Fruits, Vegetables and Health:

A Scientific Overview

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FOREWORD

THE SCIENTIFIC BASE supporting the health benefits of fruit and vegetable consumption is rapidly expanding. Our understanding of the complex interactions between the many food components in fruits and vegetables that confer those benefits is also continually evolving. Although our knowledge of the mechanisms involved is seemingly in its infancy, research is confirming what we have intuitively known—eating fruits and vegetables is important.

When it comes to the effect of fruit and vegetable consumption on health, the whole may be more than the sum of the parts. Foods and food patterns appear to act synergistically such that the influences of each are additive, and possibly more than additive. The benefits of fruit and vegetable consumption are generally shown more consistently when whole foods and food patterns are considered, favoring a whole foods approach to diet versus consumption of individual nutrients.

This review was initiated to provide an overview of the current literature on fruit and vegetable intake in relation to health promotion and disease prevention, with an objective analysis of the strengths and limitations of the research, in an effort to identify future research needs. The review summarizes what recent studies have shown about fruit and vegetable consumption as well as dietary patterns that include fruits and vegetables. Research about possible mechanisms and interactions between food components were not within the scope of this report.

The topics chosen were those for which a recent review has not been done, and generally include topics for which the scientific literature tends to be smaller. In 2005, the World Health Organization published reviews on "Dietary intake of fruits and vegetables and management of body weight" (http://www.who.int/dietphysicalactivity/publications/f&v_weight_management.pdf), and on "Dietary intake of fruits and vegetables and risk of diabetes and cardiovascular diseases" (http://www.who.int/dietphysicalactivity/publications/f&v_cvd_diabetes.pdf). In 2007, the World Cancer Research Fund evaluated the literature on diet and cancer, which included an extensive review of fruit and vegetable consumption and cancer. That report titled "Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective" can be found at www.dietandcancerreport.org.

IFAVA gratefully acknowledges **Diane Hyson, Ph.D., R.D., Associate Professor, University of California, Sacramento,** for her review of the literature and preparation of this scientific overview. Her efforts are greatly appreciated.

The following individuals provided their expertise in reviewing this document. PBH extends its sincere thanks to them for their time and critical appraisal of the content.

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Introduction

IT HAS ALWAYS BEEN WIDELY ACCEPTED that fruits and vegetables are "good for you" but there are now ample scientific data to support a close association between fruit and vegetable consumption and a variety of health outcomes. There has been an impressive increase in the number of high quality scientific studies related to specific health benefits of fruits and vegetables since January, 2002.

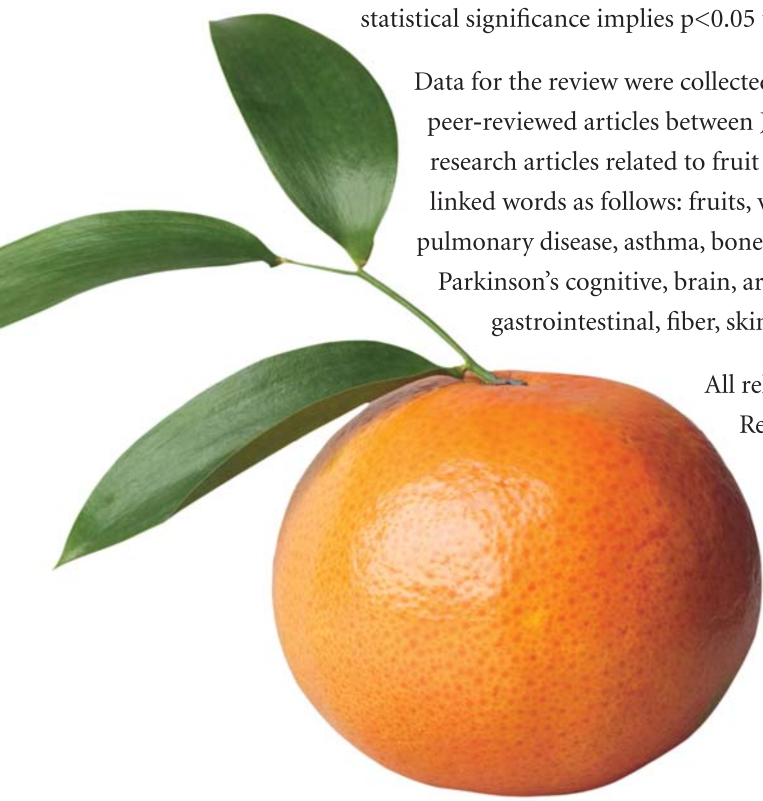
Exciting new evidence suggests that intake of fruits and vegetables may be important in pulmonary and bone health. The effects of diet and lifestyle on eye health, cognitive function, aging, and neurodegenerative diseases are also being actively studied and there are new data suggesting potential mechanisms by which fruits and vegetables might positively influence these processes.

In general there are advances in the scientific literature toward characterizing individual phytochemicals and other bioactive components in fruits and vegetables and identifying how these agents might affect biological processes known to increase disease risk. There are now more sophisticated endpoints and technologies available and the emphasis has broadened from a focus on overall antioxidant properties of fruits and vegetables to anti-inflammatory and cell-signaling potential.

The purpose of this literature review is to provide an overview of recent studies related to fruit and vegetable consumption and health. The emphasis is on investigations of whole food sources rather than supplements or individual nutrients in fruits and vegetables. The goal of the review is to evaluate a potential independent effect of collective intake of fruits or vegetables or a combination of these two categories, rather than highlighting individual fruits and vegetables or contrasting the effects of fruits versus vegetables. However, if a specific fruit or vegetable is highlighted as statistically important in a study, these findings are included in the current report. In general, statistical significance implies $p<0.05$ unless indicated.

Data for the review were collected from database searches of Pubmed and Biosis Previews for peer-reviewed articles between January, 2002 and August 2006. Key search terms used to find research articles related to fruit and vegetable intake and health/disease included individual and linked words as follows: fruits, vegetables, fruits and vegetables, pulmonary, chronic obstructive pulmonary disease, asthma, bone, osteoporosis, eye, cataracts, aging, neurodenerative, Alzheimer's, Parkinson's cognitive, brain, arthritis, inflammatory, birth defects, folate, diverticulosis, gastrointestinal, fiber, skin health, skin wrinkling, life span and longevity.

All relevant articles involving humans are included in the review. Results from animal studies are presented only if preliminary data are applicable. The topics are presented in the order of volume of available data.



Pulmonary Health

Several early observational studies suggested a positive association between fruit and vegetable intake (particularly fruit) and pulmonary function. Recent evidence has added to these data and further demonstrates a potential role for fruit and vegetable consumption in maintaining healthy pulmonary function in well-adult populations and improving lung function in those with established pulmonary disorders. It is known that lung tissues are particularly susceptible to oxidative damage due to high and continual exposure to oxygen. Fruits and vegetables are potentially important in this context because of their high antioxidant and phytochemical content according to the theory that antioxidant mechanisms are important in protecting lungs from exposure to daily oxidative stress.

Chronic Obstructive Pulmonary Disease (COPD)

Several investigations have focused on the association between intake of fruit and vegetables and development of chronic obstructive pulmonary disease (COPD). COPD, including emphysema and chronic bronchitis, is of particular interest as it is among the leading causes of death worldwide. Smoking is the major risk factor for this condition but there are convincing data to suggest that environmental factors, including diet, have an important influence on the risk of developing COPD.

Most studies of the relationship between diet and pulmonary function or disease risk use common endpoints to assess pulmonary function including spirometric measurements of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Some studies focus on the effects of whole foods on pulmonary function, but many more have been designed to determine if intake of individual nutrients, particularly vitamins C, E and β-carotene are specifically associated. While the latter provide useful data, it is important to understand the effects of consuming the combination of multiple nutrients, fiber, and other bioactive compounds within the matrix of the whole fruit or vegetable and their potential interaction in eliciting a physiologic response.

A prospective trial of men, reported in 2002, examined the association of dietary intake with COPD risk[1]. Data collected by diet history and cross-checked food frequency interviews of five cohorts of the Seven Countries Study from Finland, Italy and the Netherlands (n=2917 men) were analyzed to classify dietary variables into tertiles. The baseline data were collected 20 years prior to determining the subsequent cause of death. The goal of the study was to determine if several baseline dietary factors were associated with death from chronic bronchitis, lung emphysema, or asthma during 20 years of follow-up.

It was found that higher fruit intake was consistently associated with lowered mortality from COPD-related causes and that the trend was statistically significant when age, country of residence, and smokings were considered. The association was still present but lost statistical significance when the data were adjusted for potential confounders including BMI, total energy, and alcohol intake. The authors also determined that consumption of vegetables and the antioxidant nutrients vitamins C and β-carotene did not correlate with COPD mortality but vitamin E intake did appear to be protective when data were adjusted for age, country and smoking but not when BMI, total energy and alcohol intake were factored into the analysis.

The above data do not conclusively support an independent effect of fruit and vegetable intake with COPD risk. However, the limitations of dietary data collected at a single time point 20 years prior to mortality outcomes must be acknowledged. The authors of this long-term study indicate that dietary patterns did indeed shift over the 20 year follow-up period. Interestingly however, fruit intake increased, particularly in the lower tertiles of fruit intake, suggesting that the results of the study could have actually underestimated the benefits of fruit consumption.

A protective effect of fruit intake on COPD risk has been suggested on the basis of several case-control findings. One study in Southern England recruited clinic patients who were over 45 years of age and had a long-term smoking history[2]. Spirometry was used to diagnose the presence or absence of COPD. All subjects self-reported their dietary intake using validated food frequency questionnaires to compare dietary habits between COPD cases (n=150) and controls (n=160). Fruit intake of over 121 grams per day was associated with significantly reduced odds (54% reduction) of having diagnosed COPD compared to subjects eating less than 121 grams per day (p=0.04). There was also a significant trend toward lower risk of COPD with increasing vegetable consumption (types not specified). Apples (≥3 per week) were the only specific food item that emerged from the univariate analysis as being significantly protective (53% reduced odds).

Although promising, the data in this study were based on food frequency questionnaires that grouped food intake into broad categories and were self-reported. In general, case control study design is potentially limited by recall bias as well as the possibility that a disease diagnosis will alter the actual or reported intake of cases. To address this point, these investigators examined a subset of subjects who were found to have COPD upon enrolling in the study but had not been previously diagnosed. It was found that dietary intake and the inverse association between COPD and fruit and vegetable intake were similar in the newly and previously diagnosed cases, thus strengthening the findings.

A smaller, but more recent study in Turkey, found that fruits and vegetables were potentially protective against COPD in male smokers[3]. This study included 40 male smokers with COPD who were compared to 36 healthy male smokers. A research team interviewed all subjects face-to-face to estimate dietary intake using a semi-quantitative 113-item food frequency questionnaire with photographic props to improve estimates of portion size. A dietary score was assigned to each food category based on portion size and frequency of intake. It was found that the mean score for fruit and vegetable intake (as well as tea) was significantly higher in controls than cases and mean scores of fruit and vegetable intake were each independent predictors of COPD.

A significant limitation of this study however, is the small number of food categories examined, only 7 in all, and these groups were based on broadly combined items. In addition, consumption data are not quantified in the report, making it impossible to determine the amount of fruit or vegetable associated with reduced risk. Cases and controls were matched in the study but adjustments for potential dietary confounders were relatively limited. In fact, it was reported that cases consumed more salty foods and had different breakfast habits than controls. In spite of these issues, the outcomes are consistent with those of other studies suggesting that fruit and vegetable intake may be associated with reducing the risk of COPD in smokers.

Asthma

Asthma is another pulmonary disorder that may potentially be affected by fruit and vegetable consumption. Rates of asthma incidence and prevalence have been increasing over the past several decades, particularly in industrialized countries that have adopted a "Westernized" lifestyle. It is speculated that environmental and lifestyle factors are important determinants of this trend and that reduced antioxidant intake is one critical factor associated with increased susceptibility[4]. As indicated for COPD, lungs are particularly susceptible to oxidative damage due to high and continual exposure to oxygen. Oxidant stress has also been shown to activate inflammatory mediators that induce asthma in experimental models and might be potentially important in the etiology of asthma in humans[4].

A number of observational studies addressing the potential link between diet and asthma were published prior to 2002 (reviewed in [4]) and suggest that fruit intake, in particular, may improve ventilatory function, respiratory symptoms, and reduce risk of asthma. A few recent reports have added further evidence to support this association.

A report using data from the French branch of the ongoing European Prospective Investigation into Cancer and Nutrition (EPIC) provided evidence of a link between fruit and vegetable intake and prevalence of asthma in a sample of 68,535 adult women (mostly teachers) enrolled in a national health insurance plan[5]. Food frequency questionnaires including 208 food items and photographic prompts were used to determine dietary intake and categorize intake into quartiles. Asthma was prevalent in 3.1% of the cohort based on self-report using validated questionnaires completed on two separate occasions.

Adjusted analyses comparing women in the highest quartile of intake to the lowest quartile showed that of the 26 foods studied, only a few were significantly associated with reduced incidence of asthma. These included green leafy vegetables (>90 grams/day; 22% reduction), tomato (>28.2 g/d; 15% reduction) and carrots (>24.9 g/d; 19% reduction). Apple intake of >31.2 grams per day was associated with a 10% risk reduction but this effect was less robust after adjustment for other fruits and vegetables.

The authors proposed that the high content of carotenoids in foods that might be protective could account for the results of their study; early prospective work suggested that carotenoids may be important, although results of studies focused on β-carotene have not been consistent. The lack of a protective effect for vitamin C-containing fruits such as citrus fruits in this study is also discussed and the authors suggest that vitamin C is more consistently associated with healthy lung function than respiratory symptoms. This is an important distinction that may be overlooked in some reports. However, it is important to note the cross-sectional nature of these data and the self-reported asthma incidence as potential limitations of this study.

Another report from the EPIC study was based on a sub-analysis of a cohort of men and women living in and around the city of Norwich, UK[6]. Using questionnaires as described above, data in this study included spirometric tests of ventilatory function, anthropometric measurements and plasma vitamin C levels in 550 cases and 550 matched controls. Dietary data were obtained from 7-day food diaries in which a 24-hour recall by a trained interview formed the first day.

The results showed that controls had a significantly higher intake of fruit (149.1 versus 132.1 grams per day) and that individuals in the highest quintile of intake had a significantly lower (13%) risk of diagnosed asthma than the lowest quintile. In the highest quintile (>46.3 grams fruit per day), 90% of the subjects reported eating fruit every day. Of the individual fruits, after adjustment for

confounders, only citrus remained as a significant dietary factor associated with 36% reduced risk of asthma. The only dietary nutrient associated with reduced risk was manganese, with a statistically significant (p=0.002) 14% reduction in asthma.

The strength of this study is that the investigators further refined their data by conducting several sub-analyses to determine if the observed effects would apply if the case-control comparisons were limited to individuals with asthma who had not smoked for over 20 years or those who were the under the age of 55 years. They also tested the effects of excluding nonsymptomatic asthmatics (no reported wheeze for at least 12 months) from the case group. Although these sub-analyses reduced the number of case-control comparisons by one-third, there was still a significant protective effect of fruit and citrus fruit intake in each of the sub-analyses. There was also a significant inverse trend between asthma and increased vitamin C and manganese intake in symptomatic subjects and those who had not smoked for over 20 years, but these effects were not evident in individuals with asthma who were less than 55 years old. Plasma vitamin C levels were only protective in symptomatic asthmatics.

This was a well-controlled study that used 7-day food records, controlled for a number of confounders, and factored in potential differences between asymptomatic and symptomatic subjects as well as the potential impact of a long-term smoking history. This is one of the few studies to suggest a potential role of dietary manganese in reducing risk of asthma.

There is growing interest in the relationship between dietary intake and lung function in children in both healthy and diseased (with asthma) populations. A large prospective study in Italy, as part of the International Study on Asthma and Allergies in Childhood (ISAAC) initiative was conducted to evaluate the association between asthma and diet in boys (n=2103) and girls (n=2001) ages 6-7 years[7]. Information on several respiratory symptoms including shortness of breath, wheezing and allergic rhinitis (sneezing/running or blocked nose) as well as risks for asthma was collected at two time points separated by a 1 year period. At the second time point, dietary data were also collected using a semi-quantitative food frequency questionnaire that included 18 food items that were classified into 5 categories ranging from "never" to >4 servings per week. It was found that the consumption of fruit, summer tomatoes and citrus fruit was significantly associated with reduced occurrence of wheezing and shortness of breath over the 12 month period. When chronic and nocturnal cough were also considered as endpoints, these three foods remained significant and cooked vegetables were also protective. The authors acknowledge the potential limitations of using a food frequency questionnaire with relatively few food items and the possibility of parental bias in completing the questionnaires. The results of this study are consistent with some findings but not others as discussed below.

A very large cross-sectional multicenter study involving over 20,000 children, ages 7-11, from 25 areas in Central and Eastern Europe was conducted to test the hypothesis that low intake of fresh fruit, vegetables and fish would be associated with increased risk of respiratory disorders[8]. The goal was to correlate dietary factors with defined outcomes related to cough and wheezing in the subjects. Parents completed standardized questionnaires including questions regarding risk factors and nutrition information adapted from WHO and ISAAC tools as well as a food frequency survey from the British survey of adults to determine frequency and seasonality of fruit and vegetable consumption. Data were adjusted for several known confounders including environmental exposures and nutritional factors.

The authors found that winter cough was more likely to be reported in children consuming 2 servings of fruit per week compared to those with reported intake of more than 4 servings/week in the summer (14% higher cough) and winter (19% higher). However, intake of fruits and vegetables was not associated with any other outcomes including wheezing and persistent cough. It was interesting to note that while the effects of fruits and vegetables were only moderately associated, intake of fish (1 serving per month) was consistently associated with lowered cough and wheezing symptoms in this study. The authors discuss a slight, but puzzling, increase in respiratory symptoms associated with vegetable intake in some countries. They proposed that the explanation might be that parents may feed their children more vegetables when respiratory symptoms are present thus resulting in reverse causality.

The strength of this study is the large number of subjects. However, dietary intake data were self-reported and not detailed enough to determine if particular categories of fruits and vegetables were more significant than others. In addition, the indicators of pulmonary function were subjective, based on parent reports of symptoms and do not include measurements of lung capacity.

The "Children's Health Study" was also based on the hypothesis that low intake of vitamins, fruit, vegetables, and juice would be associated with an adverse effect on lung function[9]. The study included an examination of dietary intake and pulmonary function in a prospective cohort of 2566 children, ages 11-19 years, living in 12 communities in Southern California within 200 miles of Los Angeles. The majority of children were non-Hispanic white from middle-class families with health insurance. Food frequency questionnaires, reportedly completed by the children, included 131 food items and were used to group foods and determine the relationship between food and nutrient intake and measured pulmonary function in the subjects. Self-report of diagnosed asthma was used and respiratory infections within 1 month of testing were documented.

Average fruit and vegetable intake was below the recommended guidelines, averaging 1.5-2 servings of vegetables per day, 1 serving of fruit per day and 0.8 servings of fruit juice. Average total intake of these three categories was 3.2 and 3.5 servings per day for boys and girls, respectively. The authors found that boys reporting no intake of any fruit juice, citrus or other fruit juice had significant deficits in FVC and FEV_1 compared to children reporting any intake. This relationship was not found in girls and there was no significant association between fruit, vegetable or combined intake of both on lung function level in either gender. It was noteworthy, however, that low intake (10^{th} decile or below) of antioxidant vitamins associated with these food groups including vitamin C and to a lesser extent vitamin A (in girls) was associated with reduced lung volume and measures of flow. Low intake of vitamin E was associated with reduced lung function in boys but not girls. The lowest deciles of intake for vitamin C and E were below the recommended dietary allowance for each but vitamin A intake in the lowest decile was above recommended intake. The presence of asthma (reported "ever asthma" in 23% of subjects) did not affect any of the reported associations.

The authors noted that the results of their study conflict with earlier findings in children that suggest that fresh fruit, green vegetable, and salad consumption were associated with higher FEV_1 in children in England and Wales but plasma vitamin C levels were not[10]. The authors of the Children's Health Study acknowledge the potential limitations of the cross-sectional data and possible confounders. Furthermore, their report did not indicate control for physical conditioning effects. These limitations may account for the differential effects between this study and others, although in general, evidence that individual vitamin intake is associated with lung function has not been consistent.

The inconsistency in the data relating diet to asthma in children was further demonstrated by more conflicting results in a recent cross-sectional study in the United Kingdom. There was no association between asthma prevalence and fruit intake in 11,562 children ages 4-6 years, living in the United Kingdom based on data provided by parents of the study subjects[11]. It is possible that confounders and study design involving parental input are unique features of studies involving children.

Another study of diet in relation to asthma using semi-quantitative food frequency data from 598 Dutch children ages 8-13 years did not find an association between fruit or vegetable intake or citrus fruit and several endpoints related to asthma[12]. However, the authors suggest a potential inverse association between self-reported presence of current asthma and dietary intake of total vegetables and citrus fruits ($p=0.10$).

Pulmonary Function in Healthy Populations

There are very few recent studies that examine the effect of fruit and vegetables in adults without pulmonary disorders. One report from the "Health Survey for Scotland" suggested an association between fruit and vegetable intake and improved respiratory function in healthy adults[13]. Dietary and pulmonary health data for over 6000 randomly selected Scottish residents were collected by computer-assisted personal interview and pulmonary function tests conducted by a nurse at each subject's home. A subset of subjects (n=1146) provided blood samples for analysis of antioxidant vitamins.

The analysis showed a dose-response relationship between more frequent fruit and green vegetable consumption and higher FEV after adjustment for several confounders. Eating fresh fruit once a day compared to eating fresh fruit less than once a month was associated with significantly improved pulmonary capacity. Reported frequency and duration of phlegm production, wheezing and shortness of breath were used as general markers of respiratory symptoms. Fruit intake of more than once per day was associated with reduced symptoms and symptoms were even lower in subjects who consumed fruit more frequently. Plasma levels of vitamin C were positively associated with pulmonary function and higher plasma vitamin E was associated with reduced phlegm production.

Summary: Pulmonary health

Collectively, the data relating fruit and vegetable intake to improved pulmonary status in healthy and diseased children and adults are promising but subject to inconsistencies. Many investigators have taken great care to control for confounding variable known to affect lung health but it is likely that unknown dietary and lifestyle confounders have important effects. There is clearly a need for controlled clinical intervention studies using whole foods to further examine the components and foods that might reduce risk of pulmonary diseases and improve general lung function.

Bone Health

The loss of bone mass is associated with osteoporosis and has been labeled by some as a global epidemic[14]. In the United States alone, it is estimated that 10 million individuals have osteoporosis and predictions are that 1 in 3 women and 1 in 10 men will develop it in their lifetime. While genetic factors affect calcium and bone metabolism, environmental factors including diet are also important. Historically, studies of the relationship with diet have focused on the importance of adequate calcium and vitamin D intake although it is increasingly evident that other dietary components including potassium, magnesium, vitamins A and C and others, may have indirect but significant effects on bone health as well.

A link between fruit and vegetable consumption and bone integrity was first suggested several decades ago[14]. Early cross sectional studies showed a correlation between potassium and magnesium and bone density but mechanistic and detailed studies relating intake of fruits and vegetables to bone health were relatively limited. There has been renewed interest in this area in recent years and several studies have been published since 2002. New data show that fruit and vegetable consumption is associated with positive effects on a variety of bone indices and urinary calcium excretion[15]. The majority of studies demonstrating an association between bone health and fruit and vegetable intake are observational. Many reports focus on nutrients associated with fruits and vegetables or the effects of dietary patterns that include fruits and vegetables rather than actual fruit and vegetable intake, although a few recent reports have addressed the latter.

A cross-sectional study reported in 2006 showed that higher fruit and vegetable intake was associated with improved markers of bone status in males and females of various ages ranging from 16-83 years[16]. The data were derived from three unrelated studies in the United Kingdom that used common methodologies for assessment of diet and bone parameters. Dietary intake was determined from 7-day food diaries with photographic prompts for portion size. The analysis was based on total weight of fruits or vegetables or combined intake consumed each day. Bone status was assessed using measurements of whole body bone mineral content, bone area, and bone mineral density as well as each of these measurements at several sites including lumbar spine, total hip, femoral neck, and trochanter.

The analysis showed a positive association between fruit and vegetable intake and one or more of the above measurements in all age groups except in young women (n=90; mean age 30 years) and older men (n=67; mean age 67.9). In general, lumbar spine measurements in adolescent girls (n=101; mean age 17.4) and older women (n=67; mean age 67.9) and femoral neck measurements in adolescent boys (n=111; mean age 16.8) were most likely to be positively associated with fruit and vegetable intake. Statistical modeling suggested that doubling fruit intake would result in an increase in bone mineral content and bone mineral density of approximately 5% in older women. In adolescent boys in particular, fruit intake and combined fruit and vegetable intake was associated with greater bone measurements at nearly all of the sites measured. This and other work suggests that dietary effects may be more pronounced during periods when bone turnover is greater including rapid growth during adolescence (males having highest turnover) and bone loss later in life.

The data in this report are a compilation of records from three separate studies conducted at different times with different goals, sampling methods, instrumentation, technicians, and settings. Seven-day food records were used and efforts were made to improve their accuracy by using food photographs for portion size estimation and supplementary questions for clarification. This methodology is an improvement upon studies which are limited to self-recorded intake of shorter duration and provides some advantages over 24 hour recalls. Dietary data did not include potato intake or details of fruits and vegetables included in composite dishes unless specified by the subject. Furthermore, nuts were included in total fruit intake. However, the strength of this study is the variety of ages included in the analysis. The authors also suggest that their use of size adjustment for bone mineral content improves the accuracy of this measure.

A cross-sectional study focused on 56 pubertal white girls, ages 8-13 years showed that fruit and vegetable intake might be important in bone health in this age group[17]. Dietary intake of fruits and vegetables was classified as either high (≥3 serving/d) or low (<3 servings/d) based on three individual days of recorded food intake within a 24-month period. Average combined daily intake of fruits and vegetables in the high group was 4.0 servings (1.6 fruit/2.4 vegetable) versus 1.7 servings (0.6 fruit/1.1 vegetable) in the low group. The high intake group had significantly higher dietary content of vitamin A, vitamin C, potassium and magnesium, although both high and low groups were below requirements for vitamin A and magnesium. Both groups were comparable but below recommended intake for calcium, and phosphorus. Vitamin D and protein were comparable and adequate for each group. A higher percentage of individuals in the low intake group were found to be inadequate for vitamin C and calcium compared to the high intake group.

The bone analyses showed that girls in the high intake group of fruits and vegetables had significantly larger bone area of the whole body and wrist compared to those eating fewer servings. Bone mineral content also tended to be higher for whole body and at the wrist (p=.07 and 0.09, respectively) but bone mineral density did not differ between the two groups. Urinary calcium excretion and plasma parathyroid concentrations were lowered with high fruit and vegetable intake although serum markers of bone turnover did not differ between the two groups.

These data provide general support for the potential of fruit and vegetable intake to promote increased bone size and reduce urinary calcium excretion, although not all markers of bone density were significantly increased and not all bone markers were significantly different between groups. As the authors indicate, their study is relatively small in size and included a white, relatively affluent population. The intake data were based on reports of parents and children and although photographic and portion size prompts were used, there were only 3 days of recorded intake over a 12-24 month period and may not accurately reflect the consistent diet of these girls.

Another study conducted in a young population was based on data collected from 85 boys and 67 girls, ages 8-20 years, in a seven year prospective study in Saskatchewan, Canada[18]. Over a period of seven years, subjects were required to provide dietary data two to four times a year via serial 24-hour recalls; anthropometry and physical activity data twice a year; a bone scan once a year. The authors used the data in statistical models to determine which factors had an important effect on total body bone mineral content based on biological age (versus chronological age) as subjects progressed from childhood to adolescence.

They found that in boys, but not girls, fruit and vegetable intake was an important independent predictor of accrued total body bone mineral content. These findings, although based on self-reported intake using 24 hour recalls, are consistent with other data and are strengthened by the longitudinal design and a follow-up period of seven years. The lack of an effect in female subjects might be due, in part, to underreporting of dietary intake, a phenomenon described previously in this age group as discussed by the authors.

A study of dietary factors and bone health in adolescents ages 12 and 15 in Northern Ireland (n=1345) was published in 2004 as part of the Young Hearts 2000 cross-sectional survey in that country[19]. Dietary assessment of each subject was comprehensive and included a personal interview and observation by a nutritionist, a review of school food sources consumed by the subjects and detailed efforts to include intake of fruits and vegetables provided in mixed/composite dishes. Intake was divided into tertiles of low, medium, and high intake.

The 12 year-old girls (n=328) consumed the highest quantity of fruit (178 grams ± 164/day) and were the only group to consistently demonstrate a positive association between bone density and fruit intake. Bone density in the heel but not the forearm (distal radius) was significantly higher in 12 year old girls with high fruit intake (>196.71 g/day) compared to low (<83.83 grams). The authors suggest that the heel has a greater content of trabecular bone with higher turnover than bone in the forearm and therefore might be more susceptible to dietary factors. An important strength of this study is the detailed characterization of the diet. However, it would have been useful to have a greater number of varied sites to assess bone density in these subjects.

A number of studies have shown that fruits and vegetables are an important part of dietary patterns associated with improved bone health. While most of the work is observational, an ancillary study was conducted that was a retrospective analysis of data from one clinical trial, the Dietary Approaches to Stopping Hypertension (DASH) study. The DASH study involved a 3-month intervention in hypertensive adults[20]. The DASH diet emphasized fruits and vegetables as well as low fat dairy products, whole grains and lean protein, thus providing significantly lower total and saturated fat and cholesterol, and greater potassium, calcium, magnesium, dietary fiber and protein than the control diet in this study. All foods were provided to the 186 men and women, over 50% of whom were

African American (n=91 in DASH group, mean age 48; n=95 control, mean age 52). Each group followed their respective diets for 3 months. The study was also designed to test the effect of varying sodium content within the background of either the DASH or control diet so subjects were randomly exposed to three levels of sodium throughout the study.

It was found that the DASH diet reduced serum markers of bone turnover, regardless of sodium intake. Although this study did not test for the independent effects of fruits and vegetables specifically, the authors postulated that the high potassium, magnesium and calcium content of the DASH diet in addition to the antioxidants, phytochemicals and lower acidity of fruits and vegetables could be significant factors in potential protection of bone health.

Observational studies of dietary patterns have indicated that including fruits and vegetables as part of a dietary regime is positively correlated with bone health. A study of 1407 premenopausal Japanese farm women living in 5 rural districts in Japan found that fruit and vegetable intake may be important[21]. Diet information from a self-administered semi-quantitative questionnaire of 147 items was used to classify the women's diet into 30 food groupings. These were further divided for factor analysis into 4 broad dietary patterns to determine which pattern might be associated with bone density in the forearm of the study subjects.

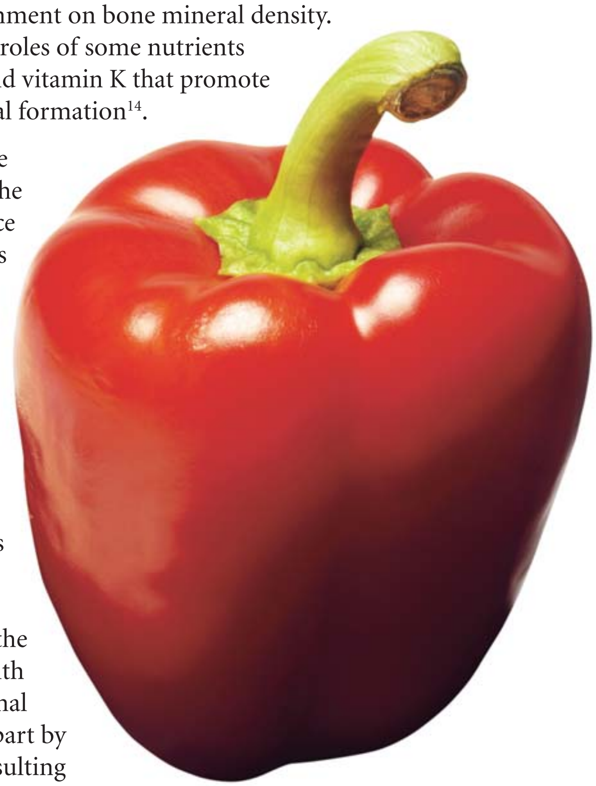
The analysis showed that women in the upper quintile of the dietary pattern designated as the "Healthy Diet" had significantly higher bone mineral density than the lowest quintile. The Healthy Diet pattern included green and white vegetables, fruit, mushrooms, fish, shellfish, processed fish, seaweed, and soy products and was positively correlated with content of protein, potassium, magnesium, calcium, phosphorus, vitamin C, vitamin K, vitamin D and alcohol. In contrast, there was a tendency for women in the upper quintile of the Western diet pattern to have lower bone mineral density (p=0.08). This diet included higher intake of fats, oils, meat, processed meat, and seasoning and was positively correlated with fat but negatively for carbohydrate content.

The use of a single marker of bone density and the self-reported diet and menopausal status are limitations of this study. However, the finding that inclusion of fruits and vegetables in the diet appears to maintain higher bone mineral density is consistent with reports of reduced rates of bone turnover associated with fruit and vegetable intake.

Dietary potassium, magnesium and vitamin C intake have been used as surrogate markers for fruit and vegetable intake in a number of studies of bone health. Recent reports based on a subset of women enrolled in the Aberdeen Prospective Osteoporosis Screening Study in Scotland included data from 891 women who completed food frequency questionnaires and had bone density and bone resorption measurements at baseline and 5 to 7 years later[22]. The average age at baseline and follow-up was 47.5 and 53.9 years, respectively.

In women who were still premenopausal and not taking hormone replacement therapy (n=146), dietary intake of vitamin C, potassium and magnesium was associated with higher bone mineral density and reduced loss of bone density at femoral but not lumbar sites. It is noteworthy that the association of vitamin C, potassium and magnesium with improved bone mineral density was not present in women who were no longer menstruating and thus presumed to be menopausal or experiencing estrogen withdrawal. It was also found that vitamin A intake was not associated with improved bone density.

The nutrients provided by fruits and vegetables suggest a protective effect of these foods, although fruit and vegetable consumption was not tested directly in the above study. It is possible that vitamin C and potassium might be markers for fruit and vegetable intake but other components, including phytochemicals and vitamin K, may also account for the positive effects on markers of bone health. The mechanisms by which consumption of fruits and vegetables may be protective to bone are not known. Antioxidants in fruits and vegetables including vitamin C and β-carotene attenuate the negative impact of an oxidative environment on bone mineral density. There are also specific roles of some nutrients including vitamin C and vitamin K that promote bone cell and structural formation[14].



It is known diet has the potential to influence the body's acid-base balance and that bone minerals provide a buffering effect. The balance of bone dissolution and resorption is important in bone integrity. Dietary protein of animal origin is rich in sulfur-containing amino acids that generate acidic metabolites and lower pH. It is believed that the acid load associated with habitual intake of animal protein is buffered in part by dissolution of bone resulting

in reduced bone density[19]. On the other hand, fruits and vegetables are rich in potassium citrate and generate basic metabolites to help buffer acids and thereby may offset the need for bone dissolution and thus potentially preserve bone. A number of studies suggest that increased fruit and vegetable intake favors an alkaline environment which is associated with enhanced bone resorption and reduced bone mineral dissolution.

The same authors addressed the effects of alkalinity versus acidity in the diet using the data of women from the Aberdeen Prospective Osteoporosis Screening Study in Scotland as described above. They used dietary intake data to calculate predicted net endogenous acid production (NEAP), and potential renal acid load (PRAL), both of which would be expected to increase bone loss[23]. Dietary data from over 3000 women, most of whom were menopausal, were examined for a potential correlation between several nutrients and bone density and resorption markers.

Results showed that lower intakes of fruits and vegetables were associated with increased predicted NEAP and PRAL. Fruit intake in the highest quartile averaged 319 grams/d versus 167 in the lowest; vegetable intake in the highest quartile was 201 grams per day versus 153 grams. Potassium intake was significantly and linearly associated with markers of bone turnover (lowest intake associated with highest turnover/loss). Femoral bone mineral density (but not lumbar density) also correlated with potassium intake with those in the highest quartile of intake having significantly higher bone mass. However, potassium intake between baseline and 5-7 years of follow-up did not affect bone density change during this period.

The data from this study were based on a 99-item food frequency questionnaire that was self-administered but checked at follow-up appointments. The strength of the study was the longitudinal design which improves accuracy compared to cross-sectional and case-control studies. There was no assessment of a direct correlation between fruit and vegetable intake and bone status but the data suggest that surrogate markers including predicted dietary acidity and potassium content are important in bone health, particularly in women who have experienced the onset of estrogen loss.

The results of a 6-day pilot intervention study designed to alter renal net endogenous acid production were published very recently[24]. The study involved 40 healthy men and women, average age 63.7 years, who were randomized to either an alkali "meat plus fruits and vegetables" diet or an acid-producing "meat plus cereal grains" diet. The free-living subjects were provided all food supplements prepared in a metabolic kitchen. Serum and 24 hour urinary measurements were collected for each subject at baseline and after 44 and 60 days on the diet.

It was found that altering the renal net acid excretion over a period of 60 days impacted several biochemical markers of bone turnover and calcium excretion. In particular, the acidity of the diet had a significant effect on increasing NTX, a urinary marker of bone breakdown and increasing the amount of calcium excreted in the urine. These short-term data are consistent with earlier studies but there is clearly a need for more controlled, longer term dietary intervention studies to clarify the mechanisms of how fruits and vegetables might affect bone health.

Summary: Bone Health

In conclusion, while several observational studies show the possibility of a link between fruit and vegetable intake and potential risk reduction for osteoporosis, there are very few clinical trials to confirm cause and effect. Mechanistic studies provide clues to several plausible components in fruits and vegetables and how they might act to improve bone health. It is known that fruits and vegetables have an alkalizing effect on acid-base balance in the body, thus favoring an environment that would reduce urinary calcium excretion and promote bone resorption over breakdown. Further work is needed to confirm that these effects are mediated in the long term with consumption of whole fruits and vegetables.

Aging and Cognition

Aging is associated with neuronal and behavioral decline, characterized by changes in multiple receptor and other cellular systems[25]. Oxidative stress and inflammation are considered significant mediators in both healthy aging of the brain and in age-related neurodegenerative diseases such as Alzheimer's and Parkinson's disease[26]. The manifestations of these processes in both humans and animals include altered cognitive behavior such as memory deficits and use of spatial learning as well as motor decline including decreased balance, loss of muscle strength, and impaired coordination[25]. Animal studies and some human experiments have suggested that fruits and vegetables, due to their bioactive components, have the potential to attenuate several age-related processes. The antioxidant and anti-inflammatory properties of several phytochemicals have been consistently demonstrated. However, recent *in vitro* work has suggested that some classes of phytochemicals also act in cell signaling and thus may protect against aging by mechanisms beyond oxidative and inflammatory processes[27].

Several studies in animals prior to 2002 demonstrated that fruit extracts were able to reverse or retard various age-related cognitive and motor deficits in rats[28]. Recent work has added to early studies suggesting that fruit consumption in particular, but also vegetable intake, may be associated with delaying or preventing age-related decline in several parameters. The majority of available data is focused on animal and mechanistic studies although a few observational studies in aging men and women have been conducted.

Animal studies not only provide evidence of a mediating effect of fruits and vegetables on certain aspects of aging but also mechanistic data to define how these foods might exert the observed effects. Several studies from the laboratory of Joseph et al. have used rat models to examine the effects of selected fruit and vegetable extracts on behavioral, cognitive and motor decline in healthy aging. Early work from this lab focused on fruits and vegetables with high antioxidant activity and found that strawberry and spinach extracts attenuated age-related cognitive and neuronal decline in rats over several months (6-15 months; reviewed in[29]). They also completed work to show that these extracts as well as blueberry extracts were effective in reversing existing cognitive deficits in aged rats. However, blueberry was the only extract to also improve motor function in these aging animals.

Examination of the brain tissue from these and other animals showed evidence of reduced inflammatory and oxidative processes in the supplemented groups, although the changes were not of sufficient magnitude to predict the observed increases in performance or attenuation of age-related processes. Thus, Joseph et al. extended their work to examine cell signaling processes in a transgenic mouse model of Alzheimer's disease[30]. The mice, shown to produce beta amyloid resulting in brain lesions and behavioral deficits characteristic of Alzheimer's disease, were fed the blueberry extract for an 8-month period. It was found that blueberry supplementation had a significant effect. Transgenic mice fed blueberry extract exhibited cognitive performance equivalent to that of normal nonsupplemented mice and were significantly improved compared to nonsupplemented transgenic mice.

Of further importance, this work showed no difference in the deposition of lesions/plaque in the brain between the animals suggesting that alternate mechanisms, other than improving brain physiology, may be important. A subsequent study showed that blueberry supplementation in the transgenic mice increased concentrations of cell signaling kinases thought to be involved in converting short-term memory to long-term memory[31]. In addition, blueberry supplementation appeared to increase other aspects of cell signaling including increased muscarinic receptor activity that is also known to be important in cognitive function.

A very recent study involved aging rats provided with Concord grape juice at high and low concentrations of 10% and 50%, respectively, for 9 weeks and tested for a variety of age-related parameters at various points in the study[26]. Grape juice has been well characterized and is known to contain a variety of flavonoids with bioactivity. It was found that cognitive performance was the most improved on the lower concentration of grape juice whereas higher concentrations were necessary to improve motor performance. Preliminary mechanistic studies showed that 10% grape juice supplementation was associated with the most effective increase in muscarinic receptor sensitivity in aging rats.

Although the collective findings in animals have yet to be extended to humans, this work raises the possibility that components in fruits and vegetables have the potential to exert important effects on brain tissue and ultimately improve performance in both healthy aging and neurodegenerative diseases associated with aging. Work in humans is relatively limited as described below.

A recent report was based on a subset analysis of a large cohort of women enrolled in the Nurses Health Study, a prospective trial initiated in 1976 involving women living in 11 states in the USA[32]. The investigators determined average fruit and vegetable intake of 13,388 women who self-reported intake via biennial quantitative food frequency questionnaires over a period of 10-16 years. Cognitive performance was assessed on two occasions; at baseline to establish cognitive performance and 2 years later to determine cognitive decline. These assessments were completed by telephone interviews using several validated tests that were averaged for a composite score. Tests of episodic memory were also conducted, as a predictor for eventual risk of Alzheimer's.

The analysis showed that baseline cognitive performance was stronger in women who reported the highest intake of cruciferous vegetables compared to those with lower intake (highest vs. lowest quintile; absolute servings not specified). However, no other dietary factor was associated with cognitive performance including combined fruit and vegetable, fruit or vegetable intake alone, or any other classification of fruits or vegetables.

A dose-response protection from cognitive decline was determined for total vegetable intake and green leafy vegetables, particularly for episodic memory tests. Intake of cruciferous vegetables was associated with attenuated cognitive decline as well, but only for women in the fourth and fifth quintile of intake compared to lower intake. Cognitive decline between baseline and follow-up was not related to any other dietary factors.

The authors made an effort to control for over 20 possible confounders in this study and their findings are strengthened by the prospective design and long term follow-up. However, measurements of cognitive function, while well validated in this model, were somewhat limited and assessment of decline was based on only one follow-up measure conducted after 2 years. In addition, dietary intake was determined using semi-quantitative food frequency questionnaires at periodic intervals which may result in potential misclassification and not reflect dietary intake with complete accuracy.

Two observational studies have evaluated the relationship between dietary antioxidants and risk of Alzheimer's disease. It is believed that oxidative stress plays a key role in the development of Alzheimer's because of the characteristic lesions associated with free radical damage and the attenuation of these processes with supplementation of some antioxidants. To date, there are no clinical trials that specifically address the role of dietary fruits and vegetables although there are trials to investigate the association between dietary antioxidants in food and risk of Alzheimer's disease.

A prospective study of 5395 individuals (mean age 67.7 at baseline), living in the Netherlands and followed for 6 years was published in 2002[33]. It was found that baseline dietary intake of vitamins C and E as well as the use of antioxidant supplements was associated with reduced risk of developing Alzheimer's during the follow-up period, with a stronger protective effect in subjects who were smokers. Flavonoid and β-carotene intake was also protective in smokers but not in nonsmokers. Although fruit and vegetables are rich in these protective components the effect of whole fruits and vegetables on Alzheimer's risk was not tested directly in this study.

A protective effect of vitamin E, and possibly vitamin C, was found in a shorter prospective study (3.2 year follow-up) of a cohort from the Chicago Health and Aging Project. The investigation included 3838 men and women who completed a food frequency questionnaire at the approximate midpoint of the follow-up period to evaluate the association between several nutrients and subsequent incidence of Alzheimer's. Dietary intake of vitamin C was inversely associated with risk of Alzheimer's in the fourth quintile of intake compared to that of the lowest quintile but was not statistically significant for a trend. The authors indicate that the effect of vitamin C is suggestive of a protective effect and warrants further study. As in the above study, fruit and vegetable consumption was not tested directly but the combination of these two studies suggests that further work needs to be done to confirm the link between fruit and vegetable intake and Alzheimer's disease.

Summary: Aging and Cognition

In conclusion, the variety of processes associated with aging and amplified in neurodegenerative diseases of aging are complex and not completely understood. The available data suggest the potential of fruits and vegetables to modulate some of these processes but there is extensive work to be done to fully characterize the effects of fruit and vegetable consumption on aging.

Cataracts and Eye Health

Many investigators have highlighted the importance of oxidative mechanisms in the etiology of cataracts in humans. Early case-control data suggested a potential inverse association between fruit and vegetable intake and risk of cataracts. Since 2002, many studies have focused on studying individual antioxidant nutrients while only a few have examined the relationship between fruit and vegetable intake and risk of cataracts.

A recent sub-analysis of data from the Women's Health Study, a large prospective study of female health professionals in the US, was conducted to determine the potential association between fruit and vegetable intake and subsequent risk of cataract development over a 10 year follow-up period[34]. A semi-quantitative food-frequency questionnaire including 29 vegetable and 15 fruit items was completed by 35,724 healthy professional women over the age of 45 years. Data regarding the occurrence and extraction of cataracts during the follow-up period was confirmed by provision of medical records or completion of a questionnaire by ophthalmologists and optometrists treating each subject.

Relative risk of developing cataracts during the 10-year study was only slightly reduced in the women in the highest quintile of fruit and vegetable intake (10 servings/day) compared to those in the lowest quintile of intake (2.6 servings/day) with a significant trend after adjusting for other lifestyle factors such as smoking, alcohol use, medical and family history, multivitamin use, BMI, menopausal status and use of hormones. However, there was no difference in the rate of cataract extraction between those with high and low intakes of fruits and vegetables.

The strength of this study was the collection of prospective data which is less subject to recall error by subjects than retrospective or cross-sectional studies. However, self-reported data using semi-quantitative food frequencies to record fruit and vegetable which may limit or misclassify some of the available data. Another potential limitation of this study and other dietary and lifestyle studies is that unknown differences between the women with high and low fruit intake may have accounted for some of the observed results in spite of best efforts to adjust for known confounders.

Another study of women (n=479) included a subset of an ongoing trial, the Harvard Nurses Health Study, to determine if diet quality was associated with risk of cataract[35]. The outcome measure was the presence or absence of nuclear opacities. Usual consumption of several food groups including fruits, vegetables and whole grains was determined by averaging self-reported intake from four semi-quantitative food frequency questionnaires completed over a 10 year period. Diet quality and adherence to the *Dietary Guidelines for Americans* was assessed using an adaptation of the Healthy Eating Index (HEI) score developed by the USDA. Cataract status was assessed using a detailed eye exam and several standardized tests including a previously validated grading system to assess for nuclear opacities.

Fruit and vegetable intake did not differ between women with and without nuclear opacities; average fruit intake was 2.5 servings/day and average vegetable intake was approximately 4 servings per day in either group. Women in the upper third and fourth quartiles of fruit intake (median intake of 2.7 and 3.9 servings per day in the third and fourth quartile, respectively) had a slightly lower reduction of risk for the prevalence of nuclear opacities. However, when adjusted for multiple confounders including age, smoking, hypertension, sun exposure, alcohol use, vitamin C supplementation, and physical activity there was no significant effect of fruit intake.

Women who adhered more closely to the *Dietary Guidelines for Americans* were less likely to have nuclear opacities than women who had lower diet quality. Dietary variety and the intake of fruit and milk were the most important individual predictors of reduced nuclear opacity, although fruit was not important in statistical models that analyzed the effect of the entire dietary pattern rather than individual components. The authors concluded that multiple aspects of the diet, in accordance with the *Dietary Guidelines for Americans*, are more important in reducing risk of cataracts than emphasizing one particular food group or component over another.

As suggested earlier, the use of food frequency questionnaires on a biennial basis increases the potential of misclassifying dietary intake as discussed above. However the use of 4 records over a 10 year period and

the completion of eye examinations after collection of dietary data are two strengths of this study.

Another report addressed the link between diet and eye health using macular pigment optical density as a marker[36]. Participants in this study (n=98, 66% female, age range 45-73) completed a 122-item food frequency questionnaire. An adaptation of a commercially available dietary screening tool was used to categorize fruit and vegetable intake as either low (<3 servings of fruit and vegetables/day), medium (3-4 servings /day) or high (≥ 5 servings per day). The aim of the study was to correlate diet and serum carotenoid levels with the amount of macular pigment in the retina. Macular pigment may have health benefits including protection against age-related macular degeneration. It is known that the principle components of pigment in the human retina include three isoforms of carotenoids: lutein, zeaxanthin, mesozeaxanthin. Visual acuity and retinal integrity were assessed using standardized assessments including the Early Treatment of Diabetic Retinopathy Study Chart and the Amsler Grid. Macular pigment optical density (MPOD) was measured at 4 loci using a validated optical system.

The results showed that high intake of fruits and vegetables was associated with significantly higher MPOD compared to measurements in subjects with lower fruit and vegetable intake. Diet and serum concentrations of carotenoids were also positively associated with MPOD. The authors of this study caution that their findings may not be applicable to all populations. Their study subjects were primarily white from New Hampshire and Southern Maine and highly educated with annual household incomes > $50,000 annually. In addition, over half of the study subjects reported consuming 5 or more fruits and vegetables per day. Thus, it is important to determine if the findings of this study apply to a sample that is more representative of the American population.

Summary: Cataracts and Eye Health

While available data relating fruit and vegetable intake to eye health and cataracts are primarily observational, there is sufficient evidence to suggest that further study is warranted, including clinical intervention trials of fruit and vegetable supplementation in order to delineate the true effect of fruit and vegetable intake on eye-related health and disorders.

Arthritis

Arthritis, or joint inflammation, is the leading cause of disability in the United States, limiting the activities of more than 16 million adults[37]. Rheumatoid arthritis (RA) is among the most common forms of joint inflammation and affects an estimated 2.1 million Americans. RA involves inflammatory processes that primarily affect the lining of the joints (synovial membrane). A combination of genetics and unknown environmental factors trigger an inflammatory response associated with a cascade of events including oxidation and production of free radicals and further generation of pro-inflammatory factors. Dietary antioxidants and anti-inflammatory components in food may be important in reducing risk or improving the course of RA. It has been suggested that these agents have the potential to limit tissue damage to the synovial membrane and attenuate progression to destruction of bone and cartilage associated with the disease. Although there are defined diagnostic criteria for RA, the disease often manifests in a gradual and progressive fashion over a course of time making it difficult to determine a clear link between diet and disease onset. Therefore, a number of studies have examined the association between diet and early predictors of RA including the presence of inflammatory polyarthritis (arthritis in several joints) and/or serum markers of RA.

A limited number of studies prior to 2002 suggested that consumption of vegetables might be associated with reduced risk of RA (reviewed in[38]). However, some of the early work was based on crudely defined dietary intake and diagnostic criteria for RA. Recent work using prospective data has suggested, although not conclusively, that fruit and vegetable intake and particularly some nutrients associated with fruit and vegetable intake might be protective.

A report based on data from a subset of the Iowa Women's Health Study used prospective data from 29,368 predominately white, married women, average age 61.4 years[39]. During the 11 year follow-up period between dietary baseline assessment and outcome analysis, 152 women were confirmed to have developed RA. Dietary data, assessed by a 127-item food frequency questionnaire, were analyzed using tertiles of intake for several nutrients and fruit and vegetable intake. It was found that total fruit consumption (> 83 servings per month) was associated with reduced risk of RA in statistical models adjusted for age and energy intake ($p=0.03$) but this association was weakened in multivariate models that adjusted for other risk factors for RA ($p=0.13$). Oranges (> 4 month) were the only individual fruit linked to reduced incidence of RA. However, the association was relatively weak ($p=0.10$) in spite of the finding that β-cryptoxanthin, a carotenoid provided by citrus fruit, was consistently highly protective. Total vegetable intake was not associated with reduced incidence of RA. However, intake of cruciferous vegetables (> 11 servings/month), particularly broccoli (> 3 servings per month), was associated with a moderate effect on RA in adjusted models ($p=0.07$).

Two limitations of this study, acknowledged by the investigators, are the homogeneity of the study population and the use of a single food frequency tool to assess dietary intake at baseline which does not allow for examination of dietary change during the study period follow-up.

Two subsequent reports from the UK, using inflammatory polyarthritis as an early predictor of subsequent RA, suggest a potential effect of fruit and vegetable intake on reducing risk of developing RA. Data for each report were obtained from the European Prospective Investigation of Cancer Incidence (EPIC) Norfolk cohort. Inflammatory polyarthritis (IP) was defined as joint inflammation that affected two or more joints and persisted for more than 4 weeks. Dietary intake was determined from 7-day food records using photographic prompts. Over a 9-year follow-up period, incident cases of IP were confirmed via the Norfolk Arthritis Register and case dietary patterns were compared to matched controls.

In the first report of this dataset, tertiles of dietary intake for 73 cases were compared to intake of 146 controls (mean age 60-61 years; 70% women)[40]. Controls were selected from the EPIC Norfolk cohort but were free of IP at baseline. For cases, the median time interval between dietary assessment and onset of symptoms was 2.1 years. Incident cases reported a lower but not statistically significant intake of fruits and vegetables. Lower intake of combined fruits and vegetables was weakly associated with a higher incidence of IP (p for trend = 0.08). However, dietary vitamin C was significantly correlated; subjects in the lowest tertile of intake (<55.7 mg/day) were three times more likely to develop IP than those in the highest tertile (>94.9 mg/day). These data do not address supplement use but because 14% of controls used vitamin C supplements compared to 6% of cases, the findings support a protective effect of vitamin C.

In a subsequent analysis of these data aimed at determining the relationship with carotenoid intake , the diets of 88 cases were compared to those of 176 controls from the EPIC-Norfolk database (mean age 61 years; 69% women)[41]. It was found that intake of vitamin C and dietary carotenoids, particularly β-cryptoxanthin and to a lesser extent, zeaxanthin, were significantly correlated with reduced risk of IP. However, vitamin C and carotenoid intake were highly correlated and adjustment for vitamin C attenuated the association with the carotenoids.

The strength of the above data is that dietary information was collected prior to the onset of symptoms and based on 7-day food diaries. However, the relatively small number of cases limits the ability to define a dose-response relationship conclusively and may not have the power to determine comprehensive effects.

Summary: Arthritis

In summary, the available data suggest that dietary antioxidants such as vitamin C may be important in reducing onset of inflammatory symptoms leading to RA. There are plausible mechanisms for a protective effect of fruits and vegetables related to inflammatory and oxidative processes associated with onset of arthritis. However, not all antioxidants or total intake of fruits and vegetables emerge as consistently protective in statistical analyses. There is a great deal more work to be done to conclusively state that intake of fruits and vegetables improves risk or prognosis of arthritis.

Diverticulosis

Diverticula are outpouchings of the colon that involve all layers of the colonic wall. Diverticulosis, or the presence of several diverticula, is common in Westernized countries affecting 50% or more of the population over the age of 60 years[42]. The majority of individuals with diverticulosis remain asymptomatic throughout their lifetime. However, an estimated 10-25% of affected individuals will manifest diverticulitis, the most common complication of the divericulosis. Diverticulitis occurs when fecal matter obstructs the neck of diverticula resulting in bacterial overgrowth and possible progression to inflammation, mucosal ulceration and potential hemorrhage.

The association between low fiber diets and the presence of diverticulosis has been well described[43]. Low volume stools, prolonged transit time, straining at the stool and constipation are all associated with low fiber intake. The consequent increase in intraluminal pressure of the colon is believed to be a key factor in herniation of the colon as well as altered collagen synthesis decreasing the strength of the circular muscle of the colon.

Early work in the 1990's showed that intake of fruit and vegetable fiber was inversely associated with risk of diverticulosis in a large prospective study of male health professionals. While there have been no recent intervention or prospective trials in this area, a high fiber diet including fruits and vegetables remains an important aspect of therapy for diverticulosis[44]. In a 2002 position paper by the American Dietetic Association fruits and vegetables were highlighted as important sources of fiber related to gastrointestinal health[44]. High fiber intake prevents the formation of additional diverticula in symptomatic and asymptomatic individuals and lowers intraluminal pressure to reduce the risk exacerbating existing diverticulosis.

Birth Defects

The effect of folic acid supplementation on reducing the risk of neural tube defects of the brain and spine, including spina bifida and anencephaly, is well documented[45]. Public health strategies aimed at achieving the recommended intake of folic acid to reduce birth defects include efforts to combine folic acid supplements with food sources of folate from a healthy and varied diet.

Fruits and vegetables are an important source of dietary folate and their consumption has been associated with increased plasma levels of folate. A recent study including folate data from a subset of middle-aged (47-49 years) and older subjects (71-74 years) in the Hordaland Homocysteine Study in Norway was reported[46]. Food frequency data (169 food items), including 27 questions related to fruit and vegetable intake, were divided into quartiles to determine the association between diet and plasma folate levels in 5533 men and women. There was a significant correlation between increased plasma folate concentration and increased intake of vegetables, fruit, and orange juice. The effect was consistent across age and gender and observed in both supplement and nonsupplement users. The difference in plasma folate concentration between lowest and highest quartiles of intake was approximately 37%. The strength of this study is that folate intake was not based on enriched or fortified foods due to strict regulations prohibiting their production and use in Norway. The majority of folate was derived from natural folate in food sources while vitamin supplement use ranged from 10-21%.

Various studies have shown that plasma folate concentration may increase by 13%, 15%, 23% and 27% after short term feeding experiments with fruits and vegetables (reviewed in[46]. These data indirectly implicate fruits and vegetables as being protective based on their potential to increase the amount of folate available for the neurodevelopment of the fetus. Red blood cell folate also rises with increasing fruit and vegetable intake (from 1 to 7 servings/day) suggesting a longer term effect of fruit and vegetable consumption on folate status[47].

Summary: Birth Defects

In summary, the majority of the data showing a protective effect of folate on birth defects are related to folic acid supplements and not based on natural folate intake. However, a number of studies demonstrate the importance of fruit and vegetable intake on plasma folate levels suggesting their potential contribution to reducing birth defects.

Conclusion

Since 2001, a variety of studies have been conducted to examine the relationship between fruit and vegetable intake and health and disease prevention. The recent data adds to earlier work suggesting that fruits and vegetables appear to have health-promoting properties. In the past 5 years, studies have included a greater emphasis on investigating mechanisms and understanding the bioactive compounds in these foods. However, the majority of evidence linking fruit and vegetable intake to health continues to be observational and data in some areas are conflicting. There is clearly a need for controlled, clinical intervention trials in order to confirm that consumption of fruits and vegetables reduces risk of disease as well as more mechanistic studies to characterize the components and processes that mediate protective effects in humans.

FRUITS AND VEGETABLES—Report Card of Health Benefits

CONDITION	STRENGTH OF EVIDENCE	ASSESSMENT OF EVIDENCE
Pulmonary Function	Diverse human data	Plausible
COPD	Few human studies	Suggestive
Asthma	Growing but conflicting studies	Watching
Bone Health	Growing	Plausible
Aging and Cognition	Limited human data	Watching
Neurodegenerative Diseases	Limited human data	Plausible
Cataracts and Eye Health	Few human studies	Suggestive of moderate effect
Arthritis	Limited human data	Plausible, watching
Diverticulosis	Human data	Convincing for fiber
Birth Defects	Human data	Convincing for folate

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