ALINEA

NUTRITION

NOVEMBER 2020

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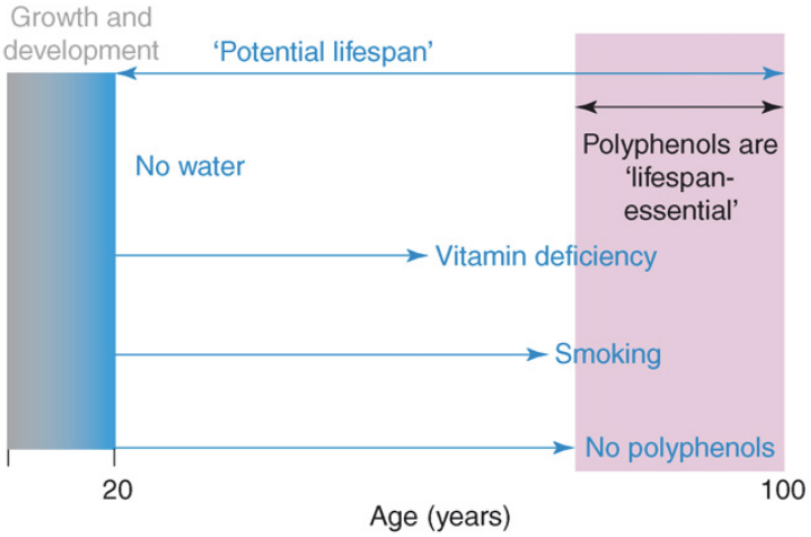
TABLE OF CONTENTS

Shishtar E, Rogers GT, Blumberg JB, Au R, Jacques PF. Long-term dietary flavonoid intake and risk of Alzheimer disease and related dementias in the Framingham Offspring Cohort. Am J Clin Nutr. 2020;112(2):343–53.

What We Know, Think We Know, or Are Starting to Know

It seems fitting that in the year that the pioneer of the epidemiology of diet and dementia Professor Martha Clare Morris passed away, a number of studies have been published which build a further case for the role of diet in long-term brain health [(1-3)]. The age-related increase in dementia incidence rises sharply from the 6th decade of life: incidence in the 80-84yo age group is double that of the 70-74yo old age group [(4)]. What dietary factors might contribute to preserving brain health over an increasing lifespan?

Interestingly, two antioxidant researchers - Birgit Holst and Gary Williamson - have proposed a particular term to describe the importance of polyphenols: "lifespan essential" [(5)]. Their conceptual framework for thinking about polyphenols in this way is illustrated in the graph, below: as we do not technically need polyphenols as nutrients, we can survive without them in a way that we could not without vitamins. However, as polyphenols have important biological activity that differ to vitamins, their particular health effects may be important for increasing the quality of healthy life years within the lifespan.



Do these potential mechanisms potentially explain long-term associations? Flavonoids constitute the major human dietary source of polyphenols, with the primary food sources including fruits, vegetables, fruit juices, tea, red wine, coffee, and chocolate [(6)]. In an early cohort to examine flavonoids intake and brain health, flavonoid intake of up to 360mg/d was associated with significant protection against cognitive decline over a 10yr period [(7)]. In the US Nurses Health Study, the effect of high flavonoid intake delayed cognitive ageing by 2.5yrs, i.e., people aged 75yo scored similar to 73yo [(8)]. These cohort studies suggest a protection of cognitive function - does this translate to lower incidence of disease? The present study investigated the effects of flavonoids on incidence of Alzheimer' s Disease and dementia over 20yrs.

The Study

The Framingham Offspring Study Cohort [FOS] began in 1970 with 5,124 participants (the study consisted of the children of participants from the original, now infamous Framingham Heart Study which established a link between blood cholesterol and heart disease).

Participants in the FOS underwent physical examination every 4yrs together with completing a semiquantitative food frequency questionnaire [FFQ]. The FFQ was validated* in a previous study by the Harvard nutritional epidemiology research group. Dietary intake was analysed at the 5th to 9th examinations [every 4yrs between 1991 and 2014]. The FFQ from the 5th examination was considered baseline for the present study. Flavonoid intake was updated at each subsequent dietary assessment, and calculated as an average intake over the period.

Participants were required to be free from Alzheimer' s Disease and dementia at baseline, be >50yrs of age, and have a completed baseline FFQ, to be included. The exposure of interest in the study was dietary flavonoid intake: both total flavonoids and 6 subclasses of flavonoids, including flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, and flavonoid polymers [proanthocyanidins]. The primary outcome was Alzheimer' s-related dementia [ARD] and Alzheimer' s Disease [AD].

The analysis was adjusted for a number of potential confounders, e.g., age, education level, ApoE4 allele [which increases risk for AD], smoking status, cholesterol levels, intake of marine omega-3 fatty acids, etc.

*Geek Box: Validity

We have discussed the concepts of reproducibility and validity in epidemiology in previous Deepdives, however, repetition always bears fruits in understanding. 'Reproducibility' is how well any instrument - in our case a food frequency questionnaire [FFQ] - is the consistency of the FFQ over time in the same individual. 'Validity' is the accuracy with which the FFQ compares to an independent measure of diet. Both are important concepts for nutritional epidemiology, but validity in particular given that a common criticism of nutritional epidemiology is that the dietary assessments are unreliable. The 'gold standard' validation process is to have a randomly selected subgroup within the overall cohort complete a 7-day food record, where all food intake is weighed and measured. A food record is currently the most accurate way of measuring diet in a free-living population. As all food is weighed and measured, this is considered the closest to "true" intake as can be achieved. If more than a single 7-day food record is conducted, this also allows for any potential seasonal variation in dietary intake to be accounted for. Also, day-to-day variation in food intake tends to be larger than dietary variation over the long-term [i.e., we tend to eat similar foods over time, but what we eat on Sunday may differ to Monday each week], which means that the 7-day food records may introduce variation when compared with the FFQ. To deal with this, the researchers can calculate the variation in an individuals' food record ['within-person', and the variation between one individual and others ['between-person']. The ratio of the within-person and between-person variance can then be used to correct the day-to-day variability in the 7-day food records. The answers from the FFQ can then be compared to the data from the 7-day food records, to obtain what is known as the 'correlation coefficient' or 'coefficient of variation' [CV].

*Geek Box: Validity...continued

The CV reflects the proximity with which the FFQ answers correlate to the 7-day food record data, and is expressed as a value between -1 to +1. For nutritional epidemiology, it is common for correlations to be in the 0.50 to 0.70 range. A CV of 0.70 or over would be quite high for nutritional epidemiology. For example, if the CV for saturated fat is 0.65, this indicates a relatively high correlation of the measure of saturated fat in the FFQ with saturated fat intake in the measured food record. Now, two more points on FFQ, i.e., the 'semi-quantitative' design and the emphasis on frequency. In a semi-quantitative FFQ, portion sizes of foods are also specified in addition to the question on frequency of consumption, i.e., rather than give frequency options for 'bread' the questionnaire will state '2 slices of bread' or '250mi milk' or 'half-cup rice'. These average quantities are provided within a question on frequency, with up to 9 frequency categories [from <1 serving/month to >6 servings/day]: the high categories on frequency is because research indicates that portion sizes vary less than frequency of intake. Having more frequency options therefore better captures variation of dietary intake, and more reflects average intake over time - which is the exposure that is most relevant for long-term diet and disease relationships. To calculate levels of intake of a nutrient [or non-nutrient, as in the present study], the frequency of consumption of a food item is multiplied by the nutrient content of the specified portion size. Whenever you are reading a prospective cohort study, it is important to look to the validation method for the dietary assessment [most studies now use FFQ], and check the CV for the nutrient or food which is the exposure of interest in that study: a higher CV indicates more validity in the dietary assessment, and therefore in any relationship between that nutrient/food and the outcome of interest.

Results: 2,801 participants were available for the final analysis. Mean age at baseline was 59.1yrs, and 52% of participants were female, the cohort was highly educated with 60.4% having a college degree, and there was low overall smoking prevalence.

The statistically significant results are reported here:

- ***ARD:***
    - ***Flavonols:*** Compared to consuming <6.4mg/d, consuming >14.2mg/d was associated with a 46% [HR 0.54, 95% CI 0.32-0.90] relative risk reduction.
    - ***Anthocyanins:*** Compared to consuming <4mg/d, consuming >16.4mg/d was associated with a 76% [HR 0.24, 95% CI 0.15-0.39] relative risk reduction.
    - ***Flavonoid polymers [proanthocyanidins]:*** Compared to consuming <60.4mg/d, consuming >179.3mg/d was associated with a 42% [HR 0.58, 95% CI 0.35-0.94]
- ***AD:*** The results were similar for AD: both flavonols and anthocyanins were associated with a 50% [HR 0.50, 95% CI 0.28-0.88]and 80% [HR 0.20, 95% CI 0.11-0.36] relative risk reduction for AD, respectively. However, the association with flavonoid polymers [proanthocyanidins] was not significant for AD.

  Because cognitive decline and the underlying processes of disease may begin years prior to diagnosis, a sensitivity analysis was conducted which used a 10yr cutoff between the final dietary assessment and diagnosis of ARD. In this analysis, the highest intake of total flavonoids of >296.8mg/d was associated with a 42% [HR 0.58, 95% CI 0.32-1.08] reduction in risk compared to <122.6mg/d.

The Critical Breakdown

Pros: The FFQ used in the study was validated against two 7-day diet records, and the correlation coefficient for certain flavonoid-containing foods was high: 0.83 for red wine, 0.70 for apples/pears, 0.76 for oranges, 0.78 for orange juice. Repeated FFQ over 5 examination periods between 1991-2014 were conducted, allowing for an average intake to be determined over the study period. The repeated examinations also allowed for relevant potential confounders - like smoking status or dietary intake of omega-3 fatty acids - to be updated. It also allowed for changes in cognitive function to be addressed. Participants were free from disease at baseline, thus the assessment of diet preceded the incidence of disease, and the follow-up period was lengthy with an average of ~20yrs, with up to 26yrs total follow-up.

Cons: There was no direct evaluation of the validity of flavonoid intake from the FFQ used in the current study. Instead, flavonoid intake was calculated from multiplying the frequency of flavonoid-containing food intake by the levels of flavonoids in the US Department of Agriculture database. The USDA database is robust, however, there is no direct correlation coefficient of flavonoid intake in the dietary assessment in this study. There was a relatively low incidence of the outcomes which may have weakened the ability to detect associations. It is possible that residual confounding from lifestyle factors earlier in life may have influenced dementia/AD risk. The cohort was White and well-educated, and the results may not generalise to other population groups.

Key Characteristic

Many of the previous studies investigating the relationship between flavonoid intake and dementia/AD have been limited by the dietary assessment, in particular the quantification of flavonoid intake. It remains a limitation, to be addressed in future research, that the validity of FFQ for measuring flavonoid intake is not known. However, the USDA database provides a more robust database which covers multiple flavonoid subclasses and a more complete database of flavonoid-containing foods. In addition, the collection of up to 5 FFQ over an average of 20yrs [separated by 4yrs between each assessment] in the present study allowed for a cumulative average of flavonoid intake to be calculated, reflecting average dietary intake over the time period. The mean dietary intake of total flavonoids in this study was substantially higher than in previous cohorts. Thus, the multiple dietary assessments over a long follow-up period, the high correlations with flavonoid food sources in the FFQ used in the study, and the use of a robust database of flavonoids to calculate intake, make this study the best assessment of flavonoid intake to date. But there remains room for improvement, in particular direct validation of FFQ' s to measure flavonoid intake.

Interesting Finding

Of the individual flavonoid subclasses, the strongest association with reduced risk of ARD and AD was for anthocyanins, with a 78% and 80% reduction in risk for ARD and AD, respectively. The tight confidence intervals in relation to both findings suggest a minimum reduction in risk that is of a large magnitude. The greatest contribution to anthocyanin intake was from blueberries and strawberries, which collectively accounted for 40% of anthocyanin intake. In the Nurses Health Study, regular consumption of blueberries and strawberries [>1-2 servings per week] was associated with a significant reduction in rate of cognitive ageing [8]. And in the Chicago Health and Ageing Project, consumption of >1 serving/week strawberry intake was associated with a 34% [HR 0.66, 95% CI 0.46-0.95] lower risk of AD compared to those consuming none or <1/month consumption [9]. This indicates that food source and/or the specific flavonoid subclass may be an important factor to consider. In this study, the primary source of flavonoids was tea, apples, and orange juice, which may be as concentrated sources of anthocyanins compared to blueberries or strawberries. Most of the intervention studies showing improvements in cognitive function have used anthocyanin-rich drinks [10-14]. While each flavonoid subclass exerts biological activity, a case could be made that anthocyanins in particular, derived from concentrated food sources, may have a particular benefit for brain health.

Relevance

The present study is one of a trio of studies from the Framingham Offspring Cohort published this year on the relationship between flavonoids and dementia. Another of the publications examined the link between flavonoid intake and brain MRI scans, finding that high flavonoid intake was associated with reduced volume of white matter hyperintensities, a marker of damage to brain tissues, which could explain reductions in dementia/AD risk [2]. The third study examined the effects of flavonoid intake on cognitive test scores, which did not find a significant protective effect against cognitive decline [3]. Other cohort studies have demonstrated a benefit with cognitive scores [8,9], as have short-term intervention studies [10-14], so the effect of flavonoids on cognitive performance remains to be fully teased out in further research.

Nonetheless, a body of evidence is starting to converge. The use of brain MRI scans provides an important strand of evidence to link dietary intake to structural changes in the brain relevant to healthy brain ageing.

The interest in flavonoids as an exposure of interest, evident in the Framingham Offspring Cohort and other studies, also appears to be generating improved dietary assessment of flavonoid intake.

From a combination of animal and human mechanistic research, it appears that the effect of flavonoids is due to a number of mechanisms [6]:

- Stimulation of brain pathways which promote growth, survival, and repair of brain cells in areas of the brain responsible for learning and memory;
- Increased brain blood flow;
- Anti-inflammatory effects in the brain.

These mechanisms provide biological plausibility, together with evidence from intervention studies showing improvements in cognitive domains of memory and learning, which may explain long-term protection against dementia and AD. This is a promising area of research with potentially important implications for a disease with no currently effective pharmaceutical treatment.

Application to Practice

One of the more encouraging findings in relation to the 'minimum effective dose' for flavonoids, and anthocyanins in particular, is that these doses are readily available through accessible foods. For example, the dose of blueberry anthocyanins used in intervention studies equates to ~150-200g blueberries. Factoring in the 'minimum effective frequency' of >1-2 servings per week observed in prospective cohort studies, regular consumption of these ranges is accessible. Factoring in other flavonoid-rich foods - dark-skinned berries, citrus fruits and apples, dark-skinned vegetables, dark chocolate, red wine, coffee and tea - consumption of a flavonoid-rich diet is also accessible. Importantly, it is low-to-no risk in application.

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