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Fruit and Vegetable Intake and Mortality: Results from Two Prospective Cohort Studies of US Men and Women and a Meta-Analysis of 26 Cohort Studies

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Abstract

Background—Optimal intake levels of fruit and vegetables for maintaining long-term health is uncertain.

Methods—We followed 66,719 women from the Nurses' Health Study (1984-2014) and 42,016 men from the Health Professionals Follow-up Study (1986-2014) who were free from cardiovascular disease (CVD), cancer and diabetes at baseline. Diet was assessed using a validated semi-quantitative food frequency questionnaire at baseline and updated every 2 to 4 years. We also conducted a dose-response meta-analysis, including results from our 2 cohorts and 24 other prospective cohort studies.

Results—We documented 33,898 deaths during the follow-up. After adjustment for known and suspected confounding variables and risk factors, we observed nonlinear inverse associations of fruit and vegetable intake with total mortality and cause-specific mortality due to cancer, CVD and respiratory disease (all $P_{\text{nonlinear}}$ <0.001). Intake of approximately 5 servings per day of fruit and vegetables, or 2 servings of fruit and 3 servings of vegetables, was associated with the lowest mortality, and above that level, higher intake was not associated with additional risk reduction. Compared to the reference level (2 servings/day), daily intake of 5 servings of fruit and vegetables was associated with hazard ratios [95% confidence interval (CI)] of 0.87 (0.85-0.90) for total

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mortality, 0.88 (0.83-0.94) for CVD mortality, 0.90 (0.86-0.95) for cancer mortality, and 0.65 (0.59-0.72) for respiratory disease mortality. The dose-response meta-analysis that included 145,015 deaths accrued in 1,892,885 participants yielded similar results (summary risk ratio of mortality for 5 servings/day=0.87, 95% CI, 0.85-0.88; $P_{nonlinear}$ <0.001). Higher intakes of most subgroups of fruits and vegetables were associated with lower mortality except for starchy vegetables such as peas and corn. Intakes of fruit juices and potatoes were not associated with total and cause-specific mortality.

Conclusions—Higher intakes of fruit and vegetable were associated with lower mortality; the risk reduction plateaued at approximately 5 servings of fruit and vegetables per day. These findings support current dietary recommendations to increase intake of fruits and vegetables, but not fruit juices and potatoes.

Keywords

Fruit; Vegetable; Mortality; Cardiovascular disease; Cancer; Diet

Introduction

Suboptimal intake of fruit and vegetable ranked among the top dietary contributors to the burden of disease and premature death in the US[1] and worldwide.[2] Despite recommendations in dietary guidelines to increase fruit and vegetable intake,[3-5] the current average intake among US adults, one serving of fruit and 1.5 servings of vegetables per day, remains far from optimal.[6]

During recent decades, recommendations for fruit and vegetable intake have been evolving in the US. In the early 1990s, the '5-a-day' campaign was launched to increase daily intake of fruit and vegetables to five servings or more in the US.[7] In 2007, the '5-a-day' message was dropped in favor of the 'Fruit and Veggies - More Matters' campaign in the US. The Healthy US-Style Eating Pattern recommended by the 2015-2020 Dietary Guidelines for Americans contains 2½ servings of vegetables and 2 servings of fruit per day.[3] The recommended fruit and vegetable intakes also vary around the world. The World Health Organization,[8] the World Cancer Research Fund[9] and the National Health Service of England[10] recommend five servings of fruit and vegetables per day, while the recommendations are six servings per day in Denmark and 8.5 servings per day in Australia.[11, 12] These recommendations were largely based on studies that quantify the dose-response relationship between fruit and vegetable intake and disease risk. To comprehensively evaluate the net effects of fruit and vegetable intake on long-term health, information on mortality can be useful. However, evidence on the dose-response relationship between fruit and vegetable intake and mortality is limited and inconsistent. Recently, two meta-analyses investigated the dose-response relationship between fruit and vegetable intake and mortality, but reached different conclusions regarding the intake levels that were associated with the maximum benefits.[13, 14] Wang el al. suggested no further reduction in mortality among those who consumed more than five servings of fruit and vegetables per day,[14] whereas Aune et al. found that most of the reduction in mortality was achieved by five servings per day, but an additional small reduction was suggested up to daily intake of 10 servings.[13]

Current dietary recommendations generally treat all types of fruits and vegetables the same although they are heterogeneous in nutritional properties.[15-17] For example, the Dietary Guidelines for Americans recommend increasing intakes of dark-green, red and orange, and starchy vegetables equivalently.[3] In addition, various dietary recommendations include fruit juices and potatoes in the fruit and/or vegetable groups despite their relatively higher glycemic load and different nutrient content compared to other fruit and vegetables. Thus, it is important to investigate the potentially distinct health effects of various subgroups of fruit and vegetables, as well as fruit juices and potatoes.

We therefore examined the associations of fruit and vegetable intake with total and cause-specific mortality in two large ongoing prospective cohort studies with many repeated measurements of diet during up to 30 years of follow-up, the Nurses' Health Study (NHS) and Health Professionals' Follow-up Study (HPFS). We also conducted a dose-response meta-analysis that includes published data on fruit and vegetable intake and total mortality combined with results from the NHS and HPFS. We hypothesized that higher intakes of fruits and vegetables are associated with lower mortality in a non-linear dose-response manner.

Methods

Data Sharing

The data from the NHS and the HPFS are available through a request for external collaboration and upon approvals of a letter of intent and a research proposal. Details on how to request an external collaboration with the NHS and the HPFS can be found at https://www.nurseshealthstudy.org/researchers and https://sites.sph.harvard.edu/hpfs/for-collaborators/.

Study population

The NHS is a prospective cohort study that consisted of 121,700 registered female nurses aged 30 to 55 years in 1976. The HPFS is a prospective cohort study that recruited 51,529 male health professionals aged 40 to 75 years in 1986. For this analysis, the baseline was defined as 1984 for the NHS and 1986 for the HPFS, when comprehensive dietary questionnaires were first administered. At baseline and during the follow-up of both cohorts, questionnaires have been mailed to participants biennially to inquire about lifestyle risk factors, other exposures of interest, and newly diagnosed diseases. The end of follow-up was defined as 2014 for both cohorts. The cumulative follow-up of the two cohorts exceeds 90% of potential person-time. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Return of completed self-administered questionnaires was accepted by the institutional review boards as implied informed consent.

We excluded participants with a history of diabetes, cardiovascular disease (CVD) or cancer, missing information on fruit and vegetable intake, or implausible total energy intake (<800 or >4200 kcal/d for men and <600 or >3500 kcal/d for women) at baseline. After exclusions, the analytical population consisted of 66,719 women and 42,016 men.

Dietary assessment

Dietary information was collected at baseline and updated every 2 to 4 years with validated semi-quantitative food frequency questionnaires (SFFQs).[18] Participants reported their usual intake (never to ≥6 times per day) of a standard portion size (e.g., 0.5 cup of strawberries, 1 banana and 0.5 cup of cooked spinach) of fruit and vegetables over the preceding year on each SFFQ. Frequencies and portions of each individual fruit and vegetable item were converted to average daily intake for each participant. The reproducibility and validity of these SFFQs in measuring food intake have been documented in detail.[18] The SFFQ performed reasonably well in ranking intakes of individual fruit and vegetable [19, 20]. For example, the average Pearson correlation coefficients corrected for within-person weekly variation comparing SFFQ-measured intakes to those measured by multiple 7-day food records was 0.74 for fruits and 0.46 for vegetables in our previous validation study in the HPFS [20]. Nutrient values were calculated based on the Harvard University Food Composition Database, which is updated every 4 years [21]. We calculated average daily nutrient and total energy intakes by multiplying the frequency of intake of each item by its nutrient content and summing across all foods. For this analysis, we used dietary information collected a total of eight times in the NHS and seven times in the HPFS. To assess the overall quality of diet, we applied a modified version of the Alternate Healthy Eating Index[22] (excluding components for fruit, vegetables and alcohol) that scored eight components of a healthy dietary pattern including whole grains, sugar-sweetened beverages and fruit juice, nuts and legumes, red/processed meat, *trans* fat, long-chain n-3 polyunsaturated fatty acids, polyunsaturated fatty acids and sodium.

Ascertainment of death

We performed systematic searches of state vital records and the National Death Index, supplemented by reports from family members or postal authorities. More than 98% of the deaths in each cohort were identified.[23] The classification of the cause of death was mostly based on review of medical records. A physician reviewed medical records and death certificates to classify the cause of death according to the eighth and ninth revisions of the International Classification of Diseases.

Statistical analysis

To best represent long-term intake and dampen within-person variation in the NHS and HPFS cohorts, we calculated cumulative average intakes of fruit and vegetables up to the start of each two-year follow-up interval. The main exposures of interest included intakes of fruit and vegetables combined, total fruits, and total vegetables. In this study, tofu and soybeans, French fried potatoes, whole or mashed potatoes, juices and foods with small serving sizes (red chili sauce, garlic, and mushrooms) were not included in the fruit and vegetables. Because the diagnosis of intermediate outcomes, including hypertension, hypercholesterolemia, diabetes, CVD, and cancer, in a follow-up cycle resulted in a subsequent change in fruit and vegetable intake, we stopped updating diet before the diagnosis of an intermediate outcome. Secondarily, we analyzed subgroups of fruit and vegetables, including green leafy vegetables, non-starchy vegetables, starchy vegetables, cruciferous vegetables, citrus fruit, and vitamin C rich and β carotene rich fruit and vegetables. We also examined the associations of intakes of fruit juices and potatoes with mortality in secondary analyses. We categorized intakes of fruit and vegetables and their subgroups, fruit juices and potatoes into quintiles, quartiles or tertiles based on their population distributions.

Person-years of follow-up were calculated from baseline to the earliest of time of death, loss to follow-up or the end of follow-up. Cox proportional hazards models were applied to estimate hazard ratios (HRs) and their 95% CIs of mortality comparing participants in each category to the lowest category of intake with simultaneous adjustment for age, race/ethnicity, physical activity level, smoking status, alcohol intake, multivitamin use, aspirin use, family histories of myocardial infarction, diabetes and cancer, total energy intake, menopausal status and hormone use in women, baseline body-mass index (BMI), baseline histories of hypertension and hypercholesterolemia, and the modified Alternate Healthy Eating Index. To quantify a linear trend across categories of intake, we assigned the median within each category and modeled this variable continuously; the Wald test was used for statistical significance. We examined the possibly non-linear relation between fruit and vegetable intake and mortality non-parametrically with restricted cubic splines with 3 knots [24] and used 2 servings of fruit and vegetables/day, 0.5 servings of fruit/day and 1.5 servings of vegetables /day as reference levels for calculating relative risk. We tested nonlinearity in the dose-response relationship between fruit and vegetable intake and mortality by comparing the model with only the linear term to the model with the linear and the cubic spline terms and using the likelihood ratio test. Although a significant *P*-value for nonlinearity indicated that a nonlinear dose-response relationship fitted the data better than a linear relationship, we also presented *P*-values for linearity for the purpose of comparison with previous publications. We examined whether the association between fruit and vegetable intake and mortality varied by subgroups defined by smoking status, baseline age, baseline BMI, and baseline histories of hypercholesterolemia and hypertension. The interaction between these stratification variables and intake level was evaluated using the likelihood ratio test for the cross-product terms of dichotomous stratification variables and indicator variables for quintiles of fruit and vegetable intake. We performed sensitivity analyses to test the robustness of our findings. First, we conducted lagged analyses by excluding the first 4 years of follow-up data and adding a 4-year lag period between assessment of dietary intake and each follow-up period to address concern that chronic disease occurrence in the years that preceded death may influence dietary behavior. Second, we continued updating diet and repeated the dose-response analysis instead of stopping updating diet before the diagnosis of an intermediate outcome. Third, we examined the dose-response relationship of fruit and vegetable intake assessed at baseline with total mortality. Lastly, we repeated the doses-response analysis in a study population without excluding participants with histories of CVD, cancer and diabetes at baseline and further adjusted for the baseline histories of the three diseases in the model. An inverse-variance-weighted fixed-effect meta-analysis was used to combine the results across the two cohorts. We performed the data analyses using SAS software version 9.4 (SAS Institute, North Carolina) at a two-tailed α value of 0.05.

Dose-response meta-analysis

We performed systematic searches in Medline and Embase (through September 2018) using both truncated free texts and Mesh terms relevant to "Fruit", "Vegetables", "Death", and "Mortality " (Table I in the Supplement). In addition, we manually searched the bibliographies of key retrieved articles and relevant reviews. The included studies met the following criteria: 1) prospective design, 2) fruit and /or vegetable intake as exposure, 3) total mortality as the outcome, 4) detailed information on dietary assessment method, 5) at least three categories of fruit and/or vegetable intake, 6) relative risks (RRs) and the corresponding confidence intervals (CIs) available, and 7) description of covariables in the statistical models available. The data extraction was done by two authors (DDW and YL) independently. The following information was extracted: author, year of publication year, cohort name, country /region, length of follow-up period, sample size, baseline age, number of deaths, dietary assessment method, fruit and vegetable intake categories/levels, RRs (95% CIs) and covariables in the fully adjusted model. To assess the risk of bias of the included studies, we used the Newcastle-Ottawa scale[25, 26]. We assigned the reported median to each intake category. If median values of each category were not reported, we assigned the midpoint of the lower and upper bounds. If the highest /lowest category of intake was open-ended, we used the width of the adjacent interval to calculate an upper or lower cut-off of the category. We converted fruit and vegetable intake in grams into servings using 80 g as a standard serving size. To examine the association between fruit and vegetable intake and total mortality, we applied a two-stage random-effects dose-response meta-analysis developed by Greenland and Longnecker[27] with the use of restricted cubic splines to flexibly model potentially nonlinear associations.[28] The first stage of the meta-analysis estimated the dose-response association between fruit and vegetable intake and the log RRs in each included study. The study-specific estimates were then combined in the second stage of this meta-analysis. The reference intake levels used in this dose-response meta-analysis were the same as those used in the restricted cubic spline models in NHS and HPFS. We applied the method described in Greenland and Longnecker[27] to convert RRs associated with categories of fruit and vegetable intake into RRs associated with a 1-serving increment in fruit and vegetable intake as inputs for the following small sample bias analysis and meta regression. Given that the conversion was based on an assumption of linear dose-response relationship, RRs generated by the conversions tended to approach the null if the actual dose-response relationship was nonlinear. We assessed bias due to small studies by using Begg’s test and Egger’s test, and visual appreciation of a funnel plot. When significant bias due to small studies was present, we examined the dose-response relationship between fruit and vegetable intake and total mortality after excluding studies with less than 500 deaths. We quantified the proportion of the total variation due to between-study heterogeneity using I^2 and the Cochran’s Q test. When heterogeneity was considered to be present, we conducted meta-regressions to explore potential sources of heterogeneity among characteristics of included studies including study quality (Newcastle-Ottawa scale), dietary assessment tools [food frequency questionnaires (FFQs) vs. other dietary assessment tools], range of intake level and statistical adjustment for confounding factors, follow-up time, and number of dietary assessments (baseline only compared with repeated measures). We conducted this meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[29] (Table II in the Supplement) and using R software version 3.6.1 (R Foundation for Statistical Computing).

Results

Characteristics of study population

During 30 years of follow-up in the NHS (1,822,058 person-years), we documented 18,793 deaths; during 28 years of follow-up in the HPFS (1,033,007 person-years), we documented 15,105 deaths. Participants with a higher intake of fruit and vegetables were older and more likely to use multivitamin, and had higher total energy intake, dietary quality, physical activity level and prevalence of hypercholesterolemia, but were less likely to be current smoker and had lower alcohol intake (Table 1). In women, fruit and vegetable intake was positively associated with prevalence of current menopausal hormone use and family histories of myocardial infarction, diabetes, and cancer. The average intakes of fruit and vegetables were generally stable over time in the two cohorts (Figure I in the Supplement).

Fruit and vegetable intake and total mortality in NHS and HPFS

Table 2 shows a nonlinear inverse association between intake of fruit and vegetables and total mortality ($P_{\text{nonlinear}}$ <0.001). Compared to the lowest quintile of fruit and vegetable intake, HRs (95% CI) of total mortality were 0.95 (0.92-0.99) for the second quintile, 0.89 (0.86-0.92) for the third quintile, 0.88 (0.85-0.91) for the fourth quintile, and 0.89 (0.86-0.93) for the fifth quintile in the fully adjusted model. Intake of approximately 5 servings of fruits and vegetables daily was associated with the lowest total mortality and above that level, higher intakes were not associated with further risk reductions (Figure 1). The restricted cubic spline analysis yielded a HR of 0.87 (95% CI, 0.85-0.90) associated with comparing 5 servings/day of fruit and vegetable intake to the reference intake level (2 servings/day). The intakes of total fruits and total vegetables were each inversely associated with total mortality in a significantly nonlinear manner (both $P_{\text{nonlinear}}$ <0.001, Table 2 and Figure 1). The HRs of total mortality did not decrease further above approximately 2 servings of fruit and 3 servings of vegetables per day; the HRs (95% CI) were 0.88 (0.86-0.91) for 2 servings of fruit per day and 0.94 (0.92-0.97) for 3 servings of vegetables per day (reference intake levels: 0.5 servings of fruit/day and 1.5 servings of vegetables /day, Figure 1).The association between fruit and vegetable intake and total mortality was generally consistent across different subgroups defined by age, smoking, BMI, hypertension and hypercholesterolemia (all $P_{\text{interaction}}$ >0.05, Table III in the Supplement). The nonlinear dose-response relationships between intakes of fruit and vegetables remained largely unchanged in the four sensitivity analyses (Figure II in the Supplement).

Dose-response meta-analysis on fruit and vegetable intake and total mortality

The dose-response meta-analysis included 25 publications from 24 prospective cohort studies[30-53] and the results from the NHS and the HPFS (Figure III in the Supplement). The results from the Shanghai Women's Health Study were in two publications[45, 53]. During follow-ups ranging from 4.6 to 30 years, 145,015 deaths accrued in 1,892,885 participants from 29 countries / territories in North and South America, Europe, Asia, Africa and Australia (Table IV in the Supplement and Figures IV-VI in the Supplement). Based on the

Newcastle-Ottawa scale, 17 studies obtained a score of at least seven and were considered at low risk of bias (Table V in the Supplement). Similar to the findings in the NHS and HPFS, the lowest risk of total mortality was observed for a daily intake of approximately 5 servings of fruit and vegetables, 2 servings of fruit and 3 servings of vegetables, and above those levels, higher intake was associated with minimal additional risk reduction (all $P_{\text{nonlinear}}$ <0.001, Figure 2). The summary RRs (95% CI) were 0.87 (0.85-0.88) for 5 servings of fruit and vegetables per day, 0.88 (0.87-0.90) for 2 servings of fruit per day, and 0.93 (0.92-0.94) for 3 servings of vegetables per day (reference levels: 2 servings/day of fruit and vegetables, 0.5 servings/day of fruit, and 1.5 servings/day of vegetables). We found considerable between-study heterogeneity (Figure IV-VI in the Supplement), as well as evidence of bias due to small studies with smaller studies yielding more extreme estimates (Figures VII-IX in the Supplement). Differences in dietary assessment tools (FFQs vs. other tools), range of intake level and statistical adjustment for confounding factors were major sources of heterogeneity (Table VI in the Supplement). Studies that captured relatively wider range of long-term fruit and vegetable intake as measured by FFQs and sufficiently addressed the issue of confounding were more likely to identify non-linear dose-response relationships between fruit and vegetable intake and mortality. We found no evidence of significant bias due to small studies for the associations of fruit intake and vegetable intake with total mortality (Figures X-XI in the Supplement) and attenuated bias due to small studies for the association between fruit and vegetable intake and total mortality (Figure XII in the Supplement) after excluding studies with less than 500 deaths, while the observed nonlinear dose-response associations were largely unchanged after the exclusions (Figure XIII in the Supplement).

Fruit and vegetable intake and cause-specific mortality in NHS and HPFS

Similar to that with total mortality, the dose-response relationships of fruit and vegetable intake with cancer, CVD, and respiratory disease mortality were significantly nonlinear (Figure 1, all $P_{\text{nonlinear}}$ <0.001) and showed a threshold of approximately 5 servings per day. Compared to the reference intake level (2 servings/day), 5 servings of fruit and vegetable per day was associated with HRs (95% CI) of 0.88 (0.83-0.94) for CVD mortality, 0.90 (0.86-0.95) for cancer mortality, and 0.65 (0.59-0.72) for respiratory disease mortality. Participants who consumed about 2 servings of fruit and 3 servings of vegetables daily showed the lowest risks of cancer, CVD and respiratory disease mortality.

Intakes of most fruit and vegetable subgroups, including green leafy vegetables, non-starchy vegetables, cruciferous vegetables, citrus fruit, vitamin C rich and β carotene rich fruit and vegetables, were inversely associated with total mortality (Table VII in the Supplement), whereas a higher intake of starchy vegetables was not associated with a lower risk of mortality. Intakes of fruit juices and potatoes were not associated with total and cause-specific mortality.

Discussion

In the two prospective cohorts with many repeated measurements of diet and up to 30 years of follow-up, we observed that a higher intake of fruit and vegetables was associated a lower risk of total mortality and cause-specific mortality in a nonlinear manner. Our analysis in the NHS and the HPFS and in a meta-analysis of 26 prospective cohort studies documented that intake of approximately 5 servings of fruits and vegetables daily was associated with the lowest mortality, and higher intake was not associated with additional risk reductions in mortality. The thresholds of risk reduction in mortality were 2 servings daily for fruit intake and 3 servings daily for vegetable intake. Higher intakes of most subgroups of fruit and vegetable were inversely associated with mortality, whereas intakes of starchy vegetables, fruit juices and potatoes were not associated with mortality.

Our finding on fruit and vegetable intake and total mortality was consistent with a meta-analysis of 16 prospective cohort studies and a large investigation in 451,151 participants from 10 European countries, in which the largest risk reduction in total mortality was found for a daily intake of approximately 5 servings of fruit and vegetables.[14, 41] These nonlinear relationships with a threshold effect are biologically plausible because that the bioactive components of fruit and vegetables, such as carotenoids, vitamin C and polyphenols, have limits in absorption, transport, metabolism, or storage, and their effects may be mediated by enzyme activities that can be saturated.[54] In another recent meta-analysis, Aune et al. reported that a risk reduction was mostly achieved by five servings per day with additional but slight benefits up to 10 servings of daily intake of fruit and vegetables.[13] It should be noted that our updated meta-analysis incorporated more studies, including several recent large investigations[35, 43] and our two large cohorts, than the previous ones,[13, 14] rendering us a greater power to delineate a dose-response relationship.

Our study provided additional data supporting nonlinear associations with cause-specific mortality due to major chronic diseases, including cancer, CVD and respiratory disease, and maximal benefit with intakes of approximately 5 servings of fruit and vegetables per day also held for the cause-specific mortality. Consistent with previous studies on CVD mortality[14] and incidence of stroke[55] and coronary heart disease,[56] we found an inverse association between fruit and vegetable intake and CVD mortality. Fruit and vegetables are major sources of potassium. Increased intake of potassium intake, in particular a high potassium / sodium ratio, has been linked to low blood pressure[57]. In addition, other nutrients and bioactive compounds in fruit and vegetables, such as magnesium, fiber and polyphenols, may act synergistically or additively to delay the progression of atherosclerotic lesions, as well as reduce platelet aggregation, modulate lipid profiles and lower blood pressure.[58] Protective effects of fruit and vegetable intake against total cancer risk were uncertain, particularly for hormone dependent cancers such as breast and prostate cancer.[59] The updated report from the World Cancer Research Fund /American Institute for Cancer Research stated that evidence that high intakes of fruit and vegetables decrease the risk for cancers at different sites were only either ‘probable’ or ‘limited suggestive’.[9] Our data supported that high intake of fruit, but not vegetables, may confer a protective effect against cancer mortality. A possible explanation for this discrepancy is that the induction period for some cancers may be longer than the follow-up period in the previous studies because the development of cancer is a multistage process that takes place over several decades, while the follow-up in our cohorts might have reached the sufficiently long duration to detect the protective effects. In addition, recent evidence suggests that higher intakes of fruits and vegetables may specifically reduce subgroups of breast cancer that are more aggressive and likely to be lethal,[60] which may be missed in studies of cancer incidence.

Previous data on fruit and vegetable intake and mortality due to respiratory disease are sparse. A recent report from the European Prospective Investigation into Cancer and Nutrition found an inverse association between fruit and vegetable intake and respiratory disease mortality in men only,[61] while our data suggested a strong inverse association for respiratory disease mortality in both men and women. Several lines of evidence suggested that higher fruit and vegetable intake may improve lung function and prevent respiratory obstructive disease through anti-oxidative and anti-inflammatory pathways.[62, 63] In addition, our previous study found that a healthy dietary pattern high in fruit and vegetables was associated a lower risk of chronic obstructive pulmonary disease.[64] Of note, these findings are novel and therefore require confirmation in further studies. While some evidence suggests a role of fruit and vegetable intake in delaying cognitive function decline and preventing dementia,[65, 66] we did not find an association between fruit and vegetable intake and neurodegenerative disease mortality.

Our findings suggest that subgroups of fruits and vegetables may have heterogeneous health impacts. Higher intake of starchy vegetables may not confer the same health benefits as other fruits and vegetables. These findings are consistent with previous studies on multiple disease outcomes, including coronary heart disease and type 2 diabetes, as well as body weight and hypertension.[15, 17, 67, 68] The observed null association for intakes of starchy vegetables may be due to their higher glycemic load which has been related to elevated risks of major chronic diseases.[69] In addition, starchy vegetables such as peas and corn are often processed by canning in the US, which may lead to a pronounced loss of antioxidant activity.[70] Higher intakes of fruit juices and potatoes were not associated with decreased mortality. We previously linked higher intakes of potatoes and fruit juices to body weight gain and increase risk of type 2 diabetes.[17, 71] Beyond their high glycemic load values and reduced nutrient content during production, juices, as fluids, may lead to more rapid and pronounced increases in postprandial blood glucose and insulin than whole fruits and vegetables without significantly enhancing appetite.[72] It should be noted that certain types of juice, such citrus juice, may have higher levels of antioxidant activity and ability of lowering atherogenic lipids than other juices.[73] Similarly, potatoes have high glycemic load values due to their predominantly starch content.[74] Our findings do not support the current Dietary Guidelines for Americans and federal nutrition assistance programs' positions on treating all types of fruit and vegetables the same and including juices and potatoes into the fruit and vegetable groups, without considering their potentially differential nutritional properties and health effects.[3]

Our results have several limitations. First, the magnitude of the observed associations could be underestimated due to reverse causation, because people with chronic disease and poor health might change their diets toward a diet generally perceived to be healthier. However, we excluded participants with known major chronic diseases at baseline and stopped updating diet at the beginning of the interval in which participants had the intermediate disease outcome. In addition, our findings remain largely unchanged when we excluded the first 4 years of follow-up or added a 4-year lag period between dietary assessment and each follow-up period. Secondly, although our SFFQs collected detailed information on fruit and vegetable intakes, measurement errors are inevitable in estimates of food and nutrient intakes. It is possible that participants within the range of higher intake levels tended to over-report their fruit and vegetable intake, which may limit our ability to clearly distinguish the intakes of vs. higher than five servings per day. Therefore, we cannot entirely rule out the possibility of some modest benefits above five servings of fruit and vegetable intake per day, although the results for intake higher than five servings per day may be less robust. However, our adjustment for energy intake and use of prospectively collected, cumulatively averaged intake using many repeated dietary assessments reduced the impact of measurement errors.[18] Thirdly, even though we adjusted for many potential confounders, residual confounding could not be ruled out. Fourthly, because our study was observational in nature, causality cannot be established. However, confounding is likely to be better controlled in the NHS and HPFS than in most studies because of the relatively homogenous socioeconomic status of the study populations due to their similar education levels and occupations and the use of repeatedly measured confounding factors. In addition, our results were largely consistent with those from existing observational studies and randomized clinical trials on diet high in fruit and vegetables and major chronic diseases including CVD, diabetes and cancer[75-78]. Lastly, as a limitation shared by all meta-analyses on published data[79], the measurement of exposure, including the definitions of fruit and vegetables and their serving sizes and the dietary assessment tools, varied across the studies in our dose-response meta-analysis. However, complementary to the meta-analysis, our original data analysis in the NHS and the HPFS that defined fruit and vegetables using the same criteria and measured intake levels using the same tools yielded concordant results. The strengths of the current study included a large sample size, high follow-up, and repeated assessments of dietary and lifestyle variables during a long follow-up for up to three decades.

In summary, we found an inverse association between fruit and vegetable intake and mortality in two large prospective cohorts with detailed and repeated dietary measurements and long follow-up. The lowest risk of mortality was observed for approximately five servings/day of fruit and vegetable intake, but above that level, the risk did not decrease further. An updated meta-analysis of 26 prospective cohort studies including the Nurses' Health Study and Health Professionals' Follow-up Study yielded similar results. These findings support current dietary recommendations to increase intakes of fruits and vegetables, and that the succinct '5-a-day' message is consistent with available evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms:

NHS	Nurses' Health Study
HPFS	Health Professionals' Follow-up Study
CVD	cardiovascular disease
SFFQ	semi-quantitative food frequency questionnaire
HR	hazard ratio
CI	confidence interval
BMI	body mass index
RR	relative risk
FFQ	food frequency questionnaire

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Clinical Perspective

What Is New?

- A higher intake of fruit and vegetables was associated lower total and cause-specific mortality in a nonlinear manner in both an original data analysis in two prospective cohorts of US men and women and a meta-analysis of 26 prospective cohort studies.
- The lowest risk of mortality was observed for approximately 5 servings per day of fruit and vegetable intake, but above that level, the risk did not decrease further.
- The thresholds of risk reduction in mortality were 2 servings daily for fruit intake and 3 servings daily for vegetable intake.

What Are the Clinical Implications?

- These findings support current dietary recommendations to increase intakes of fruits and vegetables, and that the succinct '5-a-day' message is consistent with available evidence.

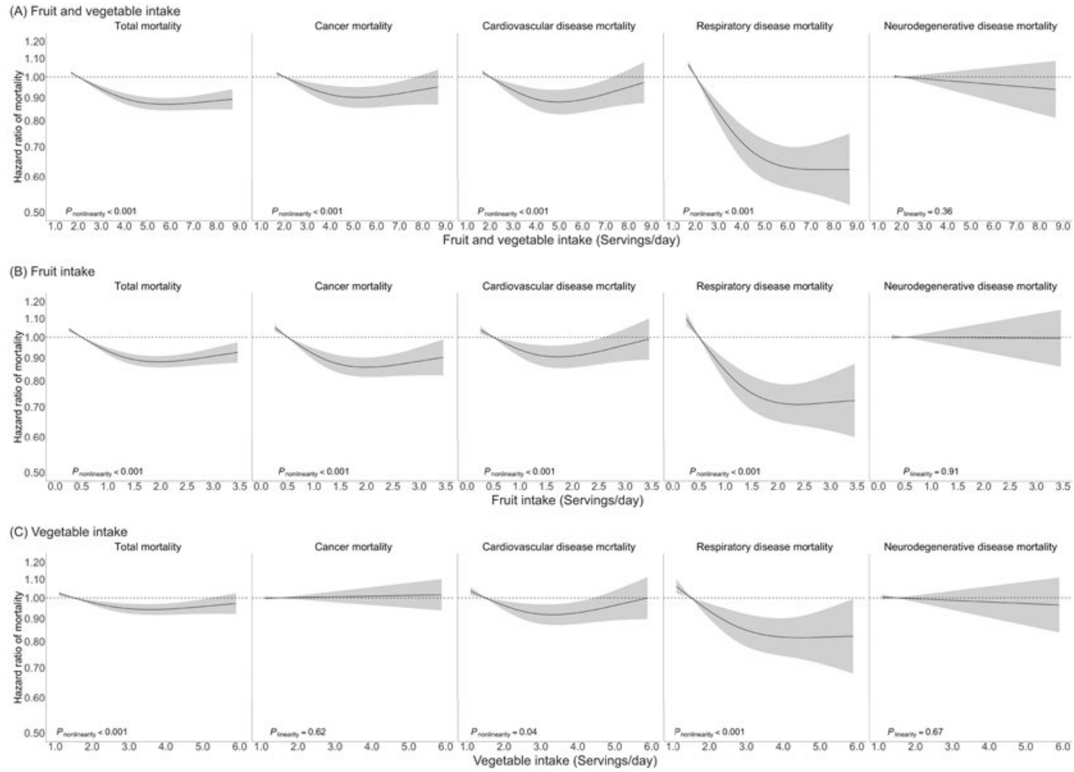

Figure 1.

Dose-response association between fruit and vegetable intake and mortality in the Nurses' Health Study and the Health Professionals Follow-Up Study. (A) Dose-response associations of combined fruit and vegetable intake with total and cause-specific mortality. (B) Dose-response associations of fruit intake with total and cause-specific mortality. (C) Dose-response associations of vegetable intake with total and cause-specific mortality.

Dose-response associations of fruit and vegetable intake with total and cause-specific mortality were estimated by restricted cubic spline Cox proportional-hazards model in a dataset that pooled data from both the Nurses' Health Study and the Health Professionals Follow-Up Study.

Multivariable model adjusted for age (in month), Caucasian (yes vs. no), moderate-vigorous physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, ≥6 hours per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, current ≥25 cigarettes/d), alcohol intake (women: 0, 0.1-4.9, 5.0-14.9, ≥15 g/d; men: 0, 0.1-4.9, 5.0-29.9, ≥30 g/d), multivitamin use (yes vs. no), current aspirin use (yes vs. no), family history of myocardial infarction (yes vs. no), family history of diabetes (yes vs. no), family history of cancer (yes vs. no), total energy intake (quintiles), menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users), baseline body-mass index (<23, 23-24.9, 25-29.9, 30-34.9, ≥35 kg/m^2), history of hypertension (yes vs. no), history of hypercholesterolemia (yes vs. no), the modified Alternate Healthy Eating Index (quintiles). All models, except that for total fruit and vegetable intake, also mutually adjusted for fruit intake and vegetable intake (in quintiles).

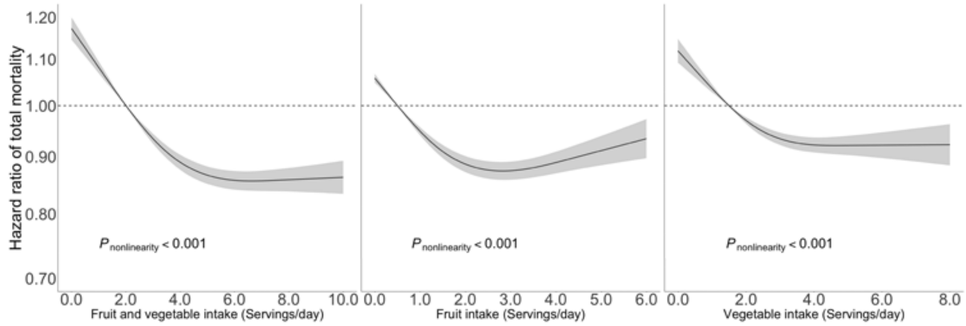

Figure 2.

Association between fruit and vegetable intake and total mortality in the dose-response meta-analysis based on 24 published studies, the Nurses' Health Study and the Health Professionals' Follow-Up Study. Dose-response relationship between fruit and vegetable intake and total mortality was estimated by the two-stage dose-response meta-analysis with the use of restricted cubic splines.

Table 1.

Age-adjusted characteristics of men and women across levels of fruit and vegetable intakes *.

	Quintiles of fruit and vegetable intake				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Nurses' Health Study					
Person-years	364165	364492	364462	364562	364377
Intake level, servings/day	2.0±0.5	3.3±0.3	4.2±0.3	5.3±0.4	7.9±1.9
Baseline age, year	48.5±7.0	49.2±7.1	49.8±7.1	50.3±7.1	51.1±7.0
Baseline BMI, kg/m^2	25.0±4.9	24.8±4.5	24.8±4.5	24.8±4.4	24.7±4.4
Alcohol, g/day	5.8±11.1	5.8±10.4	5.9±10.1	5.8±9.7	5.6±9.3
Modified Alternate Healthy Eating Index †	33.2±8.0	33.7±8.1	34.5±8.2	35.3±8.4	36.9±8.6
Moderate/vigorous physical activity, h/wk	2.3±1.9	2.5±2.0	2.8±2.0	3.0±2.1	3.5±2.4
Current smoking, %	17.9	13.2	11.3	9.3	8.1
Premenopausal, %	11.8	12.2	12.0	11.8	11.6
Current menopausal hormone use, %	25.2	26.4	27.5	28.1	28.3
Multivitamin use, %	51.7	55.0	56.2	57.7	58.8
Aspirin use, %	50.1	51.7	52.3	52.1	51.7
Family history, %					
Myocardial infarction	9.6	9.6	9.5	9.3	9.6
Diabetes	28.6	28.7	28.7	28.7	29.4
Cancer	13.6	14.0	14.4	14.7	15.4
Baseline history, %					
Hypercholesterolemia	8.9	7.8	7.0	7.1	7.7
Hypertension	24.2	20.4	18.1	17.6	18.1
Health Professionals Follow-Up Study					
Person-years	206434	206624	206764	206971	206214
Intake level, servings/day	1.9±0.5	3.2±0.3	4.2±0.3	5.4±0.4	8.4±2.4
Baseline age, year	50.1±8.7	51.0±8.9	51.7±9.1	52.4±9.2	53.4±9.4
Baseline BMI, kg/m^2	25.6±3.3	25.5±3.2	25.4±3.2	25.3±3.1	25.4±3.5
Alcohol, g/day	12.1±16.7	12±15.7	11.5±15.1	11.1±14.2	10.4±13.8
Modified Alternate Healthy Eating Index	32.1±7.7	33.8±7.6	34.7±7.6	36.1±7.7	37.7±7.5
Moderate/vigorous physical activity, h/wk	2.2±3.2	2.7±3.6	3.1±4.0	3.6±4.3	4.4±4.9
Current smoking, %	10.3	7.3	5.8	4.4	3.9
Multivitamin use, %	47.7	49.4	51.3	52.4	53.1
Aspirin use, %	53.1	54.4	54.4	53.7	51.2
Family history, %					
Myocardial infarction	31.0	31.3	31.3	31.6	33.3
Diabetes	18.9	20.5	20.7	20.4	20.5
Cancer	34.2	33.9	35.7	34.9	34.9
Baseline history, %					
Hypercholesterolemia	9.7	9.7	9.6	9.9	11.6

	Quintiles of fruit and vegetable intake				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Hypertension	18.9	18.3	17.0	16.4	18.2

*Values are means ± standard deviations for continuous variables and percentages for categorical variables. All variables except age were age-standardized.

†The modified Alternate Healthy Eating Index included eight component scores for whole grains, nuts and legumes, long-chain n-3 polyunsaturated fats, total polyunsaturated fats, sugar-sweetened beverage and juices, red/processed meat, trans fat and sodium.

Table 2.

Associations between fruit and vegetable intakes and total mortality in the Nurses' Health Study and the Health Professionals Follow-Up Study.

	Quintiles of intake					P_{trend}	
	Q1	Q2	Q3	Q4	Q5	Linear*	Non-linear†
All fruits and vegetables							
NHS							
Median (IQR), servings/day	2.1 (1.7-2.5)	3.3 (3.0-3.5)	4.2 (4.0-4.5)	5.3 (5.0-5.7)	7.3 (6.6-8.5)		
Deaths / person-years	3853/364165	3702/364492	3702/364462	3634/364562	3902/364377		
Incidence rate, per 10^4 person-years	106	102	102	100	107		
Age-adjusted model	Ref.	0.86 (0.82, 0.90)	0.78 (0.74, 0.81)	0.72 (0.69, 0.75)	0.72 (0.69, 0.75)	<.001	<.001
Multivariable-adjusted model	Ref.	0.96 (0.91, 1.00)	0.90 (0.86, 0.94)	0.87 (0.83, 0.92)	0.89 (0.84, 0.93)	<.001	<.001
HPFS							
Median (IQR), servings/day	2.0 (1.6-2.4)	3.2 (2.9-3.4)	4.2 (3.9-4.4)	5.4 (5.0-5.8)	7.6 (6.8-9.1)		
Deaths / person-years	2800/206434	2910/206624	2915/206764	3088/206971	3392/206214		
Incidence rate, per 10^4 person-years	136	141	141	149	164		
Age-adjusted model	Ref.	0.91 (0.86, 0.96)	0.81 (0.77, 0.86)	0.80 (0.76, 0.84)	0.80 (0.76, 0.84)	<.001	<.001
Multivariable-adjusted model	Ref.	0.95 (0.90, 1.00)	0.88 (0.83, 0.92)	0.89 (0.84, 0.94)	0.90 (0.85, 0.95)	<.001	<.001
Pooled							
Age-adjusted model	Ref.	0.88 (0.85, 0.91)	0.79 (0.77, 0.82)	0.75 (0.73, 0.78)	0.75 (0.73, 0.78)	<.001	<.001
Multivariable-adjusted model	Ref.	0.95 (0.92, 0.99)	0.89 (0.86, 0.92)	0.88 (0.85, 0.91)	0.89 (0.86, 0.93)	<.001	<.001
Fruits							
NHS							
Median (IQR), servings/day	0.4 (0.3-0.6)	0.9 (0.8-1.0)	1.3 (1.2-1.4)	1.8 (1.6-2.0)	2.7 (2.4-3.3)		
Deaths / person-years	3918/365137	3454/363630	3576/364225	3694/366632	4151/362434		
Incidence rate, per 10^4 person-years	107	95	98	101	115		
Age-adjusted model	Ref.	0.77 (0.74, 0.81)	0.72 (0.69, 0.75)	0.67 (0.64, 0.70)	0.68 (0.65, 0.71)	<.001	<.001
Multivariable-adjusted model	Ref.	0.89 (0.85, 0.93)	0.88 (0.84, 0.92)	0.86 (0.82, 0.90)	0.90 (0.86, 0.95)	0.004	<.001
HPFS							
Median (IQR), servings/day	0.4 (0.2-0.5)	0.9 (0.7-1.0)	1.3 (1.2-1.5)	1.9 (1.7-2.1)	3.1 (2.6-3.8)		
Deaths / person-years	2580/199654	2851/213708	2918/206857	3180/207037	3576/205751		
Incidence rate, per 10^4 person-years	129	133	141	154	174		

	Quintiles of intake					P_{trend}	
	Q1	Q2	Q3	Q4	Q5	Linear*	Non-linear†
Age-adjusted model	Ref.	0.87 (0.82, 0.92)	0.79 (0.75, 0.83)	0.76 (0.72, 0.80)	0.74 (0.70, 0.78)	<.001	<.001
Multivariable-adjusted model	Ref.	0.94 (0.89, 1.00)	0.90 (0.86, 0.96)	0.90 (0.85, 0.95)	0.88 (0.83, 0.94)	<.001	<.001
Pooled							
Age-adjusted model	Ref.	0.81 (0.79, 0.84)	0.75 (0.72, 0.78)	0.71 (0.68, 0.73)	0.70 (0.68, 0.73)	<.001	<.001
Multivariable-adjusted model	Ref.	0.91 (0.88, 0.95)	0.89 (0.86, 0.92)	0.88 (0.84, 0.91)	0.90 (0.86, 0.93)	<.001	<.001
Vegetables							
NHS							
Median (IQR), servings/day	1.4 (1.1-1.6)	2.2 (2.0-2.3)	2.8 (2.7-3.0)	3.6 (3.4-3.8)	5.0 (4.5-5.8)		
Deaths / person-years	3933/364056	3838/364319	3645/364560	3617/364618	3760/364504		
Incidence rate, per 10^4 person-years	108	105	100	99	103		
Age-adjusted model	Ref.	0.92 (0.88, 0.96)	0.82 (0.79, 0.86)	0.78 (0.75, 0.82)	0.78 (0.75, 0.82)	<.001	<.001
Multivariable-adjusted model	Ref.	1.02 (0.97, 1.06)	0.96 (0.92, 1.01)	0.94 (0.90, 0.99)	0.95 (0.90, 1.00)	0.004	<.001
HPFS							
Median (IQR), servings/day	1.3 (1.0-1.5)	2.1 (1.9-2.2)	2.7 (2.5-2.9)	3.5 (3.3-3.8)	5.1 (4.5-6.0)		
Deaths / person-years	3034/206139	2939/206729	2930/206908	3056/206820	3146/206411		
Incidence rate, per 10^4 person-years	147	142	142	148	152		
Age-adjusted model	Ref.	0.92 (0.88, 0.97)	0.86 (0.82, 0.91)	0.87 (0.83, 0.92)	0.85 (0.81, 0.89)	0.002	<.001
Multivariable-adjusted model	Ref.	0.96 (0.91, 1.01)	0.93 (0.88, 0.98)	0.96 (0.91, 1.02)	0.95 (0.90, 1.00)	0.17	0.01
Pooled							
Age-adjusted model	Ref.	0.92 (0.89, 0.95)	0.84 (0.81, 0.87)	0.82 (0.80, 0.85)	0.81 (0.78, 0.84)	<.001	<.001
Multivariable-adjusted model	Ref.	0.99 (0.96, 1.03)	0.95 (0.92, 0.98)	0.95 (0.92, 0.99)	0.95 (0.91, 0.98)	0.002	<.001

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professional Follow-up Study; IQR, inter-quartile range

Multivariable model adjusted for age (in month), Caucasian (yes vs. no), moderate-vigorous physical activity (0, 0.1-0.9, 1.0-3.4, 3.5-5.9, ≥6 hours per week), smoking status (never, past, current 1-14 cigarettes/d, current 15-24 cigarettes/d, current ≥25 cigarettes/d), alcohol intake (women: 0, 0.1-4.9, 5.0-14.9, ≥15 g/d; men: 0, 0.1-4.9, 5.0-29.9, ≥30 g/d), multivitamin use (yes vs. no), current aspirin use (yes vs. no), family history of myocardial infarction (yes vs. no), family history of diabetes (yes vs. no), family history of cancer (yes vs. no), total energy intake (quintiles), menopausal status and hormone use in women (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users), baseline body-mass index (<23, 23-24.9, 25-29.9, 30-34.9, ≥35 kg/m^2), baseline history of hypertension (yes vs. no), baseline history of hypercholesterolemia (yes vs. no), the modified Alternate Healthy Eating Index (quintiles). The models for intake of vegetables or fruits also mutually adjusted for each other.

Results for NHS and HPFS from the multivariate model were combined using the fixed-effect model.

*Test for linear trend calculated by assigning the median intake in each quintile and modeling this as a continuous variable in regression models.

†Test for nonlinear relationship was evaluated with a likelihood ratio test comparing the model with fruit and vegetable intake as a linear term and cubic restricted spline variables to the model with covariates only. Nonlinear tests are presented when significant deviation from linearity was detected ($P<0.05$), based on the likelihood ratio test, comparing the model with only the linear term with the model with the linear and the cubic spline terms. A significant P-value for nonlinearity indicated that a nonlinear dose-response relationship fitted the data better than a linear relationship. The restricted cubic spline Cox proportional hazards regressions were performed in the NHS and the HPFS separately, and in a dataset that pooled data from both the NHS and the HPFS.