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# Vegetarian Dietary Patterns: Mortality, Colorectal Cancer, and Food Consumption

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# Vegetarian Dietary Patterns: Mortality, Colorectal Cancer, and Food Consumption

By

Michael John Orlich

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A Dissertation in partial fulfillment of
the requirements for the degree of
Doctor of Philosophy in Epidemiology

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Each person whose signature appears below certifies that this dissertation in his/her opinion is adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

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ABSTRACT OF THE DISSERTATION

Vegetarian Dietary Patterns:
Mortality, Colorectal Cancer, and Food Consumption

by

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Doctor of Philosophy program in Epidemiology
Loma Linda University, June 2014
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**Objective**

Vegetarian dietary patterns represent longstanding, real-world diets consumed by a minority of persons. Studies of important health outcomes of such diets, particularly for all-cause mortality and colorectal cancer risk, have yielded inconsistent results. We sought to examine these outcomes (mortality and colorectal cancer incidence) in a large North-American cohort. We also sought to further characterize potentially important differences in the food consumption patterns of these diets.

**Design**

Baseline diet was measured by a quantitative food frequency questionnaire among more than 96,000 Seventh-day Adventists in the US and Canada, enrolled from 2002-2007. Dietary patterns were defined, based on the reported consumption of key foods, along a continuum of animal food avoidance. Mortality through 2009 was obtained by record linkage with the National Death Index. Cancer incidence data through 2011 was obtained by record linkage with state cancer registries. Cox regression of time-to-event was used as the primary analytic approach for both mortality and colorectal cancer incidence outcomes.

**Results**

Vegetarian dietary patterns demonstrated reduced consumption of sweets, added fats, refined grains, and caloric beverages and increased consumption of a variety of plant foods. Vegetarian dietary patterns together were associated with a reduction in risk of all-cause mortality (HR=0.88, 95% CI 0.80-0.97). Reductions were seen for vegans, lacto-ovo-vegetarians, and pesco-vegetarians separately. Effects were stronger in men. Some beneficial associations were seen for cardiovascular, renal, and endocrine cause of mortality but not for cancer mortality. Vegetarian dietary patterns were also associated with a reduction in colorectal cancer incidence (HR=0.79, 95% CI 0.65-0.95).

**Conclusion**

Vegetarian dietary patterns in the Adventist Health Study 2 are associated with reduced all-cause mortality and reduced incidence of colorectal cancers. These diets demonstrate notable differences in the consumption of a variety of food groups, beyond those animal foods which define them.

# CHAPTER ONE

# INTRODUCTION

## The Challenge of Nutritional Epidemiology

The impact of diet upon health, longevity, and the risk of disease is a question of great importance to public health. As a lifelong, daily exposure for all people, yet one which can vary greatly, the potential impact of diet upon health seems intuitively to be very large. However, those same factors, the long-term nature of the exposure and its complexity, make the impact of diet upon health and disease extremely difficult to study, particularly when the effects of interest may be of modest strength and may be manifest only after long periods of time.

Traditionally, nutrition science has focused a great deal of attention on the nutrient as a sort of fundamental component of the discipline, one which can be precisely defined and quantified and one which can be tied to specific biochemical mechanisms in normal physiology and in pathological states. This approach has worked well, particularly for diseases caused by the deficiency of a particular nutrient and for the practice of acute clinical dietetics. However, it is less clear that a nutrient focus is as useful in the context of chronic-disease nutritional epidemiology, where the effect on health and disease may be due to many chemical compounds in foods that fall outside of classical nutrient definitions, where the effects of specific nutrients may be small and difficult to detect, and where the nutrients occur in complex inherently-defined mixtures (i.e. foods) that may make the isolated effects of specific nutrients very difficult to determine. Studies of the effects of specific foods likely represent a good alternative in many cases to nutrient-based approaches, although even with this approach, it can be difficult to isolate the effect of a specific food or food group.

## Dietary Patterns

Another alternative is to define specific patterns of eating, which may differ from other patterns across a variety of foods and nutrients, and study their relative effects. One challenge in this approach is defining dietary patterns that can be readily distinguished from other patterns, that differ across a number of foods in a fashion suggestive of plausible health impacts, and that bear some relationship to what people actually eat, or are likely to eat, in daily life. Differing approaches to defining dietary patterns have been employed. These include partially data-driven methods of pattern analysis as well as a priori methods based on dietary theories or patterned after the diets of certain regions or cultures (e.g. the "Mediterranean" diet).

## Vegetarian Dietary Patterns

Vegetarian dietary patterns are excellent candidates for study of this sort. Vegetarian diets of different types have constituted an alternative approach to eating throughout much of history and across many societies. They are thus "real world" diets consumed by millions of people on a daily basis, not just a theoretical construct consisting of an amalgamation of discrete nutrient or food recommendations as are many dietary patterns (e.g. the "prudent" diet). They are generally easy to define, and they would seem to be familiar to many people. They have been chosen for their perceived ethical, philosophical, aesthetic, religious, and environmental merits as well as for their perceived health benefits. For these reasons, vegetarian dietary patterns have been the subject of considerable study (much of which will be reviewed in subsequent chapters), and they continue to represent an important area of study in nutritional epidemiology.

## Specific Aims

This dissertation builds upon earlier work by further characterizing vegetarian dietary patterns in the Adventist Health Study 2 (AHS-2) cohort and examining their association with mortality and colon cancer. The specific aims of this dissertation are thus the following: 1) to better characterize the vegetarian dietary patterns of the AHS-2 in terms of their patterns of food consumption, 2) to examine the association of vegetarian dietary patterns in AHS-2 with mortality from all causes and from major categories of causation, and 3) to examine the association of these dietary patterns with the risk of colorectal cancers.

# CHAPTER TWO

# LITERATURE REVIEW

## Studies of Vegetarians

While vegetarian diets date from antiquity, the scientific study of such diets is relatively recent[1]. Because vegetarian diets are defined by their avoidance of certain common types of food, primarily meats, and because much of early nutrition science dealt with deficiency states, earlier studies of vegetarian diets often focused on the nutritional adequacy of the dietary patterns. As the nutrient profiles of vegetarian diets, including nutrients of special concern, were better understood, and as evidence began to emerge associating vegetarian diets with reductions in risk for certain disease states, the research focus has gradually largely shifted to the study of the long-term health impacts of vegetarian diets. This shift in emphasis in the scientific literature has been demonstrated quantitatively[2].

One center of early scientific research into vegetarian diets was Loma Linda University, a Seventh-day Adventist institution. The Seventh-day Adventist teachings promote a vegetarian diet as ideal for the promotion of health; consequently, a significant minority of Adventists has historically adopted vegetarian diets.

In the 1950s and 1960s, Hardinge and colleagues published a series of papers comparing several nutritional aspects of vegetarian and nonvegetarian diets in adults, adolescents, and pregnant women (primarily lacto-ovo vegetarians, but also including "pure vegetarian", or vegan, adults) (N=200)[3-7]. These studies generally demonstrated vegetarian diets to be adequate in terms of the mean intake of protein and several micronutrients. Vegetarians (especially vegans) had notable reductions in body weight, despite rather comparable energy intakes[3]. Vegetarians (especially vegans) were also found to have reduced serum cholesterol levels[6].

Also in the 1950s, investigators at Loma Linda University, primarily Lemon and Walden, working with Wynder from Sloan Kettering made a number of comparisons of Seventh-day Adventists and others, finding notably reduced incidence of heart disease in the Adventist men compared to their counterparts and reduced incidence of many types of cancer[8,9]. In 1958, Lemon and colleagues surveyed a group of about 47,000 California Adventists[10]. In 1960, approximately 23,000 of these were enrolled in the American Cancer Society's (ACS) Cancer Prevention Study, led by Hammond[11]. A variety of hereditary and environmental factors that might contribute to cancer risk were assessed, and they were followed for incident cancers, along with the other members of the ACS cohort. This study is now often referred to as the Adventist Mortality Study (AMS). The AMS and other investigations in the 1950s and 1960s demonstrated an overall longevity advantage[11] and reduced mortality from respiratory diseases[12], coronary heart disease[13], and a number of cancers[10] for Seventh-day Adventists compared to the general population. Some of the cancer findings were attenuated when comparison was made to a more demographically similar reference group[14-16]. Interestingly, a comparison of Seventh-day Adventist physicians to other physicians did not show similar advantages[17]. Such early findings prompted further study regarding possible contributing factors[17]. It was clear from the beginning that the very low rates of smoking among Adventists were responsible for the lion's share of their advantageous outcomes, particularly the sharply reduced risk of respiratory and epithelial cancers. Still, there was interest in the potential contributions of other factors, such as vegetarian dietary patterns, since some advantage persisted for the Adventists even when compared to only the non-smokers of the ACS cohort[17,18].

Thus, beginning in 1974, Phillips and colleagues enrolled a cohort of approximately 34,000 California Seventh-day Adventists, now referred to as the Adventist Health Study 1 (AHS-1) with the intent of examining in greater detail the potential contributions of dietary and other lifestyle factors in disease prevention[18]. While the AMS had used only the ACS Cancer Prevention Study instrument to assess lifestyle factors, the dietary assessment of which was quite abbreviated, the AHS-1 used a rather detailed food frequency questionnaire to more closely assess the usual diet of participants[19]. A number of important findings originated with AHS-1, particularly the apparent protective effect of nuts for cardiovascular disease[20-22] and an identification of several factors that incrementally contribute to notable differences in longevity[23]. Findings from the AHS-1 that relate vegetarian diets to mortality and colon cancer are reviewed below.

A few other cohorts have been designed to evaluate the potential health effects of vegetarian diets, principally in the UK and Germany. These are briefly described here. Fraser offers a fuller review of these studies and their findings[24,25]. In the Health Food Shoppers study[26], about 10,000 subjects were recruited in the UK between 1973-79. Subjects were from health food store customers, health magazine subscribers, and health food societies. Importantly, vegetarian status was determined merely by a question asking whether the participant was a vegetarian, not by enquiring about their consumption of animal foods. A little more than 40% reported being vegetarian. The Oxford Vegetarian Study[27] was another UK study of similar size, approximately 11,000 members, recruited between 1980 and 1984. Recruitment was through the Vegetarian Society of the UK, using word of mouth and media campaigns, with each vegetarian cohort member recruiting a nonvegetarian member from among his family, friends, or acquaintances. The Heidelberg Vegetarian Study[28] was small, with less than 2000 participants. Participants were recruited between 1978-1981 in Germany, by means of an advertisement in vegetarian magazines. These three European cohorts, together with the Adventist Mortality Study and Adventist Health Study 1, were considered together in a pooled analysis examining mortality from all causes, from cardiovascular disease, and from cancers[29-31].

More recently, two major cohorts have been designed to study the possible effects of vegetarian diets on the risk of chronic diseases, and particularly cancer. The first is the Adventist Health Study II (AHS-2), which is the subject of this dissertation. Briefly, AHS-2 is funded by the National Cancer Institute with the specific aim of investigating links between dietary practices, and especially those related to vegetarian dietary patterns, and the risk of major cancers. Recruitment for the study was between 2002 and 2007, when Seventh-day Adventist church members were recruited from congregations throughout the US and Canada. More than 96,000 participants were successfully recruited. A special effort was made to recruit blacks, as a group in which diet and health has not been studied adequately. As a result, nearly one fourth of the cohort is black (African American, African, or black Caribbean). A detailed questionnaire was developed, which includes a quantitative food-frequency questionnaire with more than 200 food items as well as other questionnaire sections related to demographics, non-dietary lifestyle habits, personal health history, family health history, and reproductive and gynecologic history. A calibration study of more than 1000 persons completed multiple 24-hour food recalls, underwent biometric and laboratory testing, and provided biological specimens. This sample has been used to validate the FFQ in terms of its ability to accurately estimate intakes of foods[32] and nutrients[33]. The validity is relatively high, particularly for foods of animal origin[32], which are used to define vegetarian dietary patterns. See Butler et al. for a more detailed description of the cohort and its recruitment[34]. AHS-2 is an advance over AHS-1 (and AMS) in a number of important respects. Firstly, it is approximately three times as large as AHS-1, providing greater power for examining important cancer endpoints, for subgroup analyses, and for analysis of the associations of less popular dietary patterns, such as the vegan diet. Secondly, it is more diverse geographically and ethnically, and thus more representative of the general North American population; its relatively large number of black participants will allow for study of this important subgroup, in particular. Thirdly, there are methodological advances, with a more detailed questionnaire and a sizeable validation/calibration sample, allowing for the potential to correct for dietary measurement error and allowing for increased confidence in the validity of findings.

The second of the two major new cohorts studying vegetarian dietary patterns is the Oxford-based British cohort of the large European Prospective Investigation into Cancer and Nutrition (EPIC). The EPIC study is a coordinated collaboration of 10 individual cohorts in a number of European countries, with about one half million total participants, recruited in the 1990s[35]. The Oxford cohort, or EPIC-Oxford, intentionally recruited a large number of persons consuming vegetarian diets. Recruitment was primarily by mailings to vegetarian societies, advertisements in health periodicals, etc., though some was done through the offices of general medical practitioners[36]. Approximately 65,000 participants were recruited; of these, about half reported not eating meat (except for fish in one subgroup)[36]. EPIC-Oxford adapted the detailed semi-quantitative FFQ of the Nurses Health Study for dietary measurement[36]. As with AHS-2, EPIC-Oxford represents a substantial advance over its predecessor studies (Health Food Shoppers and Oxford Vegetarian) in terms of both its much larger size and thus power and in methodological rigor. In addition to EPIC-Oxford, there is another modern UK cohort that has a sizeable proportion of vegetarians, the UK Women's Cohort Study. This cohort is comprised of approximately 35,000 adult British women, of whom 28% self-classify as vegetarian but only 18% are defined as vegetarian based upon their responses to questions of the frequency of foods consumed[37].

## Characterization of Vegetarian Diets

The term "vegetarian" admits a variety of definitions[2]. While the name itself suggests a definition by what is included or emphasized in the diet (i.e. "vege"), vegetarian diets are often defined by what foods are omitted from the diet, namely meats and sometimes other foods of animal origin. This variability in defining vegetarian diets should not be surprising, as many dietary definitions suffer from similar uncertainty, particularly in every-day use. It is hard to give a rigorous definition for the term "vegetable", many biological fruits are not considered "fruit" in typical dietary usage, and many use the term "meat" in a way that does not include fish (and sometimes not fowl) while others use it food all animal flesh foods. A number of vegetarian diets have been labeled, that are more or less strict in their definitions. The term "vegan" has been defined by some to exclude the use of any animal products, such as honey or leather; whereas others use the term to designate those vegetarians that avoid all meats, dairy products, and eggs. The terms lacto-vegetarian, ovo-vegetarian, and lacto-ovo-vegetarian have been used to describe vegetarian diets that include animal foods. The most common of these labels is that of lacto-ovo-vegetarian, which describes a diet that omits all meats, but may include dairy products, eggs, or both. Vegans and lacto-ovo-vegetarians together can be considered "true vegetarians" or "strict vegetarians" (although that term has also been used as a synonym for vegan) or just "vegetarians", in that of these diets omit all meats (including fish and fowl). More liberal usages of vegetarian can include diets might include fish but exclude other meats (pesco-vegetarians, or pescaterians) or those is which meat eating is quite infrequent, but not avoided entirely (vegetarians). These latter diets may bear some resemblance to a number of traditional diets of island peoples or where meat consumption was a prized but not common event. Persons who consume these pesco-vegetarian or semi-vegetarian diets may self-identify as vegetarians, but be excluded by more strict definitions.

In the EPIC-Oxford study, four dietary patterns have been defined (meat-eaters, fish-eaters, vegetarians, and vegans) based on four questions of the form, "Do you eat any… (meat, fish, dairy products, eggs)"[36]. In that study, the last two groups are sometimes considered together (due to power limitations) as vegetarians or the last three groups together as non-meat-eaters. In AHS-2, five groups have been defined (nonvegetarians, semi-vegetarians, pesco-vegetarians, lacto-ovo-vegetarians, and vegans), based on the reported frequency of consumption of a number of meat, dairy product, and egg-containing food items[38]. In this study, the latter four groups are sometimes considered together (due to power limitations) as vegetarians. One can appreciate that there are some differences in the definitions and usage of terms between these two studies.

Both AHS-2 and EPIC-Oxford define vegetarian dietary patterns on the basis of exclusion or infrequent consumption of categories of food of animal origin. This approach to dietary pattern definition allows for potentially large heterogeneity within each dietary pattern, and does not immediately predict relative average intake of all foods or nutrients by dietary pattern. For example, both the nonvegetarian and lacto-ovo-vegetarian dietary patterns may include milk, but it is not clear which group might consume more milk. Given this, an important backdrop to findings that relate such dietary patterns to health outcomes is a fuller characterization of each dietary pattern. This may be done in terms of both foods consumed and nutrient intake.

In terms of nutrient intake, both AHS-2 and EPIC-Oxford have previously published nutrient profiles by dietary pattern. Davey et al. report mean levels of nutrient intake for the four EPIC-Oxford dietary patterns, for both men and women[36]. Nutrients intake levels reported included dietary energy; percent of energy as carbohydrate, protein, total fat, saturated fats, polyunsaturated fats, and alcohol; non-starch polysaccharide (fiber); and several of the most common vitamins and minerals. There was considerable variation between the groups for both macronutrients and micronutrients. Often levels for vegetarians and fish-eaters was intermediate between vegans and meat-eaters. “The mean intake of saturated fatty acids in vegans was approximately 5% of energy, less than half the mean intake among meat-eaters (10–11%). Vegans had the highest intakes of fibre, vitamin B1, folate, vitamin C, vitamin E, magnesium and iron, and the lowest intakes of retinol, vitamin B12, vitamin D, calcium and zinc."[36] Rizzo et al. report nutrient profiles by dietary pattern in AHS-2[39]. These include the nutrients reported by EPIC-Oxford as well as some more specific nutrient reporting, particularly in specific types of fatty acids and sources of protein. Again, substantial differences were observed among the dietary patterns, with vegans and nonvegetarians often the most divergent, with lacto-ovo-, pesco-, and semi-vegetarians having intermediate values in many cases. "Non- vegetarians had the lowest intakes of plant proteins, fiber, beta carotene, and magnesium compared with those following vegetarian dietary patterns, and the highest intakes of saturated, trans, arachidonic, and docosahexaenoic fatty acids."[39] Some methodological differences--particularly that reported AHS-2 micronutrients are often for total intake (including supplements), whereas supplements appear to generally not be included in the EPIC-Oxford results (but also issues of adjustment and of course dietary pattern definitions)—do not always allow for direct comparison between these published nutrient intakes; still, some comparisons are instructive. As stated by Rizzo, "When comparing unadjusted energy intakes of AHS-2 US lacto-ovo vegetarians with UK vegetarians (data not shown)… Energy percentage intakes of poly- unsaturated fatty acids were higher by 67.7% for men and 80.8% for women. Energy percentage intakes for saturated fatty acids were lower by 25.7% for men and 25.1% for women. Dietary fiber intakes, measured in grams per day, were 62.1% higher for men and 60% higher for women in US vegetarians than the corresponding non-starch polysaccharide values in the United Kingdom."[39]

A description of foods consumed is reported in some detail for the EPIC-Oxford cohort in several published papers[40-43]. Food consumption patterns are examined for the entire EPIC study, reported by individual country cohort, based on a random sample of participants; one paper first describes the consumption of meats (not including fish)[40], and a second reports the consumption of vegetables, fruits, and other plant foods[41]. For the UK cohort, results are listed as "general population" (i.e. meat-eaters) and "health conscious" (i.e. fish-eaters, vegetarians, and vegans, together". For meat intake, "health conscious" participants, not surprisingly, consume far less meat than UK "general population" participants, or members of the other country cohorts. Crude total daily meat consumption was 15.9 g in women and 18.1 g in men, for "health conscious" participants[40]. Vegetable and fruit consumption was considerably higher in the UK "health conscious" than in the UK "general population", and it was also higher than the consumption of fruits and vegetables in other northern European countries and similar (but still lower, in some cases) to the amounts consumed in the more southern/Mediterranean countries[41]. A characterization of foods consumed by the participants of AHS-2, for each dietary pattern, has not yet been published, but is included in this dissertation. Together with the nutrient profiles by dietary pattern, it should provide a fairly detailed description of how these dietary patterns differ from each other and how the diets of AHS-2 vegetarians compare to those of EPIC-Oxford vegetarians.

## Vegetarian Diets and Mortality

The mortality of man and the limits of lifespan are among the most essential of human concerns, and their contemplation has served as the fount of poetry and art, philosophy and religion, science and medicine. To have a long life is as basic a human desire as to have a happy one. Both medicine and public health strive to prevent or defeat those maladies that would bring death before its proper time. More prosaically, in studying the health of populations and the health effects of exposures or interventions, no single measure is as important as mortality, or its cognate, longevity. Mortality from all causes, or if more appropriate, mortality from natural causes, inherently sums together all of the ultimate effects, positive or negative, of an exposure, and converts dissimilar risks to a unified scale. In epidemiology, mortality as an outcome also has the distinct advantage of accurate measurement, thorough reporting, and easily accessible data. Further information from the death certificate regarding the causes to which death was attributed can provide a relatively easy way to investigate disease outcomes, though this may be a poor surrogate for disease incidence. A number of studies of vegetarian dietary patterns have examined the relationship of such dietary practices to mortality or longevity.

As described above, prior studies of cohorts of Seventh-day Adventists in California have made important contributions to the study of the possible health effects of vegetarian diets. We now review previous findings from these studies regarding mortality, primarily all-cause mortality. Most early publications from AMS and AHS-1 which examined mortality (from all causes or from cancers), compared the Adventist study population to the general population or a demographically similar control population, noting greater longevity among the Adventists[11,44]. Such differences were attributed to a number of potential causes, based on notable differences in lifestyle practices. The near absence of tobacco smoking was evidently the most important factor, particularly for the reduced mortality from respiratory diseases and smoking-related cancers[10-12]. The notably different dietary practices, with a much higher prevalence of vegetarianism, of Adventists from those of the general population were also noted as a possible contributor to the increased longevity of the Adventists[17,45]. However, the first analysis that directly analyzed the association of dietary factors to all-cause mortality in AMS was in 1984[46]. 28 food items were examined for a relationship to mortality from all causes. Of these, green salads had an inverse association to higher mortality, and eggs and meat both had a direct association to higher mortality[46]. While the analysis was not directly comparing vegetarians and nonvegetarians, the meat findings are relevant to this classification. Next, nonvegetarians were found to have a higher adjusted mortality from fatal ischemic heart disease (primarily in men) compared to vegetarians[47]. In 1986, Snowdon and Phillips publish results for all-cause mortality for increasing levels of meat consumption, compared to a vegetarian diet; in men, there was a significant adverse association of meat eating with mortality, compared to vegetarians[48] (and again by Snowdon in 1988[49]). These were all AMS results, with up to 21 years of follow-up in the latter papers. AHS-1 results began to be published in 1989, with some aspects of disease-specific mortality being reported on in the 1990s. Fraser first published results of an analysis of the association of vegetarian dietary patterns with all-cause mortality in 1999[50]. Compared to nonvegetarians, vegetarians had reduced mortality from all causes. The age-sex-adjusted hazard ratio was 0.80 (95% CI: 0.74-0.87)[50]. Multivariate adjusted lifetable analysis showed a longevity gain of vegetarians over nonvegetarians of 2.52 years in women ($p<0.001$) and 3.21 years in men ($p<0.001$)[50]. A subsequent analysis identified five major factors contributing to increased longevity in AHS-1: vegetarian diet, never having smoked, regular exercise, maintaining a normal body weight, and eating nuts regularly (and hormonal therapy in women). In this analysis, when other factors were all at high risk, the increase in life expectancy for vegetarians compared to nonvegetarians was 2.38 years (95% CI: 1.12-3.63) in men and 1.65 years (95% CI: 0.65-2.65) in women[23].

We now briefly review findings for vegetarian dietary patterns and mortality in the European cohorts. In the Heidelberg study of German vegetarians, after 5 years of follow-up, the study's vegetarian subjects had lower than expected mortality compared to the general population, but no significant differences were seen comparing the "strict" and "moderate" vegetarian groups within the study[28]. After 11 years follow-up, standardized mortality ratios (SMRs) (unless otherwise specified, all standardized mortality, morbidity, or incidence ratios are comparisons against the general population of the relevant country) for the participants remained at approximately 50 (i.e. 50% relative reduction), and strict vegetarians appeared to show a greater reduction in ischemic heart disease mortality than did moderate vegetarians[51]. After 21 years of follow up, the SMR for the cohort remained low at 59 (95% CI: 54-64); adjusted hazard ratio for all-cause mortality for vegetarians (previously labeled "strict vegetarians") compared to nonvegetarians (previously labeled "moderate vegetarians") was 1.10 (95% CI: 0.89-1.36), a null finding, whereas for mortality from ischemic heart disease, there was a non-significant apparent reduction (HR=0.70, 95% CI 0.41-1.18)[52]. In Britain, in the Health Food Shoppers cohort, after 7 years of follow-up, there was a significant reduction in ischemic heart disease mortality for vegetarians compared to nonvegetarians, strongest among men, but no significant difference for all-cause mortality[26]. Results were similar after an additional five years of follow-up time: SMRs for all cause mortality were 53.0 for vegetarians and 57.0 for nonvegetarians but for IHD mortality were 42.8 for vegetarians and 60.1 for nonvegetarians[53]. After 17 years of follow-up, the association of vegetarian diets to all-cause mortality was null; the adjusted mortality ratio was 1.04 (95% CI: 0.93-1.16)[54]. In the Oxford Vegetarian Study, after 12 years of follow up, the adjusted death rate ratios for non-meat-eaters compared to meat-eaters was 0.80 (95% CI: 0.61-0.99), and effects the association tended to persist when analysis was restricted to never-smokers[27]. In 1999, results were published from an analysis which pooled the above five cohorts (AMS, AHS-1, Health Food Shoppers, Oxford Vegetarian, and Heidelberg); the pooled death rate ratio for deaths from all causes in vegetarians compared to nonvegetarians, based on 8330 deaths, was 0.95 (95% CI: 0.82-1.11)[55]. There was a significant reduction in deaths from ischemic heart disease for vegetarians compared to nonvegetarians, with a death rate ratio of 0.76 (95% CI: 0.62-0.94)[55]. Subsequently, mortality among vegetarians and nonvegetarians has been examined in the EPIC-Oxford cohort. Again, death rates were much lower than expected for the general population (SMR=52%; 95% CI: 50%, 54%). There was no difference between vegetarians and nonvegetarians for all-cause mortality, the adjusted death rate ratio being 1.03 (95% CI: 0.90, 1.16), but there was a non-significant apparent reduction for death from ischemic heart disease, 0.81 (95% CI: 0.57, 1.16)[56]. A meta-analysis, which includes the above studies and two other small studies (one Dutch and one Japanese), estimated a summary risk ratio for all-cause mortality of 0.91 (95% CI: 0.66-1.16)[57].

Lastly, we mention two recent publications not among vegetarians. Because vegetarian dietary patterns are generally defined by the omission of meat from the diet, evidence of a possible effect of meat on increasing mortality are relevant to the discussion. If increased meat consumption leads to increased mortality, the avoidance of meat by vegetarians may lead to a reduction in mortality, perhaps conditional up what foods take the place of meat in the diet. In that light, two recent publications are here reported that found a direct association between increased consumption of red and processed meats and higher all-cause mortality. Both were in large cohort studies. The first reported findings from the Nurses Health Study and Health Professionals Follow-up Study. Among 23,926 deaths, the adjusted hazard ratios for each daily serving of meat was 1.13 (1.07-1.20) for unprocessed red meat and 1.20 (1.15-1.24) for processed red meat[58]. Findings were also significant for both cardiovascular and cancer mortality. The authors reported that "substitutions of 1 serving per day of other foods (including fish, poultry, nuts, legumes, low-fat dairy, and whole grains) for 1 serving per day of red meat were associated with a 7% to 19% lower mortality risk"[58]. They also went on to estimate how restrictions in red meat consumption might have impacted total deaths; they concluded that "9.3% of deaths in men and 7.6% in women in these cohorts could be prevented at the end of follow-up if all the individuals consumed fewer than 0.5 servings per day (approximately 42 g/d) of red meat"[58]. The second was from the NIH-AARP cohort of over 500,000 persons. After 10 years of follow up with a total 47,976 male deaths and 23,276 female deaths, the results were as follows: comparing the highest quintile of meat intake with the lowest quintile, in men the hazard ratio was 1.31 (95% CI, 1.27-1.35) for red meat and for 1.16 (95% CI, 1.12- 1.20) processed meat, and in women the HR was 1.36 (95% CI, 1.30-1.43) for red meat and 1.25 (95% CI, 1.20-1.31) for processed meat. No similar association was seen for white meat[59].

## Vegetarian Diets and Colorectal Cancer

Notions that diet may contribute to the cause or prevention of bowel cancer are not new. Prominent health reformers of the 19th century and before advocated for whole grains and worried about constipation. Concepts of putrefaction and autointoxication in the bowel due to unwholesome dietary practices were given prominence by John Harvey Kellogg, among others. Denis Burkitt warned that the lack of roughage in the Western diet might explain the disproportionate burden of gastrointestinal maladies, including bowel cancers, in Britain compared to his observations in African populations. Evidence from other early ecologic studies pointed to higher rates of colon and rectal cancers in Western countries than in other parts of the world, suggesting possible dietary risk factors such as fat and fiber intakes[60]

The following is a roughly chronological review of findings about colorectal cancer from the early studies of Seventh-day Adventists. Wynder and Lemon first found that Adventists admitted to certain hospitals had somewhat fewer than expected cases of colorectal cancer than other persons admitted to the same hospitals[9]. Early comparisons of the colonic microflora of vegetarian and nonvegetarian Adventists and of vegetarian Adventists and others did not appear to reveal major differences[61,62] When compared with both the general California population and with non-smokers in Hammond's American Cancer Society study[63], AMS members were found to have SMRs of approximately 65% for colorectal cancer[18], an age adjusted mortality ratio of approximately 0.60 when compared to a demographically similar group of the ACS study[14], and an SMR of 74% compared to a US population standardized by age, sex, and education[16]. An early examination showed lower fecal mutagen activity among vegetarian Adventists in New York compared to a higher-risk New York population[64]. A Healthy Habit Index appeared to strongly predict colorectal cancer mortality among AMS men (but not women), even among those who never smoked, suggesting a lifestyle factor other than smoking, such as diet, might be influencing colorectal cancer risk[44]. Vegetarians were found to have lower quantities of fecal bile acids than nonvegetarians[65]. In another study, vegetarian Adventists were found to have reduced rates of colonic mucosal proliferation[66]. Analysis of AMS large bowel cancer mortality by frequency of meat intake failed to find an association[67]. Again, after 21 years follow-up time in the AMS, there was no association between frequency of consumption of meat, cheese, milk, or green salad and colorectal cancer mortality, though there was a positive association of increased coffee consumption and increased colon and rectal cancer mortality[68]. All of these findings relate only to mortality from colorectal cancer (or to risk factors states like mucosal proliferation), because information on incident cancers was not available to the investigators. Except in cancers with a very high fatality rate, cancer-specific mortality may be a poor surrogate for cancer risk, as issues related to detection and treatment may mask possible effects on incidence.

The first results from AHS-1 for incident cancers were published in 1994. After 6 years of follow-up, the number of cases and standardized morbidity ratios for colon and rectum cancers for men and women were as follows: male colon, 62 cases, SMR=0.64 (95% CI: 0.45-0.88); male rectum, 25 cases, SMR=0.51 (95% CI: 0.29-0.84); female colon, 95 cases, SMR=0.76 (95% CI: 0.57-0.98); female rectum, 37 cases, SMR=0.71 (95% CI: 0.44-1.06)[69]. Singh and Fraser then examined the association of meat consumption with colon cancer. In a multivariate-adjusted survival analysis, they found a positive association of total meat intake (for ≥ once/week vs. no meat consumption) with colon cancer (RR=1.85, 95% CI: 1.19-2.87)[70]. Similar associations were found for both red and white meat, and an inverse association with legume intake was observed[70]. A number of plant foods were later found to be associated with a decreased risk of (self-reported) incident colorectal polyps[71].

We now return to the European cohorts with vegetarians and examine results for colorectal cancer in these studies. As with the AMS, the Health Food Shoppers, Oxford Vegetarian, and Heidelberg studies only had information on cancer mortality, not incidence. The Heidelberg study, as described above, was small, and thus there were few colorectal cancer deaths at early follow-up[28]. After 11 years follow-up, there were still only 6 total deaths from colon and rectum cancer, so SMRs for the entire cohort had very wide confidence intervals and comparisons of vegetarians and nonvegetarians was not possible[51]. After 21 years of follow-up, there were 8 deaths from colorectal cancer among vegetarians and 7 among nonvegetarians, yielding SMRs of 41 (95% CI: 21-81) for vegetarians and 70 (95% CI: 34-144) for nonvegetarians. Early publications for the Health Food Shoppers study did not report colorectal cancer mortality, no doubt due to lack of power[26,53]. After 17 years of follow-up time, there were 25 deaths from colorectal cancer in men and 37 in women, with SMRs of 0.64 (95% CI: 0.42-0.95) and 0.87 (95% CI: 0.61-1.20), respectively. The mortality ratio for colorectal cancer comparing vegetarians to nonvegetarians (adjusted for age, sex, and smoking history) was 1.04 (95% CI: 0.93-1.16), a null finding[54]. In the Oxford Vegetarian Study, colorectal cancer mortality data was not initially reported[27], but in their pooled analysis, Key et al. report a death rate ratio for colorectal cancer of 0.94 (95% CI: 0.49-1.80) for vegetarians compared to nonvegetarians in the Oxford Vegetarian Study (based on 38 deaths)[55]. In the pooled analysis of five studies previously described, the overall death rate ratio, based on 278 deaths from colorectal cancers, was 0.99 (95% CI: 0.77-1.27). Subsequently, in the EPIC-Oxford study, colorectal cancer incidence has been examined. The findings are certainly interesting. Among nonvegetarians (including fish-eaters), there were 220 cases of colorectal cancer, and the Standardized Incidence Ratio (SIR) was 84 (95% CI: 73-95); among vegetarians there were 70 cases, with an SIR of 102 (95% CI: 80-129)[72]. In Cox regression analysis with adjustment for age, sex, and smoking, the Incidence Rate Ratio (IRR) for vegetarians compared to nonvegetarians was 1.49 (95% CI: 1.09-2.03)[72]. When fish-eaters and vegetarians were compared to meat-eaters, the IRR for fish-eaters was 0.64 (95% CI: 0.37-1.10) and for vegetarians was 1.39 (95% CI: 1.01-1.91)[72]. Thus, whereas the early small European studies had failed to show a significant association of vegetarian diets with colorectal cancer mortality, the EPIC-Oxford study showed a significant association between vegetarian diets and increased colorectal cancer incidence.

Again, because meat avoidance is the basis of most definitions of vegetarian dietary patterns, it seems appropriate to briefly review the state of evidence relating meat consumption to colorectal cancer. Most evidence of this type comes from studies of nonvegetarians with varying levels of consumption of meat, but it is nonetheless likely relevant. The literature on meat consumption and colorectal cancer is not comprehensively reviewed here, but a few important references are given. In their 2007 report, *Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer*, the World Cancer Research Fund and American Institute of Cancer Research review the evidence that both red meat and processed meat are linked to an increased risk of colorectal cancer and judge it to be "convincing"[73]. This judgment is maintained in their 2011 Continuous Update Project report[74]. A 2011 meta-analysis provided the following summary estimates for the risk of colorectal cancer per 100g intake: for red meat, the pooled RR (from 8 studies) was 1.17 (95% CI: 1.05-1.31) and for processed meat (from 9 studies), 1.18 (95% CI: 1.10-1.28)[75]. Two of the largest studies examining this relationship have been the NIH-AARP study and the EPIC study, each of which has about 500,000 participants. In the NIH-AARP study, comparing the highest to lowest quintile of intake, the adjusted hazard ratios for incident colorectal cancer were 1.24 (95% CI: 1.12-1.36) for red meat and 1.20 (95% CI: 1.09-1.32) for processed meat[76]. In the EPIC study (in which the EPIC-Oxford cohort is included), comparing the highest to the lowest categories of intake, the hazard ratio for colorectal cancer incidence for red and processed meat was 1.35 (95% CI: 0.96-1.88), whereas for fish it was 0.69 (95% CI: 0.54-0.88), and there was no association for poultry[77]. In a pooled analysis of UK cohorts (including EPIC-Oxford), "Odds ratios (95% confidence intervals) for a 50 g/day increase were 1.01 (0.84–1.22) for red meat, 0.88 (0.68–1.15) for processed meat, 0.97 (0.84– 1.12) for red and processed meat combined, 0.80 (0.65– 1.00) for poultry, 0.92 (0.70–1.21) for white fish and 0.89 (0.70–1.13) for fatty fish." In summary, large cohorts have tended to demonstrate a moderate increased risk of colorectal cancer with increasing consumption of red and processed meats, meta-analysis has supported this relationship, and expert opinion considers the evidence convincing. Such relationships have not been found, however, in a pooled analysis of UK cohorts, including EPIC-Oxford.

## Risk Factors and Intermediates

Brief attention is paid here to the relationship of vegetarian dietary patterns to several other outcomes; might be considered risk factors, intermediate outcomes, or markers of mechanisms for ischemic heart disease (IHD) (and mortality from the same) or colorectal cancer. Those considered here are obesity/BMI, hypertension, hypercholesterolemia, the metabolic syndrome, diabetes mellitus, and fasting insulin and C-reactive protein (CRP). Please see **Appendix 1** (Orlich and Fraser, AJCN, in press) for a more detailed review of several of these (and other) outcomes in AHS-2.

Obesity is a known risk factor for both IHD mortality and colorectal cancer. While members of the British cohorts are on average thinner than those of the American Adventist cohorts[31], it has been consistently found that vegetarians (especially vegans) have lower BMI than nonvegetarians in these cohorts[31,36,78-80]. In AHS-2, vegans have a BMI 5 points lower than nonvegetarians[81], with other vegetarian groups having intermediate values. Hypertension is a well-established risk factor for IHD mortality. In the calibration sample of the AHS-2, vegetarians have an adjusted lower prevalence of hypertension compared to nonvegetarians both in whites[82] and in blacks[83]. LDL cholesterol is a risk factor for IHD mortality, and vegetarian diets have often been associated with reduced total cholesterol and LDL[84,85]. In EPIC-Oxford, for example, vegetarian diets have been found to be associated with lower levels of total cholesterol and non-HDL; there were also small reductions in HDL, but the total cholesterol/HDL ratio was reduced[86,87]. The metabolic syndrome is a constellation of cardiometabolic risk factors, characterized by abdominal obesity, elevated blood pressure, elevated fasting glucose, low HDL, and elevated triglycerides. In an analysis within the AHS-2 calibration sample, all components of the metabolic syndrome were found to be more favorable for vegetarians than for nonvegetarians, except for HDL, where there was no significant association[88]. Prevalence of the metabolic syndrome (meeting 3 of the 5 possible criteria) was significantly lower among vegetarians than nonvegetarians (OR=0.44, 95% CI: 0.30-0.64)[88]. Diabetes mellitus is a risk factor both for IHD mortality and for colorectal cancer. Adjusted self-reported prevalent and incident diabetes mellitus in lower in vegetarians than in nonvegetarians in AHS-2[81,89]. For lacto-ovo-vegetarians the odds ratio for prevalent diabetes was 0.54 (95% CI: 0.49-0.60)[81] and for incident diabetes was 0.62 (95% CI: 0.50-0.76)[89]. Vegetarian diets were also associated with a lower prevalence of diabetes mellitus in AHS-1[90]. Jaceldo-Siegl et al. (in unpublished analysis) have examined the relationship between vegetarian dietary patterns and certain disease markers in the serum. Both fasting serum insulin and CRP were significantly lower among vegetarians than nonvegetarians[91]. These may relate mechanistically to both atherosclerotic disease and to colorectal cancer.

## Summary

In summary, much of the evidence for the possible health effects comes from two streams of research. The first is a series of studies of North American (Californian, prior to AHS-2) Seventh-day Adventists, and the second is a series of European studies, primarily of British vegetarians. The earlier studies in both streams were smaller (though the Adventist studies were considerably larger than the early European studies) and had certain methodological limitations. The EPIC-Oxford study and the Adventist Health Study-2 surpass prior studies in terms of size and methodological rigor. Partial characterizations of the eating patterns of those defined as vegetarians in these studies have been done, but a characterization of foods consumed by AHS-2 vegetarians and nonvegetarians is needed. Evidence suggests that AHS-2 and EPIC-Oxford vegetarians may differ in potentially important respects regarding the foods they consume. The evidence for decreased mortality from ischemic heart disease among vegetarians seems clear and consistent from both streams, but that is less clear for mortality from all causes. The earlier Adventist studies demonstrate reduced mortality and improved longevity for vegetarians, whereas there seems to be no such association in EPIC-Oxford. Similarly, the evidence of an association of vegetarian dietary patterns and colorectal cancer risk is unclear. Meat intake was linked to higher colorectal cancer risk in AHS-1, but in EPIC-Oxford, vegetarian diets were actually associated with an increased risk of colorectal cancer, a surprising result given the state of evidence linking red meat and colorectal cancer risk. Findings from AHS-2 both for all-cause mortality and for risk of colorectal cancer will be important in clarifying these relationships.

**CHAPTER THREE**

# PATTERNS OF FOOD CONSUMPTION AMONG VEGETARIANS AND NONVEGETARIANS

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## Abstract

Vegetarian dietary patterns have been associated with a number of favorable health outcomes in epidemiologic studies, including the Adventist Health Study 2. Such patterns may vary and need further characterization regarding foods consumed. We aimed to characterize and compare the food consumption patterns of several vegetarian and nonvegetarian diets. Diet was measured by food frequency questionnaire among more than 89,000 members of the Adventist Health Study 2 cohort. Vegetarian dietary patterns were defined *a priori*, based on the absence of certain animal foods in the diet. Foods were categorized into 58 minor food groups comprising 17 major food groups. Adjusted mean consumption of each food group for the vegetarian dietary patterns was compared to that for the nonvegetarian pattern. Mean consumption was found to differ significantly across the dietary patterns for all food groups. Vegetarians demonstrated an increased consumption of many plant foods including fruits, vegetables, avocados, non-fried potatoes, whole grains, legumes, soy foods, nuts, and seeds. Conversely, consumption by vegetarians was lower for meats, dairy products, eggs, refined grains, added fats, sweets, snack foods, and non-water beverages. Thus, while vegetarian dietary patterns in the Adventist Health Study 2 have been defined based on the absence of animal foods, they also differ greatly with respect to the consumption of many other food groups. These differences in food consumption patterns may be important in helping to explain the association of vegetarian diets with several important health outcomes.

# Introduction

Given a number of challenges facing the epidemiologic investigation of diet and chronic disease relationships at the nutrient level, more attention has been recently given to dietary patterns[1]. However, defining patterns that differ in important ways and may thus have differing effects on health can be challenging. Two broad approaches have been used to define dietary patterns, data-driven approaches using pattern analysis methods and hypothesis-driven approaches using *a priori* definitions or scoring systems[2].

Investigators in the Adventist Health Studies have utilized a hypothesis-driven approach to define dietary patterns according to an index of animal food avoidance. The vegetarian-spectrum dietary patterns derived from this approach have been predictive of a number of important differences in health status, including obesity[3], the metabolic syndrome[4], diabetes mellitus type 2[3,5], hypertension[6], and mortality[7]. In the Adventist Health Study 2 (AHS-2) five vegetarian-spectrum dietary categories have been defined in order of increasing avoidance of animal food consumption: nonvegetarian, semi-vegetarian, pesco-vegetarian, lacto-ovo-vegetarian, and vegan.

It is important to characterize how these patterns may differ with respect to a variety of potentially important foods and nutrients. In a previous paper, Rizzo and colleagues characterized these dietary patterns with respect to their nutrient profiles[8]. Here we analyze their differences in terms of the consumption of key foods and food groups.

## Methods

### *Study Population*

Adventist Health Study 2 (AHS-2) is a cohort of more than 96,000 Seventh-day Adventist men and women recruited from the United States (US) and Canada between 2002-2007.[9] See Butler et al. for a detailed explanation of the cohort characteristics and formation.[9] Written informed consent was obtained upon enrollment. The institutional review board of Loma Linda University approved the study.

Of 96,060 subjects with completely processed dietary data, the following exclusions were applied: improbable response patterns in questionnaire data (e.g. identical high-frequency responses to all questions on a page) (n=251); greater than 69 missing values in dietary data (n=2052); estimated energy intake (prior to imputation) greater than 4500 kcal/day (n=2143); age missing or <25 years (n=262); missing value for sex (n=33); missing value for race (n=997); estimated energy intake (after imputation) less than 2092 kJ/day (500 kcal/day) or greater than 18,693 kJ/day (4500 kcal/day) (average n=867). After all exclusions, there remained five analytic datasets for use in multiple imputation analysis with an average of 89,455 subjects.

### *Dietary Data*

Dietary measurement in AHS-2 has been previously described in detail[10,11]. A self-administered quantitative food frequency questionnaire (FFQ) was used at baseline to assess usual dietary intake during the previous year. As described by Jaceldo et al.: "The FFQ was originally designed to include foods commonly consumed by US Adventists and was later revised to reduce the respondents' fatigue and to accommodate foods specific to black Adventists of US and Caribbean origin. All versions of the FFQ consist of two major sections: 1) a food list that includes 130-141 items of fruits, vegetables, legumes, grains, oils, dairy, fish, eggs and beverages and 2) 63-79 items of commercially prepared products, such as dietary supplements, dry cereals and vegetarian protein products that require respondents to examine food labels."[10] For each hard-coded food item, estimates of both frequency of consumption (7 to 9 categories) and serving size (3 categories: standard, ½ or less, and 1½ or more) were elicited. Similarly, for each write-in food item, participants were asked about frequency of consumption (7 to 9 categories) and serving size (either 3 categories as above or write in the usual serving size). Frequency categories ranged from never or rarely up to 2-6 servings per day depending on food type. Portion sizes included a given standard serving (e.g. cup, tablespoon, slice), and pictures portraying serving sizes of common foods or beverages were included with the questionnaire to assist participants in estimating portion sizes.[11]

Daily food intake estimates (in grams or kiloJoules) were calculated using the product-sum method; see Jaceldo et al. for details.[10] Energy and nutrient conversions were computed using the Nutrition Data System for Research version 4.06 or 5.0 (NDS-R, Nutrition Coordinating center, Minneapolis, MN, USA) and were based on the NDS-R 2008 database. Considerable attention was given to obtaining information on foods not found in the NDS-R database as previously described[10].

The FFQ was previously validated against six 24-hour dietary recalls for intake of nutrients[11] and selected foods and food groups[10]. On average, energy-adjusted de-attenuated validity correlations were 0.60 in whites and 0.52 in blacks across fifty-one nutrients.[11] For foods and food groups, the average de-attenuated validity correlation was 0.59 in whites and 0.43 in blacks.[10]

### *Dietary Pattern Definitions*

As described by Orlich et al.: "Dietary patterns were determined according to the reported intake of foods of animal origin. Thus, vegans consumed eggs/dairy, fish, and all other meats <1 time/month; lacto-ovo-vegetarians consumed eggs/dairy ≥1 time/month but fish and all other meats <1 time/month; pesco-vegetarians consumed fish ≥1 time/month but all other meats <1 time/month; semi-vegetarians consumed non-fish meats ≥1 time/month and all meats combined (fish included) ≥1 time/month but ≤1 time/week; lastly, nonvegetarians consumed non-fish meats ≥1 time/month and all meats combined (fish included) >1 time/week."[7]

### *Categorization of Foods*

Similar food items were grouped with consideration given to biological distinctions (e.g. fruits), commonly accepted food categories (e.g. vegetables), and certain diet-disease hypotheses (e.g. processed meats) to create 58 non-overlapping minor food groups. These were further clustered into 17 major food groups. (See Supplemental Table 1.)

Whenever possible, both hard-coded and write-in food items on the questionnaire contributed to the food groups as whole foods, rather than at the ingredient level. For example, the item "French bread" contributed its entire gram weight and energy content to the food group "refined-grains"; rather than breaking it down to its constituent ingredients (e.g. flour, oil, water, etc.) and placing these into separate food groups. This was done for the vast majority of food items. A few hard-coded food items (e.g. pizza) seemed by nature to warrant categorization at the ingredient level. For such items, a representative recipe was developed and used to divide the item into its constituent ingredients (e.g. flour, oil, cheese, tomato, etc.), which were each then placed into appropriate food groups.

Several of the groups constitute very minor components of the diet, may not generally be thought of as "food", or do not seem to aid in comparative characterizations of food patterns, and thus these groups were not included in the comparative analyses highlighted in the results section. Groups omitted were the following: water from recipes, mixed foods, condiments, yeast, salt, and supplements (see Supplemental Table 1).

### *Covariates*

Other variables (all measured at baseline) were age (in years); sex (male, female); race (black, non-black). Participants self-identified their race/ethnicity in one or more of 21 categories. Those self-identifying as at least part black/African American, West Indian/Caribbean, African, or other black were categorized as black for this analysis and all others as non-black.

### *Statistical Analysis*

For the entire sample, unadjusted descriptive statistics were calculated for each food group. Adjusted mean values of all food groups were calculated for each dietary pattern.

Mean values were adjusted for age, sex, and race by direct standardization, using the entire analytic sample as the standard distribution. These dietary-pattern mean values were also standardized to a 8368 kJ/day (2000 kcal/day) diet as follows: Intake values of each food item for each participant were divided by the total daily energy intake of the participant and multiplied by 8368 to yield the standardized intake; these standardized intakes were used to compute the mean values by dietary pattern. Significance testing for differences across dietary patterns was conducted as follows. For each food group, the null hypothesis was that none of the adjusted mean values of the four vegetarian groups differed from the adjusted mean value of the nonvegetarian group. This was tested by computing a Chi-square test with four degrees of freedom using the variances of each adjusted mean value. A nominal alpha value of 0.05 was selected. This process was repeated for a total of 66 unique significance tests (for 55 minor groups plus 11 major groups that were not identical to minor groups); thus a Bonferroni correction for multiple testing was applied, which yielded a corrected alpha of 0.05/66 = 0.0008. Multiple imputation of missing values was done for the small amount of missing data in the dietary variables used to calculate vegetarian status and food categories as we have evidence that many of the missing data are non-zero; a guided multiple imputation approach was utilized where possible.[12,13] Analyses were performed using SAS 9.3 (SAS Institute, Cary NC) and R version 2.13.1[14] with the Hmisc package[15].

# Results

## *Food Consumption for the Entire Sample*

**Table 1** displays unadjusted measures of the consumption of select major and minor food groups for the entire analytic sample. Daily consumption for each is described by giving the mean value, standard deviation, $10^{th}$ percentile, $25^{th}$ percentile, median, $75^{th}$ percentile, $90^{th}$ percentile, and the percentage of responses that indicated zero intake. The mean, SD, and quantiles are given in units of mass (grams). The energy density of each food group is also listed to allow for approximate conversion from mass in grams to energy content in kilocalories.

**Table 1.** Measures of daily food group consumption for all participants*

| Food | Mean (g) | SD (g) | 10th %ile (g) | 25th %ile (g) | Median (g) | 75th %ile (g) | 90th %ile (g) | %zero† (%) | Density‡ (kJ/g) |
|---|---|---|---|---|---|---|---|---|---|
| Major food groups | | | | | | | | | |
| fruit | 330.2 | 292.6 | 70.7 | 145.6 | 261.8 | 421.2 | 644.9 | 0.4 | 2.76 |
| vegetables | 327.1 | 230.8 | 107.0 | 173.8 | 276.3 | 415.8 | 596.6 | 0.0 | 1.42 |
| avocados | 7.0 | 14.1 | 0.0 | 0.0 | 4.3 | 6.4 | 27.4 | 42.6 | 5.19 |
| potatoes | 38.2 | 32.8 | 9.0 | 15.1 | 28.9 | 52.6 | 79.0 | 1.9 | 5.44 |
| grains | 296.4 | 179.4 | 104.8 | 163.8 | 262.0 | 388.8 | 532.8 | 0.1 | 7.45 |
| legumes | 62.0 | 63.0 | 10.2 | 23.2 | 43.3 | 80.9 | 134.5 | 3.9 | 4.98 |
| soy foods & meat analogues | 125.2 | 166.0 | 0.0 | 22.6 | 67.8 | 165.0 | 309.1 | 10.7 | 4.39 |
| nuts & seeds | 23.6 | 25.7 | 3.0 | 6.9 | 16.1 | 31.4 | 51.8 | 2.5 | 24.98 |
| meat | 27.9 | 41.0 | 0.0 | 0.0 | 11.4 | 41.2 | 81.5 | 37.2 | 8.12 |
| dairy products | 146.3 | 209.6 | 0.9 | 15.3 | 65.6 | 204.9 | 361.2 | 9.7 | 3.39 |
| eggs | 9.6 | 15.9 | 0.0 | 0.0 | 4.1 | 17.5 | 26.2 | 26.1 | 8.41 |
| added fats | 41.3 | 30.1 | 10.7 | 20.1 | 34.9 | 54.8 | 79.4 | 0.2 | 24.23 |
| sweets | 39.4 | 53.6 | 0.4 | 10.0 | 23.0 | 46.8 | 97.4 | 6.8 | 11.05 |
| snack foods | 3.6 | 5.9 | 0.0 | 0.6 | 2.0 | 4.3 | 9.1 | 19.5 | 26.69 |
| beverages | 419.7 | 473.2 | 33.3 | 115.0 | 282.4 | 555.3 | 964.0 | 3.6 | 1.17 |
| water | 1122.9 | 594.6 | 236.9 | 592.3 | 1066.1 | 1539.9 | 1599.1 | 2.3 | 0.00 |

**Table 1.** Measures of daily food group consumption for all participants (continued)

| Food | Mean (g) | SD (g) | 10th %ile (g) | 25th %ile (g) | Median (g) | 75th %ile (g) | 90th %ile (g) | %zero (%) | Density (kJ/g) |
|---|---|---|---|---|---|---|---|---|---|
| Minor food groups | | | | | | | | | |
| citrus | 73.0 | 103.8 | 0.0 | 8.8 | 37.0 | 105.2 | 163.0 | 11.2 | 1.88 |
| berries | 14.1 | 28.8 | 0.3 | 1.6 | 6.4 | 14.4 | 34.8 | 9.7 | 1.63 |
| other fruit | 232.6 | 213.4 | 48.0 | 101.7 | 181.8 | 294.8 | 457.6 | 0.6 | 2.72 |
| dried fruit | 10.6 | 20.9 | 0.0 | 0.7 | 3.3 | 12.5 | 27.1 | 22.5 | 11.59 |
| tomatoes | 120.1 | 105.0 | 25.2 | 52.6 | 95.9 | 156.0 | 235.6 | 0.4 | 1.17 |
| leafy greens | 42.9 | 48.0 | 3.8 | 12.1 | 30.0 | 55.9 | 96.2 | 4.1 | 0.92 |
| cruciferous vegetables | 30.2 | 32.7 | 5.7 | 11.4 | 19.5 | 39.1 | 68.1 | 2.8 | 1.26 |
| onions | 26.6 | 29.7 | 2.4 | 6.3 | 17.8 | 39.8 | 60.6 | 1.4 | 1.80 |
| other vegetables | 107.4 | 110.2 | 24.5 | 44.0 | 78.6 | 133.7 | 214.1 | 0.1 | 1.88 |
| avocados | 7.0 | 14.1 | 0.0 | 0.0 | 4.3 | 6.4 | 27.4 | 42.6 | 5.19 |
| sweet potatoes | 5.2 | 9.1 | 0.0 | 0.0 | 4.0 | 6.0 | 8.6 | 34.5 | 3.77 |
| white potatoes | 22.9 | 23.0 | 5.0 | 7.4 | 14.8 | 36.2 | 52.5 | 5.8 | 3.72 |
| fried potatoes | 10.1 | 17.4 | 0.0 | 0.0 | 6.6 | 10.0 | 21.2 | 38.3 | 10.17 |
| whole grains | 187.3 | 150.1 | 35.4 | 73.9 | 148.8 | 262.8 | 385.2 | 0.9 | 7.53 |
| refined grains | 105.9 | 95.0 | 21.9 | 42.1 | 79.0 | 139.6 | 220.7 | 0.6 | 7.11 |
| mixed grains | 3.2 | 14.2 | 0.0 | 0.0 | 0.0 | 0.0 | 7.5 | 76.7 | 12.43 |
| legumes | 62.0 | 63.0 | 10.2 | 23.2 | 43.3 | 80.9 | 134.5 | 3.9 | 4.98 |
| meat analogues | 45.2 | 54.3 | 0.0 | 9.3 | 31.3 | 61.6 | 103.9 | 16.2 | 7.53 |
| soybeans & tofu | 16.5 | 33.5 | 0.0 | 0.0 | 6.0 | 12.8 | 57.7 | 41.4 | 5.77 |
| soymilk | 63.6 | 139.5 | 0.0 | 0.0 | 0.0 | 70.1 | 236.7 | 59.2 | 1.84 |

**Table 1.** Measures of daily food group consumption for all participants (continued)

| Food | Mean (g) | SD (g) | 10th %ile (g) | 25th %ile (g) | Median (g) | 75th %ile (g) | 90th %ile (g) | %zero (%) | Density (kJ/g) |
|---|---|---|---|---|---|---|---|---|---|
| Minor food groups (continued) | | | | | | | | | |
| peanuts | 2.5 | 6.0 | 0.0 | 0.0 | 1.2 | 1.8 | 7.7 | 38.2 | 25.02 |
| peanut butter | 5.3 | 7.8 | 0.0 | 1.1 | 2.3 | 6.9 | 12.7 | 19.2 | 24.60 |
| tree nuts | 10.0 | 15.6 | 0.0 | 1.4 | 4.1 | 13.3 | 25.5 | 13.9 | 25.56 |
| mixed nuts | 2.8 | 6.5 | 0.0 | 0.0 | 1.3 | 2.0 | 8.4 | 41.0 | 24.85 |
| seeds | 3.0 | 7.7 | 0.0 | 0.0 | 0.0 | 2.2 | 9.3 | 52.3 | 23.81 |
| unprocessed red meat | 7.2 | 17.1 | 0.0 | 0.0 | 0.0 | 8.0 | 20.7 | 64.0 | 10.96 |
| processed red meat | 0.7 | 2.8 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 84.2 | 12.43 |
| unprocessed poultry | 9.5 | 18.4 | 0.0 | 0.0 | 0.0 | 11.0 | 33.1 | 51.6 | 7.95 |
| processed poultry | 0.6 | 1.7 | 0.0 | 0.0 | 0.0 | 0.6 | 1.4 | 71.5 | 4.52 |
| fatty fish | 3.5 | 8.3 | 0.0 | 0.0 | 0.0 | 5.7 | 8.6 | 64.9 | 7.61 |
| other fish | 6.5 | 12.9 | 0.0 | 0.0 | 0.0 | 9.5 | 16.0 | 51.2 | 5.44 |
| regular milk products | 57.9 | 131.7 | 0.0 | 0.0 | 9.0 | 45.4 | 191.8 | 26.2 | 2.72 |
| reduced milk products | 67.6 | 152.1 | 0.0 | 0.0 | 6.7 | 80.8 | 205.5 | 49.0 | 1.88 |
| cheese | 20.8 | 27.0 | 0.0 | 3.9 | 12.4 | 26.5 | 53.4 | 13.2 | 10.08 |
| eggs | 9.6 | 15.9 | 0.0 | 0.0 | 4.1 | 17.5 | 26.2 | 26.1 | 8.41 |
| butter | 2.7 | 6.9 | 0.0 | 0.0 | 0.2 | 1.9 | 8.3 | 29.4 | 29.96 |

**Table 1.** Measures of daily food group consumption for all participants (continued)

| Food | Mean (g) | SD (g) | 10th %ile (g) | 25th %ile (g) | Median (g) | 75th %ile (g) | 90th %ile (g) | %zero (%) | Density (kJ/g) |
|---|---|---|---|---|---|---|---|---|---|
| Minor food groups (continued) | | | | | | | | | |
| solid fats | 9.3 | 13.3 | 0.0 | 0.9 | 5.2 | 12.9 | 22.3 | 19.0 | 29.37 |
| salad dressings | 18.1 | 17.7 | 1.6 | 5.2 | 13.2 | 26.7 | 40.8 | 8.0 | 13.72 |
| liquid fats | 10.7 | 12.6 | 1.1 | 2.9 | 6.6 | 14.1 | 24.7 | 1.4 | 36.99 |
| coconut milk | 0.5 | 3.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 92.5 | 8.45 |
| dairy desserts | 19.4 | 37.4 | 0.0 | 0.0 | 10.6 | 18.5 | 67.7 | 35.1 | 5.23 |
| other desserts | 20.1 | 30.9 | 0.0 | 3.6 | 12.1 | 22.4 | 49.6 | 8.8 | 16.69 |
| snack foods | 3.6 | 5.9 | 0.0 | 0.6 | 2.0 | 4.3 | 9.1 | 19.5 | 26.69 |
| coffee | 73.3 | 183.9 | 0.0 | 0.0 | 0.0 | 25.6 | 253.0 | 66.2 | 0.08 |
| tea | 34.3 | 109.0 | 0.0 | 0.0 | 0.0 | 11.9 | 76.2 | 63.4 | 0.04 |
| soda | 132.7 | 329.3 | 0.0 | 0.0 | 23.8 | 127.8 | 372.0 | 47.4 | 0.79 |
| fruit juice | 139.5 | 202.2 | 0.0 | 16.7 | 71.0 | 212.8 | 318.3 | 15.4 | 1.88 |
| meal replacement drinks | 18.0 | 78.8 | 0.0 | 0.0 | 0.0 | 0.0 | 18.1 | 85.2 | 3.35 |
| alcoholic beverages | 4.5 | 47.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 95.4 | 2.59 |
| hot cocoa | 10.9 | 44.5 | 0.0 | 0.0 | 0.0 | 0.0 | 20.1 | 76.4 | 2.80 |
| non-dairy milk | 6.5 | 40.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 94.5 | 2.09 |
| drinking water | 1122.9 | 594.6 | 236.9 | 592.3 | 1066.1 | 1539.9 | 1599.1 | 2.3 | 0.00 |

[*] Unadjusted values. Not standardized to a 8368 kJ/day (2000 kcal/day) diet.
[†] Percentages of participants who reported no intake of the food.
[‡] Energy density of the food group in kiloJoules per gram.

Mean values are consistently higher than median values, indicating a right-skewed distribution of consumption. This is much accentuated in foods that have high percentages of zero consumption; in these cases, the median value is sometimes zero, whereas the mean value better represents the non-zero responses.

### *Food Consumption by Dietary Pattern: Major Food Groups*

For each dietary pattern, the amounts consumed (in grams) of both major and minor food groups, adjusted for age, sex, and race and standardized to 8368 kJ/day (2000 kcal/day), are provided in Supplemental Table 2. P values for all major food groups are less than 0.0001, indicating that the vegetarian dietary patterns differ significantly (i.e. $p < $ Bonferroni-corrected alpha of 0.0008) from the nonvegetarians in their consumption of all major food groups.

**Figure 1** illustrates graphically the differences in consumption of major food groups among the dietary patterns, portrayed as the relative mean consumption of each food group for each vegetarian dietary pattern compared to the mean consumption of that food group by nonvegetarians, after adjustment for age, sex, and race and standardization to 2000kcal/day.

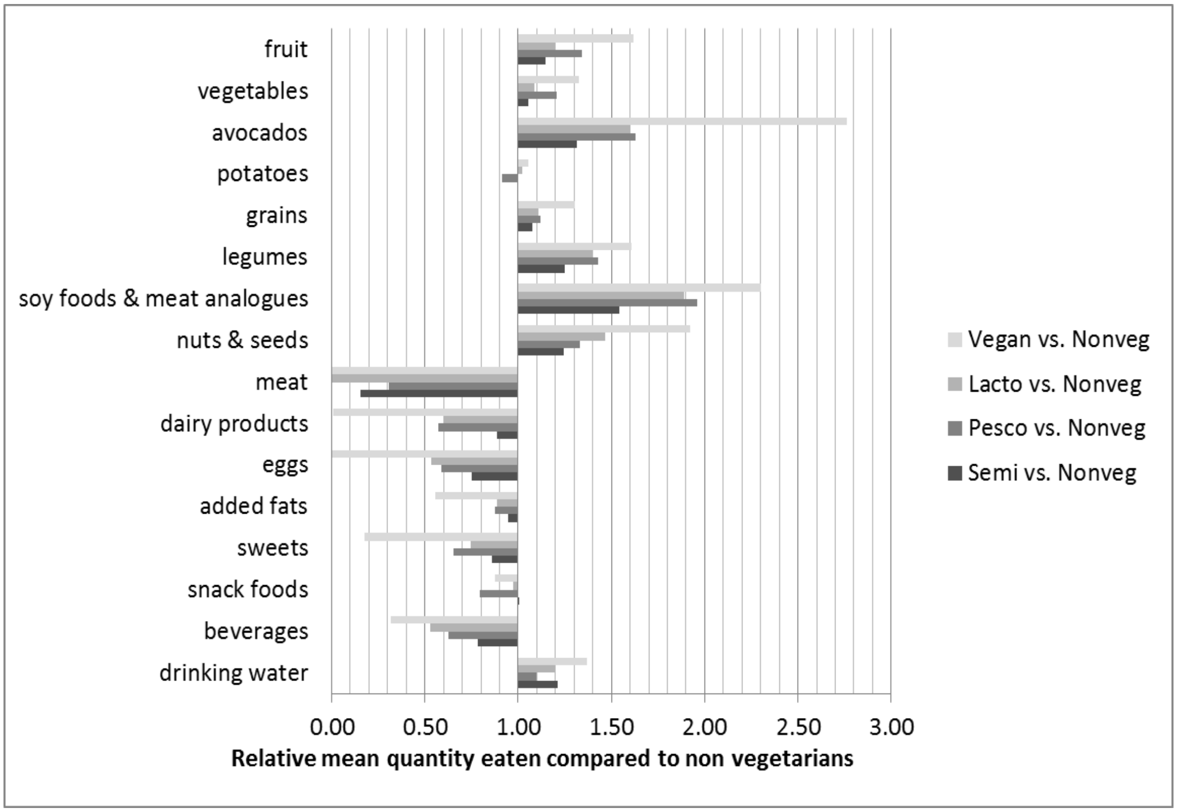


**Figure 1.** Comparative consumption of major food groups by vegetarians and nonvegetarians. The relative mean quantity (in grams) eaten by each vegetarian group compared to nonvegetarians is shown for each major food group after adjustment for age (7 categories), sex, and race (black vs. non black) by direct standardization and after standardization to a 8368 kJ/day (2000 kcal/day)diet. Abbreviations: lacto, lacto-ovo-vegetarian; pesco, pesco-vegetarian; semi, semi-vegetarian; nonveg, nonvegetarian.

As expected, given the definitions of the dietary patterns, vegetarian groups eat less meat, eggs, and dairy products than nonvegetarians. Vegans and lacto-ovo-vegetarians eat negligible amounts of meats, and pesco-vegetarians and semi-vegetarians eat much less meat than nonvegetarians. Vegans eat the least amount of eggs and dairy products and nonvegetarians the greatest, with other vegetarian groups consuming intermediate amounts. Vegetarians also consume lesser quantities of added fats, sweets, snack foods, and non-water beverages: In each case, vegans consume the least of these foods, nonvegetarians consume the most, and other vegetarian groups consume intermediate amounts. Vegans consume less than one third the quantity of non-water beverages daily than nonvegetarians and less than one fifth the amount of sweets. On the other hand, vegetarians consume more of most other major groups of foods of plant origin than do nonvegetarians, including legumes, soy foods and meat analogues, nuts and seeds, grains, potatoes, avocadoes, fruits, and vegetables. For almost all major plant food groups—legumes, soy foods and meat analogues, nuts and seeds, grains, potatoes, avocadoes, fruits, and vegetables —vegans consume the highest amounts of daily energy from these food groups, nonvegetarians consume the lowest amounts, and other vegetarian groups consume intermediate amounts.

### *Food Consumption by Dietary Pattern: Minor Food Groups*

As with the major food groups, the four vegetarian dietary patterns differ significantly from the nonvegetarian dietary pattern in their consumption all minor food groups examined. **Table 2** presents the relative mean daily consumption of each minor

**Table 2.** Adjusted relative mean daily consumption of minor food groups for four vegetarian dietary patterns compared to nonvegetarians. *,†

| Minor food group | Vegan | Lacto-ovo vegetarian | Pesco-vegetarian | Semi-vegetarian |
|---|---|---|---|---|
| citrus | 1.70 | 1.28 | 1.35 | 1.20 |
| berries | 1.75 | 1.36 | 1.42 | 1.18 |
| other fruit | 1.55 | 1.15 | 1.32 | 1.12 |
| dried fruit | 2.58 | 1.63 | 1.64 | 1.37 |
| tomatoes | 1.17 | 1.15 | 1.11 | 1.11 |
| leafy greens | 1.39 | 1.06 | 1.28 | 1.03 |
| cruciferous vegetables | 1.51 | 1.06 | 1.24 | 1.02 |
| onions | 1.27 | 0.98 | 1.21 | 1.01 |
| other vegetables | 1.44 | 1.06 | 1.28 | 1.02 |
| avocados | 2.76 | 1.60 | 1.63 | 1.31 |
| sweet potatoes | 1.45 | 0.96 | 1.32 | 0.94 |
| white potatoes | 1.32 | 1.23 | 1.00 | 1.13 |
| fried potatoes | 0.45 | 0.69 | 0.60 | 0.79 |
| whole grains | 1.85 | 1.36 | 1.33 | 1.25 |
| refined grains | 0.60 | 0.79 | 0.85 | 0.84 |
| mixed grains | 1.46 | 1.21 | 1.21 | 1.25 |
| legumes | 1.61 | 1.40 | 1.43 | 1.25 |
| meat analogues | 1.22 | 1.74 | 1.68 | 1.58 |
| soybeans & tofu | 4.75 | 2.55 | 2.78 | 1.60 |
| soymilk | 2.71 | 1.88 | 2.03 | 1.50 |
| peanuts | 0.80 | 0.92 | 1.07 | 0.95 |
| peanut butter | 1.39 | 1.49 | 1.07 | 1.31 |
| tree nuts | 2.52 | 1.71 | 1.56 | 1.36 |
| mixed nuts | 0.97 | 1.10 | 1.21 | 1.04 |
| seeds | 3.73 | 1.74 | 1.59 | 1.38 |
| unprocessed red meat | 0.00 | 0.00 | 0.00 | 0.10 |
| processed red meat | 0.00 | 0.00 | 0.01 | 0.05 |
| unprocessed poultry | 0.00 | 0.00 | 0.00 | 0.24 |
| processed poultry | 0.00 | 0.00 | 0.00 | 0.12 |
| fatty fish | 0.00 | 0.00 | 1.19 | 0.13 |
| other fish | 0.00 | 0.00 | 0.87 | 0.10 |
| regular milk products | 0.01 | 0.45 | 0.47 | 0.77 |
| reduced milk products | 0.00 | 0.67 | 0.63 | 0.96 |
| cheese | 0.05 | 0.83 | 0.69 | 1.00 |
| eggs | 0.00 | 0.54 | 0.59 | 0.75 |
| butter | 0.02 | 0.49 | 0.59 | 0.75 |
| solid fats | 0.38 | 0.91 | 0.73 | 0.99 |
| salad dressings | 0.40 | 0.89 | 0.80 | 0.94 |
| liquid fats | 1.22 | 1.02 | 1.24 | 1.00 |

**Table 2.** Adjusted relative mean daily consumption of minor food groups for four vegetarian dietary patterns compared to nonvegetarians. (continued)

| Minor food group | Vegan | Lacto-ovo vegetarian | Pesco-vegetarian | Semi-vegetarian |
|---|---|---|---|---|
| coconut milk | 1.18 | 0.55 | 1.77 | 0.63 |
| dairy desserts | 0.00 | 0.71 | 0.62 | 0.87 |
| other desserts | 0.36 | 0.79 | 0.68 | 0.85 |
| snack foods | 0.87 | 0.97 | 0.79 | 1.01 |
| coffee | 0.07 | 0.27 | 0.38 | 0.74 |
| tea | 0.89 | 0.62 | 1.35 | 0.72 |
| soda | 0.07 | 0.37 | 0.30 | 0.67 |
| fruit juice | 0.72 | 0.89 | 1.06 | 0.98 |
| meal replacement drinks | 0.00 | 0.73 | 0.77 | 0.94 |
| alcoholic beverages | 0.02 | 0.12 | 0.27 | 0.39 |
| hot cocoa | 0.00 | 0.69 | 0.87 | 0.74 |
| non-dairy milk | 4.94 | 2.66 | 2.69 | 2.17 |
| drinking water | 1.37 | 1.19 | 1.10 | 1.21 |

* The relative mean quantity (in grams) eaten by each vegetarian group compared to nonvegetarians is shown for each food group after adjustment for age (7 categories), sex, and race (black vs. non black) by direct standardization and after standardization to a 8368 kJ/day (2000 kcal/day) diet.

† $P < 0.0001$ for each food group. P-value is for a Chi-square test with four degrees of freedom testing the null hypothesis that all four vegetarian dietary patterns have the same mean consumption of a food group as the nonvegetarians.

food group for the four vegetarian dietary patterns, compared to the nonvegetarian pattern (assigned the referent value of 1.00 for each food group), adjusted for age, sex, and race and standardized to 8368 kJ/day (2000 kcal/day). See Supplemental Table 2 for the absolute quantities consumed.

Vegetarians, and particularly vegans, consumed moderately more citrus fruits, berries, and other fresh fruits than nonvegetarians; the differences were even greater for dried fruits. Vegetarians ate only modestly more tomatoes. For leafy greens, cruciferous vegetables, onions, and other vegetables, vegans and pesco-vegetarians consumed greater quantities of all of these, whereas lacto-ovo-vegetarians and semi-vegetarians consumed quantities similar to the nonvegetarians. Vegetarians, particularly vegans, consumed considerably more avocados than nonvegetarians.

Among starchy foods, the situation is more nuanced. Vegetarians eat lesser amounts of fried potatoes than do nonvegetarians. Vegans and pesco-vegetarians eat more sweet potatoes than nonvegetarians, whereas lacto-ovo-vegetarians and semi-vegetarians eat slightly less. Vegetarians, except for pesco-vegetarians, eat more (non-fried) white potatoes than do nonvegetarians. Vegetarians eat more whole grains and mixed grains than nonvegetarians; however, vegetarians eat less refined grains.

Among plant protein food groups, vegetarians eat considerably more legumes, meat analogues, soybeans and tofu, and soymilk than do nonvegetarians. Vegetarians consume moderately more peanut butter, but similar amounts of peanuts. Vegetarians consume more tree nuts and seeds than nonvegetarians, with vegans consuming notably increased amounts.

The semi-vegetarian group consumes considerably less processed red meat, unprocessed red meat, processed poultry, unprocessed poultry, fatty fish, and other fish than nonvegetarians. Pesco-vegetarians eat similar amounts of fatty fish and other fish as the nonvegetarians and much more than semi-vegetarians. Consumption of meats, particularly processed meats, is quite low even in the nonvegetarians (Supplemental Table 2). Vegans consume either none or trivial amounts of eggs, cheeses, reduced milks, and regular milks, as expected ; semi-vegetarians consume only modestly less than nonvegetarians, and pesco-vegetarians and lacto-ovo-vegetarians consume moderately less than nonvegetarians.

While vegetarians consume less added fats overall, differences emerge within this category. Much less butter is consumed among the vegetarian groups, particularly the vegans. Vegetarians also consume notably lesser amounts of solid fats (i.e. margarines and shortenings) than nonvegetarians and lesser amounts of salad dressings. On the other hand, vegans and pesco-vegetarians consumed more liquid fats (i.e. oils) than nonvegetarians. Coconut milk consumption was greatest among pesco-vegetarians, followed by vegans and nonvegetarians, and lowest among lacto-ovo-vegetarians and semi-vegetarians. Among the sweets, vegetarians (especially vegans) eat lesser amounts not only of dairy desserts but also of other desserts than nonvegetarians. Vegetarians, particularly vegans and pesco-vegetarians, also eat lesser amounts of snack foods.

Among beverages, vegetarians (especially vegans) consume dramatically less soda, coffee, and alcohol than nonvegetarians. Differences in consumption of fruit juice are less striking, but vegans consume the least. Vegans, lacto-ovo-vegetarians, and semi-vegetarians consume modestly less herbal tea than nonvegetarians, and pesco-vegetarians modestly more. The consumption of both meal replacement drinks and hot cocoa is dramatically less among vegans than among the other dietary patterns. Non-dairy milk (principally rice milk, as soymilk is categorized elsewhere) is highest in vegans, lowest in nonvegetarians, and intermediate in other groups. Vegetarians also drink moderately higher quantities of water.

## Discussion

This investigation provides an important characterization of how several vegetarian dietary patterns differ from a nonvegetarian dietary pattern as to the types of foods consumed. In a prior paper examining nutrient profiles, the dietary patterns all had similar total food intakes in terms of both gram weight and energy(8). Comparisons of food consumption were also adjusted for any differences in total energy intake by standardizing to a 8368 kJ/day (2000 kcal/day) diet. Thus, it is expected that vegetarians would eat more of certain foods of plant origin to make up for the lack of animal protein foods. However, it is difficult to predict which plant foods might be increased, and it is likely that the health consequences of vegetarian diets might be contingent on this question. This analysis provides helpful insight into this issue in a large group of North American vegetarians.

It is notable that the vegetarian dietary patterns had moderate to large increases in consumption of a broad spectrum of foods of plant origin including legumes, soy foods and meat analogues, nuts and seeds, grains, potatoes, avocadoes, fruits, and vegetables, rather than a concentrated increase in only a few food groups. Such diversity would be expected to be helpful in terms of nutritional adequacy. This is consistent with the analysis of nutrient profiles of vegetarian diet patterns by Rizzo et al[8]. In addition, this increased consumption of many plant foods would be expected to result in higher intakes of a variety of phytochemicals, many of which are hypothesized to have health benefits. Furthermore, evidence exists linking increased consumption of a number of these plant foods to health benefits. Consumption of nuts has been linked to reductions in cardiovascular disease and increased longevity[16-18]. Increased consumption of fruits and vegetables may be linked with a lower risk of certain cancers[19].

It might be expected that lacto-ovo-vegetarians would have an increased consumption of dairy products and eggs compared to nonvegetarians, to make up for the lack of meat in the diet. In fact, their consumption of these foods was reduced. Pesco-vegetarians and semi-vegetarians also consumed reduced quantities of dairy products and eggs compared to nonvegetarians. Thus dairy and egg consumption tended to correlate with meat consumption.

Perhaps more noteworthy still are the foods consumed less by vegetarians in this study apart from meats, eggs, and dairy products—primarily added fats, sweets, snack foods, non-water beverages, and refined grains. This is interesting both for its potential health impact and in terms of insight into the dietary decision making of the vegetarians in this cohort.

Vegetarians consumed reduced quantities of butter and solid fats, but comparable or increased quantities of liquid fats (i.e. oils). This is consistent with dietary recommendations to replace solid fats with oils[20], based on evidence that substituting unsaturated fatty acids for saturated fatty acids reduces heart disease risk[21,22]. Sweets and caloric beverages such as soda and fruit juices are high in simple sugars in the form of sucrose, fructose, and high-fructose corn syrup. Some evidence links increased sugar consumption, and particularly fructose, to an increased risk of dyslipidemia, insulin resistance, visceral adiposity, and hepatic steatosis[23-26]. Decreased consumption of these food groups might be responsible for some of the favorable associations previously demonstrated for vegetarians in this cohort including lower body mass index, reduced prevalence of the metabolic syndrome, and reduced incident diabetes mellitus type II[4,5].

The food consumption patterns of vegetarians observed here may provide some insight into their dietary decision-making. As previously noted, we defined the vegetarian dietary patterns on the basis of avoidance of certain foods of animal origin. We believe this is consistent with common self-designations among our target population and the general public. It is not unusual for people to self-designate as vegans or vegetarians, for example. However, this analysis demonstrates clear food consumption patterns among vegetarians that go well beyond avoidance of meats or other animal foods. Specifically, the patterns of food consumption among vegetarians are quite consistent with what is currently understood to constitute healthful food choices. The Dietary Guidelines for Americans in 2010, for example, emphasized increased consumption of fruits and vegetables, recommended decreased consumption of added sugars and solid fats, and favored whole grains over refined grains[20]. The food consumption of the vegetarians in this study, on average, is very consistent with such dietary guidelines. This would appear to demonstrate that persons in this study choosing a vegetarian diet also consciously make other healthful dietary choices. It is consistent with a health motivation for choosing a vegetarian diet.

These patterns may not be generalizable to all vegetarians. People elect vegetarian diets for a variety of reasons, including the desire for better health, ethical concerns, environmental considerations, and religious beliefs. These underlying motivations may influence the choice of foods consumed, beyond the avoidance of meats and other animal foods. While we do not have data to establish it, it is our belief that a desire for improved health and a belief that vegetarian diets are more healthful, partly informed by religious understandings, is a major motivator for many Seventh-day Adventists to choose vegetarian diets. This health/religious motivation may also lead to the increased consumption of healthful plant food groups and the decreased consumption of added fats, sweets, snack foods, caloric beverages, and refined grains. In other vegetarian populations where motivations may differ, food choices may differ as well. For example, a vegetarian whose primary motivation is the avoidance of animal suffering may not necessarily drink less soda than a nonvegetarian. Such differences could lead to some heterogeneous results among studies of the health effects of vegetarian diets.

The EPIC (European Prospective Investigation into Cancer and Nutrition)-Oxford cohort (also referred to as the EPIC British "health conscious" cohort) is an important study of British vegetarians. There have been some differences in the results of studies of the association of vegetarian diets with certain health outcomes in the EPIC-Oxford study and the Adventist Health Studies, particularly for all-cause mortality and colon cancer, for which vegetarians in the Adventist Health Studies had reduced risk, but vegetarians in EPIC-Oxford did not[7,27]. Observed differences in food consumption patterns between the two populations could be important to identify, as they might suggest possible explanations for these differing results. It has been noted that the intakes of vitamin C and dietary fiber are substantially higher among AHS-2 vegans than among EPIC-Oxford vegans[7]. Mean unadjusted consumption in gram weight for fruits and vegetables has been reported for a random sample of EPIC-Oxford cohort members as follows: all vegetables, 220.9 g; leafy green vegetables, 18.4 g; cabbages, 36.2 g; onions and garlic, 13.4 g; all fruits, 261.0 g; citrus fruits, 57.0 g[28]. Similar unadjusted means for the AHS-2 cohort (see Table 1) compare as follows: all vegetables, 48% higher (327.1 g); leafy green vegetables (non cruciferous), 133% higher (42.9 g); cruciferous vegetables, 17% lower (30.2 g); onions, 99% higher (26.6 g); all fruits, 27% higher (330.2 g); citrus fruits, 28% higher (73.0 g). While this is not a comparison of vegetarians from the two cohorts specifically, both cohorts have about half vegetarians and half nonvegetarians, and the AHS-2 cohort members overall clearly have a considerably higher intake of most fruits and vegetables than members of the EPIC-Oxford cohort.

These differences in health outcomes and in food consumption patterns may shed light on the types of vegetarian diets that are likely to be optimal. While vegetarian diets have meat avoidance in common, they may differ in what takes its place in the diet. The AHS-2 vegetarian dietary patterns described here may provide good examples of healthy approaches to replacing meat in the diet, primarily by an increased consumption of a variety of whole plant foods. Given their association with reduced chronic disease risk and increased longevity, they probably provide a helpful illustration of what constitutes healthy plant-based dietary approaches. Future dietary guidelines might use this information to formulate recommendations.

In conclusion, we find that in the AHS-2 cohort, vegetarian dietary patterns are associated not only with reductions in the consumption of meats, eggs, and dairy products, but also with increased consumption of a variety of plant foods and with a reduced consumption of added fats, sweets, snack foods, non-water beverages, and refined grains.  Vegetarian dietary patterns similar to those demonstrated in this population represent important, real-world dietary options with multiple simultaneous features that might be expected to confer health benefits such as protection against obesity and certain cardio-metabolic diseases.  Furthermore, these vegetarian dietary patterns have previously been associated with such beneficial outcomes.  They may play an important role as models for dietetic counseling about healthy vegetarian diets and for future nutritional guidelines.

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**Supplemental Table 1.** Categorization of food items

| Major groups | Minor groups | Select food items* |
|---|---|---|
| Fruits | Citrus fruits | oranges, grapefruit |
| | Berries | strawberries, blueberries, raspberries, blackberries |
| | Other fruits | grapes, peaches, nectarines, plums, apricots, cantaloupe, persimmons, apples, pears, bananas, fruit salad, cherries |
| | Dried fruits | raisins, prunes, dates |
| Vegetables | Tomatoes | tomatoes, tomato soup, tomato sauce, tomato juice |
| | Leafy greens (non-cruciferous) | dark green lettuce, romaine lettuce, loose leaf lettuce, iceberg lettuce, spinach, chard |
| | Cruciferous vegetables | cabbage, brussel sprouts, kale, collards, mustard greens, turnip greens, poke salad, broccoli, cauliflower |
| | Onions | onions |
| | Other vegetables | bell peppers, carrots, peas, corn, okra, winter squash, green beans, carrot juice |
| Avocados | Avocados | avocado, guacamole |
| Potatoes | Sweet potatoes | sweet potatoes, yams |
| | White potatoes (not fried) | white or red potatoes (baked, boiled) |
| | Fried potatoes | French fries, hash browns, fried potatoes |
| Grains | Whole-grains | whole grain bread, rolls, buns, or oatmeal bread; oatmeal, cooked brown rice, millet, granola, muesli, whole-grain commercial cereals, whole grain flour |
| | Refined-grains | white bread, rolls, buns, or French bread; cornbread, Johnnycakes, cream of wheat, grits, corn porridge, homemade gluten steaks, refined-grain commercial cereals, refined flours, white rice |
| | Mixed grains | mixed-grain (i.e. mix of whole-grain and refined-grain) commercial cereals, mixed-grain flours |
| Legumes | Legumes (not soy) | refried beans, bean or lentil soup, navy beans, kidney beans, red beans, garbanzos, pigeon peas, cow peas, black-eyed peas, field peas, pinto beans, black beans, great northern beans, lima beans, white beans, fava beans, butter beans, lentils, split peas, gungo beans |
| Soy foods & meat analogues | Meat analogues | meat analogues, imitation cheese |
| | Soybeans & tofu | soybeans, tofu, soybean curd |
| | Soy milks | soy milks |
| Nuts & seeds | Peanuts | peanuts |
| | Peanut butter | peanut butter |
| | Tree nuts | almonds, cashews, walnuts |
| | Mixed nuts | mixed nuts, trail mix |
| | Seeds | seeds |

**Supplemental Table 1.** Categorization of food items (continued)

| Major groups | Minor groups | Select food items |
|---|---|---|
| Meats | Unprocessed red meats | beef, lamb, hamburger, pork (chops, ribs) |
| | Processed red meats | processed beef, lamb (e.g. sausage, salami, bologna), pork (bacon, sausage, ham, lunch-meat) |
| | Unprocessed poultry | chicken or turkey (roasted, stewed, broiled, fried, in casserole, burrito, etc.) |
| | Processed poultry | processed chicken or turkey (turkey bologna, turkey ham) |
| | Fatty fish | salmon |
| | Other fish | white fish (cod, salt fish, sole, haddock, halibut, snapper, catfish), tuna, tuna salad |
| Dairy Products | Regular milks | milk (whole or 2%), evaporated milk, regular yogurt, other dairy products (cream, sour cream, etc.) |
| | Reduced milks | low-fat milk (1% or skim), low-fat yogurt |
| | Cheeses | American processed cheese, cheddar cheese, low fat cheese, mozzarella, ricotta, cottage cheese, cream cheese, cheese spreads |
| Eggs | Eggs | eggs |
| Added fats | Butter | butter |
| | Solid fats | vegetable shortening, margarine |
| | Salad dressing | mayonnaise or Miracle Whip (regular & low calorie), low calorie salad dressing, other oil salad dressing, regular creamy salad dressing (Ranch, Thousand Island, etc.) |
| | Liquid fats | olive oil, corn oil, sunflower oil, safflower oil, canola oil, other vegetable oil, oil salad dressings |
| | Coconut milk | coconut milk |
| Sweets | Dairy desserts | ice cream, ice milk, frozen yogurt, milk shakes |
| | Other desserts | doughnuts, cinnamon rolls, pastries, sweet pies, cookies, cakes |
| Snack foods | Snack foods | popcorn, chips, pretzels |
| Beverages (not water) | Coffee | regular coffee, decaffeinated coffee |
| | Tea | herbal teas |
| | Sodas | sodas and soft drinks (including regular, diet, and caffeine free) |
| | Fruit juices | orange juice, apple juice |
| | Meal replacement drinks | meal replacement drinks such as Slimfast, Instant Breakfast, Ensure, protein drinks |
| | Alcoholic beverages | wine, beer or wine coolers, liquor |
| | Hot cocoa | ovaltine or hot chocolate |
| | Non-dairy milk | rice milk (write in) |
| Water | Drinking water | drinking water (including sparkling, but not counting coffee or tea) |

**Supplemental Table 1.** Categorization of food items (continued)

| Major groups | Minor groups | Select food items |
|---|---|---|
| Other | Mixed foods | Foods/recipes not separately classified[†,‡] |
| | Condiments | Components of recipes designated as condiments (spices, seasonings, etc.) [†,§] |
| | Yeast | Brewer's or nutritional yeast |
| | Salt | Salt |
| | Supplements | Vitamins, minerals, and other dietary supplements[†] |
| | Water from recipes | water as an ingredient in recipes whose other ingredients were separately categorized[†, ǀ] |

[*] Non-comprehensive list of food items included in each food group; primarily foods listed on the food-frequency questionnaire as hard-coded items. Food groups may contain other foods from write-in items.

[†] In the absence of specific hard-coded food items on the questionnaire that belong to this food group, a brief description of items classified in the group is given.

[‡] A small number of write-in foods or complex ingredients of those foods were not able to be categorized easily, due to their heterogeneous nature, and were left in this "mixed foods" category. Examples include the non-tuna portion of tuna casserole and a write-in "veggie loaf".

[§] The "condiments" category includes certain spices, seasonings, or sauces not elsewhere classified; examples include "Baco Bits" and "McKay Chicken Seasoning".

[ǀ] For the few food items categorized at the ingredient level, rather than as whole foods, water was often an ingredient. It did not seem sound to include this water, a component of only a few foods, with drinking water, so a "water from recipes" category was created.

**Supplemental Table 2.** Daily mean food group consumption (g/day) according to dietary pattern, minimally adjusted*,†.

| Foods | Vegan | Lacto | Pesco | Semi | Nonveg |
|---|---|---|---|---|---|
| Major food groups | | | | | |
| fruit | 483.1 | 357.0 | 400.3 | 343.0 | 298.8 |
| vegetables | 424.1 | 347.2 | 386.0 | 337.0 | 319.9 |
| avocados | 14.7 | 8.5 | 8.7 | 7.0 | 5.3 |
| potatoes | 42.2 | 40.9 | 36.5 | 39.9 | 40.0 |
| grains | 371.6 | 315.6 | 319.8 | 306.6 | 285.3 |
| legumes | 84.4 | 73.4 | 75.2 | 65.5 | 52.5 |
| soy foods & meat analogues | 202.9 | 166.4 | 172.6 | 136.2 | 88.1 |
| nuts & seeds | 36.0 | 27.5 | 25.0 | 23.4 | 18.8 |
| meat | 0.0 | 0.0 | 18.2 | 9.1 | 59.2 |
| dairy products | 2.1 | 120.5 | 114.4 | 177.8 | 200.3 |
| eggs | 0.0 | 7.6 | 8.3 | 10.6 | 14.1 |
| added fats | 25.9 | 41.0 | 40.6 | 43.7 | 46.3 |
| sweets | 8.6 | 37.0 | 32.2 | 42.5 | 49.5 |
| snack foods | 3.5 | 3.9 | 3.2 | 4.1 | 4.0 |
| beverages | 187.8 | 314.2 | 372.8 | 466.8 | 597.3 |
| water | 1629.3 | 1421.3 | 1304.9 | 1445.8 | 1191.0 |
| Minor food groups | | | | | |
| citrus | 108.5 | 81.5 | 86.3 | 76.4 | 63.7 |
| berries | 20.7 | 16.1 | 16.8 | 14.0 | 11.8 |
| other fruit | 334.4 | 247.0 | 284.8 | 242.3 | 215.7 |
| dried fruit | 19.5 | 12.3 | 12.4 | 10.4 | 7.6 |
| tomatoes | 137.3 | 134.8 | 130.0 | 129.9 | 117.2 |
| leafy greens | 58.9 | 44.9 | 54.5 | 43.6 | 42.5 |
| cruciferous vegetables | 44.5 | 31.4 | 36.7 | 30.3 | 29.6 |
| onions | 34.2 | 26.3 | 32.5 | 27.2 | 26.9 |
| other vegetables | 149.1 | 109.7 | 132.4 | 106.1 | 103.8 |
| avocados | 14.7 | 8.5 | 8.7 | 7.0 | 5.3 |
| sweet potatoes | 7.6 | 5.0 | 6.9 | 4.9 | 5.2 |
| white potatoes | 28.9 | 27.0 | 21.9 | 24.8 | 21.9 |
| fried potatoes | 5.8 | 8.9 | 7.7 | 10.2 | 12.9 |
| whole grains | 292.8 | 214.0 | 210.6 | 197.8 | 157.9 |
| refined grains | 74.5 | 98.1 | 105.7 | 105.2 | 124.5 |
| mixed grains | 4.3 | 3.5 | 3.5 | 3.7 | 2.9 |
| legumes | 84.4 | 73.4 | 75.2 | 65.5 | 52.5 |
| meat analogues | 43.4 | 62.1 | 59.7 | 56.4 | 35.6 |
| soybeans & tofu | 40.2 | 21.6 | 23.6 | 13.6 | 8.5 |
| soymilk | 119.3 | 82.8 | 89.4 | 66.2 | 44.1 |
| peanuts | 2.1 | 2.4 | 2.7 | 2.4 | 2.6 |
| peanut butter | 6.3 | 6.7 | 4.9 | 5.9 | 4.5 |
| tree nuts | 17.8 | 12.1 | 11.0 | 9.6 | 7.1 |
| mixed nuts | 2.5 | 2.9 | 3.2 | 2.7 | 2.6 |
| seeds | 7.3 | 3.4 | 3.1 | 2.7 | 2.0 |

**Supplemental Table 2.** Daily mean food group consumption (g/day) according to dietary pattern, minimally adjusted (continued)

| Foods | Vegan | Lacto | Pesco | Semi | Nonveg |
|---|---|---|---|---|---|
| Minor food groups (continued) | | | | | |
| unprocessed red meat | 0.0 | 0.0 | 0.0 | 1.6 | 16.1 |
| processed red meat | 0.0 | 0.0 | 0.0 | 0.1 | 1.4 |
| unprocessed poultry | 0.0 | 0.0 | 0.0 | 5.2 | 21.7 |
| processed poultry | 0.0 | 0.0 | 0.0 | 0.2 | 1.3 |
| fatty fish | 0.0 | 0.0 | 7.5 | 0.8 | 6.3 |
| other fish | 0.0 | 0.0 | 10.7 | 1.3 | 12.3 |
| regular milk products | 0.7 | 38.3 | 40.0 | 65.1 | 84.2 |
| reduced milk products | 0.0 | 60.8 | 56.8 | 87.1 | 90.4 |
| cheese | 1.4 | 21.3 | 17.7 | 25.6 | 25.7 |
| eggs | 0.0 | 7.6 | 8.3 | 10.6 | 14.1 |
| butter | 0.1 | 1.9 | 2.3 | 2.9 | 3.9 |
| solid fats | 3.9 | 9.5 | 7.7 | 10.4 | 10.5 |
| salad dressings | 8.5 | 18.7 | 16.8 | 19.8 | 21.1 |
| liquid fats | 12.7 | 10.6 | 12.8 | 10.3 | 10.3 |
| coconut milk | 0.7 | 0.3 | 1.0 | 0.3 | 0.6 |
| dairy desserts | 0.0 | 18.1 | 15.9 | 22.1 | 25.5 |
| other desserts | 8.6 | 18.9 | 16.3 | 20.4 | 24.1 |
| snack foods | 3.5 | 3.9 | 3.2 | 4.1 | 4.0 |
| coffee | 9.9 | 36.1 | 50.6 | 99.0 | 134.4 |
| tea | 37.2 | 25.8 | 56.2 | 30.0 | 41.8 |
| soda | 15.3 | 83.1 | 66.0 | 149.1 | 223.4 |
| fruit juice | 108.4 | 133.3 | 159.4 | 146.8 | 149.9 |
| meal replacement drinks | 0.0 | 16.4 | 17.4 | 21.0 | 22.4 |
| alcoholic beverages | 0.2 | 1.0 | 2.3 | 3.3 | 8.4 |
| hot cocoa | 0.0 | 9.4 | 11.8 | 10.1 | 13.5 |
| non-dairy milk | 16.9 | 9.1 | 9.2 | 7.4 | 3.4 |
| drinking water | 1629.3 | 1421.3 | 1304.9 | 1445.8 | 1191.0 |

[*] Adjusted for age (7 categories), sex, and race (black, non- black) by direct standardization and standardized to a 8368 kJ/day (2000 kcal/day) diet. Abbreviations: lacto, lacto-ovo vegetarian; pesco, pesco vegetarian; semi, semi vegetarian; nonveg, nonvegetarian.

[†] $P < 0.0001$ for each food group. P-value is for a Chi-square test with four degrees of freedom testing the null hypothesis that all four vegetarian dietary patterns have the same mean consumption of a food group as the nonvegetarians.

# CHAPTER FOUR

# VEGETARIAN DIETARY PATTERNS AND MORTALITY IN ADVENTIST HEALTH STUDY 2

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## Abstract

**Importance:** Some evidence suggests vegetarian dietary patterns may be associated with reduced mortality, but the relationship is not well established.

**Objective:** To evaluate the association of vegetarian dietary patterns with mortality.

**Design:** Prospective cohort study. Mortality analysis by Cox proportional hazards regression, controlling for important demographic and lifestyle confounders.

**Setting:** Adventist Health Study 2 (AHS-2) is a large North American cohort.

**Participants:** 96,469 Seventh-day Adventist men and women recruited between 2002 and 2007, from which an analytic sample of 73,308 participants remained after exclusions.

**Exposures:** Diet assessed at baseline by a quantitative food frequency questionnaire and categorized into 5 dietary patterns: nonvegetarian, semi vegetarian, pesco vegetarian, lacto-ovo vegetarian, and vegan.

**Main outcomes and measures:** The relationship between vegetarian dietary patterns and all-cause and cause-specific mortality; deaths through 2009 were identified from the National Death Index.

**Results:** There were 2570 deaths among 73 308 participants during a mean follow-up time of 5.79 years. The mortality rate was 6.05 (95%CI, 5.82-6.29) deaths per 1000 person-years. The adjusted hazard ratio (HR) for all-cause mortality in all vegetarians combined vs nonvegetarians was 0.88 (95%CI, 0.80-0.97). The adjusted HR for all-cause mortality in vegans was 0.85 (95%CI, 0.73-1.01); in lacto-ovo–vegetarians, 0.91 (95%CI, 0.82-1.00); in pesco-vegetarians, 0.81 (95%CI, 0.69-0.94); and in semi-vegetarians, 0.92

(95%CI, 0.75-1.13) compared with nonvegetarians. Significant associations with vegetarian diets were detected for cardiovascular mortality, noncardiovascular noncancer mortality, renal mortality, and endocrine mortality. Associations in men were larger and more often significant than were those in women.

**Conclusions and Relevance:** Vegetarian diets are associated with lower all-cause mortality and with some reductions in cause-specific mortality. Results appear to be more robust in males. These favorable associations should be considered carefully by those offering dietary guidance.

## Background

The possible relationship between diet and mortality remains an important area of investigation. Previous studies have identified dietary factors associated with mortality. Those found to correlate with reduced mortality include nuts[1-4], fruit[5,6], cereal fiber[2], polyunsaturated fatty acids (PUFAs)[2], ω-3 PUFAs[3], green salad[7], Mediterranean dietary patterns[8-11], "healthy" or "prudent" dietary patterns[10,12,13], plant-based diet scores[14], plant-based low carbohydrate diets[15], and vegetarian diets[4,16,17]. Associations with increased mortality have been found for a high glycemic load[2], meat[6,7], red meat[18,19], processed meat[18,19], eggs[7], potatoes[5], increased energy intake[20], and animal-based low carbohydrate diets[15].

Vegetarian dietary patterns may contain many of the above-listed foods and nutrients associated with reduced mortality while having reduced intakes of some foods associated with increased mortality. Vegetarian dietary patterns have been associated with reductions in risk for several chronic diseases such as hypertension[21,22], the metabolic syndrome[23], diabetes mellitus[24,25], and ischemic heart disease (IHD)[17,26], which might be expected to result in lower mortality. Vegetarian diets represent common, real-world dietary patterns, and are thus attractive targets for study.

Previous studies of the relationship between vegetarian dietary patterns and mortality have yielded mixed results. In the first Adventist Health Study, a study of 34,198 California Seventh-day Adventists[27], vegetarian dietary patterns were associated with reduced all-cause mortality and increased longevity.[4,17] In contrast, the European Prospective Investigation into Cancer and Nutrition–Oxford (EPIC-Oxford) cohort study did not show an all-cause mortality advantage for British vegetarians (among 47,254 vegetarian and nonvegetarian participants),[28] and pooled results have shown reductions only for IHD mortality.[16]

Our objective, in light of the potential benefits of vegetarian diets and the existing uncertainty in the literature, was to evaluate the possible association of vegetarian dietary patterns with reduced mortality in a large American cohort including many vegetarians.

## Methods

### *Study Population*

Adventist Health Study 2 (AHS-2) is a cohort of 96,469 Seventh-day Adventist men and women recruited at churches in the United States and Canada between 2002 and 2007.[29] Butler et al[29] provided a detailed explanation of the cohort formation and characteristics. Written informed consent was obtained from all participants upon enrollment. The study was approved by the institutional review board of Loma Linda University.

Exclusions were applied in the following order: missing data for questionnaire return date, birthdate, sex, or race (n=1702); age younger than 25 years (n=434); estimated energy intake (not including write-in items) less than 500 kcal/day or more than 4500 kcal/day, improbable response patterns (e.g. identical responses to all questions on a page), or more than 69 missing values in dietary data (n=4961); non-US residents (n=4108); or history of a specific prior cancer diagnosis (except non-melanoma skin cancers) or of cardiovascular disease (CVD) (coronary bypass, angioplasty/stent, carotid artery surgery, myocardial infarction, or stroke; or angina pectoris or congestive heart failure treated in the past 12 months) (n=11,956). After exclusions, there remained an analytic sample of 73,308.

### *Mortality Data*

Mortality data through December 31, 2009, were obtained from the National Death Index. International Statistical Classification of Diseases, 10th Revision (ICD-10) codes for the underlying cause of death were used for causal classification. Unnatural causes of death (ICD-10 letters U, V, W, X, and Y) were considered as censoring events. Deaths associated with IHD were identified as ICD-10 I20-25; CVD deaths, as those starting with the letter I; and cancer deaths, as those starting with the letter C. Noncardiovascular, noncancer deaths were identified as all natural deaths not classified as CVD or cancer deaths. Infectious disease deaths were identified as those starting with the letters A or B; neurologic deaths, the letter G; respiratory deaths, the letter J; renal deaths, the letter N; and endocrine deaths, the letter E. Stroke deaths were identified using the code I60-69; diabetes mellitus deaths, E10-14; and renal failure deaths, N17-19.

### *Dietary Data*

Usual dietary intake during the previous year was assessed at baseline by a self-administered quantitative food frequency questionnaire of more than 200 food items. Dietary patterns were determined according to the reported intake of foods of animal origin. Thus, vegans consumed eggs/dairy, fish, and all other meats less than 1 time/mo; lacto-ovo–vegetarians consumed eggs/dairy 1 time/mo or more but fish and all other meats less than 1 time/mo; pesco-vegetarians consumed fish 1 time/mo or more but all other meats less than 1 time/mo; semi-vegetarians consumed non-fish meats 1 time/mo or more and all meats combined (fish included) 1 time/mo or more but no more than 1 time/wk; and last, nonvegetarians consumed non-fish meats 1 time/mo or more and all meats combined (fish included) more than 1 time/wk. For some analyses, the 4 vegetarian categories (vegan, lacto-ovo-vegetarian, pesco-vegetarian, and semi-vegetarian) were combined as "vegetarian." The food frequency questionnaire was previously validated against six 24-hour dietary recalls for intake of nutrients[30] and selected foods/food groups.[31] Validity correlations for red meat, poultry, fish, dairy, and eggs were 0.76, 0.76, 0.53, 0.86, and 0.64, respectively, in whites and 0.72, 0.77, 0.57, 0.82, and 0.52, respectively, in blacks.[31] Mean duration of adherence to dietary patterns was calculated for respondents to a follow-up questionnaire in which participants were asked to characterize their consumption of meat and dairy products at that time and in previous decades.

### *Covariates*

Other variables, all measured at baseline were as follows (**Table 1** footnotes for category specification): sex (dichotomous), race (dichotomous), geographic region (6 levels), personal income (4 levels), educational level (4 levels), marital status (dichotomous), smoking (8 levels), alcohol use (5 levels), exercise (i.e. "vigorous activities, such as brisk walking, jogging, bicycling, etc., long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath") (5 levels), sleep (3 levels), menopausal status of women (dichotomous), hormone therapy in postmenopausal women (dichotomous), dietary energy (7 levels: <1000kcal, 1000-

1499kcal,1500-1999kcal, 2000-2499kcal, 2500-2999kcal, 3000-3999kcal, and ≥4000kcal), body mass index (calculated as weight in kilograms divided by height in meters squared) (9 levels: <18, 18-<20, 20-<23, 23-<25, 25-<27,27-<30, 30-<35, 35-<40, ≥40).

**Table 1. Comparison of Vegetarian With Nonvegetarian Dietary Patterns With Respect to All-Cause and Cause-Specific Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009**

| | Deaths, Hazard Ratio (95% CI) | | | | |
|---|---|---|---|---|---|
| Characteristic | All-Cause | Ischemic Heart Disease | Cardiovascular Disease | Cancer | Other |
| All (N = 73 308), No. of deaths[a,b] | 2560 | 372 | 987 | 706 | 867 |
| Vegetarian | 0.88 (0.80-0.97) | 0.81 (0.64-1.02) | 0.87 (0.75-1.01) | 0.92 (0.78-1.08) | 0.85 (0.73-0.99) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Men (n = 25 105), No. of deaths[a] | 1031 | 169 | 390 | 273 | 368 |
| Vegetarian | 0.82 (0.72-0.94) | 0.71 (0.51-1.00) | 0.71 (0.57-0.90) | 1.02 (0.78-1.32) | 0.83 (0.66-1.04) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Women (n = 48 203), No. of deaths[a,c] | 1529 | 203 | 597 | 433 | 499 |
| Vegetarian | 0.93 (0.82-1.05) | 0.88 (0.65-1.20) | 0.99 (0.83-1.18) | 0.87 (0.71-1.07) | 0.88 (0.72-1.08) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |

[a] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/wk, 21-60 min/wk, 61-150 min/wk, and ≥151 min/wk), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night).

[b] Also adjusted by sex (male and female), menopause (in women) (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[c] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

Race was included as a potentially important covariate. Participants self identified their race/ethnicity in 1 or more of 21 categories. Those self-identifying as black/African American, West Indian/Caribbean, African, or other black were categorized as black for this analysis and all others were categorized as non-black.

### ***Statistical Analysis***

Baseline descriptive statistics were calculated according to the 5 dietary-pattern categories. Means and percentages were adjusted for age, sex, and race by direct standardization, using the entire analytic sample as the standard distribution. Age-sex-race standardized mortality rates were computed by dietary pattern. Analyses of mortality were performed using Cox proportional hazards regression with attained age as the time variable and left truncation by age at study entry. Covariates were selected on an a priori basis as likely confounders based on prior studies and suspected relationships. Menopausal status and hormone therapy were represented in models as nested covariates (i.e. sex + sex × menopause + sex × menopause × hormone therapy). Covariates were tested for possible interaction with the diet variable and for suspected interactions between selected covariates. The proportional hazards assumption was evaluated using Schoenfeld residuals, log(—log) plots, and attained-age interaction terms. Significant non-proportionality of hazards was present for race and marital status, so attained-age interaction terms for these variables were retained in the models. Residual methods were used to evaluate possible outliers and influential data points; no data points required removal. Multiple imputation of missing values was done for the small amount of missing data in the dietary variables used to calculate vegetarian status and for all covariates; a guided multiple imputation approach was used when possible,[32] as we have evidence that many of the missing dietary data are true zeroes.[33] Analyses were performed using commercial software SAS 9.3 (SAS Institute, Inc.). Guided multiple imputation was performed using R, version 2.13.1,[34] and the Hmisc package[35].

## Results

### *Baseline Characteristics*

Among the 73,308 individuals in our analytic sample, 5548 (7.6%) were vegans, 21,177 (28.9%) were lacto-ovo-vegetarians, 7194 (9.8%) were pesco-vegetarians, 4031 (5.5%) were semi-vegetarians, and 35,359 (48.2%) were nonvegetarians. **Table 2** presents characteristics of the participants at baseline according to the 5 dietary patterns. Percentages and means were age-sex-race standardized as appropriate. Vegetarian groups tended to be older, more highly educated, and more likely to be married, to drink less alcohol, to smoke less, to exercise more, and to be thinner. The proportion of blacks was highest among pesco vegetarians and lowest in lacto-ovo vegetarians. Of postmenopausal women, far fewer vegans were receiving hormone therapy. Mean reported duration of adherence to current dietary pattern (not included in Table 2) was 21 years for vegans, 39 years for lacto-ovo vegetarians, 24 years for pesco vegetarians, 19 years for semi-vegetarians, and 48 years for nonvegetarians.

Table 2. Standardized Distribution of Baseline Characteristics Among 73 308 Adventist Health Study 2 Participants According to Dietary Pattern[a]

| Characteristic | No. (%) | | | | |
|---|---|---|---|---|---|
| | Vegetarian | | | | |
| | Vegan | Lacto-Ovo | Pesco | Semi | Nonvegetarian |
| Participants | 5548 (7.6) | 21 177 (28.9) | 7194 (9.8) | 4031 (5.5) | 35 359 (48.2) |
| Age, mean (SD), y | 57.9 (13.6) | 57.5 (13.9) | 58.8 (13.7) | 57.8 (14.1) | 55.9 (13.1) |
| Sex, women | 3533 (63.8) | 13 644 (64.9) | 4925 (68.0) | 2785 (69.7) | 23 315 (65.3) |
| Race, black | 1139 (21.0) | 2823 (13.6) | 2745 (39.1) | 711 (17.8) | 12 362 (34.0) |
| Marital status, married | 4227 (75.6) | 16 634 (76.3) | 5081 (73.1) | 2868 (71.5) | 24 575 (70.3) |
| Personal income, $1000/y | | | | | |
| ≤20.0 | 2736 (48.8) | 8414 (38.4) | 2762 (37.7) | 1696 (41.0) | 13 911 (40.3) |
| 20.1-50.0 | 1983 (36.3) | 8520 (41.2) | 2818 (38.7) | 1570 (39.2) | 14 253 (39.6) |
| 50.1-100.0 | 646 (11.8) | 3238 (15.9) | 1282 (18.3) | 616 (16.2) | 5777 (16.0) |
| ≥100.0 | 182 (3.1) | 1005 (4.6) | 332 (5.3) | 148 (3.6) | 1417 (4.1) |
| Educational level | | | | | |
| High school or less | 968 (16.7) | 3005 (13.9) | 1426 (18.4) | 859 (21.3) | 8455 (24.4) |
| Trade school, associate degree, or some college | 2175 (39.4) | 7534 (35.7) | 2755 (38.1) | 1605 (39.2) | 15 014 (42.2) |
| Bachelor degree | 1341 (24.4) | 5386 (25.3) | 1575 (23.0) | 858 (21.3) | 6857 (19.2) |
| Graduate degree | 1063 (19.5) | 5251 (25.1) | 1439 (20.5) | 708 (18.3) | 5032 (14.1) |
| Geographic region | | | | | |
| West | 1117 (19.6) | 4696 (20.8) | 1446 (21.9) | 950 (22.5) | 7262 (21.9) |
| Northwest | 854 (14.2) | 3765 (15.2) | 882 (14.2) | 663 (14.6) | 4056 (12.7) |
| Mountain | 188 (3.2) | 866 (3.6) | 199 (3.2) | 178 (4.1) | 1453 (4.5) |
| Midwest | 1103 (19.6) | 3860 (18.3) | 970 (14.1) | 802 (19.8) | 6704 (19.2) |
| East | 556 (10.7) | 2212 (12.0) | 1493 (18.0) | 415 (11.4) | 5347 (13.7) |
| South | 1731 (32.8) | 5778 (30.1) | 2204 (28.6) | 1022 (27.7) | 10 536 (28.0) |
| Postmenopausal[b] | 2056 (54.7) | 7667 (53.7) | 2669 (53.1) | 1572 (53.7) | 11 647 (52.9) |
| Hormone therapy[c] | 166 (8.2) | 1312 (19.6) | 381 (16.7) | 312 (25.0) | 2131 (22.8) |
| Alcohol consumption | | | | | |
| None | 5487 (98.8) | 20 484 (96.8) | 6720 (92.5) | 3722 (92.4) | 29 502 (83.4) |
| Rare | 33 (0.6) | 386 (1.8) | 257 (4.0) | 176 (4.2) | 2652 (7.5) |
| Monthly | 11 (0.2) | 112 (0.5) | 68 (1.1) | 42 (1.1) | 1083 (3.1) |
| Weekly | 13 (0.3) | 154 (0.7) | 119 (1.9) | 76 (2.0) | 1652 (4.7) |
| Daily | 3 (0.1) | 41 (0.2) | 31 (0.5) | 14 (0.3) | 470 (1.3) |
| Smoking | | | | | |
| Never | 4697 (85.0) | 18 748 (88.2) | 6092 (84.1) | 3312 (81.4) | 26 866 (75.7) |
| Quit, y | | | | | |
| ≥30 | 335 (5.6) | 1019 (4.6) | 393 (5.3) | 264 (6.5) | 2076 (6.4) |
| 20-29 | 262 (4.7) | 606 (3.2) | 310 (4.4) | 157 (4.3) | 1939 (5.5) |
| 10-19 | 156 (2.8) | 471 (2.4) | 224 (3.4) | 148 (4.0) | 1866 (5.2) |
| 5-9 | 53 (1.0) | 178 (0.8) | 82 (1.3) | 72 (1.8) | 844 (2.3) |
| 1-4 | 38 (0.6) | 110 (0.5) | 57 (0.9) | 53 (1.4) | 794 (2.2) |
| <1 | 3 (0.0) | 20 (0.1) | 11 (0.2) | 11 (0.4) | 233 (0.6) |
| Current | 4 (0.1) | 25 (0.1) | 26 (0.4) | 13 (0.3) | 741 (2.0) |
| Exercise, min/wk[d] | | | | | |
| None | 882 (15.1) | 3753 (17.3) | 1354 (18.0) | 873 (20.6) | 8061 (23.4) |
| ≤20 | 889 (16.2) | 3971 (18.6) | 1217 (16.8) | 809 (20.5) | 7196 (20.0) |
| 21-60 | 885 (16.1) | 3486 (16.5) | 1151 (16.2) | 627 (16.1) | 5684 (15.8) |
| 61-150 | 1525 (27.8) | 5619 (26.8) | 1941 (27.5) | 980 (24.5) | 8366 (23.6) |
| ≥151 | 1367 (24.8) | 4349 (20.8) | 1531 (21.6) | 742 (18.3) | 6051 (17.2) |
| Sleep, h/night | | | | | |
| ≤4 | 107 (2.1) | 252 (1.6) | 203 (2.5) | 73 (2.2) | 1250 (3.2) |
| 5-8 | 5154 (93.0) | 19 668 (93.0) | 6634 (92.2) | 3728 (92.5) | 32 283 (91.3) |
| ≥9 | 287 (4.9) | 1256 (5.4) | 358 (5.3) | 230 (5.3) | 1826 (5.5) |
| BMI, mean (SD) | 24.1 (4.7) | 26.1 (5.3) | 26.0 (5.0) | 27.3 (5.6) | 28.3 (6.1) |
| Energy intake, mean (SD), kcal/d | 1897 (729) | 1912 (735) | 1939 (772) | 1720 (713) | 1884 (773) |

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Multiple imputation of missing values was used to calculate all values. All counts are actual and unadjusted. Means and percentages were standardized by age, sex, and race, as appropriate, by the direct standardization technique using the entire analytic sample as the standard distribution.

[b] Among women only.

[c] Among postmenopausal women.

[d] Exercise defined as "vigorous activities, such as brisk walking, jogging, bicycling, etc, long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath."

### ***Mortality***

The mean (SD) follow-up time was 5.79 (1.31) years.  During this time there were 2570 deaths among 73,308 participants, and the overall mortality rate was 6.05 (95% CI, 5.82-6.29) deaths per 1000 person-years.  **Table 3** gives the age-sex-race standardized mortality rates by dietary pattern.  Vegans, lacto-ovo-vegetarians, and pesco-vegetarians had significantly lower mortality rates compared withy nonvegetarians.

Table 3. Age-Sex-Race Standardized Mortality Rates Among 73 308 Adventist Health Study 2 Participants According to Dietary Pattern

| Characteristic | No. of People | Time, Person-years | Mean Time, y | Deaths | Death Rate, Deaths/1000 Person-years (95% CI)[a] | *P* Value[b] |
|---|---|---|---|---|---|---|
| Vegetarian[c] | | | | | | |
| Vegan | 5548 | 32 810.3 | 5.92 | 197 | 5.40 (4.62-6.17) | .009 |
| Lacto-ovo | 21 177 | 124 660.5 | 5.88 | 815 | 5.61 (5.21-6.01) | .001 |
| Pesco | 7194 | 41 225.7 | 5.73 | 251 | 5.33 (4.61-6.05) | .004 |
| Semi | 4031 | 23 714.6 | 5.86 | 160 | 6.16 (5.03-7.30) | .30 |
| Nonvegetarian | 35 359 | 202 098.4 | 5.72 | 1147 | 6.61 (6.21-7.03) | |
| All participants | 73 308 | 424 509.4 | 5.79 | 2570 | 6.05 (5.82-6.29) | |

[a] Adjusted for age, race, and sex by direct standardization.

[b] From *Z* tests that test null hypotheses of no difference from the nonvegetarian death rate.

[c] Dietary pattern classified after multiple imputation of missing values. Values for number of people, person time, mean time, deaths, and death rate represent the mean of values from 5 imputed data sets; thus, summed values for number of people, person-time, and deaths may not equal the value for all participants.

Table 1 reports the comparison of the multivariate-adjusted risk of death for all vegetarians combined with that for nonvegetarians. Vegetarians had 0.88 (95% CI, 0.80-0.97) times the risk of all-cause mortality of nonvegetarians. In men, the hazard ratio (HR) was 0.82 (95% CI, 0.72-0.94) and in women, 0.93 (95% CI, 0.72-1.05). Significantly reduced risk in the combined sexes was also seen for other mortality (i.e. non-CVD noncancer) (HR, 0.85; 95% CI, 0.73-0.99), but not clearly for IHD mortality (0.81; 0.64-1.02), CVD mortality (0.87; 0.75-1.01), or cancer mortality (0.92; 0.78-1.08). For men, CVD mortality (0.71; 0.57-0.90) and IHD mortality (0.71; 0.51-1.00) achieved significance, and other mortality had a notable but non-significant reduction (0.83; 0.66-1.04). In women, there were no significant reductions in these causal categories of mortality, although the effect estimates for IHD mortality, cancer mortality, and "other" mortality were moderately less than 1.0. Results (not included in table) for stroke were, for both sexes combined, HR, 1.10 (95% CI, 0.82-1.47); for men, 0.83 (0.52-1.31); and for women, 1.27 (0.89-1.80).

**Table 4** reports the comparison of the multivariate-adjusted risk of death for 4 categories of vegetarians compared with nonvegetarians.

**Table 4. Associations of Dietary Patterns With All-Cause and Cause-Specific Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009**

| Characteristic | Deaths, Hazard Ratio (95% CI) | | | | |
|---|---|---|---|---|---|
| | All-Cause | Ischemic Heart Disease | Cardiovascular Disease | Cancer | Other |
| All (N = 73 308), No. of deaths[a,b] | 2560 | 372 | 987 | 706 | 867 |
| Vegetarian | | | | | |
| Vegan | 0.85 (0.73-1.01) | 0.90 (0.60-1.33) | 0.91 (0.71-1.16) | 0.92 (0.68-1.24) | 0.74 (0.56-0.99) |
| Lacto-ovo | 0.91 (0.82-1.00) | 0.82 (0.62-1.06) | 0.90 (0.76-1.06) | 0.90 (0.75-1.09) | 0.91 (0.77-1.07) |
| Pesco | 0.81 (0.69-0.94) | 0.65 (0.43-0.97) | 0.80 (0.62-1.03) | 0.94 (0.72-1.22) | 0.71 (0.54-0.94) |
| Semi | 0.92 (0.75-1.13) | 0.92 (0.57-1.51) | 0.85 (0.63-1.16) | 0.94 (0.66-1.35) | 0.99 (0.72-1.36) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Men (n = 25 105), No. of deaths[a] | 1031 | 169 | 390 | 273 | 368 |
| Vegetarian | | | | | |
| Vegan | 0.72 (0.56-0.92) | 0.45 (0.21-0.94) | 0.58 (0.38-0.89) | 0.81 (0.48-1.36) | 0.81 (0.53-1.22) |
| Lacto-ovo | 0.86 (0.74-1.01) | 0.76 (0.52-1.12) | 0.77 (0.59-0.99) | 1.01 (0.75-1.37) | 0.89 (0.69-1.15) |
| Pesco | 0.73 (0.57-0.93) | 0.77 (0.45-1.30) | 0.66 (0.44-0.98) | 1.10 (0.73-1.67) | 0.60 (0.39-0.93) |
| Semi | 0.93 (0.68-1.26) | 0.73 (0.33-1.60) | 0.75 (0.43-1.32) | 1.15 (0.65-2.03) | 1.03 (0.62-1.71) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Women (n = 48 203), No. of deaths[a,c] | 1529 | 203 | 597 | 433 | 499 |
| Vegetarian | | | | | |
| Vegan | 0.97 (0.78-1.20) | 1.39 (0.87-2.24) | 1.18 (0.88-1.60) | 0.99 (0.69-1.44) | 0.70 (0.47-1.05) |
| Lacto-ovo | 0.94 (0.83-1.07) | 0.85 (0.59-1.22) | 0.99 (0.81-1.22) | 0.85 (0.67-1.09) | 0.93 (0.75-1.17) |
| Pesco | 0.88 (0.72-1.07) | 0.51 (0.26-0.99) | 0.90 (0.66-1.23) | 0.86 (0.61-1.21) | 0.81 (0.58-1.15) |
| Semi | 0.92 (0.70-1.22) | 1.09 (0.60-1.98) | 0.93 (0.64-1.34) | 0.85 (0.56-1.30) | 0.97 (0.64-1.47) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |

[a] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/week, 21-60 min/week, 61-150 min/week, and ≥151 min/week), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night).

[b] Also adjusted by sex (male and female), menopause (in women) (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[c] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (postmenopausal women) (not taking hormone therapy, taking hormone therapy).

Pesco vegetarians had significantly reduced risk in both sexes combined for all-cause mortality (HR, 0.81; 95% CI, 0.69-0.94), IHD mortality (0.65; 0.43-0.97), and other mortality (0.71; 0.54-0.94); in men for all-cause mortality (0.73; 0.57-0.93), CVD mortality (0.66; 0.44-0.98), and other mortality (0.60; 0.57-0.93); and in women for IHD mortality (0.51; 0.26-0.99). Lacto-ovo vegetarians had significantly reduced risk in both sexes combined for all-cause mortality (HR, 0.91; 95% CI, 0.82-1.00) and in men for CVD mortality (0.77; 0.59-0.99). Vegans had significantly reduced risk in both sexes combined for other mortality (HR, 0.74; 95% CI, 0.56-0.99) and in men for all-cause mortality (0.72; 0.56-0.92), IHD mortality (0.45; 0.21-0.94), and CVD mortality (0.58; 0.38-0.89).

**Table 5** presents the results of multivariate-adjusted Cox analyses for several more specific categories of mortality within the broad "other" mortality of table 1 (i.e. non-CVD, non-cancer mortality), comparing all vegetarians with nonvegetarians. In men and women combined, vegetarians had a significantly reduced risk of renal mortality (HR, 0.48; 95% CI, 0.28-0.82) and endocrine mortality (0.61; 0.40-0.92); in men, vegetarians had reduced risk of renal mortality (0.42; 0.19-0.91) and endocrine mortality (0.48; 0.25-0.92); and in women, non-significant reductions for both renal mortality (0.57; 0.28-1.19) and endocrine mortality (0.76; 0.44-1.30). Forty of 67 renal deaths were associated with renal failure (for both sexes combined, HR, 0.26; 95%CI, 0.12-0.57; for women, 0.39; 0.13- 1.17; and for men, 0.21; 0.07-0.63). Sixty-seven of 104 endocrine deaths were associated with diabetes mellitus (for both sexes combined, HR, 0.53; 95%CI, 0.32-0.89; for women, 0.78; 0.41-1.48; and for men, 0.27; 0.11-0.66).

Table 5. Comparison of Vegetarian With Nonvegetarian Dietary Patterns With Respect to Categories of Noncancer, Noncardiovascular Mortality From a Cox Proportional Hazards Regression Model Among Participants in the Adventist Health Study 2, 2002-2009

| Characteristic | Hazard Ratio (95% CI) | | | | |
|---|---|---|---|---|---|
| | Infectious[a] | Neurologic[a] | Respiratory[a] | Renal[a] | Endocrine[a] |
| All (N = 73 308), No. of deaths[b,c] | 64 | 182 | 172 | 67 | 104 |
| Vegetarian | 0.93 (0.53-1.62) | 0.93 (0.67-1.29) | 0.95 (0.68-1.32) | 0.48 (0.28-0.82) | 0.61 (0.40-0.92) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Men (n = 25 105), No. of deaths[b] | 31 | 80 | 72 | 34 | 41 |
| Vegetarian | 0.85 (0.39-1.86) | 0.86 (0.53-1.40) | 1.13 (0.67-1.92) | 0.42 (0.19-0.91) | 0.48 (0.25-0.92) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| Women (n = 48 203), No. of deaths[b,d] | 33 | 102 | 100 | 33 | 63 |
| Vegetarian | 0.97 (0.44-2.11) | 0.97 (0.63-1.49) | 0.88 (0.57-1.36) | 0.57 (0.28-1.19) | 0.76 (0.44-1.30) |
| Nonvegetarian | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] | 1 [Reference] |

[a] The most common specific causes of mortality for each category: infectious (septicemia, *International Statistical Classification of Diseases*, *10th Revision* [*ICD-10*] code A41, 32 deaths); neurologic (Alzheimer disease, *ICD-10* G30, 93 deaths; Parkinson disease, *ICD-10* G20, 34 deaths); respiratory (influenza and pneumonia, *ICD-10* J10-18, 59 deaths; emphysema and chronic obstructive pulmonary disease, *ICD-10* J43-44, 49 deaths; interstitial lung disease, *ICD-10* J84, 29 deaths); renal (renal failure, *ICD-10* N17-19, 40 deaths); and endocrine (diabetes mellitus, *ICD-10* E10-14, 67 deaths).

[b] Adjusted by age (ie, attained age as time variable), race (black, nonblack), smoking (current smoker, quit <1 year, quit 1-4 years, quit 5-9 years, quit 10-19 years, quit 20-29 years, quit ≥30 years, and never smoked), exercise (none, ≤20 min/wk, 21-60 min/wk, 61-150 min/wk, and ≥151 min/wk), personal income (≤$20 000/y, >$20 000-$50 000/y, >$50 000-$100 000/y, and >$100 000/y), educational level (up to high school graduate, trade school/some college/associate degree, bachelor degree, and graduate degree), marital status (married/common-law and single/widowed/divorced/separated), alcohol (nondrinker, rare drinker [<1.5 servings/mo], monthly drinker [1.5 to <4 servings/mo], weekly drinker [4 to <28 servings/mo], and daily drinker [≥28 servings/mo]), geographic region (West, Northwest, Mountain, Midwest, East, and South), and sleep (≤4 h/night, 5-8 h/night, and ≥9 h/night).

[c] Also adjusted by sex (male and female), menopause (premenopausal [including perimenopausal], postmenopausal), and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

[d] Also adjusted by menopause (premenopausal [including perimenopausal], postmenopausal) and hormone therapy (in postmenopausal women) (not taking hormone therapy, taking hormone therapy).

A sensitivity analysis in which body mass index was added to the model generally had only modest effect on the results. Overall HRs for vegetarians were then 0.90 (95% CI, 0.82-0.98) for both sexes combined, 0.83 (0.72-0.96) for men, and 0.95 (0.84-1.06) for women. The adjustment for body mass index did not consistently move results toward the null. Mortality results adjusted for body mass index affected statistical significance in the following instances. For all vegetarians combined compared with nonvegetarians: IHD mortality in men (HR, 0.77; 95%CI, 0.54-1.10), endocrine mortality in both sexes combined (HR, 0.71; 95%CI, 0.46-1.09), and diabetes mortality in both sexes combined (HR, 0.65; 95% CI, 0.38-1.11). For specific vegetarian dietary patterns compared with nonvegetarians: vegans, all-cause mortality in both sexes combined (HR, 0.84; 95%CI, 0.72-1.00) and IHD mortality in men (0.50; 0.24-1.06); lacto-ovo–vegetarians, all-cause mortality in both sexes combined (0.92; 0.84-1.02) and CVD mortality in men (0.81; 0.63-1.05); pesco-vegetarians, IHD mortality in both sexes combined (0.69; 0.45-1.05), other mortality in both sexes combined (0.77; 0.60-1.00), CVD mortality in men (0.68; 0.45-1.04), and other mortality in men (0.65; 0.43- 1.00). Additional adjustment by dietary energy intake resulted in negligible changes. Formal tests for interaction of the diet variable (vegetarian vs nonvegetarian) with sex revealed significant interaction for CVD mortality ($P = .01$), but no significant interaction for all-cause mortality or other categories of mortality.

## Comment

These results demonstrate an overall association of vegetarian dietary patterns with lower mortality compared with the nonvegetarian dietary pattern. They also demonstrate some associations with lower mortality of the pesco vegetarian, vegan, and lacto-ovo vegetarian diets specifically, compared with the nonvegetarian diet.

Some associations of vegetarian diets with lower cardiovascular mortality and lower non-cardiovascular, non-cancer mortality were observed. Vegetarian diets have been associated with more favorable levels of cardiovascular risk factors,[17,22-25,36,37] and nutrient profiles of the vegetarian dietary patterns suggest possible reasons for reduced cardiovascular risk, such as lower saturated fat and higher fiber consumption[38]. Analysis within the non-CVD, non-cancer category revealed notable reductions in mortality with underlying cause classified as endocrine or renal (diabetes mellitus and renal failure, in particular). These apparent protective associations seem consistent with previously published findings showing an association of vegetarian diets with reduced risk of incident diabetes[25] and of prevalent diabetes, hypertension, and the metabolic syndrome.[21,23,24]

No significant associations with reduced cancer mortality were detected. The heterogeneous nature of cancer may obscure specific diet-cancer associations in analyses of combined cancer mortality, and lack of significance may reflect insufficient power to detect weaker associations at early follow up. Early analyses of vegetarian dietary patterns and cancer incidence in AHS-2 demonstrated significantly reduced risks of female-specific and gastrointestinal cancers[39].

Effects were generally stronger and more significant in men than women. Previous studies[40-42] among Adventists have demonstrated effect modification by sex of the association of vegetarian diets with reduced ischemic heart disease mortality. It is possible that within dietary groups the diets of men and women differ in important ways;

however, a recent evaluation[38] of the nutrient profile of the dietary patterns in this cohort did not reveal striking differences. Alternatively, the biological effect of dietary factors on mortality may be different in men and women. Future analysis will evaluate possible effect modification by sex for particular foods or nutrients, which may suggest sex-specific mechanisms.

Strengths of this study include the large number of participants consuming various vegetarian diets; the diverse nature of this cohort in terms of sex, race, geography, and socioeconomic status, enhancing generalizability; the low use of tobacco and alcohol, making residual confounding from these unlikely; the shared religious affiliation of the cohort, which may lead to greater homogeneity across several possible unmeasured confounders, enhancing internal validity; and precise dietary pattern definitions based on measured food intake rather than self-identification of dietary patterns.

This analysis is limited by relatively early follow-up. If dietary patterns affect mortality, they may do so with moderate effect sizes, via complex pathways, and with long latency periods. Early follow-up analysis may thus have bias toward the null, and true associations may remain undetected. Observed mortality benefits may be affected by factors related to the conscious lifestyle choice of a vegetarian diet other than dietary components. Potential for uncontrolled confounding remains. Dietary patterns may change over time, whereas the analysis relies on a single measurement of diet at baseline. Caution must be used in generalizing results to other populations in which attitudes, motivations, and applications of vegetarian dietary patterns may differ; dietary pattern definitions used may not reflect some common uses of these terms.

Further study of the possible association with mortality of specific foods and nutrients that characterize the different diet-pattern groups is a major future goal of the AHS-2 study.  Later follow-up may yield more statistically robust results, allow direct comparisons between vegetarian groups, enable subgroup analysis, particularly by race/ethnicity, and allow for analysis by more specific causes of mortality.

The lack of similar findings in British vegetarians[28] remains interesting and this difference deserves careful study.  In both studies, the nonvegetarians are a relatively healthy reference group. In both, the nutrient profiles of vegetarians differ in important ways from those of nonvegetarians, with vegetarians (especially vegans) consuming less saturated fat and more fiber[38,43]. It appears that British vegetarians and U.S. Adventist vegetarians eat somewhat differently[44].  For instance, the vegetarians in our study consume more fiber and vitamin C than those of the EPIC-Oxford cohort:  Mean dietary fiber in EPIC-Oxford vegans was 27.7 g/day in men and 26.4 g/day in women compared with 45.6 g/day in men and 47.3 g/day in women in AHS-2 vegans; mean vitamin C in EPIC-Oxford vegans was 125 mg/day in men and 143 mg/day in women compared with 224 mg/day in men and 250 mg/day in women in AHS-2 vegans[38,43].   Individuals electing vegetarian diets for ethical or environmental reasons may eat differently from those who choose vegetarian diets primarily for reasons of perceived superiority for health promotion.  We believe that perceived healthfulness of vegetarian diets may be a major motivator of Adventist vegetarians.  More important, other large cohort studies have linked increased red and processed meat consumption to higher mortality,[18,19,45] and our findings build on this work by demonstrating reduced mortality in those consuming low-meat dietary patterns.  Notably, the findings of the present study are similar to those of prior North American Adventist cohorts, demonstrating a consistent association over several decades and replicating prior results in a population with greater geographic and ethnic diversity[46].

In conclusion, in a large American cohort we found that vegetarian dietary patterns were associated with lower mortality. The evidence that vegetarian diets, or similar diets with reduced meat consumption, may be associated with a lower risk of death should be considered carefully by individuals as they make dietary choices and by those offering dietary guidance.

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# CHAPTER FIVE

# VEGETARIAN DIETARY PATTERNS AND THE RISK OF COLORECTAL CANCERS

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Keywords: Dietary Pattern, Vegetarian, Colorectal Cancer, Colon Cancer

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## Abstract

**Importance:** Colorectal cancers are a leading cause of cancer mortality, and their primary prevention by diet is highly desirable. The relationship of vegetarian dietary patterns to colorectal cancer risk is not well established.

**Objective:** To evaluate the association between vegetarian dietary patterns and incident colorectal cancers.

**Design:** Prospective cohort study. Analysis was by Cox proportional hazards regression, controlling for important demographic and lifestyle confounders.

**Setting:** Adventist Health Study 2 (AHS-2) is a large North American cohort.

**Participants:** 96,798 Seventh-day Adventist men and women recruited between 2002 and 2007, from which an analytic sample of 77,712 participants remained after exclusions.

**Exposures:** Diet assessed at baseline by a quantitative food frequency questionnaire and categorized into four vegetarian dietary patterns (vegan, lacto-ovo-, pesco-, and semi-) and a nonvegetarian dietary pattern.

**Main outcomes and measures:** The relationship between vegetarian dietary patterns and incident cancers of the colon and rectum; colorectal cancer cases were identified primarily by state cancer registry linkages.

**Results:** During a mean follow-up of 7.8 years, there were 405 cases of colon cancer and 93 cases of rectal cancer. The adjusted hazard ratio (HR) in all vegetarians combined versus nonvegetarians was 0.79 (95% CI 0.65-0.95) for all colorectal cancers, 0.79 (95% CI 0.64-0.98) for colon cancer, and 0.76 (95% CI 0.49-1.17) for rectal cancer. The adjusted HR for colorectal cancer in vegans was 0.84 (0.60, 1.19), in lacto-ovo-vegetarians was 0.81 (0.65, 1.01), in pesco-vegetarians was 0.59 (0.41, 0.84), and in semi-vegetarians was 0.95 (0.64, 1.39) compared to nonvegetarians. Effect estimates were similar for men and women and for blacks and non-blacks.

**Conclusions and relevance:** Vegetarian diets are associated with lower incidence of colorectal cancers, overall. If such associations are causal, they may be important for primary prevention.

## Introduction

Colorectal cancer remains the second leading cause of cancer mortality in the United States[1]. While much attention has focused on improving screening for and treatment of colorectal cancer, enhancing primary prevention of colorectal cancer through risk factor reduction remains an important objective.

Dietary factors have been implicated as important sources of modifiable risk for colorectal cancer[2]. Among dietary factors thought to influence colorectal cancer risk, the evidence that red meat and processed meat consumption is linked to increased risk[3-6] and that foods containing dietary fiber are linked to decreased risk has been judge to be convincing[2,7]. The evidence for a link to decreased risk has been judged probable for garlic, milk, and calcium[2]. Evidence for other dietary components is considered limited[2].

Vegetarian dietary patterns might be expected to be associated with a lower risk of colorectal cancer, given that they differ from nonvegetarian diets in the amount of meat (including red and processed meat) consumed. Vegetarian diets may also be higher in fiber-containing foods[8]. Such diets have also consistently been associated with lower BMI[9-12], and evidence convincingly links increased adiposity to increased colorectal cancer risk[2,7,13]. However, surprisingly, British vegetarian diets have been associated with an increased risk of colorectal cancer[14].

The Adventist Health Study 2 (AHS-2) is a large North American cohort with a substantial proportion of vegetarians. Vegetarian dietary patterns in AHS-2 have been associated with a number of beneficial health outcomes including lower mortality[15]; lower prevalent obesity[10], hypertension[16,17], metabolic syndrome[18], and diabetes mellitus type II[10]; and lower incidence of diabetes mellitus type II[19]. Preliminary investigations have demonstrated vegetarian dietary patterns to be associated with reduced incidence of all cancers combined and of cancers of the gastrointestinal tract[20], but not with reduced mortality from all cancers[15]. Results from a previous cohort (AHS-1) found meat intake to be associated with increased risk of colon cancer and legume consumption with decreased risk[21].

We hypothesized that vegetarian dietary patterns in AHS-2 would be associated with reductions in risk for cancers of the colon and rectum. In this analysis, we examine that hypothesis.

## Methods

### *Study Population*

Study participants were recruited between 2002-2007 across all US states and Canadian provinces. Recruitment took place in Seventh-day Adventist churches. A total of 96,798 persons enrolled. See Butler et al. for a detailed description of the formation and characteristics of the cohort[22]. The study was approved by the institutional review board of Loma Linda University; written informed consent was obtained.

Of the 96,798 participants, linkage with cancer registries was possible for 90,844 participants in 48 states. Among these, the following exclusion criteria were applied: age less than 25 years or missing data for age or sex (n=446); improbable response patterns in questionnaire data (e.g. identical high-frequency responses to all questions on a page) (n=369); greater than 69 missing values in dietary data (n=1720); estimated energy intake less than 500 kcal/day or greater than 4500 kcal/day (n=3174); a history of prior cancer (except for non-melanoma skin cancer) (n=7402); consent not returned (n=17); no cancer diagnosis date (n=4). After all exclusions, there remained an analytic sample of 77,712 participants.

### *Outcome Data*

Information on incident cancers was obtained primarily via linkage with state cancer registries. At the time of this analysis, linkage has been achieved for 48 states. The linkage was through the end of 2011 for 33 states, 2010 for 10 states, 2009 for 3 states, and 2008 for 2 states. The procedure for record linkage varied according to state regulations. Whenever possible, a programmer from our team was sent to conduct the record linkage at each registry. Potential matches were identified based on a three-stage process, which included a probabilistic screen, confirmation by a deterministic algorithm based on defined criteria, and if this was inconclusive, a manual review. When state regulations did not allow for our programmer to conduct the linkage, we supplied the state with identifying information necessary to match participants to cancer cases.

ICD-10 coding was used to identify cases of colorectal cancer. The following definitions were applied: colon cancer, ICD-10 = C18.0-C18.9 (but not C18.1) or C19.9; rectal cancer, ICD-10 = C20.9. Carcinomas *in situ* were not considered to be cases.

In addition to the record linkages with cancer registries, each participant was sent a follow-up questionnaire biennially, which asked whether the participant had been diagnosed with cancer. These responses were compared to the information from the registry linkages. When participants reported a new cancer that was not found in the registry linkage, the participant was called and clarifying questions were asked. When indicated, medical records were requested and reviewed by the principal investigator to ascertain whether the self-reported cancer could be verified.

### ***Dietary Data***

Diet was assessed at baseline by means of a detailed, quantitative food frequency questionnaire. Frequency and quantity of consumption were queried for more than 200 food items. Jaceldo-Siegel et al. provide detailed descriptions of the methods of dietary measurement using the questionnaire and its validation by repeated 24-hour recalls[23,24]. Validity correlations for red meat, poultry, fish, dairy and eggs were 0.76, 0.76, 0.53, 0.86, and 0.64, respectively, in Whites, and 0.72, 0.77, 0.57, 0.82, and 0.52, respectively, in Blacks[24].

Five vegetarian and nonvegetarian dietary patterns were defined *a priori* according to the absence of intake of particular animal foods. As described by Orlich et al.: "Dietary patterns were determined according to the reported intake of foods of animal origin. Thus, vegans consumed eggs/dairy, fish, and all other meats <1 time/month; lacto-ovo-vegetarians consumed eggs/dairy ≥1 time/month but fish and all other meats <1 time/month; pesco-vegetarians consumed fish ≥1 time/month but all other meats <1 time/month; semi-vegetarians consumed non-fish meats ≥1 time/month and all meats combined (fish included) ≥1 time/month but ≤1 time/week; lastly, nonvegetarians consumed non-fish meats ≥1 time/month and all meats combined (fish included) >1 time/week."[15] In many analyses, the four vegetarian groups (vegan, lacto-ovo-vegetarian, pesco-vegetarian, and semi-vegetarian) were considered together as "vegetarians" and compared to the nonvegetarian dietary pattern, as the numbers of cases for specific vegetarian dietary patterns (aside from lacto-ovo-vegetarian) were relatively small.

### *Covariate Data*

Additional information was also ascertained at baseline using a questionnaire. This included a wide variety of questions related to demographics, family history, biometrics, prior or current diseases and medications, use of tobacco and alcohol, exercise and other lifestyle factors, and reproductive and gynecological information.

### *Statistical Analysis*

We used Cox proportional hazards regression to assess the relationship between vegetarian dietary patterns and the risk of colorectal cancers, controlling for likely confounders; separate analyses were conducted for all colorectal cancers, colon cancers alone, and rectal cancers alone. For individuals diagnosed with both colon and rectal cancers, the first date of diagnosis was used in analyses of all colorectal cancers. Attained age was the Cox regression time variable, with left truncation at age of study entry. Survival curves were computed using PROC PHREG in SAS, with covariates fixed at their mean values.

Covariates were selected for inclusion in the analytic models in an *a priori* fashion as likely confounders. For each analysis, three models were used, to show the effect of including additional covariates. The following variables (and categories) were included in the analytic models: age (attained age as time variable); sex (male, female); education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher); moderate or vigorous exercise (none, ≤60 min/week, >60 min/week); smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago); alcohol (none, <28 servings/mo, ≥ 28 servings/mo); family history of colorectal cancer (yes, no); history of peptic ulcer (yes, no); history of inflammatory bowel disease (yes, no); treated for diabetes mellitus within the last year (yes, no); taken aspirin at least weekly at least 2 of the last 5 years (yes, no); taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no); supplemental calcium consumption (yes, no); dietary energy (kcal); hormone therapy among menopausal women (yes, no); and BMI (<18.5, 18.5-24.9, 25-29.9, ≥30). Participants self-identified their race/ethnicity in one or more of 21 categories. Those self-identifying at least in part as black/African American, West Indian/Caribbean, African, or other black were categorized as black for this analysis and all others as non-black. Covariates were tested for possible interaction with the diet variable and for suspected interactions between selected covariates.

A sensitivity analysis was performed to assess robustness to potential inadequate model specification, since covariate category specification was limited by the number of events: A propensity score analysis was used, in which covariates (often with a larger number of specified categories) were used to compute a propensity for the vegetarian dietary pattern; this propensity score was then used as a covariate in Cox regression models in lieu of other covariates.

The proportional hazards assumption was evaluated using Schoenfeld residuals, log(-log) plots, and attained-age interaction terms. Residual methods were used to evaluate possible outliers and influential data points; no data points required removal. Multiple imputation of missing values was done for the small amount of missing data in the dietary variables used to calculate vegetarian status and for most covariates; a guided multiple imputation approach was utilized where possible,[32] as we have evidence that many of the missing dietary data are true zeroes.[33] Analyses were performed using SAS 9.4 (SAS Institute, Cary NC). Guided multiple imputation was performed using R version 2.13.1[25] and the Hmisc package[26].

## Results

During an average follow-up period of 7.8 years (total of 608,051 person-years of follow-up) among 77,712 study participants, there were 405 cases of colon cancer and 93 cases of rectal cancer.

**Table 1** compares the baseline characteristics of four different groups of vegetarians to nonvegetarians. Blacks are less well represented among vegetarians (particularly lacto-ovo-vegetarians) with the notable exception of pesco-vegetarians. Vegetarians are more likely to have higher education and to exercise; they are less likely to have ever smoked, to drink alcohol, to have had a colonoscopy or sigmoidoscopy (especially vegans), to take aspirin, statins, or calcium supplements, to have diabetes treated within the last year, or to have had peptic ulcers. Vegetarians have lower BMI, and lower intakes of fat, saturated fat, meat, red meat, and processed meat, but higher intake of fiber. Vegans have a lower dietary calcium intake. Energy intake is similar in all groups, with semi-vegetarians having the lowest intake and pesco-vegetarians the highest.

**Table 1.** Baseline characteristics[a] among 77,712 Adventist Health Study 2 participants according to dietary pattern.

| | Vegetarian | | | | | |
|---|---|---|---|---|---|---|
| | Vegan | Lacto-ovo | Pesco | Semi | Non vegetarian | Miss-ing[b] |
| *Categorical, %* | | | | | | |
| N | 5919 | 22723 | 7706 | 4304 | 37060 | 0 |
| Percent | 7.6 | 29.2 | 9.9 | 5.5 | 47.7 | 0 |
| Sex, women | 63.5 | 63.8 | 67.7 | 68.2 | 64.7 | 0 |
| Race, black | 21.4 | 13.9 | 39.4 | 18.6 | 33.9 | 824 |
| Education, HS or less | 17.7 | 14.2 | 20.0 | 21.4 | 25.8 | 1020 |
| Smoking, ever | 15.4 | 11.6 | 15.4 | 18.5 | 25.1 | 1545 |
| Alcohol, current | 1.1 | 3.3 | 6.6 | 8.1 | 16.2 | 1824 |
| Exercise, >60min/wk[c] | 52.5 | 47.8 | 48.8 | 43.3 | 40.2 | 3752 |
| Family history[d], yes | 8.5 | 9.7 | 7.9 | 9.1 | 8.8 | 0 |
| Endoscopy[e], ever | 30.9 | 38.8 | 39.0 | 40.3 | 41.0 | 3974 |
| Aspirin[f], ≥ weekly | 5.9 | 11.9 | 12.4 | 14.6 | 17.9 | 2044 |
| Statins[f], yes | 3.2 | 7.2 | 9.2 | 11.0 | 14.2 | 2194 |
| Supp. calcium, yes | 38.8 | 46.1 | 45.2 | 45.2 | 41.2 | 2 |
| Diabetes, current[g] | 2.7 | 3.5 | 4.9 | 6.3 | 8.6 | 207 |
| IBD, yes | 1.1 | 1.2 | 1.1 | 1.1 | 1.2 | 207 |
| Peptic ulcer, yes | 9.8 | 11.0 | 12.4 | 13.6 | 14.2 | 207 |
| *Continuous, mean (SD)* | | | | | | |
| Age, y | 58.4 (14.0) | 58.8 (14.6) | 58.2 (14.5) | 58.5 (14.6) | 55.5 (13.7) | 0 |
| BMI, kg/m$^2$ | 24.0 (4.7) | 25.9 (5.3) | 26.2 (5.1) | 27.3 (5.7) | 28.7 (6.3) | 1979 |
| energy, kcal/d | 1926 (734) | 1946 (722) | 2002 (795) | 1769 (728) | 1964 (796) | 0 |
| total fat, g/d | 62.8 (31.2) | 72.2 (32.7) | 72.5 (35.7) | 66.4 (33.4) | 76.3 (37.2) | 0 |
| saturated fat, g/d | 12.1 (6.2) | 17.4 (8.7) | 16.9 (9.2) | 17.0 (9.4) | 21.0 (11.3) | 0 |
| total meat[h], g/d | 0.0 (0.5) | 0.1 (0.7) | 15.7 (23.5) | 7.0 (4.1) | 54.5 (44.5) | 0 |
| red meat, g/d | 0.0 (0.1) | 0.0 (0.3) | 0.1 (0.8) | 1.3 (2.6) | 16.3 (24.3) | 0 |
| processed meat, g/d | 0.0 (0.0) | 0.0 (0.1) | 0.0 (0.2) | 0.2 (0.5) | 2.6 (5.0) | 0 |
| fiber, g/d | 44.2 (18.6) | 35.6 (15.9) | 37.7 (18.3) | 30.5 (15.4) | 29.3 (15.2) | 0 |
| dietary calcium, mg/d | 801 (379) | 882 (423) | 918 (462) | 820 (430) | 880 (471) | 0 |

Abbreviations: HS, high school; supp., supplemental; IBD, inflammatory bowel disease.
[a] Adjusted for age by direct standardization (except N, Percent, and Age).
[b] Dietary patterns and dietary variables, which are estimated from multiple questionnaire items, had missing values imputed in their calculation. Most other missing values indicated here were subsequently multiply imputed in the main analyses.
[c] Exercise defined as "vigorous activities, such as brisk walking, jogging, bicycling, etc., long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath."
[d] Family history of colorectal cancer.
[e] Colonoscopy or flexible sigmoidoscopy.
[f] For at least 2 of the last 5 years.
[g] Treated within the last year.
[h] All meat consumed (including poultry and fish).

Vegetarian diets were associated with reduced risk of colorectal cancer overall. **Figure 1** displays curves indicating the probability of surviving to a given age without a diagnosis of colorectal cancer (with race and sex held constant) for all vegetarians compared to nonvegetarians.

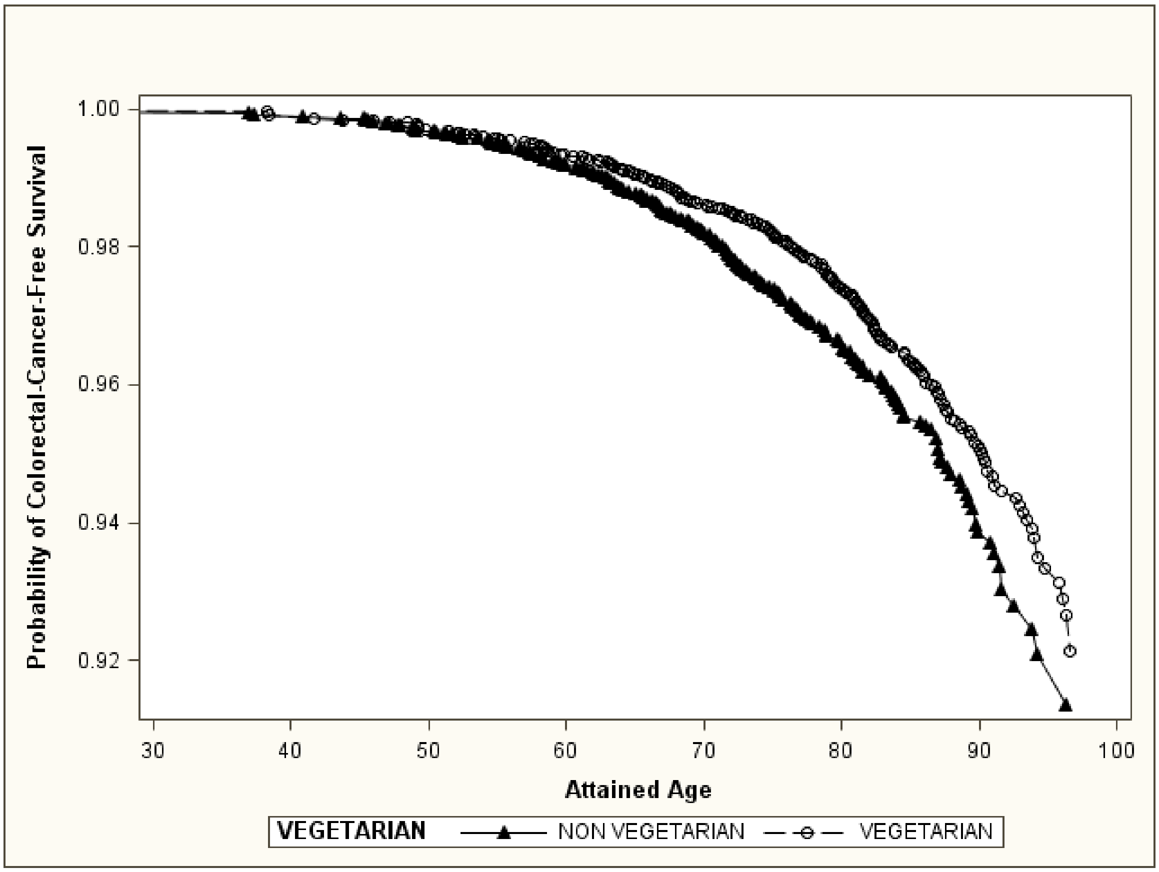


**Figure 1.** A comparison of the probability of surviving to a given age without having received a diagnosis of colorectal cancer (i.e. colorectal-cancer-free survival) for all vegetarians compared to nonvegetarians. Generated by PROC PHREG, SAS 9.4; race and sex held constant.

These show reduced colorectal cancer incidence among vegetarians across a spectrum of attained ages. **Table 2** presents results of proportional hazards regression models for all vegetarians compared to nonvegetarians, for all colorectal cancers together and for colon and rectal cancers separately. In each case, three adjustment models are presented: Model 1, with adjustment for age, sex, and race; Model 2, with additional adjustment for a variety of plausible confounders (see footnote b, Table 2); and Model 3, with additional adjustment for BMI. Since BMI may represent a causal intermediate, we consider Model 2 as the likely best model for the total effect of dietary pattern on colorectal cancers; results cited here are all for Model 2. The vegetarian dietary pattern is associated with a reduction in risk of all colorectal cancers (HR 0.79, 95% CI 0.65-0.95) and for colon cancer (HR 0.79, 95% CI 0.64-0.98). A similar point estimate of association for vegetarian diets and rectal cancer risk is seen, but is not statistically significant (HR 0.76, 95% CI 0.49-1.17). **Table 3** presents hazard ratios for colorectal cancer for those covariates from Model 3 which demonstrated a significant association. It can be seen that a number of known risk factors did demonstrate an association in this analysis.

**Table 2.** Comparison of vegetarian with nonvegetarian dietary patterns with respect to incident cancers of the colon and rectum from a Cox proportional hazards regression model among participants in the Adventist Health Study 2.

| | Dietary Pattern | N | Cases | HR (95% CI) | p value[a] |
|---|---|---|---|---|---|
| Colorectal cancers | | | | | |
| Model 1[b] | Vegetarian | 40650 | 257 | 0.80 (0.67-0.96) | 0.017 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |
| Model 2[c] | Vegetarian | 40650 | 257 | 0.79 (0.65-0.95) | 0.013 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | 40650 | 257 | 0.82 (0.67-0.99) | 0.043 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |
| Colon Cancers | | | | | |
| Model 1[b] | Vegetarian | 40650 | 211 | 0.79 (0.65-0.97) | 0.021 |
| | Nonvegetarian | 37059 | 194 | 1 (reference) | ref |
| Model 2[c] | Vegetarian | 40650 | 211 | 0.79 (0.64-0.98) | 0.029 |
| | Nonvegetarian | 37059 | 194 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | 40650 | 211 | 0.83 (0.67-1.03) | 0.094 |
| | Nonvegetarian | 37059 | 194 | 1 (reference) | ref |
| Rectal Cancers | | | | | |
| Model 1[b] | Vegetarian | 40650 | 48 | 0.83 (0.55-1.25) | 0.371 |
| | Nonvegetarian | 37059 | 45 | 1 (reference) | ref |
| Model 2[c] | Vegetarian | 40650 | 48 | 0.76 (0.49-1.17) | 0.204 |
| | Nonvegetarian | 37059 | 45 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | 40650 | 48 | 0.75 (0.48-1.17) | 0.205 |
| | Nonvegetarian | 37059 | 45 | 1 (reference) | ref |

[a] p value for Wald chi-square test of beta coefficient in the Cox model.

[b] Adjusted by age (i.e. attained age as time variable), race (black, non-black), and sex (male, female).

[c] Adjusted as in model 1 and additionally by education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), moderate or vigorous exercise (none, ≤60 min/week, >60 min/week), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), family history of colorectal cancer (yes, no), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no), prior colonoscopy of flexible sigmoidoscopy (yes, no), supplemental calcium (yes, no), dietary energy (kcal), and hormone therapy among menopausal women (yes, no).

[d] Adjusted as in model 2 and additionally by BMI (<18.5, 18.5-24.9, 25-29.9, ≥30).

**Table 3.** Variables with a significant adjusted association with colorectal cancer incidence; all variables are from a single multivariate Cox proportional hazards regression model among participants in the Adventist Health Study 2[a,b].

| Covariate | Category | HR (95% CI) | p value |
|---|---|---|---|
| Dietary pattern | Nonvegetarian | 1 (reference) | ref |
| | Vegetarian | 0.82 (0.68-1.00) | 0.046 |
| Moderate/vigorous exercise | None | 1 (reference) | ref |
| | 1-60 min/week | 0.75 (0.60-0.95) | 0.015 |
| | >60 min/week | 0.75 (0.60-0.94) | 0.012 |
| Family history of colorectal cancer | No | 1 (reference) | ref |
| | Yes | 1.46 (1.14-1.87) | 0.003 |
| Sigmoidoscopy or colonoscopy | Never | 1 (reference) | ref |
| | Ever | 0.65 (0.54-0.78) | <.0001 |
| Taking a statin medication | No | 1 (reference) | ref |
| | Yes | 0.70 (0.53-0.94) | 0.016 |
| BMI | <18.5 | 1.13 (0.61-2.08) | 0.705 |
| | 18.5-24.9 | 1 (reference) | ref |
| | 25-29.9 | 1.19 (0.96-1.48) | 0.108 |
| | 30+ | 1.40 (1.09-1.79) | 0.008 |

[a] Additionally adjusted by age (i.e. attained age as time variable), race (black, non-black), and sex (male, female), education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), supplemental calcium (yes, no), dietary energy (kcal), and hormone therapy among menopausal women (yes, no). None of these additional variables demonstrated a significant association with the outcome.

[b] From a Cox model with single random imputation of missing values.

Tables 4-6 display a similar covariate adjustment modeling strategy as Table 2. Results are here reported based on Model 2 for each table. **Table 4** presents results of analyses comparing the adjusted hazard of all colorectal cancers for the four vegetarian dietary patterns separately compared to the nonvegetarian diet. Pesco-vegetarians have a significantly reduced adjusted hazard (HR 0.59, 95% CI 0.41-0.84). Lacto-ovo-vegetarians have a reduced effect estimate that approaches significance (HR 0.81, 95% CI 0.65-1.01). **Table 5** presents sex-specific results for the dichotomous vegetarian variable and all colorectal cancers. While not reaching statistical significance, effect estimates for men and women are similar. Similarly, **table 6** presents results stratified by race; point estimates for blacks and non-blacks are similar, though only statistically significant in non-blacks.

Results for the propensity score sensitivity analyses did not differ meaningfully from the results of the standard regression modeling strategy presented above. This was true for all outcomes, even when the number of events was limited. This was true for both effect estimates and confidence intervals.

**Table 4.** Comparison of several vegetarian with nonvegetarian dietary patterns with respect to incident colorectal cancers from a Cox proportional hazards regression model among participants in the Adventist Health Study 2.

| | Dietary Pattern | N | Cases | HR (95% CI) | p value[a] |
|---|---|---|---|---|---|
| Model 1[b] | Vegetarian | | | | |
| | Vegan | 5919 | 42 | 0.90 (0.64-1.25) | 0.519 |
| | Lacto-ovo | 22722 | 148 | 0.82 (0.67-1.02) | 0.073 |
| | Pesco | 7705 | 35 | 0.59 (0.41-0.84) | 0.004 |
| | Semi | 4304 | 32 | 0.95 (0.65-1.39) | 0.805 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |
| Model 2[c] | Vegetarian | | | | |
| | Vegan | 5919 | 42 | 0.84 (0.60-1.19) | 0.332 |
| | Lacto-ovo | 22722 | 148 | 0.81 (0.65-1.01) | 0.067 |
| | Pesco | 7705 | 35 | 0.59 (0.41-0.84) | 0.004 |
| | Semi | 4304 | 32 | 0.95 (0.64-1.39) | 0.773 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | | | | |
| | Vegan | 5919 | 42 | 0.91 (0.64-1.29) | 0.584 |
| | Lacto-ovo | 22722 | 148 | 0.84 (0.68-1.06) | 0.139 |
| | Pesco | 7705 | 35 | 0.61 (0.42-0.88) | 0.008 |
| | Semi | 4304 | 32 | 0.96 (0.66-1.41) | 0.838 |
| | Nonvegetarian | 37059 | 236 | 1 (reference) | ref |

[a] p value for Wald chi-square test of beta coefficient in the Cox model.

[b] Adjusted by age (i.e. attained age as time variable), race (black, non-black), and sex (male, female).

[c] Adjusted as in model 1 and additionally by education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), moderate or vigorous exercise (none, ≤60 min/week, >60 min/week), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), family history of colorectal cancer (yes, no), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no), prior colonoscopy of flexible sigmoidoscopy (yes, no), supplemental calcium (yes, no), dietary energy (kcal), and hormone therapy among menopausal women (yes, no).

[d] Adjusted as in model 2 and additionally by BMI (<18.5, 18.5-24.9, 25-29.9, ≥30).

**Table 5.** Comparison of vegetarian with nonvegetarian dietary patterns with respect to incident colorectal cancers, stratified by sex, from a Cox proportional hazards regression model among participants in the Adventist Health Study 2.

| | Dietary Pattern | N | Cases | HR (95% CI) | p value[a] |
|---|---|---|---|---|---|
| Men | | | | | |
| Model 1[b] | Vegetarian | 14268 | 102 | 0.84 (0.62-1.12) | 0.231 |
| | Nonvegetarian | 13035 | 86 | 1 (reference) | ref |
| Model 2[c] | Vegetarian | 14268 | 102 | 0.77 (0.56-1.05) | 0.094 |
| | Nonvegetarian | 13035 | 86 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | 14268 | 102 | 0.79 (0.57-1.09) | 0.148 |
| | Nonvegetarian | 13035 | 86 | 1 (reference) | ref |
| Women | | | | | |
| Model 1[b] | Vegetarian | 26384 | 155 | 0.78 (0.62-0.98) | 0.035 |
| | Nonvegetarian | 24025 | 150 | 1 (reference) | ref |
| Model 2[e] | Vegetarian | 26384 | 155 | 0.81 (0.63-1.02) | 0.077 |
| | Nonvegetarian | 24025 | 150 | 1 (reference) | ref |
| Model 3[d] | Vegetarian | 26384 | 155 | 0.84 (0.66-1.07) | 0.159 |
| | Nonvegetarian | 24025 | 150 | 1 (reference) | ref |

[a] p value for Wald chi-square test of beta coefficient in the Cox model.

[b] Adjusted by age (i.e. attained age as time variable) and race (black, non-black).

[c] Adjusted as in model 1 and additionally by education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), moderate or vigorous exercise (none, ≤60 min/week, >60 min/week), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), family history of colorectal cancer (yes, no), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no), prior colonoscopy of flexible sigmoidoscopy (yes, no), supplemental calcium (yes, no), and dietary energy (kcal).

[d] Adjusted as in model 2 and additionally by BMI (<18.5, 18.5-24.9, 25-29.9, ≥30).

[e] Adjusted as in model 1 and additionally by education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), moderate or vigorous exercise (none, ≤60 min/week, >60 min/week), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), family history of colorectal cancer (yes, no), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no), prior colonoscopy of flexible sigmoidoscopy (yes, no), supplemental calcium (yes, no), dietary energy (kcal), and hormone therapy among menopausal women (yes, no).

**Table 6.** Comparison of vegetarian with nonvegetarian dietary patterns with respect to incident colorectal cancers, stratified by race, from a Cox proportional hazards regression model among participants in the Adventist Health Study 2.

| | Diet Pattern | N | Cases | HR (95% CI) | p value[a] |
|---|---|---|---|---|---|
| Blacks | | | | | |
| Model 1[a] | Vegetarian | 8025 | 41 | 0.88 (0.59-1.30) | 0.511 |
| | Nonvegetarian | 13018 | 65 | 1 (reference) | ref |
| Model 2[b] | Vegetarian | 8025 | 41 | 0.83 (0.55-1.24) | 0.357 |
| | Nonvegetarian | 13018 | 65 | 1 (reference) | ref |
| Model 3[c] | Vegetarian | 8025 | 41 | 0.81 (0.54-1.22) | 0.312 |
| | Nonvegetarian | 13018 | 65 | 1 (reference) | ref |
| Non-blacks | | | | | |
| Model 1[a] | Vegetarian | 32627 | 216 | 0.78 (0.64-0.96) | 0.017 |
| | Nonvegetarian | 24042 | 171 | 1 (reference) | ref |
| Model 2[b] | Vegetarian | 32627 | 216 | 0.78 (0.63-0.97) | 0.026 |
| | Nonvegetarian | 24042 | 171 | 1 (reference) | ref |
| Model 3[c] | Vegetarian | 32627 | 216 | 0.83 (0.67-1.03) | 0.092 |
| | Nonvegetarian | 24042 | 171 | 1 (reference) | ref |

[a] p value for Wald chi-square test of beta coefficient in the Cox model.

[b] Adjusted by age (i.e. attained age as time variable) and sex (male, female).

[c] Adjusted as in model 1 and additionally by education (up to high school graduate, trade school/some college/associate degree, bachelor degree or higher), moderate or vigorous exercise (none, ≤60 min/week, >60 min/week), smoking (never, quit ≥1 yr ago, current or quit < 1 yr ago), alcohol (none, <28 servings/mo, ≥ 28 servings/mo), family history of colorectal cancer (yes, no), history of peptic ulcer (yes, no), history of inflammatory bowel disease (yes, no), treated for diabetes mellitus within the last year (yes, no), taken aspirin at least weekly at least 2 of the last 5 years (yes, no), taken statins (i.e. HGMcoA reductase inhibitors) at least 2 of the last 5 years (yes, no), supplemental calcium (yes, no), prior colonoscopy of flexible sigmoidoscopy (yes, no), dietary energy (kcal), and hormone therapy among menopausal women (yes, no).

[d] Adjusted as in model 2 and additionally by BMI (<18.5, 18.5-24.9, 25-29.9, ≥30).

## Discussion

These findings together demonstrate an association between vegetarian dietary patterns and reduced risk of colorectal cancers. Significant reductions are also seen for the analysis specific to colon cancer; the analysis specific to rectal cancer is limited by power.

The study has a number of strengths. It is diverse in terms of age, sex, race, geographic location, and socioeconomic status, enhancing the relevance of its findings to the North American population. Homogeneity in certain domains of lifestyle, related to the shared religious affiliation of participants, particularly in terms of the low use of tobacco and alcohol, may enhance internal validity. Vegetarian/nonvegetarian status was determined by precise definitions based on the intake of multiple foods, rather than simple self-designation.

Limitations include the power restrictions of relatively early follow-up, particularly for separate analyses for the four vegetarian dietary patterns. Later follow-up will enhance power and allow for additional subgroup analyses. Diet was only assessed at baseline, though dietary change is less likely to be an important factor with early follow-up. The associations persisted when controlling for a number of potential demographic, hereditary, and lifestyle confounders. While analyses controlled for many potential confounders, unknown and unmeasured confounders are always possible. Measurement error may produce bias, although error in the classification of participants into major categories such as vegetarian and nonvegetarian seems unlikely to be a frequent occurrence, this being an advantage of analysis by dietary pattern over analysis by a specific food or nutrient.

These results seem consistent with prior evidence linking the consumption of red and processed meats to an increased risk of colorectal cancers[3,5,6]. While reductions in meat intake may be a primary reason for the reduced risk seen for vegetarians, an increase in various whole plant foods might also contribute. Orlich et al. describe the differences in food consumption for vegetarians compared to nonvegetarians[27]. In addition to reduced consumption of animal products, vegetarians eat less refined grains, added fats, sweets, snacks foods, and caloric beverages than nonvegetarians and increased amounts of a wide variety of plant foods[27]. Such a pattern might be expected to reduce hyperinsulinemia, which has been proposed as a possible mechanism by which diet may increase colorectal cancer risk[28-35]. The association between particular foods and colorectal cancers will be examined later in separate analyses. The relatively strong estimate of a protective association in pesco-vegetarians suggests future analysis by fish consumption and long-chain n-3 fatty acid consumption; the existing literature provides some (inconsistent) support for a possible protective association for fish consumption, particularly for rectal cancer[36]; evidence for n-3 fatty acid consumption[37] is limited and inconsistent. Adiposity could lie along a causal pathway from dietary pattern to colon cancer. Results from models including BMI (i.e. Model 3, Tables 2-5), however, did not differ strongly, suggesting that the association may be largely independent of BMI. It is also worth noting that the nonvegetarian group, against which comparisons were made, is already consuming a low-meat diet, with only 54.5 g/day total meat, including 16.3 g/day of red meat, on average. For comparison, in the NIH-AARP study, the lowest quintile of red meat consumption for a 2000 kcal/day diet was 17.8 g/day and the highest was 133.0 g/day[4]. Thus the AHS-2 nonvegetarians consumed slightly less red meat daily than the lowest quintile of the NIH-AARP cohort. Comparisons of the AHS-2 vegetarians against a more typical American high-meat-consumption dietary pattern might be expected to demonstrate stronger effects.

These findings differ markedly from those of the EPIC-Oxford cohort, the other major cohort examining the health effects of vegetarian dietary patterns. Not only did EPIC-Oxford investigators fail to find an apparent protective association for vegetarian diets and colorectal cancer, they actually found an increased risk for vegetarians, with a magnitude of approximately 50% increased risk[14]. The striking differences in results between these two studies is perplexing and in need of explanation. Biological differences between British vegetarians and North American Seventh-day Adventist vegetarians seem an unlikely explanation. Both studies attempted to control for a variety of important confounders. The approach to ascertaining vegetarian status differed in the two studies, but large measurement error of vegetarian status seems unlikely. Some of the discrepancy may be explained by dietary differences. AHS-2 cohort members eat substantially more fruits and vegetables than EPIC-Oxford participants[27,38]. AHS-2 vegans have substantially greater intake of both dietary fiber and vitamin C than their EPIC-Oxford counterparts[8,39]. Indeed, since foods containing dietary fiber may reduce the risk of colorectal cancer[2,40], such differences in diet between the groups may affect their risk. However, given that the evidence for a link between red meat and processed meat consumption and increased risk of colorectal cancer is considered convincing[2,7], the EPIC-Oxford results remain surprising. It suggests either that the potential beneficial effects of the elimination of red and processed meats by British vegetarians are overwhelmed by other potentially deleterious aspects of their vegetarian diets or that their meat avoidance is not beneficial. In fact, a UK pooling study including EPIC-Oxford cohort members did not demonstrate an association between red meat consumption and colorectal cancer risk[41]. Conversely, red meat consumption is associated with colorectal cancer risk in the entire European EPIC cohort[5]. Given currently available results, such divergent findings seem difficult to fully explain.

In conclusion, in a large North American cohort, we found that vegetarian dietary patterns were associated with lower risk of all colorectal cancer as well as colon cancer separately. The evidence that vegetarian diets similar to those of our study participants may be associated with a reduced risk of colorectal cancer, along with prior evidence of the potential reduced risk of obesity, hypertension, diabetes, and mortality, should be considered carefully in making dietary choices and in giving dietary guidance.

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# CHAPTER SIX

# CONCLUSION

Having reviewed the most relevant literature and presented the findings of the three investigations which comprise the heart of this work, I now pause to consider what contribution has been made by these analyses, what is the resultant state of knowledge about vegetarian dietary patterns in light of these findings, and what future studies may bring additional clarity. I begin with a brief summary of the findings in light of the stated aims of this dissertation.

## Summary

Given our improving but still limited understanding of vegetarian diets and their possible effects on important health outcomes, this thesis proposed a further study of vegetarian dietary patterns with the following stated aims: 1) to better characterize the vegetarian dietary patterns of the AHS-2 in terms of their patterns of food consumption, 2) to examine the association of vegetarian dietary patterns in AHS-2 with mortality from all causes and from major categories of causation, and 3) to examine the association of these dietary patterns with the risk of colorectal cancers. Having presented the relevant results in previous chapters, the following is a summary of the fulfillment of these aims.

Aim 1: While the five vegetarian-spectrum dietary patterns had been previously characterized in terms of their nutrient content, a detailed profile of foods consumed had not been published. This study created a system of major and minor food categories and quantified the level of consumption of each food category for the entire AHS-2 cohort and separately for the five dietary patterns. A comparison by dietary pattern clearly revealed that mean consumption differed substantially for the vegetarian groups compared to the nonvegetarians. In addition to lower consumption of the meats and other animal products by which they were defined, vegetarians consumed lesser amounts of sweets, added fats, refined grains, and non-water beverages and greater amounts of a wide variety of plant foods including legumes, meat analogues, nuts and seeds, whole grains, avocados, fruits, vegetables, and drinking water.

Aim 2: Results presented in chapter X demonstrate an association of vegetarian dietary patterns with reduced all-cause mortality in AHS-2. This was true for all vegetarians together as well as for vegans, lacto-ovo-vegetarians, and pesco-vegetarians separately. The results supported a reduction in mortality from cardiovascular diseases including ischemic heart disease, as well as from mortality from endocrine (primarily diabetes mellitus) and renal (primarily chronic renal failure) causes, but failed to show a significant reduction in mortality from all cancers combined. Results were much stronger in men, whereas in women they were often non-significant and closer to no association.

Aim 3: Lastly, as presented in chapter Y, there was an overall association between vegetarian dietary patterns and a reduction in risk of colorectal cancer in AHS-2. When all four vegetarian dietary patterns were considered together and compared to nonvegetarians, they had a reduction in risk of about 20%, after adjustment for plausible confounders. The effect estimate was similar for colon cancer and rectal cancer separately, though power was very limited for rectal cancer. The effect estimates were similar for men and women and for blacks and non-blacks, though power was limited in subgroup analysis. When the four vegetarian patterns were considered separately, pesco-vegetarians had a strong and significant reduction in risk, and lacto-ovo-vegetarians a moderate, nearly-significant reduction in risk.

## Limitations

Of course, the findings presented here in fulfillment of the aims of this thesis come with a number of methodological limitations, which in turn limit the conclusions that can be safely drawn. A number of limitations were mentioned in each relevant chapter, but they are summarized here in the context of the entire work.

The characterization of foods consumed is a rather straightforward description, but still comes with limitations. Firstly, these descriptive findings are limited to the AHS-2 population. They might be reasonably extrapolated to other North American Seventh-day Adventists, but other populations of vegetarians (and nonvegetarians) with different cultural and religious backgrounds and different motivations for their dietary choices might demonstrate very different patterns of foods consumed. As discussed, this appears to be the case for the British vegetarians of EPIC-Oxford. This inherent limitation also underscores the need for this analysis as an important context for comparing health-outcome results from diverse groups of vegetarians. Secondly, measurement of diet by questionnaire is imperfect; thus while, the relative comparisons are likely to be informative, absolute quantities of foods consumed cannot be taken as exact. Thirdly, there is no perfect, or even universally agreed, system for classifying foods into categories; the system presented here is a reasonable one, but other systems would present advantages as well as limitations. This makes direct comparisons problematic at times where classifications may differ. Lastly, summary measures, such as mean daily intake, are helpful in comparing groups by certain parameters (i.e. measures of central tendency, ranges, etc.), but they are limited in their ability to fully describe the variety of intakes of individuals in the group.

The limitations of the analyses of the relationship of vegetarian dietary patterns to health outcomes, mortality and colorectal cancer incidence in this case, are potentially more consequential and important. The imperfect measurement of diet by questionnaire mentioned above can lead to biased results and loss of power. However, this limitation is likely less of an issue for analysis by dietary pattern, where dietary measurement only needs to be good enough to place persons in the correct dietary pattern group. A related issue is that a person's dietary practices may change over time, whereas these findings are based on a single baseline measurement of usual dietary intake; repeated measurements of diet at intervals would be preferable. These studies are observational, and thus dietary pattern may be naturally associated with any number of other factors, which, if causally related to the outcome might confound the analysis. However, the modeling strategies employed adjusted statistically for most plausible confounders. Potential for uncontrolled confounding still exists, though substantial continued confounding does seem unlikely. Finite, and in some cases insufficient, power is a notable limitation for the analysis of these outcomes. Fewer events result in wider confidence intervals. Hence, a number of true but weaker associations may not have been detected. This is particularly important for more specific outcomes, analysis by the individual vegetarian dietary patterns, and subgroup analysis. Lastly, these results, which demonstrate that vegetarian dietary patterns are associated with reduced mortality and lower risk of colorectal cancer, may not hold in other populations of vegetarians, and may therefore have limited generalizability. This is mainly due to the potential for dietary variability within the patterns, and underscores the utility of the food consumption analysis to more clearly characterize the diets; this can be pointed to in interpretation of the outcome results, where it can be rightly said that "vegetarian dietary patterns like these" are associated with these health benefits. This limitation should be less relevant where the health association might be causally related to a reduction in meat intake, as this should be common to all vegetarian populations.

## Importance and Implications

The findings presented here represent an important contribution to our understanding of the potential health effects of vegetarian dietary patterns. The characterization of these dietary patterns in terms of foods consumed gives a better understanding of what is meant, on average, by "vegetarian diets" in the context of the Adventist Health Studies. When we examine the relationship of vegetarian dietary patterns to health outcomes in AHS-2 (and by reasonable extension, AHS-1), we now have a better idea of what those dietary patterns are like. I think that for the most part, a description of the patterns of food consumption is more useful in this regard than a nutrient profile for the same dietary pattern. It is hard to translate "a diet that was higher in vitamin C, several B vitamins, magnesium…but lower in calcium, vitamin D…etc." in a meaningful way (though such nutrient profiles, of course, have other important uses). Rather, for a result in which vegetarians are found to have a lower risk of disease X than nonvegetarians, we can say something like "those who on average ate less meat and animal products, refined grains, sweets, and non-water beverages but who ate more legumes, nuts, whole grains, fruits, and vegetables had a lower risk of disease X". This is a different (and more accurate) message than "those who ate less meat but ate whatever else they wanted had a lower risk of disease X"; without the clearer description of what the AHS-2 vegetarian diets are like, this latter message might be assumed by many people on reading or hearing that "vegetarians had a lower risk of diseases X". The foods-based message is also one that is relatively easy for people to understand and apply.

Thus, an important implication of these findings is better translational messaging of results related to vegetarian diets in AHS-2 and better health promotion and education regarding vegetarian diets and health. Findings from AHS-2 for vegetarian dietary patterns can be accurately and helpfully qualified by an "of this type" characterization. More broadly, in health promotion and education efforts in the area of vegetarian diets, a useful and important message can be framed as follows: "Are you choosing a vegetarian diet for health reasons? Do you want to choose a vegetarian diet that has been linked to many important health outcomes in scientific studies? If so, we recommend you adopt a vegetarian dietary pattern similar to that in the Adventist Health Study 2. The key components of this approach are as follows…". This links a public health nutrition and health promotion message closely and meaningfully to the most important scientific literature supporting that message. Of course, such recommendations should be qualified by the uncertainty in the scientific literature and by messages about the importance of nutrient adequacy or other important dietetic considerations.

The findings presented here about vegetarian dietary patterns and mortality are certainly important, and their contribution in the context of the existing evidence deserves careful thought. Both their consistency with and divergence from previous published findings merit comment. First, the results are quite consistent with many previous findings regarding vegetarian diets and mortality. As described in the literature review, consumption of meat and eggs was linked to increased mortality in the AMS (and green salad consumption to a decrease)[46]. Further analyses linked increasing meat intake with higher all-cause mortality in men[48,49]. Mortality from ischemic heart disease was higher in nonvegetarians (primarily in men)[47]. These AMS findings are all consistent with the current results: a decrease in overall mortality among vegetarians, the greatest effect being seen in cardiovascular disease (including ischemic heart disease) mortality, and effects being primarily in men. The vegetarian dietary pattern was also linked with increased longevity and decreased all-cause mortality in AHS-1[23,50]. Thus, there is substantial internal consistency across the more than 50 years of studies of North American Seventh-day Adventists regarding the association of vegetarian dietary patterns with decreased mortality. This consistency has been seen even as the studies have expanded in size, geographic and ethnic diversity, and quality. This type of consistency, along with rigorous attempts to adjust for potential confounding, certainly adds some credibility to the inference of a possible causal relationship between vegetarian dietary patterns and reduced mortality.

Such an inference may be somewhat challenged by inconsistencies with results of the British vegetarian studies. However, before examining that, it is important to note a major area of consistency. The individual British studies, the Adventist studies, and pooled analyses have all supported an association of vegetarian dietary patterns with lower ischemic heart disease mortality (though the finding was not significant in EPIC-

Oxford[56]). This consistent result, particularly in men, again supports a possible causal relationship between vegetarian dietary patterns and reduced deaths from ischemic heart disease. Given that, as discussed, British vegetarian dietary patterns may differ in important respects from Adventist patterns regarding the patterns of foods consumed, it tends to suggest that this consistent finding for IHD mortality may relate to the common element of these diets, a reduction in meat consumption. Despite this reduction in IHD mortality, some British vegetarian studies (and a pooled analysis[29]) have failed to show a significant reduction in all-cause mortality for vegetarians. The Health Food Shoppers study had very significant methodological limitations in its determination of vegetarian status, which may have resulted in a bias toward the null. The Oxford Vegetarian study did show a reduction in all-cause mortality for vegetarians, though the analytic approach was rudimentary[27]. Importantly, the EPIC-Oxford study showed a null result for the association of vegetarian diets to all-cause mortality[56]. It is important to note that the EPIC-Oxford cohort is a very healthy group overall, with greatly reduced mortality rates compared to the general population; so vegetarians are being compared to relatively healthy controls. However, this is generally a feature for all of the studies discussed here. The various Adventist and British/German cohorts have all had low SMRs for the cohort and are all considered “low-risk” and “healthy” populations. This is important, in that findings for vegetarians would generally be much more exaggerated if compared to nonvegetarians more typical of the general population. Again however, this is not unique to EPIC-Oxford, and is thus not a good explanation for the discrepancy. Other lifestyle differences between the populations might explain differences; if so, this would be equivalent to uncontrolled confounding in one or both cases, which might undermine causal inference. However, the most plausible explanation may be differences in diet between the British and American Adventist vegetarians. It may be that the foods substituted for meat in the diet have an important impact on all-cause mortality. Again, it is worth noting that other large cohorts have found evidence for a link between increased consumption of red and processed meats and higher mortality[58,59]; while this approach is different, these findings tend to support the plausibility of the AHS-2 findings for vegetarian diets and all-cause mortality.

In summary regarding vegetarian diets and mortality, it seems highly plausible that there may be a causal association of vegetarian diets (perhaps related to meat avoidance per se) and reduced ischemic heart disease mortality, particularly in men. It also seems plausible that certain types of vegetarian dietary patterns (similar to the Adventist patterns) may decrease overall mortality and thus improve longevity. If these plausible causal relationships are in fact true, the implications for public health are substantial. In this case, vegetarian diets of the Adventist variety should probably be promoted (at least as an option alongside other dietary patterns for which similar evidence may exist) for their overall health benefits. If adopted widely, such dietary approaches might then result in meaningful reductions in premature death at the population level.

The findings for vegetarian dietary patterns and colorectal cancer are also potentially important. The prior literature is not as robust for this endpoint. The AMS and pre-EPIC British and German studies only examined colorectal cancer mortality, which may be a poor surrogate for risk. Only AHS-1 and EPIC-Oxford were able to examine incident colorectal cancer cases. The published AHS-1 results did not analyze by dietary pattern per se, but rather by meat consumption; however, given that this compared weekly or greater meat consumption to no meat consumption and did not adjust for other dietary factors in the model, it was a nearly equivalent analysis[70]. The current findings are therefore consistent with prior AHS-1 findings for colorectal cancer. However, in the case of colorectal cancer incidence, analysis in the EPIC-Oxford cohort did not simply fail to show an association; rather, it demonstrated a significant association in the opposite direction, linking vegetarian dietary patterns to a higher risk of colorectal cancer[72]. Even here, there is one area of concordance: in both studies, pesco-vegetarians (or fish-eaters) had a reduced risk of colorectal cancer compared to nonvegetarians. However, the results for other vegetarians are starkly divergent. At the present time, there is no obvious explanation for such a divergence. Again, it may be that foods substituted for meat may have an important effect on this outcome. However, given that the literature linking red and processed meat intake to an increased risk of colorectal cancer is generally considered convincing due to its consistency in the literature, and given that vegetarians by definition (including as defined in EPIC-Oxford) eliminate red and processed meat from the diet; for vegetarians to then have a significant 50% relative increase in risk, the benefits from their avoidance of red and processed meat would have to be completely overwhelmed by contrary factors in the diet. This does not seem very plausible at present.

Given the disparities in the literature regarding vegetarian dietary patterns and colorectal cancer risk, it is difficult to resolve them and offer a coherent conclusion. At the present, it seems best to emphasize the consensus of evidence regarding the likely detrimental effects of red and processed meat, and also the likely beneficial effects of foods containing fiber, on colorectal cancer risk. It can then be said that the evidence from AHS-1 and AHS-2 is generally consistent with this consensus, and that vegetarian dietary patterns of the AHS variety seem a valid approach to possible risk reduction, consistent with all of this evidence. That leaves the EPIC-Oxford evidence as a generally contrary point, which may in the end be a chance outlier.

To summarize the importance and implications of the findings here reported, the following statements seem fair: These findings add to a consistent weight of evidence linking vegetarian dietary patterns to reduced ischemic heart disease mortality, primarily in men. The consistency of this finding across cohorts that differ in other important respects suggests that a causal relationship is likely. Thus, the adoption of vegetarian dietary patterns may be an important approach in the prevention of premature mortality from ischemic heart disease, especially in men. Vegetarian dietary patterns of the AHS variety--which are characterized not only by the absence of meat and a reduction in the consumption of other animal products, but also by a reduced consumption of added fats, refined grains, sweets, and non-water beverages and an increased consumption of legumes, nuts and seeds, meat analogues, whole grains, avocados, fruits, and vegetables—appear also to be linked with reduced overall mortality, and thus increased longevity. This same type of vegetarian diet appears to be linked to a reduction in risk for colorectal cancers, and this is consistent with evidence linking red and processed meat to higher colorectal cancer risk and foods containing fiber to lower risk. This adds to prior evidence linking these same vegetarian diets to reductions in obesity, hypertension, diabetes mellitus, and the metabolic syndrome. Given this, AHS-style vegetarian diets (with sensible attention to nutrient adequacy) can and should be recommended as a good dietary strategy (perhaps alongside other approaches with similarly robust scientific support) for living a longer and healthier life and one that might be expected to yield substantial benefits in reduced disease incidence and reduced premature mortality at the population level, if widely adopted.

## Future Work

Considering the state of knowledge regarding the health effects of vegetarian dietary patterns, including the incremental addition of the current findings, much remains to be learned. The following is an attempt to describe potential future approaches that might help to bring further clarity.

An important limitation of the current analyses for mortality and colorectal cancer incidence is that of insufficient power for many interesting analyses due to relatively early follow-up. Continued follow-up and analysis after an interval of several additional years might provide power for analysis by specific vegetarian dietary patterns (including meaningful comparisons between the vegetarian diets), by subgroup, and for less common outcome categories. However, longer follow-up times are of necessity more remote from the baseline measurement of diet, and subsequent dietary changes could lead to exposure misclassification. AHS-2 does not currently have funding for interval exposure measurements. Such funding is needed and should be pursued. If funding for a re-administration of the entire food frequency questionnaire should not materialize, a simplified approach might be considered. Brief questionnaires enquiring about a history of recent hospitalization and any new cancer diagnoses are mailed out to the cohort every two years. A few questions about meat, fish, dairy, and egg consumption could be included. While inadequate for many analyses, this should be adequate for an interval assessment of dietary patterns, and this would support analyses with time-varying exposure status.

Given that the vegetarian dietary patterns as defined may sum together a number of particular effects of specific foods, it will of course be important to do future analyses by food as well. Analysis by meat, adjusting for certain categories of plant food consumption, is an obvious relevant analysis. In addition, the apparently impressive associations of the pesco-vegetarian dietary pattern for both mortality and for colorectal cancer risk, suggest additional analysis be done for possible associations of total and fatty fish consumption with these endpoints.

One of the major elements of the preceding discussion has been an attempt to consider possible explanations for apparent discrepancies between AHS results and EPIC-Oxford results. The EPIC-Oxford results are surprising enough that a chance effect, though statistically quite improbable, could reasonably be suspected. If that were the case, no reanalysis of the published data would likely yield further clarity; however, reanalysis after several additional years would be expected to weaken or eliminate the adverse finding, if due to chance. Therefore, a reanalysis with later follow up of the EPIC-Oxford colorectal cancer and vegetarian diet association should be done. If it persists, non-chance explanations will have to be assumed. Beyond that, as previously discussed, differences for all-cause mortality between AHS-2 and EPIC-Oxford may be due to different food consumption patterns in the vegetarians of the two cohorts. To better investigate this possibility and to attempt to resolve some of the existing discrepancies, a joint analysis of the datasets should be attempted. This would not be a pooling for power. Rather, it would use appropriate dietary adjustments or reclassifications in an attempt to determine whether more specific dietary patterns or particular foods would have similar effects in both cohorts.

The characterization of the dietary patterns by foods consumed presented here provides a helpful context for the translation of diet-outcome findings and for health promotion efforts, as described above. However, the description, or message, becomes fairly complex and unwieldy when many qualifiers are added. One of the benefits of vegetarian dietary patterns is that they are relatively easy to understand. Most people, if asked to design a vegetarian diet, would know this roughly means avoiding meat and substituting some kind of plant foods. Other dietary patterns that have been described often suffer from a lack of clarity. The “prudent” patterns, which have emerged from some pattern analysis approaches, have no self-evident meaning and require fairly detailed description. Even the Mediterranean dietary pattern seems unclear to many people. The diets of people in countries around the Mediterranean Sea vary greatly, even if the focus is restricted to European Mediterranean areas. For example, the meat consumption in a number of Spanish and Italian cohorts in EPIC is much higher than in the Greek cohort[40]. For many health professionals, the Mediterranean diet has become a synonym for a list of dietary recommendation only loosely related to traditional Mediterranean cuisines. In contrast, for many average people, the term “Mediterranean” may signify typical Middle-Eastern cuisine, which may be appreciated but may seem very difficult for many to translate into a daily diet. Avoidance of this type of confusion and complexity is one of the benefits of the vegetarian dietary pattern. However, it seems from the literature and the current results that an AHS-type vegetarian dietary pattern may have important health advantages over an EPIC-Oxford-type vegetarian diet. It would be helpful if a single very simple and easy-to-understand qualifier could be added to the vegetarian dietary pattern schema that would be predictive of important outcomes. It seems to me that two related candidate qualifiers could be a “whole food” vegetarian dietary pattern or an “unrefined” vegetarian dietary pattern. I suggest that attention be given to developing these as categories or as indices that could be simultaneously analyzed alongside the current vegetarian dietary patterns, as defined. For example, if envisioning a dichotomous “refined” schema alongside a dichotomous vegetarian classification, then the categories “unrefined vegetarian”, “refined vegetarian”, and “unrefined nonvegetarian” could be compared to “refined nonvegetarian”. If such an approach was predictive, it could lead to easier messaging, needing only an explanation for what constitutes a “refined” diet. This might yield an easier, more useful health education approach than more complex dietary descriptions or indices.

Another future consideration would be exploring for heterogeneity of effect within the AHS-2 dietary patterns, as currently defined. Analysis by specific foods is one such approach that has already been mentioned. Another method could be a single-qualifier system, as described above. A third approach could be the use of data-driven pattern analysis approaches in conjunction with the existing AHS theory-driven diet categories. For example, the lacto-ovo-vegetarian category is rather large. Without evidence to support this claim, but based on personal familiarity with Seventh-day Adventist culture, I suspect that the vegan and pesco-vegetarian groups may be highly health-conscious, whereas the lacto-ovo-vegetarian group may be a mix of health-conscious vegetarians and cultural vegetarians. An approach such as cluster analysis may identify whether such natural groupings appear to exist, and if so, health-conscious lacto-ovo-vegetarians might be compared with vegans, for example. A similar approach could be taken with the nonvegetarians.

Since computer and internet technology is becoming increasingly widespread throughout the population, future nutritional epidemiology studies in Adventists should strongly consider the adoption of web-based dietary assessment tools. Such tools might arguably be able to blend aspects of a 24-hour recall with those of traditional FFQs to enhance accuracy of dietary measurement. Less debatable perhaps is the enhanced potential for repeated measurement at little marginal cost as well as easily imagined advantages for cohort communication and retention. Smart-phone technology may further enhance to potential of these approaches.

Based upon existing evidence, the most important effect of vegetarian dietary patterns may be that of the prevention (including possibly primary, secondary, and tertiary prevention) of ischemic heart disease and death from the same in men. This deserves further study. Mortality from ischemic heart disease has been reduced substantially in the general population in recent decades, and some of this likely is due to improvements in the acute treatment of myocardial infarction. In the face of effective treatments for a disease, disease-specific mortality is often a poor surrogate for incidence. Effective treatments would be expected to lessen differences in disease-specific mortality between exposure groups (e.g. vegetarian vs. nonvegetarian), assuming both exposure groups have access to this treatment. Given this, it is remarkable that an effect for vegetarian dietary patterns on cardiovascular mortality and ischemic heart disease mortality more specifically, continues to be detected. This suggests that the effect upon risk may be very strong and/or that there is an important modification of the course of already present disease. It seems very important to attempt to conduct an analysis in AHS-2 of the effect of vegetarian diets on IHD incidence, particularly in men. Separate analyses could look at the effects of vegetarian diets on IHD mortality in those with already diagnosed IHD. Funding for this research seems an important priority. Attempts at investigating the effect-modification by gender of the association of vegetarian diets with IHD mortality would be valuable, given that this sex specificity seems fairly consistent. Recent attention has been drawn to possible novel mechanisms that may relate meat and eggs in the diet to the pathophysiology of atherosclerosis, with colonic bacterial metabolism as a step in this mechanistic chain[92,93]. Measurement of serum TMAO and characterization of the microbiota of vegetarian and nonvegetarian men and women may be one approach to examining a possible sex-specific mechanistic difference[92,93]. In addition to ischemic heart disease mortality, the preliminary results reported here suggesting possibly important reductions in mortality attributable to diabetes mellitus and to chronic renal failure argue for further investigations of the effects of vegetarian dietary patterns on these disease processes.

## Concluding Remarks

Nutritional epidemiology is a challenging, though very important, discipline. It is difficult to establish causal relationships. For example, the evidence for a link between saturated fats (at least as a broad category) and ischemic heart disease, once thought to be strong, has more recently been called into question. Diet is a very complex exposure, and all approaches to analysis of diet and health outcomes have substantial shortcomings. Analysis by dietary pattern is no exception. Given this context, I would argue that vegetarian dietary patterns remain a valid and reasonable approach to dietary analysis. The consistent predictive value of the AHS dietary pattern schema supports its validity and continued usefulness. However, important discrepancies with EPIC-Oxford results for vegetarian dietary patterns underscore the point that all vegetarian diets are probably not equal in their health effects and preventive potential. Therefore, AHS results need important qualification and translation in their reporting. It needs to be consistently pointed out what type of vegetarian dietary approach has shown benefits and compared to what type of nonvegetarian dietary approach. If a simplified qualifier can be found as proposed above, much the better, but for now, a short but specific description of the food consumption patterns can be referenced.

In response to questions like "Should we all be vegetarians?"[94], AHS investigators should be clear that our findings for vegetarian dietary patterns do not directly support a positive answer, nor do I necessarily argue for this. Rather AHS-type vegetarian dietary patterns do represent an important, real-world dietary option that can be readily implemented and that has much scientific support. It is an option that should be promoted as a very good one, without arguing that it is necessarily the best. As to whether the public is well served by research and recommendations that identify dietary patterns with the label "vegetarian", this is unknown. It ultimately involves questions about what types of health promotion messages have the most positive and least negative consequences in terms primarily of health outcomes. Such questions about the effects of particular health and dietary messages involve aspects of psychology and behavior change, and while important, are not answerable from the kinds of evidence reviewed here. To a related question, "Is 'vegetarian dietary pattern' a reasonable, useful, valid label or message, based on current findings?" I would say yes, with the important qualifications previously discussed, and not necessarily claiming primacy over other dietary patterns for which support also exists.

Related questions might be asked. For example, "Will adding a small amount of meat to an otherwise equal diet have detrimental effects?" The results for analyses by AHS dietary patterns do not answer this question directly. Other types of analysis can be done which will address this; in particular an analysis by meat consumption variables, with zero meat consumption as the referent, and adjusting for a number of other potentially important dietary confounders. Conversely, questions about the effects of increasing consumption of particular plant foods, such as vegetables or legumes, adjusting for meat consumption may be examined. Modelling strategies may be devised to compare the relative strengths of associations for a given outcome with meat consumption and with plant food consumption. The dietary pattern approach considered here does not specifically address these types of questions, because a number of dietary factors vary simultaneously between the groups as previously discussed. Hence, analyses by specific food consumption with appropriate dietary adjustment strategies will be an important complement to dietary pattern analyses.,

Comparative analyses of the AHS vegetarian dietary patterns to other diet indices or dietary patterns may also be done, and may provide useful information. In particular, the strengths of association for the vegetarian dietary pattern approach discussed here for particular outcomes can be compared to that of a given alternative pattern schema or a dietary index. The degree of independence and potential for additivity for such approaches might also be assessed. Such approaches may provide additional information that might put the usefulness and importance of the vegetarian classification approach in context.  However, given the findings presented here, the dietary patterns as currently defined (especially when appropriately qualified by a description of the foods consumed), continue to represent an important approach for investigation of health outcomes and a valid dietary option that can be recommended for disease prevention.  Dietary guidelines should embrace such recommendations.

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# APPENDIX A

# VEGETARIAN DIETS IN THE ADVENTIST HEALTH STUDY 2: A REVIEW OF INITIAL PUBLISHED FINDINGS

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**Short running head:** Review of vegetarian diets in AHS-2

**Abbreviations:** AHS-2: Adventist Health Study 2; AHS-1: Adventist Health Study 1

## Abstract

The Adventist Health Study 2 is a large cohort well suited to the study of the relationship of vegetarian dietary patterns to health and disease risk.  Here we review initial published findings regarding vegetarian diets and several health outcomes. Vegetarian dietary patterns were associated with lower BMI, lower prevalence and incidence of diabetes mellitus, lower prevalence of the metabolic syndrome and its component factors, lower prevalence of hypertension, lower all-cause mortality, and, in some instances, lower risk for cancer.  Findings regarding factors related to vegetarian diets and bone health are also reviewed.  These initial results demonstrate important links between vegetarian dietary patterns and improved health.

## Introduction

Much of the current understanding of the health effects of vegetarian diets has come from a few cohort studies, especially among California Seventh-day Adventists and British vegetarians. The Adventist Health Study 2 (AHS-2) is a relatively new large cohort with a high proportion of vegetarians, which promises to add to that understanding. Here, we review the characteristics of AHS-2 and the initial published findings related to vegetarian diets.

### *Cohort Characteristics*

The Adventist Health Study 2 is a large North American cohort. Approximately 96,000 cohort members were enrolled throughout the United States and Canada between 2002 and 2007. Recruitment for the study was done in Seventh-day Adventist churches, and the vast majority of cohort members identify themselves as Adventists. There was a special effort to recruit black subjects (including African Americans and Caribbean Americans) as an important group that has been underrepresented in scientific studies of diet and health. About 27% of the cohort members are black in AHS-2, with the vast majority of others identifying as white. 65% of subjects are women. The mean age at enrollment was 57 years. A calibration sample of over 1100 participants was selected, using a two-stage weighted random process, with approximately equal numbers of blacks and whites, in which food and physical activity recalls, biometric measurements, and biological samples for laboratory analysis were obtained for the purpose of validation and calibration of the cohort questionnaire data. Butler et al. provide a more detailed description of the cohort's characteristics and recruitment(1).

### ***Dietary Patterns***

In the AHS-2, dietary patterns were defined along a vegetarian continuum, which can be thought of as an index of animal food avoidance. Cohort members were not asked to self-identify as vegetarians. Rather, they were categorized based on their reported intakes of key food items of animal origin. See **Table 1** for dietary pattern definitions. Defined thus, 7.7% of cohort members are vegan, 29.2% are lactoovovegetarian, 9.9% are pescovegetarian, 5.4% are semivegetarian, and 47.7% are nonvegetarian. For some analyses, these five dietary patterns were collapsed to yield fewer categories; for example, in some cases the four vegetarian categories (vegan, lactoovovegetarian, pescovegetarian, and semivegetarian) were combined together as "vegetarian". See **Table 2** for select demographic, lifestyle, and nutritional characteristics for each dietary pattern category at baseline.

**Table 1:** Definitions and prevalence of dietary patterns in the Adventist Health Study 2.

| | Dietary Patterns | | | | |
|---|---|---|---|---|---|
| | Vegan | Lactoovovegetarian | Pescovegetarian | Semivegetarian | Nonvegetarian |
| Prevalence (%) | 7.7 | 29.2 | 9.9 | 5.4 | 47.7 |
| All meats, including fish (servings) | <1/month | <1/month | ≥1/month | ≥1/month but ≤1/week | >1/week |
| Non-fish meat (servings) | <1/month | <1/month | <1/month | ≥1/month but ≤1/week | ≥1/month |
| Fish (servings) | <1/month | <1/month | ≥1/month | ≤1/week | any amount |
| Eggs and dairy products (servings) | <1/month | ≥1/month | any amount | any amount | any amount |

**Table 2:** Select baseline characteristics by dietary pattern category.

| | Vegan | Lactoovo vegetarian | Pesco vegetarian | Semi vegetarian | Non vegetarian |
|---|---|---|---|---|---|
| Age[1,2] | 57.9 ± 13.6 | 57.5 ± 13.9 | 58.8 ± 13.7 | 57.8 ± 14.1 | 55.9 ± 13.1 |
| Female sex[1] (%) | 63.8 | 64.9 | 68.0 | 69.7 | 65.3 |
| Race, black[1] (%) | 21.0 | 13.6 | 39.1 | 17.8 | 34.0 |
| Marital status, married[1] (%) | 75.6 | 76.3 | 73.1 | 71.5 | 70.3 |
| Education level[1] (%) | | | | | |
| High school or less | 16.7 | 13.9 | 18.4 | 21.3 | 24.4 |
| Trade, associate, some college | 39.4 | 35.7 | 38.1 | 39.2 | 42.2 |
| Bachelor degree | 24.4 | 25.3 | 23.0 | 21.3 | 19.2 |
| Graduate degree | 19.5 | 25.1 | 20.5 | 18.3 | 14.1 |
| Alcohol consumption[1] (%) | | | | | |
| None | 98.8 | 96.8 | 92.5 | 92.4 | 83.4 |
| Rare | 0.6 | 1.8 | 4.0 | 4.2 | 7.5 |
| Monthly | 0.2 | 0.5 | 1.1 | 1.1 | 3.1 |
| Weekly | 0.3 | 0.7 | 1.9 | 2.0 | 4.7 |
| Daily | 0.1 | 0.2 | 0.5 | 0.3 | 1.3 |
| Smoking[1] (%) | | | | | |
| Never | 85.0 | 88.2 | 84.1 | 81.4 | 75.7 |
| Former | 14.9 | 11.7 | 15.5 | 18.3 | 22.3 |
| Current | 0.1 | 0.1 | 0.4 | 0.3 | 2.0 |
| Exercise [1,3] (%) | | | | | |
| None | 15.1 | 17.3 | 18.0 | 20.6 | 23.4 |
| 1-20 min/wk | 16.2 | 18.6 | 16.8 | 20.5 | 20.0 |
| 21-60 min/wk | 16.1 | 16.5 | 16.2 | 16.1 | 15.8 |
| 61-150 min/wk | 27.8 | 26.8 | 27.5 | 24.5 | 23.6 |
| 151+ min/wk | 24.8 | 20.8 | 21.6 | 18.3 | 17.2 |
| Energy intake [1,2] (kcal/d) | 1897 ± 729 | 1912 ± 735 | 1939 ± 772 | 1720 ± 713 | 1884 ± 773 |
| Macronutrients (% of energy) [4,5] | | | | | |
| Carbohydrate | 58.1 ± 0.1 | 54.3 ± 0.1 | 54.5 ± 0.1 | 53.9 ± 0.1 | 51.4 ± <0.1 |
| Fat | 28.2 ± 0.1 | 31.9 ± 0.1 | 31.3 ± 0.1 | 32.2 ± 0.1 | 33.8 ± <0.1 |
| Protein | 13.6 ± <0.1 | 13.7 ± <0.1 | 14.2 ± <0.1 | 13.7 ± <0.1 | 14.7 ± <0.1 |
| Select nutrients [4,5] (g/d) | | | | | |
| Total fiber | 46.7 ± 0.1 | 37.5 ± 0.1 | 37.7 ± 0.1 | 34.9 ± 0.1 | 30.4 ± <0.1 |
| Saturated fatty acids | 11.6 ± 0.1 | 16.0 ± 0.1 | 15.8 ± 0.1 | 17.4 ± 0.1 | 19.9 ± <0.1 |
| Animal protein | 3.1 ± 0.2 | 12.2 ± 0.1 | 16.0 ± 0.2 | 17.6 ± 0.2 | 31.8 ± 0.1 |

[1] Results from reference 2. N=73,308. Adjusted for age, sex, and race (as appropriate) by direct standardization.

[2] Values are means ± SDs.

[3] Exercise defined as "vigorous activities, such as brisk walking, jogging, bicycling, etc, long enough or with enough intensity to work up a sweat, get your heart thumping, or get out of breath."

[4] Results from reference 3. N=71,751. Mean nutrient intake values standardized to 2000 kcal/day; adjusted for age, sex, and race.

[5] Values are means ± SEs.

## Health Outcomes

The main aims of AHS-2 are to examine the possible effects of dietary factors on the risk of specific cancers. These analyses for specific cancers will begin this year after the accrual of further incident cases to provide sufficient power. Meanwhile, several early publications from AHS-2 have examined the relationship of diet to certain other health outcomes. Here we review findings relating diet to prevalent obesity, prevalent metabolic syndrome, prevalent hypertension, prevalent diabetes mellitus, incident diabetes mellitus, bone density and fracture risk, mortality, and incident cancer (considered as all cancers combined and by organ system). **Table 3** provides a summary of selected results.

**Table 3:** Summary of the association of vegetarian dietary patterns with selected health outcomes in Adventist Health Study 2.

| | Dietary Patterns | | | | |
|---|---|---|---|---|---|
| Health Outcome[1] | Vegan | Lactoovo vegetarian | Pescovegetarian | Semivegetarian | Nonvegetarian |
| Cross-sectional findings | | | | | |
| BMI[2] (4) ($kg/m^2$) | 23.6 ± 4.4 | 25.7 ± 5.1 | 26.3 ± 5.2 | 27.3 ± 5.7 | 28.8 ± 6.3 |
| Diabetes[3], (4) [OR (95% CI)] | 0.51 (0.40,0.66) | 0.54 (0.49,0.60) | 0.70 (0.61,0.80) | 0.76 (0.61,0.80) | Referent |
| Prevalence (%) | 2.9 | 3.2 | 4.8 | 6.1 | 7.6 |
| Hypertension, [OR (95% CI)] | | | | | |
| Non-blacks[4] (5) | 0.37 (0.19,0.74) | 0.57 (0.36,0.92) | 0.92 (0.70,1.50) | | Referent |
| Blacks[5] (6) | 0.56 (0.36,0.87) | | 0.94 (0.54,1.63) | Not reported | Referent |
| Metabolic syndrome[6,7] (7) [OR (95% CI)] | 0.44 (0.30,0.64) | | Not reported | | Referent |
| Prevalence[6] (%) | 25.2 | | 37.6 | | 39.7 |
| Prospective findings | | | | | |
| Diabetes[8], (8) [OR (95% CI)] | 0.38 (0.24,0.62) | 0.62 (0.50,0.76) | 0.79 (0.58,1.09) | 0.49 (0.31,0.76) | Referent |
| *n* | 3545 | 14,099 | 3644 | 2404 | 17,695 |
| Incident cases (%) | 0.54 | 1.08 | 1.29 | 0.92 | 2.12 |
| All cancers[9], (9) [HR (95% CI)] | 0.84 (0.72,0.99) | 0.93 (0.85,1.02) | 0.88 (0.77,1.01) | 0.98 (0.82,1.17) | Referent |
| *n* | 4922 | 19,735 | 6846 | 3881 | 33,736 |
| No. of events | 190 | 878 | 276 | 182 | 1413 |
| All-cause mortality[10], (2) [HR (95% CI)] | 0.85 (0.73,1.01) | 0.91 (0.82,1.00) | 0.81 (0.69,0.94) | 0.92 (0.75,1.13) | Referent |
| *n* | 5548 | 21,777 | 7194 | 4031 | 35,359 |
| No. of events | 197 | 815 | 251 | 160 | 1147 |

[1] Numbers in parentheses are reference numbers.
[2] Values are means ± SDs.

**Table 3:** Summary of the association of vegetarian dietary patterns with selected health outcomes in Adventist Health Study 2. (continued)

[3] Logistic regression model, adjusted for age, sex, race, BMI, physical activity, education, income, sleep, television watching, and alcohol consumption.

[4] Pescovegetarians and semivegetarians considered together as partial vegetarians, due to small numbers of both categories. Logistic regression model, adjusted for age, gender, and exercise.

[5] Vegans and lactoovovegetarians considered together as vegetarians, due to the small number of vegans. Logistic regression model, adjusted for age, gender, education, and physical activity.

[6] Vegans and lactoovovegetarians considered together as vegetarians, due to the small number of vegans; pescovegetarians and semivegetarians considered together as semi vegetarians, due to the small number of both categories.

[7] Logistic regression model, adjusted for age, sex, ethnicity, physical activity, smoking, alcohol consumption, and dietary energy.

[8] Logistic regression model, adjusted for age, sex, race, BMI, physical activity, education, income, sleep, television watching, smoking, and alcohol consumption. (2-yfollow-up.)

[9] Cox proportional hazards regression model, adjusted for age, race, family history of cancer, education, smoking, alcohol consumption, age at menarche, pregnancies, breast feeding, oral contraceptive use, hormone replacement therapy, and menopausal status. (4.14-y average follow-up.)

[10] Cox proportional hazards regression model, adjusted for age, sex, race, smoking, exercise, personal income, educational level, marital status, alcohol, geographic region, menopause (in women), and hormone therapy (in postmenopausal women). (5.79-y average follow-up.)

### *Obesity*

As in earlier studies (10-12), vegetarians in AHS-2 have lower body mass index levels. Among 60,903 participants, the crude mean baseline BMI (kg/m$^2$) was 23.6 for vegans, 25.7 for lactoovovegetarians, 26.3 for pescovegetarians, 27.3 for semivegetarians, and 28.8 for nonvegetarians (4). After adjustment for age, sex, and race, mean BMI was 24.1 for vegans, 26.1 for lactoovovegetarians, 26.0 for pescovegetarians, 27.3 for semivegetarians, and 28.3 for nonvegetarians among 73,308 participants(2).

### *Metabolic Syndrome*

Rizzo et al. examined the relationship of dietary patterns to metabolic syndrome and its component risk factors in the calibration sample of the AHS-2 (n=773). Diets were considered in three categories: vegetarian (vegan plus lactoovovegetarian), semivegetarian (pescovegetarian plus semivegetarian) and nonvegetarian. In ANCOVA analysis, adjusting for age, sex, ethnicity, smoking, alcohol intake, physical activity, and dietary energy intake, significant differences between the dietary groups were found for all the metabolic syndrome components except HDL (triglycerides, diastolic blood pressure, systolic blood pressure, waist circumference, BMI, and glucose), with vegetarians having more favorable levels in each case (7). Considering metabolic syndrome as a whole, the prevalence was 25.2%, 37.6%, and 39.7% for vegetarians, semivegetarians, and nonvegetarians respectively, and in logistic regression analysis adjusting for the same potential confounders, vegetarians had 0.44 (95%CI: 0.30,0.64) times the odds of having metabolic syndrome as nonvegetarians (7).

### *Hypertension*

Pettersen et al. (5) examined the relationship of dietary patterns to prevalent hypertension among whites in the calibration sample (n=500). Diets were considered in four categories: vegans, lactoovovegetarians, partialvegetarians (pescovegetarians plus semivegetarians), and nonvegetarians. In a logistic regression analysis controlling for age, gender, and exercise, the adjusted ORs of having hypertension were 0.37(95%CI: 0.19,0.74) and 0.57(95%CI: 0.36,0.92) for vegans and lactoovovegetarians, respectively, compared to nonvegetarians (5). Additional adjustment for BMI (a possible causal intermediate) attenuated the results to 0.53(95%CI: 0.25,1.11) and 0.86(95%CI: 0.51,1.45) respectively. A subsequent analysis (6) demonstrated similar findings in black subjects (N=592). In a logistic regression analysis adjusting for age, gender, education, and physical activity, the OR for prevalent hypertension among vegetarians (vegans and lactoovovegetarians combined) was 0.56 (95%CI: 0.36,0.87) compared to nonvegetarians.

### *Diabetes Mellitus*

The relationship of vegetarian diets to both prevalent and incident diabetes mellitus has been examined in AHS-2. Prevalence of diabetes (type II) was 2.9% among vegans, 3.2% among lactoovovegetarians, 4.8% among pescovegetarians, 6.1% among semivegetarians, and 7.6% among nonvegetarians (4). In logistic regression analysis, compared to nonvegetarians, the multivariate adjusted (for age, sex, ethnicity, education, income, physical activity, television watching, sleep habits, alcohol use, and BMI) odds ratio for prevalent diabetes (type II) was 0.51 (95%CI: 0.40,0.66) for vegans, 0.54 (95%CI: 0.49,0.60) for lactoovovegetarians, 0.70 (95%CI: 0.61,0.80) for pescovegetarians, 0.76 (95%CI: 0.65,0.90) for semivegetarians (4).

Among 41,387 participants who did not report having diabetes mellitus at baseline, diabetes incidence was calculated from a response to a follow-up questionnaire at two years. The percent who had reported developing diabetes was 0.54% in vegans, 1.08% in lactoovovegetarians, 1.29% in pescovegetarians, 0.92% in semivegetarians, and 2.12% in nonvegetarians (8). In multivariate adjusted (for age, gender, education, income, television watching, physical activity, sleep, alcohol use, smoking, and BMI) logistic regression analysis, the OR for developing diabetes compared to nonvegetarians was 0.38 (95%CI: 0.24,0.62) for vegans, 0.62 (95%CI: 0.50,0.76) for lactoovovegetarians, 0.79 (95%CI: 0.58,1.09) for pescovegetarians, and 0.49 (95%CI: 0.31,0.76) for semivegetarians (8). Similar analyses stratified by race found reductions in odds among blacks for the vegan 0.30 (95%CI: 0.11,0.84) and lactoovovegetarian 0.47 (95%CI: 0.27,0.83) dietary patterns and among non-blacks for the vegan 0.43 (95%CI: 0.25,0.74), lactoovovegetarian 0.68 (95%CI: 0.54,0.86) and semivegetarian 0.50 (95%CI: 0.30,0.83) dietary patterns(8).

### *Osteoporosis*

The relationship of diet to osteoporosis risk is complex, and scientific understanding of it is incomplete. In particular, there is conflicting evidence regarding the relationship of protein intake (particularly animal protein) with bone density and fracture risk (13-18). Thorpe et al. examined the relationship of protein-rich foods of both animal and plant origin to the incidence of wrist fracture over 25 years among 1865 women who were participants in both the AHS-1 and AHS-2 (19). Higher consumption of protein rich foods of both animal and plant origin were found to be protective. In Cox proportional hazards regression analysis, among those with the lowest consumption of animal protein (vegetarians), those who consumed protein-rich plant foods more than once per day had a hazard ratio of 0.32 (95%CI: 0.13,0.79) for wrist fracture compare to those consuming plant protein foods less than three times per week (19). Similarly, among those with the lowest consumption of plant protein foods, those consuming meat more than four times per week had a hazard ratio for wrist fracture of 0.20 (95%CI: 0.06,0.66) compared with those not consuming meat (19).

Dairy products are generally thought to be good sources of dietary protein and calcium, raising the concern that reduced dairy product consumption among vegetarians, particularly vegans, may increase the risk of osteoporosis. Many vegetarians (and many nonvegetarians) use soymilk or other types of milk substitutes to replace dairy consumption. Matthews et al. examined whether soymilk consumption might confer similar benefits on bone health as dairy product consumption (20). Among 337 postmenopausal white women from AHS-2 evaluated for osteoporosis by broadband ultrasound attenuation of the calcaneus, the multivariate adjusted OR for osteoporosis for those consuming one or more servings of dairy products per day compared to those consuming dairy less than twice per week was 0.38 (95%CI: 0.17,0.86) (20). These analyses come from a logistic regression model in which both soymilk consumption and dairy product consumption were included. The OR for those consuming one or more servings of soymilk daily compared to those not consuming soymilk was 0.44 (95%CI:

0.20,0.98) (20). Thus, soymilk appeared to be associated with improved bone health to a similar degree as dairy products, suggesting it may provide a useful alternative to dairy in certain vegetarian diets. This may be related to the protein content of soymilk and, in the case of many fortified soymilks, the calcium content. The protein content of unfortified soymilk is 3.27g/100g, as compared to 3.15g/100g for whole milk; the calcium contents of unfortified and fortified soymilks are 25mg/100g and 123mg/100g respectively, as compared to 113mg/100g for whole milk (21).

### *Cancer*

Tantamango-Bartley et al. have recently published an initial analysis of the association of dietary patterns with cancer incidence in AHS-2 (9). Because this was early follow-up, there was not yet sufficient power to analyze the effect on specific cancers. However, interesting results were demonstrated in analyses of all incident cancers and of cancers categorized by organ system. Among 69,120 participants included in the analysis there were 2939 incident cancers. In multivariate adjusted (for age, race, family history of cancer, eductation, smoking, alcohol, age at menarche, pregnancies, breastfeeding, oral contraceptives, hormone replacement therapy, and menopause status) Cox proportional hazards regression analyzes comparing all vegetarians combined (vegans, lactoovovegetarians, pescovegetarians, and semivegetarians) to nonvegetarians, significant reductions in risk were found for all cancers HR=0.92 (95%CI: 0.85,0.99) and gastrointestinal system cancers HR=0.76 (95%CI: 0.63,0.90) (9). When the four vegetarian groups were compared separately to the nonvegetarian referent group, reduced risk was found in vegans for all cancers

HR=0.84 (95%CI: 0.72,0.99) and female-specific cancers HR=0.66 (95%CI: 0.47,0.92) and in lactoovovegetarians for gastrointestinal system cancers HR=0.75 (95%CI: 0.60,0.92) (9).

### ***Mortality***

A longevity advantage for those consuming vegetarian diets was previously demonstrated in the AHS-1 cohort(12,22). On the other hand, a reduction in all-cause mortality has not been associated with vegetarian dietary patterns in the EPIC-Oxford cohort(23). Orlich et. al examined the possible association of vegetarian dietary patterns to all-cause mortality and broad categories of cause-specific mortality in AHS-2(2). After a mean follow-up of 5.79 years (N=73,308), Cox proportional hazards regression analysis (adjusting for age, race, sex, smoking, exercise, education, marital status, alcohol, geographic region, menopause, and hormone therapy) demonstrated reduced all-cause mortality for all vegetarians compared to nonvegetarians, HR=0.88 (95%CI: 0.80,0.97). For specific dietary patterns, the hazard ratios were 0.85 (95%CI: 0.73,1.01) for vegans, 0.91 (95%CI: 0.82,1.00) for lactoovovegetarians, 0.81 (95%CI: 0.69,0.94) for pescovegetarians, and 0.92 (95%CI: 0.75,1.13) for semivegetarians. Effects were stronger in men and less often significant in women. Apparent beneficial associations were seen in some cases for mortality from cardiovascular, renal, and endocrine diseases.(2)

## Discussion

Because of its relatively large number of vegetarians, AHS-2 is a valuable cohort for the study of the possible effects of vegetarian dietary patterns on various health outcomes. The initial published results, reviewed above, demonstrate a number of apparent health benefits of vegetarian diets. Vegetarian diets in AHS-2 are associated with lower BMI levels, lower prevalence of hypertension, lower prevalence of the metabolic syndrome, lower prevalence and incidence of diabetes mellitus, and lower all-cause mortality. Initial analyses also show possible moderate reductions in the rates of certain cancer outcomes for some vegetarians. The bone health research presented here links inadequate protein levels to an increased risk of osteoporosis and fractures; however, it appears to show that plant sources of protein, like animal sources, decrease this risk.

As with all observational research, caution must be exercised in inferring causation from the results reviewed here. While appropriate attempts at adjustment for possible confounders were made in each case, it remains possible that some uncontrolled confounding may explain all or part of these findings. Measurement error is another challenge and potential source of bias in nutritional studies(24), but this would seem less likely to affect analyses by broad dietary pattern than analyses according to the intake of specific foods or nutrients.

While large, high-quality clinical trials examining the effects of vegetarian dietary patterns on major health outcomes have not been conducted as they have for the Mediterranean dietary pattern(25,26), small interventional studies provide indirect support for some findings presented here, particularly in regard to reduced weight(27-

32), improvements in serum lipid levels(31-35), and improvements in control of diabetes mellitus(27,38,39) with vegetarian diets.

The dietary patterns described here are defined according to the avoidance of certain foods of animal origin. However, the demonstrated associations may not always be related to reduced animal product consumption. They may also result from an increase in nutritional components related to plant foods, such as the increased fiber intake (Table 2). There may also be considerable heterogeneity of food and nutrient consumption within each vegetarian-spectrum dietary pattern, as we have previously discussed(40), so additional analyses by food, nutrient, or dietary indices will be of value. As with all diets, vegetarian diets should be carefully planned for nutritional adequacy. Nutrients of possible concern for vegetarian diets include vitamin B12 (particularly for vegans), iron, calcium, zinc, vitamin D, and protein(41). Rizzo et. al analyzed the nutrient profiles of the five dietary patterns described here in detail(3) and reported considerable variation by diet pattern. In no case were mean values of potentially marginal nutrients less adequate among vegetarians than nonvegetarians, but some individuals in the tails of the distributions may have had inadequate intakes.

### ***Potential Mechanisms***

While analysis by dietary pattern is advantageous in terms of real-world relevance and avoids many of the problems of reductionist models, a major disadvantage of this approach is its remoteness from specific mechanistic hypotheses. Various mechanisms, known and unknown, may link vegetarian dietary patterns to improved health outcomes, and a full discussion of these is beyond the scope of this brief review; however, we offer a few comments.

Adiposity is a core feature of the metabolic syndrome and an important risk factor for diabetes mellitus, cardiovascular disease, and certain cancers. Thus, the stepwise increase of BMI levels from vegan (lowest) to nonvegetarian (highest) presented here is noteworthy and may serve as an important intermediate in pathways of causation leading from dietary pattern to disease. The reason for this BMI gradient is not well understood. Caloric intakes are similar among the 5 dietary pattern groups(3). Significant differences in BMI persist after control for both dietary energy intake and physical activity(7). Vegetarian diets may result in differences in energy absorption and utilization that lead to differences in BMI. The results for diabetes mellitus reviewed here are interesting in that significant reductions in risk for vegetarians remained after controlling for BMI. Some of this remaining effect may still be mediated by differences in adiposity not fully captured by BMI (central adiposity, visceral adiposity); however, mechanisms entirely independent of adiposity may also be in effect.

Differences in the intake of specific nutrients may mediate some of the effects of vegetarian dietary patterns. For example, vegetarians have higher intakes of potassium(3), considered an important micronutrient for the prevention of hypertension. Tantamango-Bartley et al. provide a discussion of many possible mechanisms linking vegetarian dietary patterns to reduced cancer risk(9); in particular, they discuss the possibility that increased soy consumption among vegetarians could be relevant to their finding of a reduction in risk for female-specific cancers among vegans(9).

### *Ongoing AHS-2 Research*

The primary aim of AHS-2 is to investigate potential connections between dietary factors and the risk of specific cancers. To this end, we are attempting record linkages with the cancer registries of all fifty states and all Canadian provinces, something that to our knowledge has not previously been done. This process is well advanced, and we anticipate important publications on the relationship of diet to specific major cancers starting in 2014. We are hopeful that these ongoing and future analyses will add to our understanding of the relationship of vegetarian dietary patterns to health and longevity.

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