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Glenn AJ, Lo K, Jenkins DJA, Boucher BA, Hanley AJ, Kendall CWC, Manson JE, Vitolins MZ, Snetselaar LG, Liu S, Sievenpiper JL. Relationship Between a Plant-Based Dietary Portfolio and Risk of Cardiovascular Disease: Findings From the Women's Health Initiative Prospective Cohort Study. J Am Heart Assoc. 2021 Aug 17;10(16):e021515.

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

In the early 2000's, David Jenkins and colleagues at the University of Toronto developed the 'Portfolio Diet' pattern, a dietary pattern designed to emphasise inclusion of multiple foods with evidence for lowering blood cholesterol levels [(1)]. In addition to the well-established effects of a low saturated fat [SFA] intake for lower LDL-cholesterol [LDL-C], the Portfolio Diet added:

- Viscous [soluble] fibres at doses of ~10g per 1,000kcal, primarily from oats and barley beta-glucans and psyllium, and additionally eggplant/aubergine and okra.
- Plant sterols at doses of 1g/1,000kcal, added from sterol-enriched margarines.
- Soy protein at doses of ~22g/1,000kcal, added from soy milk and soy-based meat alternatives.
- Nuts at doses of 14g/1,000kcal, added from almonds.

In a 2003 study with controlled diets, where the Portfolio Diet was compared to 20mg of the first approved statin, lovastatin [20mg was the starting dose for this statin], the Portfolio Diet resulted in a 28.6% decrease in LDL-C compared to a 30.9% reduction with lovastatin [(2)]. Promising results for diet, especially where overall effects of lifestyle interventions to reduce LDL-C are, on average, underwhelming [(3)].

In 2010, based on evidence for cardiovascular benefits of plant-sourced monounsaturated fats [MUFA], the Portfolio Diet pattern was modified to include an option of replacing ~15% of the energy from carbohydrates in the originally diet with MUFA from olive or canola oils and avocado [(4)]. While this modified version did not alter the LDL-C lowering effect of the diet, the high-MUFA version did result in a ~12% increase in HDL-C compared to the low-MUFA original diet [(4)].

Overall, this makes for a promising cardio-protective dietary pattern. However, one of the major challenges of nutrition research is the temporal aspect of relationships between diets and disease. The major chronic diseases of interest to our field, i.e., cardiovascular disease [CVD], type-2 diabetes [T2D], etc., typically take years to develop and diet may influence this progression for years in advance of an overt disease diagnosis.

This means that nutrition research faces a temporal dilemma; observational prospective cohorts provide the only real option as a research design to regularly investigate "hard" clinical outcomes of a disease [e.g., coronary heart disease events and mortality] over longer periods of time. Conversely, randomised controlled trials [RCTs] typically end up investigating effects of diet on risk factors for that disease [e.g., LDL-C] over shorter periods of anywhere between 3–12 months.

And while RCTs can certainly investigate hard endpoints, this typically requires that participants are already at high risk of that disease at baseline, rather than healthy. So, what if we wanted to understand the effects of a diet developed and tested in RCTs of risk factors, on longer-term disease outcomes in participants that were healthy at baseline?

One method to achieve this is to create a "diet quality index"***** [see ***Geek Box**, below, for further details] to quantitively score a diet, and compare the effects of high to low adherence scores on disease outcomes in a longer-term cohort study. The present study was the first to do exactly this for the Portfolio Diet.

*Geek Box: Diet Quality Indices

Most approaches to dietary assessment in nutritional epidemiology focus on individual foods and nutrients as the exposure of interest. However, there are several different methods of analysing total dietary patterns or characteristics of dietary patterns, known as "diet quality indices", or "index" in the singular. This involves creating a numeric scoring system to represent the quality of the overall dietary pattern based on specific levels of intake of different food groups, foods, and nutrients, in that dietary pattern.

There are many examples of diet quality indices, including the Diet Quality Index, Healthy Eating Index and Alternate Healthy Eating Index, and the Mediterranean Diet Score. They provide a means to quantitatively assess the healthfulness of a dietary pattern, given "quality" is an ambiguous term for research purposes. The overall scoring range may then be used as a numeric variable for a statistical analysis, i.e., by comparing levels of adherence quantified numerically as "low", "moderate", or "high" adherence to that dietary pattern.

There are several ways an index may assess diet quality. Basing the index on food groups and nutrient intakes is the most common, e.g., an index may have "low-fat dairy" as a food group, and then thresholds in grams per day upon which higher or lower scores are assigned. Alternatively, polyunsaturated fats [PUFA] may have a threshold in percentages, to which higher or lower scores are assigned based on PUFA intake as percentage of total energy intake.

In contrast, dietary components associated with negative health outcomes, including sugar-sweetened beverages and fruit juices, red/processed meats, trans fats, and sodium have points scores inverse to consumption. For example, the maximum score for sodium intake in the Alternate Healthy Eating Index is awarded for <1,612mg/d sodium intake, while >5,271mg/d sodium intake results in a score of 0.

Where evidence exists of the effects of a specific diet, such as in the case of a Portfolio Diet, the diet quality index for that diet may be based on evidence from interventions of the effects of the component parts of the diet. In the case of the Portfolio Diet, the diet quality index was created by categorising the diet into 6 components: plant protein, nuts, viscous fibre, plant sterols, MUFA, and saturated fat and cholesterol sources.

One of the major advantages to scoring indices like this is that they are inherently adaptable to different dietary patterns, and may need to evolve over time with further knowledge. For example, a max score is provided in the Alternate Healthy Eating Index if trans fats are <0.5%, but due to changes in the food supply this score is often a default 10 points, and not necessarily reflective of diet quality.

There is also 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, 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 Women's Health Initiative [WHI] recruited women aged between 50–79yrs across all regions of the United States from 1993 to 1998 into either an RCT or prospective cohort study. The present study analysed the associations between adherence to the Portfolio Diet score and CVD outcomes in women from both studies combined.

The Portfolio Diet score categorised the diet into 6 components: plant protein, nuts, viscous fibre, plant sterols, MUFA, and saturated fat and cholesterol sources. Each individual component was scored from 1 ["unhealthy"] to 5 ["healthiest"], and the sum total of scores from each component constituted the total diet score. Thus, the total scores could range from 6 to 30. The diet components were assessed from the food frequency questionnaire [FFQ] designed for the WHI cohort, completed at baseline and again at year 3 of the follow-up period. The analysis used the average Portfolio Diet score from both completed FFQ's.

Participants were divided into quartiles of Portfolio Diet adherence scores with 6–14 points as the lowest and 20.5–30 as the highest; the lowest score group served as the reference group against which the risk of CVD outcomes in the highest group was compared.

The primary outcomes were total CVD, coronary heart disease [CHD; including nonfatal myocardial (MI) infarction and death from CHD], and stroke [including incidence and death from stroke]. "Total CVD" was a composite of nonfatal MI, CHD death, all stroke, coronary revascularisation, and heart failure. Secondary outcomes included heart failure [HF] and atrial fibrillation [AF]. The results were presented as hazard ratios [HR] and 95% confidence intervals [CI].

Results: The final sample for the present analysis included 123,330 women. Average age of participants at baseline was 62.6yrs and average BMI at baseline was 27.8kg/m^2. The average duration of follow-up was ~15.3yrs. 84% of the cohort were White ethnicity, 8.2% Black, 4% Hispanic, and 1.1% Asian, and participants were distributed equally across the U.S.

Association Between Portfolio Diet and Primary Outcomes

- ***Total CVD***: Based on 13,365 cases, the highest level of adherence to the Portfolio Diet had an 11% lower [HR 0.89, 95% CI 0.83 to 0.94] risk of total CVD compared to the lowest group.
- ***CHD***: Based on 5,640 cases, the highest level of adherence to the Portfolio Diet had an 14% lower [HR 0.86, 95% CI 0.78 to 0.95] risk of CHD compared to the lowest group.
- ***Stroke***: Based on 4,400 cases, the highest level of adherence to the Portfolio Diet had an 3% lower [HR 0.97, 95% CI 0.87 to 1.08] and non-significant [the upper bound of the CI crossed 1.0] risk of stroke compared to the lowest group.

Association Between Portfolio Diet and Primary Outcomes

- ***HF***: Based on 1,907 cases, the highest level of adherence to the Portfolio Diet had an 17% lower [HR 0.83, 95% CI 0.71 to 0.99] risk of HF compared to the lowest group.
- ***AF***: Based on 929 cases, the highest level of adherence to the Portfolio Diet had an 10% higher [HR 1.10, 95% CI 0.87 to 1.38] risk of AF compared to the lowest group.

Overall, the sensitivity analyses [e.g., analysing the cohort study participants only as the RCT participants had a direct intervention to change their diet, and excluding CVD events within the first 3 years of follow-up, or participants with T2D] produced similar results to the primary analysis.

However, for HF, excluding the first 3yrs of follow-up from the analysed rendered the finding for the highest level of the Portfolio Diet no longer significant; this indicates that the significant association in the overall analysis may have been influenced by participants that exhibited latent risk of HF at baseline.

Finally, the subgroup analyses [i.e., by age, ethnicity, BMI, region of the U.S., family history of CVD, smoking status, and use of cholesterol-lowering medications] were similar overall to the primary analysis, with evidence of some effect modification by smoking status [greater risk reduction in current smokers] and cholesterol-lowering medication use [greater risk reduction in those on medications].

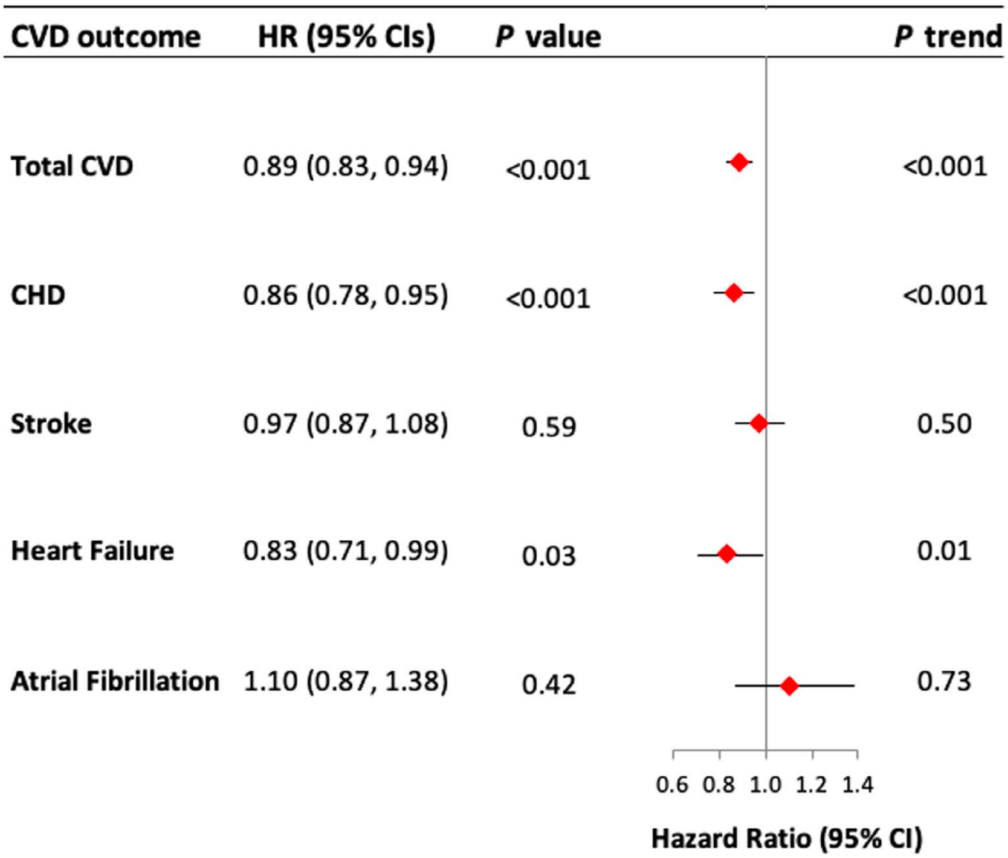

Figure *from the paper illustrating the associations between the highest adherence category of the Portfolio Diet scores compared to the lowest and risk of each of the primary outcomes [Total CVD; CHD; stroke] and secondary/exploratory outcomes [HF and AF]. The most robust associations were observed for Total CVD and CHD, while neither stroke nor AF were significant, and the finding for HF was attenuated and lost significance after excluding the first 3yrs of follow-up*

The Critical Breakdown

Pros: The objective of the study was clearly stated, and was a novel research aim being investigated for the first time. The Portfolio Diet index provided a means of capturing the characteristics of this diet for nutritional epidemiological research. The dietary assessment did at least have some repeated measures at 3yrs follow-up, rather than an isolated baseline measurement. The sample size was very large, and there was a large number of total CVD events for the analysis. The follow-up duration of ~15yrs added to the power of the study. The statistical analysis was thorough and included adjustment for a wide range of lifestyle [i.e., smoking, alcohol, education status, ethnicity, physical activity], dietary [i.e., sodium intake, total energy intake], and health related [i.e., family history of CVD, hypertension, T2D] factors that could influence the associations. The analysis also included several pertinent sensitivity analyses and subgroup analyses.

Cons: Although providing a quantitative measure of the Portfolio Diet was a positive, this was observational research and the diet could only be assessed as far as the characteristics of the population in which it was being measured would allow; intakes of plant proteins, plant sterols, and MUFA, were all quite low. This meant that even the highest quintile of points for the Portfolio Diet score corresponded to a low intake of specific food components. For example, the intervention Portfolio Diet provides ~2g/d plant sterols; the highest intake in the WHI cohort was 404mg/d. As a telling example of this, in a sensitivity analysis which compared adherence in the cohort to the maximal Portfolio Diet recommendations from RCTs, the average adherence in the cohort was 22%. No adjustment was made for PUFA in the analysis, which is a dietary factor strongly related to lower CVD risk. The cohort demographics were relatively homogenous and consisted of predominantly health-conscious postmenopausal White/Caucasian women, thus the findings should not be over generalised to other population groups. Importantly, the demographics of included and excluded participants differed, with more Black and Hispanic women not meeting inclusion criteria for the present study, which resulted in a final study sample less representative of the U.S. general population.

Key Characteristic

The design of the present study is important in the context of one of the major accusations against nutrition science; that evidence from RCTs and cohort studies are divergent [5,6]. In this context, the reliability of observational research is primarily evaluated relative to the results of RCTs [7].

However, one of the major limitations of the assumption that nutrition RCTs are more reliable than nutritional epidemiology has been the failure to consider how similar the design characteristics of both research approaches are. In particular, the most important design characteristic appears to be the source or method of dietary intake, i.e., whether we are comparing whole diets, specific foods and nutrients, or supplements [8]. We covered this in detail in a previous Research Lecture.

In their evaluation of agreement between diet-disease relationships based on 950 randomised controlled trials and 750 cohort studies, Schwingschakl *et al*. [8] showed that the strongest level of agreement between research designs was found where the source of intake was *diet* in cohort studies compared to *diet* in RCTs. This is precisely the

approach taken in the present research, comparing "apples to apples" as much as the diet of the population in the cohort would allow.

The Portfolio Diet in RCTs reliably reduces the causal risk factor for CVD in LDL-C, along with other cardio-metabolic risk factors; the present study demonstrates reductions in hard CVD endpoints associated with the characteristics of the Portfolio Diet over 15yrs. The study thus provides an example of where RCT evidence meets long-term epidemiological research in congruence.

Interesting Finding

Sticking with the theme of congruence, the present study also conducted an analysis of the individual components of the Portfolio Diet and their associations with CVD risk. Nuts, plant sterols, MUFA, and low-SFA foods were each associated with a 10%, 10%, 8%, and 11% lower risk of total CVD, respectively. For CHD, plant sterols and low-SFA foods were each associated with a 17% and 10% lower risk, respectively.

These findings bolster previous research on the specific components of diet that may yield cardio-protective benefits. The relationship between plant-sourced MUFA and low-SFA intakes goes back to the 15yr follow-up of the Seven Countries Study [(9)]. However, a really interesting aspect of these individual component findings is that both nuts and plant sterols showed up because – as we covered in a previous Deepdive – these components may actually be related.

Del Gobbo *et al*. [(10)] showed that the plant sterol content of nuts primarily explained the blood cholesterol-lowering effects of nuts. These effects have been demonstrated at levels of plant sterols of up to 275mg/d [(11)], which is even lower than the highest quintile of 404mg/d observed in the present study. The suggested maximum effective dose of phytosterols for cholesterol reduction is ~2g/d [(12)], and this is difficult to achieve through diet alone [it would be well over 100g of nuts], hence the addition of sterols to "functional foods" such as soft margarines or yogurt-based drinks.

Nevertheless, plant sterols exert effects on cholesterol metabolism that provide strong mechanistic plausibility for the lower CVD risk observed in the present study [(13)]. Indeed, the plant sterol content of unsaturated fat oils, such as sunflower, corn, and soybean oils, may provide some explanation for the benefits of these oils in lowering CVD risk in the early dietary intervention trials in the 1960's and '70's, beyond their fatty acid composition alone [(14)].

Relevance

Typically, RCTs are designed to proceed from observational associations found in epidemiology. The present study represents the inverse sequence; taking a diet designed for use in intervention trials and applying a scoring index to assess adherence to that diet in a long-term observational cohort.

In this respect, the attempt to match an intervention diet with habitual intake in the general population represents a useful approach to bridging the temporal gap between the effects of a diet on intermediate risk factors in shorter-term RCTs with relevant disease endpoints in longer-term cohort studies.

The fact that the primary outcomes were largely unaffected by various sensitivity and subgroup analyses conducted in the present study lends further weight to the findings. Let's think about these findings in turn. The 11% and 14% lower risk for the primary outcomes of total CVD and CHD, respectively, were modest but relatively robust effect estimates for "high" adherence to the Portfolio Diet scores. And as the Portfolio Diet RCTs preceded this epidemiological research, the findings in the present study have an already well-established biological plausibility given the effects of the food components on CVD risk factors.

Application to Practice

Let's recap on the full implementation of the Portfolio Diet recommendations from the intervention trials for an average 2,000kcal/d diet: 50g soy protein, 45g nuts, 20g viscous fibre, 2g plant sterols, 45g MUFAs, <7% energy from saturated fat and <200mg cholesterol per day. Some of these thresholds could be challenging for the average person in the population to meet and would require some targeted approaches to their nutrition.

Nevertheless, that is where you as nutrition and healthcare professionals may help. For example, 2g/d plant sterols are more easily achieved with yogurt-based drinks like Benecol, or soft margarines with added sterols. The levels of plant-sourced MUFA could be achieved with ~3-tablespoons/d extra-virgin olive oil or rapeseed oil.

Arguably the most challenging could be the viscous fibre intake, as aside from oats, foods that the Portfolio Diet recommends such as eggplant/aubergine and okra are possibly not quite dietary staples in the average fridge. Supplementation with psyllium husk fibres could be a helpful strategy for individuals disinclined to eat 200g/d of aubergine.

However, it is important to remember that the present study demonstrated benefits with less than stellar adherence to the full Portfolio Diet as implemented in RCTs; this is rather encouraging, and suggests that some adherence is better than none, and more is better than less. This is a principle that seems to be relatively universal when it comes to the role of nutrition in long-term health.

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