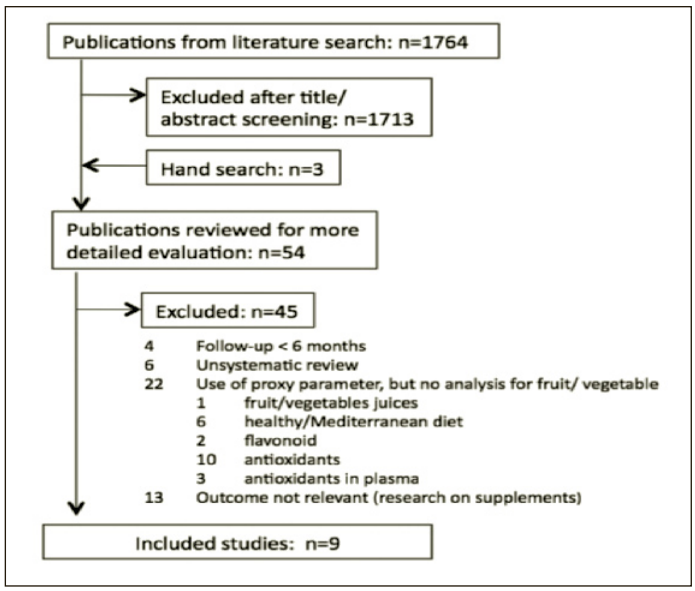
Of the nine cohort studies, three were from the US, three from France, two from the Netherlands and one from Sweden. Five studies used the incidence of dementia, AD or mild cognitive impairment (MCI) in the study population as a primary outcome parameter (10, 13-15, 18), while, in the four remaining studies, the rate of cognitive decline over time was assessed (11, 12, 16, 17).

All nine studies applied food frequency questionnaires (FFQ) to assess the dietary intake of vegetables and fruit. One study made use of bivalent nutritional questionnaires on fruit/vegetables (two portions a day vs. less) and fish consumption (once a week vs. less) (10). Four studies used semi-quantitative FFQ at administered baseline (11, 12, 15, 17). One study repeated the FFQ every fourth year (12) and in another, the FFQ was preceded by a checklist on all foods and drinks that had been consumed by the participants (15).

The definitions of high vs. low frequency of fruit and vegetable intake were heterogeneous and are displayed in table 1.

Six trials gathered information on the frequency of the consumption of fruit and vegetable separately (11-16) and five of these also analyzed the data separately (11, 12, 14-16).

Figure 1
Flow chart of the selection process



While one study found cognitive decline measured by the DECO-scale not to be associated neither with high fruit consumption nor with increased intake of vegetables (16), five other studies reported an association between a lower risk of dementia (14, 15) or a slower rate of cognitive decline (11, 12, 17) and a high intake of vegetables. None of the studies found such an association for fruit consumption. Four studies analyzed the effects of fruit and vegetable consumption in combination (10, 13, 17, 18) and found the incidence of MCI, AD and dementia, but not cognitive decline to be associated with frequent fruit and vegetable intake.

Two trials specified that approx. 3 servings (11) and 200 mg of vegetable (14) a day or more were associated with a lower risk of cognitive decline or MCI, respectively. The strongest associations between cognitive decline and vegetable consumption have been found for cruciferous vegetables, legumes and green leafy vegetables (11, 12), particularly cabbage (17), zucchini, squash, broccoli and lettuce (11).

Discussion

Our systematic review has summarized what is currently known on the relationship between fruit and vegetable intake and the risks of AD, dementia and cognitive decline. Most of the included studies show that frequent consumption of vegetables is associated with a lower risk of dementia whereas the evidence for such an association is lacking with regard to fruit intake. Since one of the nine studies found no benefit of either fruit or of vegetable intake on cognitive performance (16), results are not definitive and should taken with caution. It might nevertheless be summarized that the findings moderately support the recommendation of an intake of at least three servings (11, 12) or more than 200g (14) of vegetables per day in order to prevent AD and cognitive decline in age.

Table 1
Cohort studies reporting an association between fruit and vegetable intake and dementia, AD or cognitive decline

Study acronym or location	Study characteristics	Exposure assessment	Outcome assessment	Study results	Adjusted variables
Esprit (France) (10)	prospective cohort; follow-up: 7 y; n=1433; mean age: 72.5 y (SD 5.1)	baseline: FFQ (2 categories: fish; fruit/vegetable; 2 classes: 2x per day or less)	incidence of MCI (Artero, 2006); baseline + follow-up: interview by neurologist	HR: 1.26 (CI 95% 1.02-1.56) - fruit/ vegetable < twice a day [model 1]; HR: 1.38 (1.11-1.70) - fruit/ vegetable < twice a day [model 2]	model 1: age, education, sex, ApoE ε4 genotype; model 2: age, sex
CHAP (USA) (11)	prospective cohort; median follow-up: 5.5 y; n=3718; mean age: 73.6 y	baseline: self-administered SFFQ (139 items; 6 classes: never - daily)	baseline + follow-up: MMSE, East Boston immidiate and delayed recall, symbol digit modalities test (merged in a global score)	Rate of cognitive decline compared to the lowest quintile of vegetable intake (median of 0.9 servings/d) was slower by 0.019 SU/y , a 40% decrease in the fourth quintile (2.8 servings/d) , and by 0.018 SU/y for the fifth quintile (4.1 servings/d), or a 38% decrease in rates. Fruit consumption was not associated with cognitive change.	age, sex, race, and education
The Nurses' Health study (USA) (12)	prospective cohort; follow-up: 10-16 y; n=13388 women; mean age: 74 y	averaged intake of 4-5 SFFQ (15 fruits, 30 vegetables) over 11 years before baseline	baseline: TICS; follow-up: TICS, East Boston immediate and delayed recall, category fluency, digit span backward (merged in a global score)	Total vegetable intake (median servings: 3.1/d) was associated with less cognitive decline (mean difference Q5 vegetable comsumption vs. Q1: 0.01 (CI 95% -0.03 to 0.04). Fruits (median servings: 2.4/d) were not associated with cognition or cognitive decline. (mean difference Q5 fruit comsumption vs. Q1: -0.03 (CI 95% -0.06 to 0.01)	adjusted for age, education, history of diabetes, history of high blood pressure, body mass index, smoking, physical activity, supplement use
The Three-City Cohort Study (France) (13)	prospective cohort; follow-up: 4 y; n=8085; age ≥ 65 y	baseline: FFQ (11 categories (e.g. meat, fish); 6 classes: never - daily)	Incidence of dementia (DSM-IV) and AD (NINCSD-ADRDA); baseline: neuropsychological tests, examination by neurologist; follow-up: neurologist, committee of neurologists	Frequent (daily) consumption of fruits and vegetables was associated with a decreased risk of all cause dementia (hazard ratio [HR] 0.72, 95% CI 0.53 to 0.97)	adjusted for age, gender, education, city, income, marital status, ApoE ε4 genotype, vascular risk factors
Olmsted County (USA) (14)	prospective cohort; n=1233; median follow-up: 2.2 y; mean age: 80.8 y	baseline: self-administered FFQ (128 items; 3 classes of portion size; 10 classes of frequency: never - 6x per day)	Mild cognitive impairment; baseline + follow-up: examination by neurologist; Clinical Dementia Rating, 9 cognitive tests	The odds ratio of MCI was reduced for high vegetable intake (consumption (without legumes) ≥ 191 g/d) vs. Low (≤ 109.6 g/d) [OR=0.66 (95% CI = 0.44–0.99), p = 0.05], but not for fruit (high intake ≥ 276.8 g/d; low intake ≤ 153.4 g/d) [OR= 0.92 (0.61-1.38]	adjusted for age, years of education, and total caloric intake, sex, ApoE ε4 genotype, stroke, coronary heart disease, depressive symptoms
Rotterdam study (Netherlands) (15, 24)	prospective cohort; n=5407; mean follow-up: 6 y; age ≥ 55 y	baseline: 2-stage protocol (a. checklist on all foods, drinks consumed ≥ 2x per month in the preceding year; b. interview by dietitian; 150-item SFFQ)	incidence of dementia (DSM-III-R) and AD (NINCSD-ADRDA); baseline + follow-up: 3 stage protocol: a. MMSE, b. CAMDEX if MMSE <26, c. neurologist	High intake vegetables (no information on definition available) decreased the risk of total dementia (RR (95% Cl) 0.81 (0.68-0.97)), as well as the risk of Alzheimer's disease (RR (95% Cl) 0.82 (0.67-1.00)). No relation was found between intake of fruit and the risk of dementia.	age, sex, education and energy-intake
E3N (France) (16)	prospective cohort; n=4809; follow-up: 13 y; mean age: 65.5 y (SD 1.8)	baseline: self-administered FFQ (208 items, booklet for estimating portion sizes)	Cognitive performance (DECO scale); instrumental activities of daily living (IADL); self response to questionnaires	Cognitive decline was not associated with consumption of fruit (mean consumption 354.5 g/d (SD 199.4)) and vegetables (mean consumtion: 231.7 g/d (SD 118.7)); Highest vs. lowest tertile of vegetable consumption: OR: 1.1 (0.89-1.37); fruits: OR: 0.88 (0.7-1.09). Better instrumental activities of daily living was associated with a higher intake of vegetables (OR 0.8 (0.65-0.98)).	age, education, BMI, physical activity, energy intake, smoking, use of supplements, history of diabetes mellitus, hypertension, hypercholesterolaemia, CHD , stroke, cancer and depression
Doetinchem study (Netherlands) (17)	prospective cohort; n=2613; follow-up: 5 y; age: 43-70 y	self-administered SFFQ (178 items, photographs for estimating portion size)	Cognitive performance; baseline + follow-up: 4 tests (Verbal Learning Test, the Stroop Colour–Word Test, the Word Fluency Test and the Letter Digit Substitution Test) (merged in a global score)	Higher intake of vegetables was associated with with smaller decline in information processing speed (ß=0.07) and global cognitive functioning (ß=0.05). Total intake of fruits and vegetables, fruits and legumes were not associated with a change in cognitive function.	age, sex, education, energy intake, physical activity, smoking, systolic blood pressure, use of blood pressure lowering medication, serum HDL-cholesterol, waist circumference, coffee consumption, vitality, mental health
Harmony (Sweden) (18)	prospective cohort; n=3318; follow-up: 31.5 y; mean age: 79.8 y (SD 5.1)	baseline: FFQ (23 items, fruit/v egetable as 1 item; 4 classes on portion size)	incidence of dementia (DSM-IV) and AD (NINCSD-ADRDA), follow-up: a-telephone screening; b. clinical evaluation	Medium or high intake of fruit/ vegetables in midlilfe was associated with a decreased risk of dementia (OR=0.73 (0.53–1.00)) amd AD (OR=0.60 (0.41–0.86))	age, sex, education, smoking, alcohol drinking, angina pectoris, BMI, total food intake, marital status, exercise

Abbreviations: (S)FFQ: (semiquantitative) food frequency questionnaire, DSM-III/IV: diagnostic and statistical manual of mental disorders III/IV; NINCSD-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; MCI: mild cognitive impairment; SU: standardized units

The systematic review is reliable in so far as all of the included studies had a long duration of follow-up and large sample sizes. A review of cohort studies may represent the most adequate currently available source of respective knowledge, as respective randomized-controlled trials would be difficult to implement and are questionable from an ethical perspective. Additionally, the selection of studies that gather information on whole food consumption avoid biases of observational supplementary trials due to users of supplements being more likely to have a healthy diet in general (19).

However, several limitations have to be taken into consideration with regard to our review.

First, there is a publication bias. There are many studies that report a beneficial effect of certain nutrients on the risk of dementia whose dietary intake is mainly obtained from fruits and vegetables.

These studies do not provide direct evidence, but can support the reported findings as proxy parameters. For instance, there are studies that show that higher flavonoid intake is associated with a decreased risk of dementia and better cognitive performance (20, 21). Since the sources of flavonoid greatly vary between different populations (e.g. tea, wine, fruit, vegetables), these associations, however, do not necessarily imply a beneficial impact of frequent fruit/vegetable intake on cognition.

In the same vein, there are prospective studies reporting that consumption of antioxidants come with a decreased incidence of dementia (22-27). For example, we have included data from the Rotterdam study (15) whose outcome is supported by additional analyses, showing that dietary intake of antioxidants, including vitamin C and vitamin E, but not supplement consumption, is associated with a lower risk of AD (24). A more recent analysis of the study which represents a longer follow-up, found the association remaining significant for vitamin E only (27).

Also, studies that report vegetable and fruit consumption as an inherent part of certain dietary patterns (28) or the Mediterranean diet (29-31) which is associated with a decreased risk of AD or dementia may be considered as a proxies. What amount of the beneficial effects of antioxidants or the Mediterranean diet is due to frequent vegetable consumption cannot be determined without additional analysis of the original data.

Second, there may be a selection bias. We aimed to limit this source of error by repeating the literature search several times and iteratively adopting the search strategy each time to maximize study coverage. In addition, our double review process and the quality control were intended to reduce this bias.

Third, the included studies' heterogeneity hampered collating the outcomes into a meta-analysis. The studies differed in their outcome measures including incidence of dementia, AD, MCI or cognitive performance, applied different food frequency questionnaires and cognitive tests, varied in their definitions of frequency of vegetable and fruit consumption and adjusted for different groups of potential confounders. Particularly, only three studies adjusted for apolipoprotein E ε4 genotype and two studies failed to analytically differentiate between vegetables and fruits (see table 1). None of the studies validated the diagnosis of AD by determining biochemical or imaging biomarkers of AD. The only study which didn't find a beneficial effect of vegetable intake on cognition assessed cognitive performance via self-response (16).

Fourth, the included studies using US-American and European study cohorts cover only parts of the world population and may not be representative for Asian or African ethnicities.

The reason why the protective effect of frequent vegetable consumption appears stronger than that for fruit may be based on biological mechanisms as well as on eating habits.

Oxidative stress is one of the salient pathogenic mechanisms in AD and is largely driven by various reactive aldehydes derived from lipid peroxidation which, interfere with antioxidant and mitochondrial key enzymes (32).

Vitamin E is a non-enzymatic, lipophilic antioxidant which is essential for brain function (33), and indeed, intake of vitamin E is inversely related to the risk of AD and cognitive decline (27, 34). Important sources of vitamin E are cereals, tomatoes, spinach, seeds, nuts and sunflower oils (35). Thus, vegetables contain more vitamin E than fruits. It may be also important that vegetables are often processed and consumed with added fats such as sunflower oils that are rich in vitamin E. Added fats may also increase the absorption of vitamin E and further lipophilic nutrients with a beneficial impact on brain health including flavonoids and carotenoids.

However, randomized-controlled trials failed to provide evidence of the efficacy of vitamin E in the prevention of AD (36). Moreover, vitamin C, which is enriched in fruits (35), acts as co-antioxidant of vitamin E by reducing the alpha-tocopheryl (Vitamin E) radical and restores the antioxidant capacity of vitamin E (37). An unbalanced ratio of fruit and vegetable could disrupt the effects of vitamin E.

The differences in the nutritional composition between fruit and vegetables are not limited to vitamin E, but also relate to dietary fibres, lycopenes, ß-carotenoids or monosaccharides (35). Therefore, the explanation that the difference between the effects of fruit and vegetable on the risk of AD relies on different concentrations of vitamin E is speculative.

Alternatively, one could argue that a diet rich in vegetables may be associated with other healthy nutrients which were not adjusted for in the studies. The risk reduction of AD derived from frequent fish consumption (38), however, does not interact with the association of fruit or vegetable consumption and the risk of developing AD or dementia (13). To further uncover the reason for the differences in the beneficial effects of fruit and vegetable consumption and to test the validity of the present review, further long-term prospective studies and re-analyses of those existing studies exclusively reporting proxy parameters (e.g. flavonoids, antioxidants) might provide

definitive answers.

In conclusion, our systematic review of cohort studies suggests that a higher intake of vegetables is associated with a lower risk of dementia and a slower rate of cognitive decline. Evidence for an association between increased fruit consumption and a lower risk of dementia is, however, lacking.

Further studies should include Asian cohorts, address different life stages and accord greater attention to genetic risk factors.

Although our results imply that the 'Five a day' recommendation may necessitate compositional specification for the prevention of dementia and cognitive decline, and is not generally valid for all chronic diseases, they do not infringe on the public health importance of combined fruit and vegetable intake in other chronic diseases (2, 3). Yet, advances in predictive medicine and genetic risk assessment may support the calls of individuals for more tailored prevention concepts in the near future.

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