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

Spend any time with the research on nutrition and cardiovascular disease, then turn to nutrition and neurodegenerative disease, and a striking pattern of similarity becomes evident: what is good for the heart appears to be good for the head.

The first clues in relation to the potential role of dietary patterns in reducing risk of neurodegenerative disease came out of cardiovascular disease prevention trials. In the vaunted PREDIMED trial conducted in multiple centres across Spain, participants were randomised to consume either 60ml extra-virgin olive oil per day or 30g mixed nuts per day; the primary endpoints were cardiovascular disease [CVD] outcomes. Over 5yrs, risk of CVD was reduced by 30% compared to the control group [(1)]. However, analysis of one of the Spanish regional cohorts in PREDIMED also showed that both the olive oil and mixed nuts intervention groups scored higher on cognitive tests compared to the control group [(2)].

And what of the Dietary Approaches to Stop Hypertension [DASH] diet? The DASH diet is one of the longest standing formulated dietary patterns in nutrition research, consistently demonstrating significant reductions in blood pressure and CVD risk [(3)]. Analysis of a DASH diet also showed improved cognitive function compared to a habitual control diet, although weight loss and exercise were also part of this intervention [neither were part of the PREDIMED intervention] [(4)].

These lines of evidence pointed to the truism: what is good for the heart is good for the head. Based on these findings, the pioneering diet-dementia researchers Martha Clare Morris and Christy Tangney examined the relationship between both Med and DASH diet scores and cognitive decline in a cohort of elderly Chicago residents [(5)]. They showed that higher scores for both dietary patterns were associated with a slower rate of cognitive decline in adults aged over 81yrs [(5)].

So there are characteristics to the Med diet which may be good for the brain. The present study brings us back to the Iberian peninsula to examine this relationship.

*Geek Box: A Priori Indices in Nutritional Epidemiology

Most approaches to dietary assessment in nutritional epidemiology focus on foods and nutrients as the exposure of interest. However, there are a number of different methods of analysing total dietary patterns, or characteristics of dietary patterns. An 'a priori indices' is a fancy way of saying a scoring index to quantify the healthfulness of a dietary pattern, or to quantify specific characteristics of the diet. Such indices are considered 'a priori', because they are derived from analysing the overall wider research and deciding in advance that, for example, fruits and vegetables are healthy. An example of this type of dietary assessment would be the Alternate Healthy Eating Index 2010 [AHEI-2010]. Based on the original 1995 Healthy Eating Index, the AHEI-2010 consists of 11 dietary components with a maximum of 10-points for each component, contributing to a total score of 110. The dietary components associated with lower risk of disease, including vegetables, wholegrains, whole fruit, nuts and legumes, long-chain omega-3 fatty acids, and polyunsaturated fats, have a points score that rises with increasing consumption of the dietary component from 0 up to a maximum score of 10. In contrast, dietary components associated with negative health outcomes, including sugar-sweetened beverages and fruit juices, red/processed meats, trans fats, and sodium, are score inversely to consumption, i.e., 0 for high intakes up to 10 for low intakes. This allows for the overall healthfulness of an individual's diet pattern to be quantified in a single number, and the overall scores in a cohort can be divided into different levels and analysed in relation to disease outcomes. Diet indices have been developed for inflammation - the Dietary Inflammatory Index II - the financial cost of diet, a Mediterranean diet score, and low-carbohydrate diets. One of the major advantages to scoring indices like this is that they are inherently adaptable to different dietary patterns. However it should also be noted that they are based on judgment calls, too. For example, there is debate about whether whole-milk dairy [i.e., "full fat"] should be scored as a positive, negative, or neutral score for a dietary pattern. The MIND dietary pattern score also scores positively for red wine, which I wholeheartedly support! But some would debate the merits of any alcohol. The point to bear in mind here is that any dietary pattern score is not necessarily a sacrosanct representation of a particular dietary pattern, and they are modifiable as the wider evidence develops.

The Study

The European Prospective Investigation into Cancer and Nutrition [EPIC] Study, is a large scale prospective cohort study with cohorts recruited across nine countries; the UK, Netherlands, Denmark, Germany, Norway, Sweden, Spain, Greece, and Italy. Within the overall EPIC study, the EPIC-Spain Dementia Cohort was established based on three study centres from EPIC-Spain: Murcia, Navarra, and Gipuzkoa. Diet was assessed by a diet history questionnaire administered in 1-1 interviews by trained dietitians.

The Med dietary pattern was defined by a Med diet pattern score* [rMED], based on 9 components: 6 of which are scored positively [fruits, vegetables, olive oil, legumes, fish, cereals], and 2 are scored negatively [meat and dairy]. Intakes of these foods was divided into tertiles [i.e., thirds] of intake, and scored as 0, 1, or 2 from lowest to highest intakes for positive foods [negatively scored foods were reversed]. The sum total of points for each food constituted the rMED score.

Levels of adherence were classified as: Low [0-6 points]; Medium [7-10 points]; High [11-18 points].

The rMED score was the main exposure of interest, comparing levels of adherence. The primary outcomes were dementia and Alzheimers Disease [AD].

Results: 16,160 participants were included in the present analysis. 459 cases of dementia were recorded, of which 67% were diagnoses of AD. The mean follow-up time was 21.6yrs. Cases of dementia were more likely to be older age, have obesity, have lower educational attainment, higher intakes of fruit and dairy, and lower intake of meat.

- ***Adherence to rMED & Dementia:*** Higher rMED scores were associated with a 20% [HR 0.80, 95% CI 0.60 - 1.06] lower dementia risk [which you can see that because the confidence interval crossed 1.0, was not statistically significant]. For each 2-point increase in rMED scores, dementia risk was 8% [HR 0.92, 95% CI 0.85 - 0.99] lower.
- ***Risk By Sex:*** In women and men, each 2-point increase in rMED scores was associated with a 10% and 7%, respectively, lower risk of dementia. There was a statistically significant trend for linear lower dementia risk with increasing rMED scores in women, but not in men.
- ***Risk by Time:*** The analysis of time-varying effects of the rMED scores with dementia showed that the reduction in risk of dementia became evident only when looking at follow up over ~18yrs, when the number of cases increased exponentially with age [more under ***Interesting Finding***, below].

The Critical Breakdown

Pros: The statistical analysis was adjusted for multiple relevant factors for brain health, including education, smoking, physical activity, and coffee consumption. The analysis also modelled the effects of adherence to the rMED diet scores over time, to see if any associations were time-dependent. The follow-up time of 21.6yrs was a strength, as was the decent sample size of >16k people. The assessment and calibration of diet in the EPIC cohorts is one of the more robust dietary assessments in nutritional epidemiology.

Cons: The Med diet score is arguable rather crude given the wider literature. Particular dairy products, specifically yogurts and cheese, form a consistent part of healthy Med dietary patterns, and nuts were excluded from the positively scored foods [which is a bit of a headscratch given the PREDIMED trial]. The low number of cases overall may have weakened the power of the study to detect stronger or more precise associations between diet and dementia.

Key Characteristic

Remember the lecture on thinking about confidence intervals when we interpret research findings, particularly for epidemiology? This study presents us with a really good example of this. Let' s think about the two main findings:

- Overall dementia risk: 20% [HR **0.80, 95% CI 0.60 – 1.06**], and not 'statistically significant'
- Per 2-point diet score increase: 8% [HR **0.92, 95% CI 0.85 – 0.99]**, and 'statistically significant'

The overall score is one we may think of in terms of overall direction of effect. The point estimate is a moderate effect size for nutritional exposures, 20% lower risk [1.0 minus 0.80 = 0.20 = 20%]. But the upper-bound of the confidence interval is 1.06, and crosses the null; the rudimentary interpretation would be to say this is not statistically significant. But it is relevant. The point estimate is moderate, and the lower bound of the confidence interval is 0.60; clearly the direction of effect is toward reduced risk, whether it has achieved statistical significance or not.

However, it is is not a particularly precise estimate. Why? Primarily because the number of dementia cases was low. More cases = more power to detect more precise effects. The score per 2-point increase is one of the difficult ones; the point estimate is small, and the overall width of the confidence intervals is modest. But it is a more precise estimate.

So, how would we think about reconciling these effects? Well, have a read of the ***Interesting Finding*** first, and we' ll take this back up under ***Relevance***...

Interesting Finding

The time-course analysis indicates that the benefit of higher Med diet scores only become evident at the latter stages of the follow-up period, when more dementia cases started to occur. Recall that one of the characteristics of chronic disease is low *short-term* frequency but high *cumulative incidence*. Translated, this means that in any population cohort the amount of cases in a given year won't be high, but the amount of total cases after say 30yrs would be much higher. Contrast this with infectious diseases like Covid-19, where the short-term frequency of cases is high due to the infectious transmission of the virus in the population. This is important because it suggests that if there were more cases in the study, or if the study went on for longer [or ideally a combination of both!], then the associations between the Med diet and dementia risk may be stronger. Something for future research to think about.

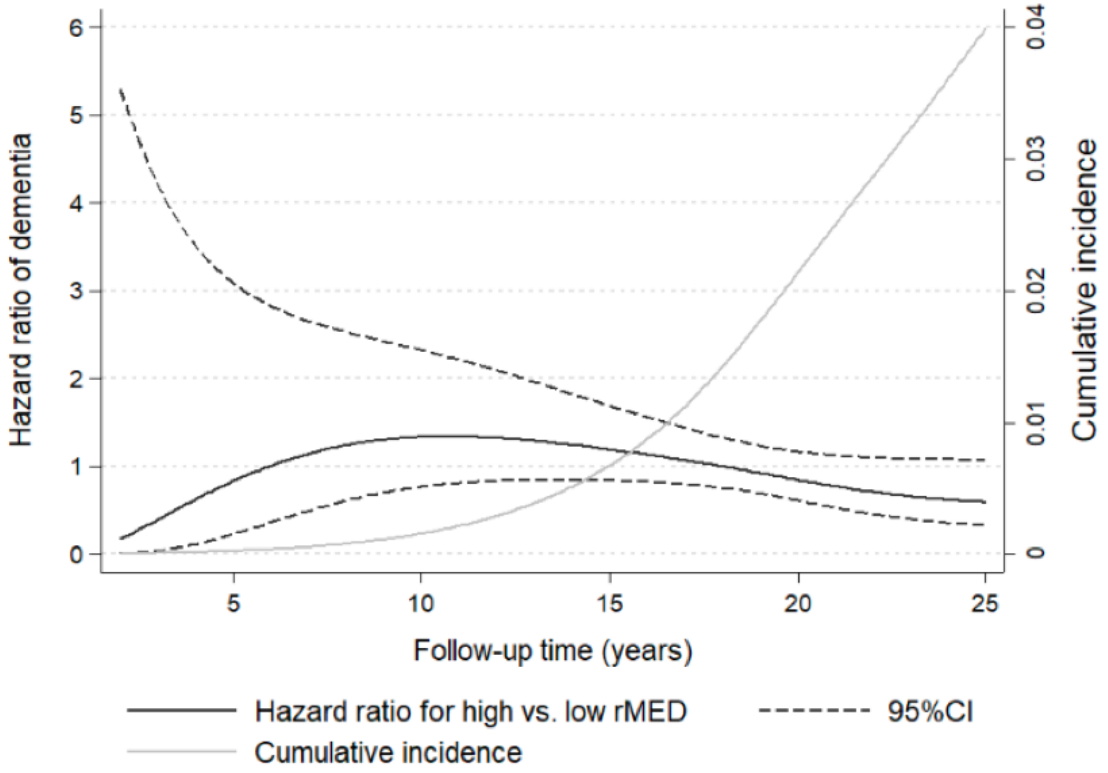

Figure *from paper illustrating the time-varying analysis. There are a couple of things to look at in this graph. On the left-hand Y-axis is the risk for dementia, and on the right-hand Y-axis is the cumulative incidence of dementia cases. The X-axis has the years of follow-up. Now, look at the grey line; you can see this exponentially increases after ~15yrs of follow-up. This is a characteristic feature of chronic disease incidence. Now, look at the solid black line; this intersects with the grey line around the ~15yr mark, and starts to dip below the 1 line on the left Y-axis [i.e., the 1.0 confidence interval, thus going below this = going to lower risk] around what would be ~18yrs.*

Relevance

First, let' s wrap up our interpretative conundrum. It is important that we think about the observed effects in relation to:

1. The fact that higher incidence of cases did not occur until >15yrs into the study;
2. The low absolute number of cases, even given No.1 above;
3. The strongest reduction in risk observed in the last 5-7yrs of the study.

Given the findings and the direction of effect, we could expect that a longer study, in a larger cohort, with more dementia incidence, would find stronger and more robust associations. So it would be premature to dismiss the findings with the usual lazy interpretation of nutrition studies like this as "not significant" or "weak effect".

Also bear in mind that the dietary pattern score used in the present study is arguably not a refined characterisation of the Med diet, based on current knowledge. It would be interesting to see the effects of a more sophisticated Med diet score in future research.

However, it is also important to bear in mind that the Med diet, or even the DASH diet, may still lack certain nutritional characteristics important for brain health. With specific regard to dementia/AD, the dietary pattern which ties these nutrient strands together is the Mediterranean-DASH Intervention for Neurodegenerative Delay [MIND] diet [(6)]. The MIND diet makes specific food-based recommendations - dark-skinned berries, red wine, dark green leafy vegetables - which are not specifically made in either Med or DASH diets.

In the Chicago MAP study, high adherence to the MIND diet recommendations was associated with delayed cognitive ageing equivalent to 7.5yrs [(7)]. In contrast, only the highest level adherence to either the Mediterranean diet or DASH diet was associated with lower risk, while even moderate adherence to the MIND diet adherence still conferred a moderate reduction in risk for cognitive decline.

So the Med diet may be good, but the MIND diet may be better when to comes to, excuse the pun, the mind.

Application to Practice

For a chronic disease with no real pharmaceutical interventions, dementia incidence is expected to quadruple by 2050 [8]. Lifestyle, diet, and healthy ageing strategies thus take on a particular importance for thinking about preserving neurological integrity over the lifespan.

There is a relatively consistent body of evidence supporting various health-promoting dietary patterns in preserving cognitive function, and associating with lower incidence of dementia/AD. Currently, food-based recommendations to prevent dementia are currently strongest for green leafy vegetables, berries, and fatty fish, reflecting the strength of evidence for specific nutrients provided by these foods, in particular EPA/DHA, vitamin E, and flavonoids. For B-vitamins, it is difficult to ascertain the prophylactic potential, but nonetheless foods like green leafy vegetables and fatty fish contain substantial levels of folate and B12, which nutrients are also commonly fortified in specific food products.

Distilling core aspects of the MIND diet, and wider literature, into food-based recommendations, the following points reflect the totality of evidence to date:

- Oily fish 1-2/week [90-120g servings]
- High dietary vitamin E for mixed tocopherols, e.g., almonds, avocado, oils, green leafy vegetables, seeds
- Flavonoid-rich foods, e.g., mixed berry intake 2-3/week, high-cacao chocolate, teas, citrus fruits, ~100ml red wine
- Adequate folate, B12, and B6 intake from green leafy vegetables, fish, and fruit [other than citrus for B6]
- Extra-virgin olive oil as main added oil, for polyphenol content

I would be inclined to recommend more of the MIND diet principles than Med diet if cognitive health is the focus.

References

1. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA; PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med. 2018;378(25):e34.
2. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, Sanchez-Tainta A, Ros E, Valls-Pedret C, Martinez-Gonzalez MÁ. Mediterranean diet improves cognition: the PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry. 2013;84(12):1318-25.
3. Sacks FM, Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. Clin Cardiol. 1999;22(7 Suppl):III6-10.
4. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, Strauman TA, Sherwood A. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension. 2010;55(6):1331-8.
5. Tangney CC, Li H, Wang Y, Barnes L, Schneider JA, Bennett DA, Morris MC. Relation of DASH- and Mediterranean-like dietary patterns to cognitive decline in older persons. Neurology. 2014;83(16):1410-6.
6. Morris M, Tangney C, Wang Y, Sacks F, Bennett D, Aggarwal N. MIND diet associated with reduced incidence of Alzheimer' s disease. Alzheimer' s & Dementia. 2015;11(9):1007-1014.
7. Morris M, Tangney C, Wang Y, Barnes L, Bennett D, Aggarwal N. MIND diet score more predictive than DASH or Mediterranean diet scores. Alzheimer' s & Dementia. 2014;10:P166-P166.
8. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi H. Forecasting the global burden of Alzheimer' s disease. Alzheimer' s & Dementia. 2007;3(3):186-191.