A CASE FOR PLANT-BASED DIET

The proven, evidence-based case in a US population group for increased emphasis on plant foods in the diet.

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Questions about behavioral choices, such as diet, are some of the most important—easy to state but difficult to test. As compared to binary behaviors such as cigarette smoking, or long-distance running, dietary choices cannot be "turned off". Such choices are either "better" or "worse" for our health. They are mandated by our physiology and are strongly influenced by culture. We must all participate, this often without considering the health effects of those choices. If there are such consequences they are likely to be hugely important at the population level, affecting quality of life years, as well as mortality rates, national health expenditures and budgets.

Recommended medical and lifestyle standards, and suggested changes from norms, require strong causal evidence. This is usually gained with three "legs" of evidence, starting with careful multivariate correlations, then proceeding to randomized trials, and then to mechanistic studies examining interactive effects. However, when considering impacts of complex lifestyles on chronic diseases that develop over decades, the second "leg" of evidence, randomized trials, is rarely possible. Randomly allocated experimental changes to people's cherished diets for decades at a time are unacceptable to most.

In this context, evidence from carefully conducted observational studies takes on added importance. Such studies seek to duplicate the results of randomized trials, but in so doing must give great attention to the validity of measuring lifestyle, and also appropriate adjustment for confounding factors (1). The evidence for beneficial effects of plant-based, compared to more animal-food based traditional American diets, is now overwhelming in its quantity, although quality needs more discernment. It is important to recall that the enduring evidence that behaviors such as cigarette smoking, and risk factors such as hypertension, and blood LDL cholesterol, are causally related to vascular and other diseases, was all initially based on high quality observational work.

The complexity of many lifestyle behaviors does provide challenges of adequate measurement accuracy and the possibility of correlations with other potentially confounding behaviors. Dietary studies, searching for cause, should be most influential when they provide extensive validation data of the dietary assessment, and include extensive adjustment for possible confounders.

While recognizing the existence of excellent quality studies seeking to establish effects of particular foods or nutrients prominent in plant-based diets, there are few large studies that examine the dietary descriptor "plant-based" as a category, rather than a sliding scale continuum (where the consumption of some meats continues). These few studies are those of vegetarians. One may consider these individuals to be at an extreme of the plant-based continuum (when defined in that way). The two largest studies of vegetarians are the Adventist Health Study-2 (2, 3), and the EPIC-Oxford study (4). Other preceding smaller studies have been important both among American

Adventists and U.K health-conscious subjects. As a group these studies appear to show sizeable health benefits that accrue among the vegetarians when compared with nonvegetarians (5). These include relative protection from many chronic (and some acute) diseases and probably also greater life expectancy. There is also evidence that plant-based diets result in a higher level of life satisfaction as well as increased quality of life years (6).

We largely focus here on methods and results of Adventist Health Study-2 (AHS-2). The study subjects are all members of a church, which may seem to limit representation, but it is in fact a very diverse group, living in all 50 states of the USA, encompassing every conceivable occupation, covering all socioeconomic strata (although tending to well-educated), and also in that 25% of the 96,000 subject cohort are African American (2, 3).

A common misconception is that the study design usually compares Adventists to non-Seventh-day Adventists, which would include many potentially confounding non-dietary differences. Rather, most published work from AHS-2 compares certain Adventists to other Adventists with different dietary habits. Only ~50% of American Adventist study group were vegetarian. This allowed a strong focus on the dietary contrast. Although analyses always included extensive adjustment for potentially confounding variables, these differences were often quite small at the level of the different dietary subgroups. It is notable that the relatively potent confounders of cigarette smoking, and alcohol consumption are largely absent from this study group.

That the study group includes some dietetically atypical subjects is also a strength. Exploration of new ideas requires some subjects who adhere to those new patterns, but many other more typical subjects to act a basis for comparison. Approximately half of Adventists are not vegetarian, and form a strong basis for comparison. Indeed AHS-2 could be considered a test of principle, a non-randomized trial of the hypothesis that less common, but still accessible, plant diets, do make a substantial difference to health experience This does not test one “plant-based” food at a time, but combinations of such foods that then form a plant-based dietary category or pattern (e.g. lacto-ovo-vegetarian, or vegan).

What have we found in AHS-2? First, AHS-2 has published extensive dietary validation results, relating questionnaire data to repeated 24-hour dietary recalls, to serum, urine and adipose biomarkers (7-10), to risk factors (11-13), and also limited work with metabolomics (14). Our dietary data has very good validity, particularly for the foods required to allocate study participants to vegetarian dietary patterns (8). It is clear that our questionnaire is identifying dietary patterns that have strong biological signals. Second, review of key AHS-2 papers relating diet patterns to cardiovascular deaths, cancer incidence, all-cause mortality , and risk factors (11-13, 15-18), will confirm extensive adjustment for potential risk factors that may confound associations with diet, and we also usually evaluate overweight as a possible mediating variable. The following paragraphs summarize key results and provide references.

Mortality and Life Expectancy

In one of the few external comparisons, AHS-2 data was compared with a non-smoking nationally representative subgroup of a U.S. Census research population (analysis conducted by Census Dept) (19). Covariate adjustment was limited but included age gender, race, education, BMI and past smoking habits. Mortality was about 30% less in the Adventists on average for each year of

age, and the greatest percentage reductions were seen at younger than older ages. The 30% reduction in mortality was also approximately true separately comparing Black subjects in AHS-2 to Black subjects in the census population. A subsequent analysis **within the Adventist group** compared vegetarian to non-vegetarian Adventists (18), and found that at younger (<75-80 year) ages the vegetarians had a clear 10-15% advantage each year of age but this disappeared in deaths at very old ages. Thus, the important benefit appeared to be in the prevention of premature deaths, thereby saving more person-years of life. A greater proportion of vegetarians survived till their 80's. Putting this together with the census study on non-Adventists, compared to the general U.S. population we calculate that vegetarian, and (the relatively low-meat consuming) nonvegetarian Adventists, respectively have 33% and 22% fewer deaths per year of age than other Americans.

The causes of death that appeared to be particularly prevented or at least delayed in the vegetarians (compared to nonvegetarian Adventists), were cardiac deaths, those related to diabetes and hypertension, chronic renal failure deaths and infectious disease deaths (18). At oldest ages only, these benefits were still present but of lesser magnitude, and somewhat counterbalanced by a mild increase in neurologic deaths, a matter needing further research (18).

Cancer Incidence

Comparing incident cancer rates between vegetarian and nonvegetarian Adventists, a significant difference over all was not demonstrated, but cancer is a very diverse category, and looking at different types, in no case was there evidence of excess cancer in the vegetarians, and good evidence of lesser rates in several more common and a few less common cancers. Even a large cohort is challenged by smaller numbers of specific cancer events and hence lower statistical power. Vegetarians as a group had lower rates of colorectal cancers, no doubt related in part to absent dietary red and processed meats(15). The vegetarian Adventists also had distinctly lower rates of lymphatic cancers (lymphoma and lymphatic leukemia), and also stomach cancer (manuscript submitted, under review). The total of all medium frequency cancers (excluding colorectal, breast and prostate) was a highly significant 18% lower in the vegetarians suggesting that other less common cancers were also probably at lower risk but were difficult to detect with available power. Candidate cancers (that just failed statistical significance) included lung, pancreas and ovarian cancers. The much more common prostate and breast cancers were of interest, in that it was only the vegan vegetarians who showed a substantial (25-30%) and significant reduction in their risk (compared to nonvegetarians) (16-17). AHS-2 is the largest (and perhaps only informative) study of vegans that is available for such analyses at present.

Biological and Mechanistic Analyses Among Vegetarians in AHS-2.

A great deal of evidence shows that vegetarians have markedly lower values of BMI, lower rates of hypertension, diabetes, and elevated LDL cholesterol, as compared to non-vegetarians. This is clearly so when we compare vegetarian to non-vegetarian Adventists (11-13, 20,21). Further, we have also shown that as compared to non-vegetarian Adventists, vegetarians also have lower C-reactive protein levels, a marker of inflammation (22). Much of this evidence is cross-sectional. The usual weakness there is the possibility of reverse causation, which however does not exist in this context . The existence of these risk factors would not cause change to a non-vegetarian diet among Adventists, rather toward a vegetarian habit, which would tend to weaken the observed associations. AHS-2 has published **longitudinal results** associating non-vegetarian dietary habits

at baseline to greater subsequent rates of new diabetes mellitus (21). Others have reported short term randomized trials associating vegetarian diets with lower blood pressures, LDL cholesterol values, and lower risk of diabetes, thus also supporting causality in most of these diet-risk factor associations.

Lastly, we have recently published molecular analyses, based on the DNA methylome and the metabolome. While much yet awaits further research, we obtained evidence that vegans and non-vegetarian Adventists had about 1000 genes where average methylation of CpG sites differed significantly (23). However, we could specifically identify (with the small sample size available) only a few of these. Most significant sites were hypo-methylated in vegans, which usually implies less gene suppression. The differentially methylated sites that we observed were in genes involved in RNA transport, ribosome assembly, protein degradation/ubiquitination, and B cell receptor signaling. Thus, differences involving protein synthesis appear as a possible focus. Further work with a larger sample is on-going.

Second, with a panel of 900 blood metabolites (14), the vegans differed significantly from Adventist non-vegetarians in more than 600 of these metabolites! In both DNA methylation and metabolomic analyses, false discovery was kept at a 5% level.

Summary

There now seems little doubt that plant-focused diets are causally associated with better physical health outcomes as well as life satisfaction. Although study designs are largely observational, it is highly unlikely that the large amount of consistent evidence from different studies in different locations can be explained by unrecognized confounding. Further, physiologic mechanisms based on established differences in body size, blood pressure, blood lipids, blood sugar and insulin (also diabetes), as well as a marker of lesser inflammation, offer further support and strongly suggest causal mechanisms. Changes at the levels of gene expression and molecules are as yet poorly understood, but that there are major differences in these, according to diet, has now been demonstrated.

Thus, we applaud the plan to recommend plant-based diets, as dietary changes in this direction are almost certain to improve public health, providing a higher degree of life satisfaction, thus more quality years, as well as lower mortality, and a substantial reduction in health care costs.

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