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5 A Day THE COLOR WAY™

PRODUCE FOR BETTER HEALTH FOUNDATION

December 15, 2003

Patricia Daniels
Director, Supplemental Food Programs Division
Food and Nutrition Service
USDA
3101 Park Center Drive, Room 520
Alexandria, VA 22302

Re: Revisions to the WIC Food Packages, 7 CFR Part 246

Dear Ms. Daniels:

The Produce for Better Health Foundation (PBH) appreciates the opportunity to provide comments on Public Notice 7 CFR Part 246, Revisions to the WIC Food Packages. PBH is the founding partner, along with the National Cancer Institute, of the National 5 A Day for Better Health Program that encourages all Americans to eat 5 to 9 servings of fruits and vegetable each day.

The WIC program represents one of the most important investments this country can make in the health of our nation's mothers and children. The WIC program serves on average 7.5 million women and children, with over 50 percent being children ages one through five. WIC is proven to be one of the premier nutrition assistance programs that saves money and promotes healthy habits for life by providing supplemental foods and nutrition education to low-income pregnant, breastfeeding and post-partum women, infants and children. The WIC food package, coupled with the nutrition education component, highlight the important role of education combined with access.

PBH strongly supports updating the WIC food package to assure that the package offerings are better aligned with current nutrition science, especially with respect to the growing body of evidence linking increased fruit and vegetable intake with the promotion of health and the prevention of a variety of chronic diseases.

As seen below, both the Dietary Guidelines for Americans as well as the Food Guide Pyramid promote the intake of at least 5 to 9 servings of fruits and vegetables daily for all Americans 2 years of age and older.

> *2000 Dietary Guidelines for Americans: Choose a variety of fruits and vegetables daily.*

EAT 5 A DAY
Member National
5 A Day Partnership

534 Limestone Road ◆ Wilmington, DE 19808, U.S.A. ◆ www.5aday.com
Phone (302) 235-2329 ◆ Fax (302) 235-5555

To promote your health, eat a variety of fruits and vegetables – at least 2 servings of fruits and 3 servings of vegetables – each day.

The Food Guide Pyramid recommends 3 to 5 servings of vegetables and 2 to 4 servings of fruits daily, for a combined total of 5 to 9 servings each day.

The 5 A Day for Better Health message is a widely recognized and easily understood message that has broad-based support from many audiences, including government agencies, the fruit and vegetable industry, and public health experts. In April 2002, HHS, three mission areas of USDA, and the National Cancer Institute signed a Memorandum of Understanding outlining their commitment to work together as part of the National 5 A Day Partnership to help Americans meet the recommendations to eat 5 to 9 daily servings of fruits and vegetables.

We urge USDA and the Institute of Medicine to base food package revisions on the Federal Guidelines put forth in the Dietary Guidelines, the Food Guide Pyramid, as well as IOM reports that have raised the requirement for a number of important nutrients, including vitamin C, vitamin K, folate, and fiber.

Below is a summary of key findings regarding fruit and vegetable intake among Americans, as well as the role of parents and caregivers on fruit and vegetable intake among infants and children. Also attached is a more detailed description of key studies pertaining to the role of increased fruits and vegetables in disease prevention.

It is important to recognize, particularly for the WIC population, the importance of role modeling and the influence of parental/caregiver food and dietary practices, especially regarding fruit and vegetable intake, on infant, child and adolescent habits. Not only does the WIC program provide an excellent opportunity to instill healthy eating practices at an early age, but for the pregnant and post-partum women it also provides an opportunity for them to role model healthy habits. The current WIC food packages for women (V, VI and VII) do very little to help pregnant and new mothers be good role models regarding fruit and vegetable intake.

Summary of Key Fruit and Vegetable Findings/Research:

Current Intake Patterns for Fruits and Vegetables Among Various Groups:

- The average American eats 1.5 servings of fruits and 3.3 servings of vegetables per day (this includes French fries) and French fries make up 20% of vegetable servings for adults 20 and older and 32% for children 2 to 19 years old.
- Only 23% of Americans get their recommended number of servings of fruit and 41% get their recommended number of vegetable servings each day.
- Several surveys, including CDC's Behavioral Risk Factor Surveillance System (Li et al, 2000), USDA's Economics Research Survey (Putnam et al, 2000), the Michigan Behavior Risk Factor Survey (Anderson et al, 2001), and research conducted by

professional market research firms (NPD, 2002) and on free-living adults (DeBoer et al, 2003) have documented that few Americans are attaining even the minimum goal of 5 servings of fruits and vegetables per day.

Disease Prevention and Fruit and Vegetable Intake:

- Higher fruit and vegetable intakes can help reduce the risk for many chronic diseases, including cardiovascular disease, cancer, lung disease, and some age-related diseases such as osteoporosis, macular degeneration, and cataracts.
- Findings from the DASH Diet, PREMIER Study, Nurses' Health Study, Health Professionals' Follow-Up Study, World Cancer Research Fund and others support the important role that fruits and vegetables play in promoting health.
- Several studies have found that eating 5 to 10 daily servings of fruits and vegetables can help reduce the risk for major chronic diseases, including cardiovascular disease and cancer.

  Numerous studies have pointed to the importance of fiber in reducing cardiovascular disease risk and in promoting weight control and weight loss. The average American consumes about 15 grams of fiber per day, an amount far less than the 25 grams recommended by the NAS for women and 38 grams recommended for men. Encouraging the consumption of fruits, vegetables, legumes and whole grains is the best way to increase one's fiber intake.

Lack of Variety of Fruit and Vegetable Intake among Americans:

- A limited number of fruits and vegetables provide the majority of these foods consumed by average Americans.
  - Only 3 vegetables (potatoes, iceberg lettuce, and canned tomatoes) accounted for almost half (48%) of vegetable consumption in the United States in 2000.
  - Only 3 fruits (oranges, apples, and bananas) contributed one-half of total daily fruit servings in 2000, according to ERS (Putnam et al, 2002).

Childhood Eating Patterns:

- USDA's Center for Nutrition Policy and Promotion documented that due to poor choices, most children have diets that 'need improvement' or are frankly 'poor,' particularly in fruits and vegetables, as judged by the Healthy Eating Index (HEI).
- An increasing body of evidence is revealing that early feeding experiences determine food preferences and habits, thus impacting on later risk for chronic disease.
- Parental diet and activity patterns strongly influence the habits of children.
- Introduction of sound eating habits early in life is likely to reduce one's risk for chronic diseases.

PBH offers the following recommendations for you to consider regarding fruits and vegetables in the WIC Food Package.

1. A wider variety of fruits and vegetables must be included in the WIC Food Package.

The current WIC Food Package is extremely poor in fruits and vegetables. Right now, the only fruit included in the five WIC food packages is fruit juice; and the only vegetable allowed is carrots permitted in the breastfeeding food package (Package VII).

PBH recommends increasing the amount of fruits and vegetables offered in food packages II through VII, and allowing substitutions of fresh, canned, and frozen fruits and vegetables for the current juice allocations. PBH recommends that USDA create a fruit and vegetable category of WIC foods, in which 100% juice is but one offering within this category, and that whole fruits and vegetables be emphasized.

PBH supports the National WIC Association position that:

Selection criteria should include fruits and vegetables high in vitamin A, vitamin C, folic acid, B6, magnesium, fiber and antioxidants, with year round availability at a low to moderate price. The inclusion of cruciferous vegetables is encouraged. Possible items would include: carrots, citrus fruits, tomatoes, sweet potatoes, greens, or broccoli. These foods would be offered in addition to any produce available through the WIC Farmers' Market Nutrition Program. (National WIC Association Position paper: WIC Food Prescription Recommendations, *2000)*

At a time with research is exploding on the important role of fruits and vegetables in promoting health and preventing disease, coupled with USDA's commitment to promoting 5 A Day, WIC Food Packages must be better aligned with current public health recommendations and include greater variety of fruits and vegetables. Current WIC Food Packages are not consistent with Federal nutrition guidance urging Americans to consume more fruits and vegetables. Nor do the packages reflect the commitment USDA has made to the 5 A Day program as detailed in the Memorandum of Understanding between USDA and the Department of Health and Human Services in April, 2002.

2. PBH strongly encourages USDA to assure that the WIC food packages only include fruits and vegetables that have been processed in a way that maintains their integrity as healthful foods. They should not include in the WIC food package fruits and vegetables that are fried or served with fatty sauces.

PBH recommends that USDA set limits on the amount of amount of added sugar, salt, saturated and trans fat that can be included in canned, dried, frozen and prepared fruits

and vegetables allowed as part of the WIC food packages. PBH would welcome the opportunity to work with USDA to help develop healthy criteria for these limits.

3. The amount of juice offered in the Food packages should be reduced.

Attached is a letter PBH sent to USDA in November 2001 outlining recommendations for reducing the amount of juice offered. Such a reduction is consistent with public health recommendations put forth by the American Academy of Pediatrics as well as the National WIC Association. This reduction will also help offset the cost of increasing whole fruit and vegetable items as recommended above.

4. The WIC Food Package must better accommodate cultural and participant preferences, regional variations of supply, and cost and administrative factors.

This recommendation is especially critical regarding fruit and vegetable offerings. Given the wide variation in cost and availability of fruits and vegetables across the country, a more flexible system will allow participants to have access to a greater variety of nutritious and economical products. For example, states should have the flexibility to substitute a more economical fruit or vegetable offering if there is an abundance of that product certain times of the year. Such a substitution would have to be made within the prescribed nutrition profile of the package.

In addition, there must be greater flexibility in the rules governing the food package to better provide for cultural differences among participants. Specifically, the WIC rules should more effectively and efficiently accommodate substitutions of nutrient-dense culturally appropriate foods. For example, cultural food package that contained tomatoes, or peppers would be more acceptable to Hispanic participants.

PBH urges USDA to consider the recommendations put forth in the National WIC Association position paper "*NWA Culturally Sensitive Food Prescription Recommendation,*" 2003 when developing guidelines and regulations regarding food package flexibility.

5. Fruit and vegetable consumption should be encouraged through WIC nutrition education programs.

While PBH recognizes that the Federal Register notice soliciting comments does not address nutrition education, PBH urges USDA to strengthen educational efforts especially with respect to promoting greater consumption of fruits and vegetables among WIC participants. Given the increasing role of fruits and vegetables in chronic disease prevention, and the importance of role modeling healthful eating habits, the WIC population would benefit greatly from expanded educational efforts surrounding fruits and vegetables.

Early in 2002, PBH began working with a research firm to conduct a series of qualitative research sessions to evaluate and further develop the concepts and materials for PBH's "5 A Day The Color Way" campaign. Overall, the creative materials have been highly effective at defining the "5 A Day The Color Way" concept to a diverse audience of consumers. A summary of the research is attached. Key findings from the focus group research showed:

The creative concepts consistently communicated the importance of eating a colorful variety of fruits and vegetables on a daily basis. Virtually all respondents reacted with genuine enthusiasm to the connection between "colors" and variety, and to the overall health-based orientation of the campaign.

- For most respondents, the concept of linking health with a colorful approach to eating was seen as "new" and a relevant, compelling message. The message clearly resonates with consumers' desire to make healthy eating choices. In particular, the Color Way logo, Color Model graphic and The Color Way Guide brochure tested as powerful tools for delivering the message, (samples attached).

PBH urges USDA to consider incorporating the "color" concept into WIC nutrition education guidance to better communicate in a specific and effective way, the importance of eating a variety of fruits and vegetables.

The Produce for Better Health Foundation looks forward to continuing efforts with USDA and the Institute of Medicine in efforts to revise the WIC food packages. This revision provides a wonderful opportunity to better promote a colorful variety of fruits and vegetables to millions of mothers, infants and children to enhance the nutritional benefits of the program and bring it in line with federal nutrition recommendations.

Sincerely,

Elizabeth Pivonka, PhD, RD
President, Produce for Better Health Foundation

Attachments:
Letter dated Nov. 8, 2001 re: WIC Juice recommendations
Fruit and Vegetable Research Findings

References

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Putnam J et al. U.S. per capita food supply trends: more calories, refined carbohydrates, and fats. *Food Review* 2002; 25:2-15.

November 8, 2001

Patricia Daniels
Director
Supplemental Food Programs Division
U.S. Department of Agriculture
Food and Nutrition Service
3101 Park Center Drive
Alexandria, VA 22302

Dear Ms. Daniels:

The **Produce for Better Health Foundation** (PBH) supports the position of the National WIC Association (NWA) in response to the draft WIC Policy Memorandum, *Categorical Nutrition Tailoring of Juice for Infants and Children.*

PBH is the catalyst for creating a healthier America through increased consumption of fruits and vegetables. The Foundation is a nonprofit organization which, in cooperation with the National Cancer Institute (NCI), sponsors the national 5 A Day – for Better Health program

To this end, PBH urges FNS to reconsider the policy on fruit juice in infants and support the NWA position outlined in the October 16, 2001 letter submitted by NWA in which NWA:

Supports delaying the issuance of juice to all infants until they are 6 months of age. We believe this policy will prevent the replacement of breastmilk or infant formula with juice, reduce the risk of nursing-bottle caries, and reduce the risk/incidence of poor health/growth outcomes due to over-consumption of juice.

- *Does not support the proposal to reduce juice without replacing it with fresh, frozen, or canned fruits and vegetables. The reduction of juice without the concomitant addition of fruits/vegetables will seriously compromise the nutritional value of the food prescription.*

  Vitamin C is essential to the integrity of the WIC food prescription. The inclusion of fruits and vegetables will provide an excellent source of vitamin C as well as additional nutrients.

- *The reduction of juice without replacement with fruits and vegetables would potentially trigger food insecurity in our nation's most needy families.*

(Note: Language in italics from Oct. 16, 2001 NWA letter to P. Daniels.)

PBH was instrumental in advocating greater prominence for fruits and vegetables in the 2000 edition of *the Dietary Guidelines for Americans.* For the first time since the guidelines were issued, a separate guideline encouraging Americans to eat more fruits and vegetables is now included. The new guideline states: "Choose a variety of fruits and vegetables daily."

Furthermore, research shows that increasing fruit and vegetable consumption reduces the risk of cancer and numerous other serious illnesses including heart disease, stroke, and diabetes. The USDA also estimates that better nutrition could reduce the costs associated with diet-related illnesses by $71 billion each year, enough savings to nearly fully fund the Department's activities each year.

The WIC program is instrumental in improving the health and nutritional status of the women, infants and children it serves and stands as a model program among the 15 nutrition assistance programs. Eliminating the important nutrients provided by fruit juice without replacing with fresh, frozen or canned fruit or vegetable items, goes directly against the very public health recommendations USDA supports – such as the Dietary Guidelines for Americans.

Please reconsider the fruit juice policy and assure that appropriate fruit and vegetable substitutions are provided to the WIC population.

Sincerely,

Elizabeth Pivonka, PhD, RD
President

cc: Douglas Greenaway, Executive Director NWA/NAWD

Cardiovascular Disease

Section Editors.

Howard Sesso, Sc.D., MPH
Department of Epidemiology, Harvard School of Public Health, Boston, MA
Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Teresa T. Fung, ScD, RD, LDN
Assistant Professor, Department of Nutrition, Simmons College, Boston, MA; and
Adjunct Assistant Professor, Department of Nutrition, Harvard School of Public Health Boston, MA

Frank Hu, M.D., Ph.D.
Dept. of Nutrition, Harvard University School of Public Health, Boston, MA

The term cardiovascular disease (CVD) encompasses coronary heart disease, stroke, hypertension, congestive heart failure, congenital defects, and other circulatory diseases which are associated with inadequate blood circulation. Nearly 62 million Americans have some form of CVD.[1] The total direct (healthcare) and indirect costs (loss in productivity) of CVD estimated for 2003 is an astounding $351.8 billion.[1] This section focuses on coronary artery disease (CAD), also known as coronary heart disease (CHD). CHD includes acute myocardial infarction (MI), other acute ischemic heart disease, angina pectoris, atherosclerotic cardiovascular disease, and all other forms of chronic ischemic heart disease.[1] Stroke and hypertension will be discussed in later sections of this document.

Coronary Heart Disease

Statistics

CHD is the leading cause of noncommunicable disease mortality globally and the major killer of Americans. In 2000, CHD accounted for 1 of every 2.5 deaths in the United States (U.S.).[1] In 2001, an estimated 699,697 deaths in the U.S. were attributable to heart disease.[2] For each person who dies of CHD, nearly 20 others are affected (a prevalence of 12,900,000 Americans).[1] For 2003, the estimated direct and indirect costs of CHD were $61.2 billion and $129.9 billion, representing 17% and 37% of the total cost of CVD respectively.[1]

Cardio-Protective Effects of a High Fruit and Vegetable Intake

The ability to explain the molecular mechanisms of atherosclerosis and the metabolic effects of bioactive compounds in foods has contributed to a greater

understanding of the pathology of CHD.[3] Fruits and vegetables contain a variety of compounds such as phytochemicals, potassium, and fiber that play roles in reducing CHD risk.[4,5,6] In addition, use of a multi-factorial approach to the study of CHD prevention and treatment strategies has enhanced the potential application of findings obtained from large prospective studies and intervention trials. In a comprehensive review of research related to CVD, the World Health Organization (WHO) expert panel report[6] categorized compounds in fruits and vegetables based upon the following three levels of evidence: convincing, probable, and possible. A "convincing" level of evidence has been established for the consumption of diets high in fruits and vegetables, as well as potassium and reduced risk of CVD. A "probable" level of evidence has been established for diets high in folate, plant sterols and stanols; and "possible" associations for flavonoid consumption and reduced risk of CVD. The strength of evidence was regarded as "insufficient" for vitamin C.

Evidence regarding the cardio-protective effects of consuming diets high in fruits and vegetables has been reported in numerous investigations. A large scale, prospective cohort study[7] using a sample of participants from the Nurse's Health Study (n=84,251) and the Health Professional's Follow-up Study (n=42,148) identified an inverse association between fruit and vegetable intake and CHD. Men and women with the highest intake of fruit and vegetables (median intake = 10.15 servings per day for women; 9.15 servings per day for men) had a 20% lower risk for CHD compared to those with the lowest intake (median intake = 2.93 servings per day for women, 2.54 servings per day for men). Each 1-serving per day increase in fruit or vegetable intake was associated with a 4% lower risk for CHD. Fruits and vegetables contributing most to the apparent protective effect were: green leafy vegetables (23% risk reduction with a 1 serving per day increase) and vitamin C-rich fruits and vegetables (6% risk reduction with a 1 serving per day increase). The Physician's Health Study found that men who consumed at least 2.5 servings per day of vegetables had a 23% reduction in CHD when compared with men consuming <1 serving per day.[8] For each additional serving per day of vegetables, the risk of CHD decreased by 17%. While an impressive risk reduction, these results were based on a more limited dietary assessment that included vegetable intake only. Even so, this study provides additional evidence that incremental increases in vegetable intake may confer CHD risk reduction benefits. The protective effect of vegetable intake persisted even when the contributions of other known coronary risk factors, such as overweight and smoking status were considered. Analysis from the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-Up Study (n=9,608) also demonstrated a strong inverse association between fruit and vegetable intake and risk of ischemic heart disease mortality and CVD mortality.[9] Individuals who reported consuming at least 3 servings per day of fruits and vegetables had 24% and 27% reductions in risk of death from ischemic heart disease and cardiovascular disease, respectively. Further, in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study,[10] a high intake of fruits, berries and vegetables (excluding potatoes) was associated with decreased mortality in men. In this study, 2,641 men were followed for a mean of 12.8 years. When compared to men with the lowest fruit, berry, and vegetable intake, men with the highest reported consumption had a 41% risk reduction for CVD-related mortality. The protective effect of fruits, berries, and vegetables on CVD mortality was attributed by varying degrees to three key nutrients,

with vitamin C explaining 19.4% of protection, folate providing 14.6% of the protective benefit, and vitamin E only 1.9%. Although the clinical significance has not yet been determined, the intake of fruits, berries and vegetables correlated with serum haptoglobin, a biomarker of inflammation, and plasma fibrinogen, which may promote blood clot formation[10] and is a known independent risk factor for CVD.[11] Considering that both fibrinogen and inflammatory markers are involved in atherosclerosis,[12] further research on the effects of fruits and vegetables on these biomarkers is warranted.

Folate, Homocysteine, and CHD

Several specific nutrients have been linked to CHD. Evidence is accumulating from case-control and prospective observational cohort studies, as well as *in vitro* and *in vivo* experiments regarding the interrelationship of folate and total homocysteine (tHcy). The role of folate in CHD prevention independent of tHcy has also been examined.[13, 14] A number of epidemiological studies have found an inverse association between either low plasma folate concentrations or low dietary folate intake and risk of CVD.[15,16] It is well established that there is a relationship between CVD (including stroke) and total plasma homocysteine (tHcy) levels.[13] High plasma tHcy (i.e., hyperhomocysteinemia) concentrations are considered to be an independent risk factor for CHD.[14] A recent meta-analysis indicated the relationship may be causal and suggested that reductions in homocysteine achievable by a higher intake of folate (0.8 mg folic acid) could decrease the risk of ischemic heart disease by 16% and stroke by 24%.[15] Folate, found in abundance in several fruits and vegetables, plays a role in the conversion of homocysteine to methionine, thereby helping to reduce homocysteine concentrations in the blood. Inadequate folate, vitamin B6 or vitamin B12 intakes may be associated with elevated tHcy levels.[16,17,18] A recent report from the Kuopio Ischemic Heart Disease Risk Factor Study found that men with the highest folate intake had a 55% reduction in risk of acute coronary events when compared to men with the lowest intake.[16] A randomized, placebo-controlled intervention trial[19] evaluated the effects of dietary forms of folate on serum folate and plasma tHcy levels. Participants (15 women and 19 men) were assigned either to a dietary group (provided with fortified cereal and instructed on ways to increase dietary folate intake to reach a target of 600 mcg/day) or a control group (given unfortified cereal and no instruction). Serum folate concentrations increased significantly (37% higher) and plasma tHcy concentrations decreased significantly (10%) in the dietary group compared to those in the control group. Data from a recent case-control study[20] (n=171) supports a potentially causal association between dietary folate and decreased risk of MI. Those subjects in the three highest quartiles of folate intake had a 43% lower risk of MI when compared to those classified in the lowest quartile of folate intake. Several studies examining nutritional and genetic factors[18,21, 22] influencing tHcy validate efforts to increase folate intake already established by some countries.

It has been proposed that folic acid improves endothelial function in CAD acutely and possibly longer-term by a mechanism largely independent of tHcy.[23,25] Endothelial dysfunction may contribute to decreased blood flow and formation of blood clots. Both of these processes lead to the development of atherosclerosis and studies indicate that endothelial dysfunction independently predicts cardiovascular events.[24] A well-controlled intervention trial demonstrated that with folic acid treatment, flow-mediated dilation improved dramatically at 2 and 4 hours after the first dose.[25] There were no

significant differences between tHcy levels during the 4 hours after the first treatment; however, tHcy was significantly decreased after 6 weeks of treatment with folic acid. The change in flow-mediated dilation was not correlated with tHcy at any point of the intervention.[25]

Antioxidants, Flavonoids, and CHD Risk Reduction

An imbalance in human antioxidant status provides an environment for the promotion of chronic diseases related to oxidative stress, including CHD. Because of differences in lifestyle, diet, genetics, and the environment, the antioxidant potential among individuals varies. Dietary antioxidants (e.g., carotenoids, vitamins C and E) and other 'functional' compounds, such as phytochemicals, may play an important role in the protection against oxidative stress-related diseases.[5, 6,26,27]

Carotenoids

There are over 500 plant-derived carotenoids, of which lutein, lycopene, beta-cryptoxanthin, alpha-carotene and beta-carotene account for most of those found in plasma.[28] High dietary intakes and blood concentrations of carotenoids are associated with potential health benefits against chronic diseases, including CVD. Cardio-protective mechanisms attributable to carotenoids include quenching of oxygen radicals and inhibiting lipid peroxidation or low density lipoprotein (LDL) oxidation.[5,26] Carotenoids may also protect vascular cells and function from oxidative injury through actions that are independent of their inhibitory roles on LDL oxidation.[5]

Individuals who consume high amounts of fruits and vegetables tend to have higher blood concentrations of carotenoids.[28] An inverse association between the blood concentration of various carotenoids, intakes of carotenoids as a group, and the risk of CHD has been shown by many prospective studies.[28] However, few studies have examined the relationship between dietary intakes of *specific* carotenoids and cardiovascular disease risk.[28] In the Nurse's Health Study, 73,286 women completed a food frequency questionnaire using blood concentrations of carotenoids as a basis for validation.[28] Foods that provided the greatest contribution to the total absolute intake of carotenoids were ascertained. Women in the highest quintile of beta-carotene and alpha-carotene intake had a 26% and 20% lower risk of CHD respectively when compared to women in the lowest quintile of intake. Randomized supplementation studies have failed to show an association between high intakes of carotenoids such as beta-carotene and reduced risk for CHD. The lack of protective effect of beta-carotene supplementation suggests that other compounds found in foods high in beta-carotene may account for the apparent risk reduction benefit observed in prospective studies. In addition, carotenoids may act additively or synergistically with other antioxidants, such as vitamin E or C, to protect against CHD.[29]

Lycopene

Lycopene, the acyclic form of beta-carotene, is a more potent antioxidant than alpha- or beta-carotene, and has been shown to have the highest oxygen-quenching rate of all the carotenoids.[30] These antioxidant properties appear to be resistant to heat and

cooking and the bioavailability of lycopene is higher in processed tomato products than fresh tomatoes.[31] One of the central mechanisms shown by lycopene to reduce risk of CHD is through inhibiting LDL oxidation.[30] Although results have not been consistent for men and women,[32] serum lycopene has also been implicated as a possible mediator between atherosclerotic progression and intima-media thickness of the common carotid artery (CCA-IMT),[33,34] a predictor of coronary events.[35] The associated benefit of lycopene remains significant after adjustment for other plant-derived compounds, including serum folate, beta-carotene, and alpha-tocopherol.[33,34]

Lutein

Using a combination of epidemiological, in vitro, and animal model findings, a strong case has recently emerged for the protective role of lutein against the development of early atherosclerosis.[36] Lutein is a carotenoid found in many fruits and vegetables. Findings from a prospective investigation[36] involving 480 participants aged 40 to 60 years in the Los Angeles Atherosclerosis Study suggest that lutein-rich foods have a beneficial effect on reducing progression of early atherosclerosis. This benefit appears to be dose-dependent, and related to an antioxidant pathway involving resistance to LDL oxidation and pathways that involve reduced inflammation, another notable mechanism of CHD initiation and progression.[12]

Flavonoids

Recently, a number of prospective studies[37,38,39] have found an inverse association between dietary flavonoids (and related phenolic compounds found in fruits, vegetables, grape juice and wine) and CHD, although this relationship has not been consistent across studies.[40] Flavonoids such as flavones, isoflavones, flavonols and flavanes are widely distributed in fruits and vegetables. Cells that are involved in immunity and inflammation (e.g., macrophages, platelets) have been shown to be affected by some flavonoids,[41] a fact which may be of great significance given that the roles of the immune system and inflammation in the development of cardiovascular disease.[42] Flavonoids are effective antioxidants because they have free radical scavenging abilities and are chelators of metal ions (e.g., iron and copper) known to catalyze free radical production.[39] Several sources indicate quercetin is the most potent antioxidant of the flavonoids.[43] In a Finnish study of 10,054 men and women, persons with higher quercetin intakes had a 21% lower risk of mortality from ischemic heart disease compared to those with the lowest intakes.[38] Of the dietary sources rich in flavonoids, apple and onion intakes were significantly associated with a decrease in ischemic heart disease mortality; oranges had a nonsignificant, but strong association. A large cohort study involving 25,372 male smokers with no previous MI provided evidence of an 11% reduction in CHD mortality associated with high flavonol and flavone intake.[39] In addition, results indicated a 23% reduction in risk of nonfatal myocardial infarction among men in the highest quintile (median 18 mg per day) compared with the lowest (median 4 mg per day) quintile of flavonol and flavone intake.[39] Other studies reported results contradictory to the findings described by these two studies, or were inconclusive with regard to the benefits of flavonoid intake.[39,40] Clearly, more research is needed in this area.

Vitamin C

Vitamin C intakes have been shown to be inversely related to systolic blood pressure,[44,45] oxidative stress,[46] and body mass index,[44] and positively related to high density lipoprotein (HDL) cholesterol,[44] and nitric oxide-mediated vasodilation,[46,47] all of which are acknowledged mediators of CHD and support the potential cardioprotective role of vitamin C. Findings from the EPIC-Norfolk study involving 19,496 males and

females aged 45 to 79 indicated that a 20 umol/L plasma vitamin C concentration change (achievable with an increase of approximately 1 daily serving of a vitamin C rich fruit or vegetable) was associated with a 32% reduction in mortality risk for CHD. Although the number of CHD events was smaller and trends were less consistent for women than for men, these data support a potential dose-response relationship between vitamin C and CHD.[44]

Dietary Patterns and CHD

Although many studies published in the literature document the effects of single nutrients, bioactive compounds, or specific foods on CHD, there are inherent advantages of examining associations between overall dietary patterns and CHD. By assessing overall dietary intake, the 'synergistic effect' of diet can be more easily detected and described for translation into practice and to establish dietary recommendations and guidelines.[48] Dietary patterns may be useful in predicting chronic disease risk factor outcomes. A recent report[3] summarized evidence from 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials through May 2002. At least three dietary strategies for which there is substantial evidence of effectiveness in preventing CHD were identified: (1) substitute nonhydrogenated unsaturated fats for saturated and trans-fats; (2) increase consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources; and (3) consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grain products. Using factor analysis on food frequency questionnaire data from the Health Professionals Follow-up Study (n=466), two primary dietary patterns, 'prudent' and 'Western' were identified as useful in assessing relationships between diet and biomarkers (i.e., plasma lipids, thrombogenic factors, indicators of glycemia, inflammatory markers, leptin, folate, homocysteine) of obesity and CVD.[49] The 'prudent' pattern, characterized by higher intakes of fruit, vegetables, whole grains, and poultry, was associated with more favorable biomarker outcomes for cardiovascular risk reduction than the 'Western' pattern, characterized by higher intakes of red meat, high-fat dairy products, and refined grains. Using dietary pattern scores, significant positive correlations were found between the Western pattern and insulin, C-peptide, leptin, and homocysteine concentration, and an inverse correlation found with plasma folate. The 'prudent' pattern was positively correlated with plasma folate and inversely correlated with insulin and homocysteine concentrations. Several studies were published between 2001and 2003 that focused on the Mediterranean dietary pattern and potential risk reduction for CHD.[50,51,52,53] In a randomized single-blind trial, 1,000 high risk cardiac patients were either assigned to follow an alpha-linoleic rich diet rich emphasizing whole grains, fruits, vegetables, walnuts, and almonds or a control diet, similar to the National Cholesterol Education Program (NCEP) prudent diet.[50] The treatment diet group experienced significantly fewer cardiovascular events than the controls. Although this study did not specifically examine fruit and/or vegetable intake as an independent variable, the findings do lend support to the cardio-protective effect of a diet high in fruits and vegetables.

Summary of Evidence

Based on this review of literature emphasizing articles published 2001-2003, the value of fruit and vegetable consumption and reduced risk of CHD has been established largely through epidemiological studies. More clinical trials and dietary intervention studies are needed to better understand the relationship of increased fruit and vegetable consumption on CHD-related markers and events such as hypertension, stroke, and MI. The overall benefit of an approximate 20% reduction in CHD supports the protective effect and current recommendations to consume more fruits and vegetables.

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Hypertension

Section Editor:
Lawrence Appel, M.D., MPH
Professor of Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland

Statistics and Background

Over 50 million adults in the United States have hypertension or high blood pressure.[1] Hypertension has been associated with dementia and cognitive impairment[2] and can lead to many degenerative diseases of vascular origin[3,4,5] such as CHD,[6,7] stroke, congestive heart failure, and kidney disease. An age-related increase[8,9] in the prevalence of hypertension has been identified in many populations, with more than half of Americans over the age of 60 years affected.[3] Hypertension is often called the silent killer because many people are asymptomatic, with an estimated 30% of those with hypertension undiagnosed.[1] Of those affected, approximately 90-95% have primary hypertension, for which the cause is likely related to adverse lifestyle factors. These individuals may be managed in part with weight loss and lifestyle and dietary modification.[1] The other 5-10% of cases of hypertension ('secondary' hypertension) are usually related to renal (kidney) or endocrine diseases, and are managed primarily through antihypertensive drug therapy.[1,10] Overall, hypertension control rates are estimated to be less than 27% nationwide.[11]

Classification of blood pressure levels are established by the Joint Commission on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[7] "Normal" blood pressure is <120 mmHg for systolic blood pressure (SBP) and <80 mmHg for diastolic blood pressure (DBP); "Prehypertension" levels are 120-139 mmHg SBP or 80-89 mmHg DBP; "Stage 1 Hypertension" is 140-159 mmHg SBP or 90-99 mmHg DBP; and the more severe "Stage 2" is SBP ≥160 mmHg or DBP ≥100 mmHg. Epidemiological data suggest that a 2 mmHg reduction in SBP[3] or DBP[12] would result in a 17% decrease in the prevalence of hypertension, a 14-15% reduction in risk of stroke and ischemic heart attacks, and a 6% reduction in the risk of CHD.

Lifestyle Modifications Can Aid Blood Pressure Control

Lifestyle modifications are recommended as an important component in blood pressure control for the general population[3], especially those with prehypertension, and for those with hypertension who may or may not take antihypertensive drugs.[6] Lifestyle changes are considered of utmost importance for those with prehypertension, due to an increased risk for progression to hypertension. Those in the 130-139 mmHg SBP and 80-89 mmHg DBP range are twice as likely to develop hypertension than those with lower values.[13] Lifestyle modifications with the corresponding average estimated range for SBP reduction[6] include: weight reduction in those who are overweight or obese[9,14,15,16] (5-20 mmHg per 10 kg), adherence to the Dietary Approaches to Stop Hypertension

(DASH) eating plan[17] (8-14 mmHg), dietary sodium reduction[17,18] (2-8 mmHg), aerobic physical activity[19] (4-9 mmHg), and moderation of alcohol consumption[20] (2-4 mmHg). Potassium intakes equal to 3500 mg/day[19] (in the DASH diet 4700 mg per day[21]) have also been shown to improve blood pressure control,[22,23,24,37] with dietary sodium-to-potassium ratio considered to be a risk factor for hypertension.[25] A diet high in fruits and vegetables is supportive of several of these lifestyle modification recommendations.

Benefits of the DASH Diet

The DASH randomized clinical trial demonstrated the important role of multiple dietary factors in blood pressure control. The DASH diet emphasizes fruits, vegetables, and low-fat dairy products, includes whole grains, poultry, fish, and nuts, and contains only small amounts of total fat, cholesterol, and saturated fat, red meat, sweets, and sugar-containing beverages.[11,17] This dietary pattern was designed to be higher in potassium, magnesium, calcium, fiber and protein and lower in saturated and total fat and cholesterol than the typical U.S. diet.[21] In participants with hypertension, the effects were equal to or greater than those of single drug antihypertensive therapy, with reductions achieved by the combined DASH diet and low sodium intake of 8.9 mmHg (SBP) and 4.5 mmHg (DBP).[17] Importantly, the DASH trial showed that factors other than sodium intake, weight, and alcohol consumption also directly affect blood pressure.[17]

Benefits associated with blood pressure reduction are possible through dietary changes that include a high intake of fruits and vegetables. In a large-scale study conducted by the PREMIER Collaborative Research Group, 810 adults with above optimal blood pressure, including persons with Stage 1 hypertension and not taking antihypertensive medications, were randomly assigned to one of three treatment groups: "established" (implemented established lifestyle recommendations, i.e., weight loss if overweight, reduced sodium intake, increased physical activity, and limited intake of alcohol), "established plus DASH", or the "advice only" comparison group.[6,26] The interventions were theory-based, behavioral interventions focusing on multiple components of lifestyle change.[26] Fruit and vegetable intake increased significantly in the established plus DASH group compared with the other two groups, with corresponding changes in urinary potassium excretion. At 6 months, one-third of the established plus DASH group participants achieved the dietary intake goal of 9 or more servings of fruits and vegetables per day compared to only 6% in the other groups. Significant reductions in SBP and DBP were seen with the established and the established plus DASH groups. The blood pressure change was consistently greater in the established plus DASH group compared to the other groups, in spite of a lack of statistical significance.

In another controlled trial, 44 hypertensive, overweight adults aged 22 to 70 years and taking one antihypertensive medication were randomly assigned to either a control group or a comprehensive "lifestyle" intervention group.[11] The lifestyle intervention was designed to promote weight loss. Participants were fed a hypocaloric version of the DASH diet that contained 100 mmol per day (2.4 g) of sodium and engaged in a supervised, moderate intensity aerobic exercise program 3 times per week. The intervention achieved significant mean reductions of 9.5 mmHg SBP and 5.3 mmHg

DBP, similar to reductions by the DASH-Sodium trial hypertensive participants (not on antihypertensive medication). Comprehensive lifestyle changes achieved reductions in blood pressure similar in magnitude to drug therapy, but also supported other outcomes such as weight loss, fitness, and reductions in serum cholesterol levels that provide health benefits in addition to blood pressure reduction alone.[11]

Increased Fruit and Vegetable Consumption Reduces Blood Pressure

Adherence to lifestyle modification recommendations is challenging and complex. To examine the feasibility and effect of a theory-based, goal-oriented and individualized educational intervention reinforcing the 5 A Day message to increase fruit and vegetable consumption in a general population, 690 healthy participants aged 25-64 years were recruited from a primary-care health center.[27] After the educational intervention, there was a significant difference in self-reported fruit and vegetable intake, with the intervention group increasing intake by a mean of 1.4 portions and the control group increasing intake by 0.1 portions. Plasma concentrations of alpha-carotene, beta-carotene, lycopene, beta-cryptoxanthin, and vitamin C showed significantly greater increases for the treatment group than the controls. SBP decreased more in the intervention group than the controls, with a significant difference in SBP of 4 mmHg and in DBP of 1.5 mmHg. These reductions have the potential to substantially decrease CVD risk at the population level.[3] In contrast to the DASH diet studies, this was not a controlled feeding trial and participants were not advised to reduce fat intake or change physical activity. These data extend results of the DASH trial, but demonstrate that individuals in the general population can adhere to dietary advice by making food choices to increase dietary intake of fruits and vegetables and positively affect blood pressure control.[27] Increased intake of fruits and vegetables may improve blood pressure regulation through a variety of mechanisms. These include protection against oxidative stress and resulting arterial damage,[28,33] protection of nitric oxide from degradation,[35] improvement in arterial stiffness,[31] inhibition of angiotensin converting enzyme (an enzyme that is involved in raising blood pressure and constricting blood vessels), and restoration of endothelial function.[34]

Oxidative Stress, Vitamin C, and Hypertension

Evidence suggests an interaction between obesity, blood pressure, insulin resistance, and CVD.[28,29] Obesity, a risk factor for hypertension, may lead to physiological imbalances that increase oxidative stress. A possible mechanism by which the DASH diet affects blood pressure is by increasing antioxidant capacity and reducing oxidative stress.[28] Several studies have examined the potential role of antioxidants and blood pressure regulation, with conflicting results regarding vitamin C.[30,31,32,33,34,35] A 17-week controlled study involving vitamin C depletion/repletion in 68 men aged 30-59 years found an inverse relationship between plasma vitamin C and blood pressure, consistent in magnitude with blood pressure changes seen in non-hypertensive individuals in the DASH study.[30,36] Subjects in the lowest quartile of plasma vitamin C had a >7 mmHg higher DBP compared to those in the highest quartile of plasma vitamin C distribution. In multivariate analysis, 25% of the variance in DBP was attributable to

plasma vitamin C alone. Plasma vitamin C was also significantly associated with SBP.[30] A recent randomized crossover study comparing 'usual' (control) diets to either the DASH diet or a low-antioxidant diet in 12 obese Stage 1 hypertensives and 12 lean normotensives also investigated the relationship of oxidative stress and blood pressure.[28] Results showed that among obese hypertensives, the DASH diet raised antioxidant capacity, lowered blood pressure, and reduced oxidative stress induced by hyperlipidemia and related metabolic syndrome parameters (e.g., insulin resistance, obesity). These findings suggest that the DASH diet may decrease blood pressure through increasing antioxidant capacity, and that the elevated blood pressure in obese subjects may be associated with an imbalance between antioxidant capacity and oxidative stress.

High Potassium Intakes Play a Role in Blood Pressure Regulation

Potassium is found in most fruits and vegetables. A recent meta-analysis of randomized controlled potassium supplement trials showed reductions of 1.8 mmHg and 4.4 mmHg (SBP) and 1.0 mmHg and 2.5 mmHg (DBP) for normotensive and hypertensive subjects, respectively.[22] Data from the Third National Health and Nutrition Examination Survey (NHANES III) involving 17,030 individuals 20 years and older examined the relationship between dietary intake and SBP, DBP, and pulse pressure.[37] In support of findings from other studies, higher dietary potassium consumption was significantly associated with lower SBP and DBP. High dietary potassium intakes were found to significantly reduce the effect of protein intake with respect to raising SBP and to decrease age-related elevations in DBP. This study emphasizes the importance of examining nutrients in the context of an overall diet and not in isolation.[38,39] Because it is often not possible to separate the effects of potassium from other nutrients that affect blood pressure, it is best to obtain potassium from whole foods, including fruits and vegetables.

Summary of Evidence

Based on a review of literature emphasizing articles published 2001-2003, both epidemiological and clinical trial data support the beneficial role of fruit and vegetable consumption as a means to lower blood pressure in the general population. Although mechanisms of action and interrelationships between bioactive compounds are still under study, these reductions, particularly in SBP, are associated with significantly decreased risk for hypertension, stroke, and CHD. These data highlight the importance of nutrition as an essential lifestyle modification to reduce hypertension risk and support recommendations to increase fruit and vegetable consumption both to prevent and treat hypertension.

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Stroke

Section Editor:
Lawrence Appel, M.D., MPH
Professor of Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland

Statistics and Background

Stroke or cerebral vascular accident (CVA) is a significant public health concern that can be measured in incidence, mortality, morbidity and cost.[1] Stroke is the result of complete ischemia (i.e., lack of blood flow) which deprives the brain of blood and oxygen. Stroke includes sub-classifications of ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage.[2,3] Most strokes are caused by infarcts of the internal carotid artery and its branches. Stroke is the third leading cause of death, with approximate direct and indirect costs estimated at $51.2 billion for 2003.[4] Stroke has an estimated prevalence of 4,700,000, affecting 700,000 Americans each year, of which 24% die.[4] Stroke is the most common basis for long-term disability, with the majority of survivors experiencing significant, permanent neurological damage and diminished performance in activities of daily living (ADL).[1,4]

Elevated blood pressure (BP) is the most modifiable of the independent risk factors for any type of stroke.[3,5,6] The risk of stroke rises progressively throughout the range of BP, including non-hypertensive or 'pre-hypertensive' range as well as the hypertensive range (systolic BP $\geq$ 140 mmHg and/or diastolic BP >90 mmHg). Elevated systolic BP (SBP) is a particularly important cause of stroke. Modest reductions in SBP or diastolic BP (DBP) can significantly reduce stroke incidence.[5] Other risk factors for stroke include age, CHD, diabetes mellitus, hyperlipidemia, physical inactivity, smoking, obesity, elevated serum hematocrit, elevated fibrinogen (a plasma protein that is converted into fibrin during blood clot formation), and elevated plasma homocysteine. Much of the research related to stroke prevention has focused on aspects of diet that influence BP or overall CVD disease risk. These factors include potassium,[7] fruit and vegetable intake,[8] nutrients that influence homocysteine metabolism (i.e., folate, vitamin B12),[9,10,11,12] and antioxidants.[13,14]

Increased Fruit and Vegetable Intake Reduces Risk for Stroke

Although most studies on stroke prevention have involved pharmacological intervention[15] or vitamin supplementation studies[16], two important studies have shown an association between fruit and vegetable intake and reduced risk of stroke.[7,8] A large prospective study involving male (n=38,683) and female (n=75,596) health professionals found that persons in the highest quintile of fruit and vegetable intake had a 31% lower risk of ischemic stroke compared with the lowest quintile of intake.[7] An increase of one daily fruit or vegetable serving was associated with a 6% lower risk for ischemic stroke.[7] Cruciferous vegetables, green leafy vegetables, citrus fruit and citrus fruit juice contributed the most to the apparent protective effect of fruits and vegetables against

stroke.[7] A more recent prospective study[8] involving 54,506 male and female participants in the Danish Diet, Cancer, and Health Study found that those in the top quintile of fruit and vegetable intake had a 28% reduction in risk of ischemic stroke compared to those in the bottom quintile of intake. A 40% lower risk for stroke was found when comparing those in the highest to lowest quintile for fruit intake, with significant reductions noted for citrus fruit.[8]

Folate, Homocysteine, and Stroke

Available evidence, albeit inconsistent, links total and plasma homocysteine to CVD risk, including stroke[9,10,11] and recurrent stroke.[12] High plasma homocysteine has been associated with a higher prevalence of silent brain infarctions and heightened progression to clinical stroke and dementia related to vascular causes.[17] Folate, abundant in many fruits and vegetables, is the primary dietary constituent involved in homocysteine regulation,[18] and therefore is being investigated as a key nutrient for stroke prevention.[16] A prospective study[19] of 369 Canadians aged 65 years and older found the risk of an adverse cerebrovascular event (i.e., vascular dementia, vascular cognitive impairment, or fatal stroke) was 2.4 fold higher in persons in the lowest quartile for folate intake compared to the highest quartile. Another prospective study[20] of 9,764 U.S. male and female participants in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study determined that those persons in the highest quartile of dietary folate intake had a 21% lower risk for stroke than those in the lowest quartile. Subjects with the highest dietary folate intake tended to have slightly lower SBP and serum cholesterol, compared to those in the lowest quartile group. In this study, the inverse associations between folate intake and stroke incidence appeared to be consistent across gender, physical activity, and tobacco use.

Oxidative Stress, Carotenoids, Vitamin C, and Stroke

Oxidative stress (an environment where the body's ability to defend against reactive oxygen species is compromised, leading to cellular damage) is thought to contribute to CVD, including stroke.[21] A study of 28 elderly subjects with acute ischemic stroke examined the association between carotenoids, oxidative stress and stroke.[13] Findings indicated that the majority of plasma carotenoids are lowered immediately after an ischemic stroke, with low lutein status associated with a poor early outcome (e.g., functional decline).[13] Deterioration of blood carotenoid status in the acute phase after stroke may occur due to oxidative stress and related lipid peroxidation.[13] In addition to lipid peroxidation, oxidative stress is associated with other factors related to stroke risk, including hypertension and endothelial dysfunction.[15] Low plasma[22] and serum[23] vitamin C has been associated with increased risk of stroke. In a study comparing 31 acute ischemic stroke patients, 26 hospitalized non-stroke patients, and 23 healthy controls, serum vitamin C concentrations decreased significantly in stroke patients compared to controls.[24] A recent report based on examination of 2,419 men aged 42-60 years in the Kuopio Ischemic Heart Disease Risk Factor Study[22] found that those with the lowest levels of plasma vitamin C had a 2.4 fold higher risk of stroke than men with the highest levels. It appears there is an interaction between plasma vitamin C, hypertension and

stroke.[22] Hypertensive and overweight men with low plasma vitamin C levels had a 2.6-fold and 2.7-fold increase in risk for stroke, respectively, when compared to those with the highest plasma vitamin C levels.[22]

Dietary Potassium May Reduce Risk of Stroke

Diets high in potassium have been associated with a decreased risk of stroke.[25,26,27] A study including participants in the NHANES I Epidemiologic Follow-Up Study (n=9,805) found those consuming a low potassium diet at baseline (<34.6 mmol potassium per day) had a 28% higher risk of stroke than other participants.[25] Another study of 43,738 men in the Health Professionals Follow-up Study that included semi-annual interviews to update dietary information found that individuals in the top quintile (who consumed approximately 9 daily servings of fruits and vegetables) of dietary potassium intake had a 38% lower risk of stroke than those in the bottom quintile (who consumed 4 servings of fruits and vegetables daily).[26] Primary sources of dietary potassium included tomatoes, spinach, bananas, and oranges.[26] Greatest benefit of a high potassium intake appears to be for those who have high BP,[26,28] and there is some evidence that the effectiveness of diuretics as a BP management treatment may be optimized with adequate potassium intake.[29] Interestingly, while some studies indicate that potassium (supplementation) may lower BP,[30] others report that the magnitude of stroke risk reduction is only partially explained by BP reduction. Other suggested mechanisms of action (e.g., inhibition of free radical formation, vascular smooth muscle proliferation, and arterial thrombosis) require further study to explain potassium's potential protective effect against stroke.[26]

Summary of Evidence

Based on a review of literature emphasizing articles published 2001-2003, fruits and vegetables and their constituents (e.g., folate, vitamin C, potassium) may decrease the risk of stroke through their BP lowering effect (as discussed in the hypertension section) and their antioxidant and homocysteine-lowering potential (as previously discussed in the CHD section). Future directions in research may determine to what degree fruits and vegetables can reduce the risk for stroke and possibly reduce the long-term disability resulting from CVA. Research is needed to determine the role and relative contribution of nutritional factors in stroke prevention and treatment.

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Diabetes Mellitus

Section Editor:

Katrina Ylonen
Department of Applied Chemistry and Microbiology, Division of Nutrition, University of Helsinki, Helsinki, Finland

Statistics and Background

Diabetes mellitus consists of a number of diseases related to defects in glucose metabolism. These include: type 1 (insulin-dependent diabetes mellitus, IDDM), type 2 (non-insulin-dependent diabetes mellitus, NIDDM), and gestational diabetes (GDM). In type 1 diabetes the body does not produce adequate amounts of insulin, whereas in type 2 diabetes and gestational diabetes defects in insulin action and cellular uptake of glucose are the mechanisms responsible for elevation of blood sugar. The prevalence of type 2 diabetes has reached alarming levels in the U.S., increasing by 27% between 1997 and 2002,[1] a change strongly related to environmental factors. These include: the rise in overweight and obesity, lifestyle (e.g., a lack of adequate physical exercise), and socioeconomic factors.[2,3] For this reason, overweight and diabetes are sometimes referred to as the 'twin epidemics' (nicknamed 'dia-besity'[4]). There is convincing evidence that excessive weight gain, particularly abdominal adiposity, is linked to the onset of type 2 diabetes.[2] Excess body fat prevents insulin from working properly, thus increasing the risk for insulin resistance and diabetes.[5] In the last decade, type 2 diabetes has undergone a transition from a disease rarely found in children to one approaching epidemic proportion in this population, accounting for up to 45% of all newly diagnosed cases of diabetes.[2] Approximately 6.5% of the U.S. population has diabetes, with 11.1 million of these cases diagnosed and an estimated 5.9 million undiagnosed.[6]

Approximately 90-95% of all cases are type 2 diabetes. These individuals are at higher risk for numerous co-morbid conditions and complications (e.g., cardiovascular disease, stroke, hypertension, blindness, kidney disease, nervous system damage, amputations, periodontal disease, and greater susceptibility to infection).[2,7] Based on 2002 estimates, the total health cost of diabetes in the U.S. was $132 billion ($91.8 direct and $40.2 billion indirect). Complications of type 2 diabetes are associated with substantial increases on the direct medical costs of type 2 diabetes.[8]

Dietary Modification May Slow Progression of Insulin Resistance and Aid in the Prevention and Treatment of Type 2 Diabetes

Lifestyle and Dietary Pattern Changes

Modifications of dietary intake have been shown to be helpful in preventing and effectively treating type 2 diabetes. The benefits of lifestyle change were illustrated by a prospective study involving middle-aged, overweight subjects (172 males and 350 females with a mean age of 55 years) who were randomly assigned to either an

intervention (counseling aimed at weight loss, reduction of fat, increase in fiber, and increase in physical activity) or a control group.[9] Those in the intervention group successfully improved in all dietary parameters assessed, including an increased fruit and vegetable intake. When compared to those in the control group, the intervention group lost more weight and had significantly greater decreases in blood insulin, triglycerides, and blood pressure. The cumulative incidence of diabetes after 4 years was significantly lower in the treatment group (11%) than in the control group (23%), with a 58% lower overall risk for diabetes onset.[9]

A recent study involving 42,504 male health professionals identified two major dietary patterns, the 'prudent' and 'western' patterns.[10] The 'prudent' pattern is higher in fruit, vegetables, fish, poultry, and whole grains, whereas the 'western' diet is higher in processed and red meats, high-fat dairy products, French fries, refined grains, and sweets. The prudent dietary pattern score was associated with a modestly lower (16%) risk reduction for type 2 diabetes, whereas the 'western' dietary pattern score was associated with a significantly higher risk.[10]

Additionally, a high fruit and vegetable intake may support weight control efforts,[11,12,13] thus potentially helping to prevent diabetes.[4,9,10,14,15,16] There is 'convincing' evidence (as defined by World Health Organization criteria) that voluntary weight loss is effective in reducing the risk of type 2 diabetes in overweight and obese individuals.[2,3,16]

Increased Fruit and Vegetable Consumption and Blood Glucose Regulation

Fruits and vegetables include several components that may reduce the risk of developing diabetes.[3,17,18] These include: dietary fiber (delays meal absorption and thereby blunts post-meal rise in blood sugar and insulin), low energy density (may aid in weight management), antioxidants (may reduce the oxidative stress that can negatively impact insulin receptor function), and magnesium (involved in insulin secretion).[3,19] A large-scale (n = 9,665) study involving male and female participants aged 25-74 years in the National Health and Examination Survey (NHANES I) found an inverse relationship between fruit and vegetable intake and incidence of diabetes.[3] Overall, those consuming 5 or more daily servings of fruits and vegetables were least likely to develop diabetes (27% risk reduction). A 39% risk reduction was seen when the effect for females was considered alone.[3] Similar findings with regard to a reduced prevalence of diabetes among those with high fruit intakes were found in a cross-sectional study of the Inuit population in Greenland.[20]

A central goal of type 2 diabetes management through dietary intervention is to improve control of blood sugar levels.[9] There is a 'probable' level of evidence (as defined by World Health Organization criteria) in the literature supporting a relationship between increased intake of fiber from fruits, vegetables, whole grain cereals and reduced risk of insulin resistance and type 2 diabetes.[2] The EPIC-Norfolk population-based cohort study (2,678 males and 3,318 females aged 45-74 years) found that intake of fruit and green leafy vegetables in particular influenced glucose metabolism.[18] Significantly lower mean glycosylated hemoglobin (HbA_{1C}, a measure of long-term blood glucose control) levels were found among those reporting higher intake of fruits and vegetables, compared to those who never or seldom consumed these foods in a given week.[18] This

beneficial effect was independent of dietary fiber and vitamin C intake, factors which may exert a protective role against diabetes risk.[18,21] A significant reduction in HbA_{1C} was also achieved in another study through a healthy eating intervention that included increased fruit servings (1.89 versus 1.68) and vegetable servings (2.24 versus 2.06).[22]

Research also supports a relationship between high dietary and plasma carotenoids and decreased insulin resistance and fasting plasma glucose.[19] A case-control study involving rural Japanese subjects examined blood levels of carotenoids in relation to blood sugar in subjects with diabetes (n=133), hyperglycemia (n=151), and two matched control groups.[23] Those with a high frequency of carrot and pumpkin intake had a 51% lower likelihood of having high HbA_{1C}. High serum levels of alpha- and beta-carotene combined, lycopene, beta-cryptoxanthin, zeaxanthin, and lutein were associated with 62%, 65%, 43%, 65% and 12% risk reductions for high HbA_{1C}, respectively. In support of findings from a previous study associating serum carotenoids with decreased insulin resistance,[24] a recent cross-sectional study involving 81 males and 101 females found that higher intakes of dietary carotenoids were associated with lower fasting plasma glucose concentrations in men. In women, plasma beta-carotene was related to lower fasting plasma glucose.

Glycemic Load and Type 2 Diabetes

There is interest in the potential relationship between glycemic load (GL) and management of type 2 diabetes.[25] GL is defined as the weighted average glycemic index of individual foods multiplied by the percentage of dietary energy as carbohydrate.[26,27] Observational studies suggest that GL appears to be an independent risk factor for type 2 diabetes,[25,28] with research affirming the beneficial impact of cereal fiber.[29,30,31] Including more fruit and vegetables in the diet aids glucose regulation and may reduce the risk of those diseases associated with the metabolic syndrome, a condition that has features in common with type 2 diabetes.[32,33,34] The potential of reducing the GL of the diet by including more fruits and vegetables[35] warrants examination.[36]

Summary of Evidence

Based on a review of literature emphasizing articles published 2001-2003, there is an increasing body of evidence for fruits, vegetables, and the nutrients found in these foods in the prevention of both insulin resistance and the development of type 2 diabetes and its complications. By assisting with weight control and providing antioxidants that protect insulin action, fruits and vegetables may confer significant protective benefits with respect to diabetes prevention and management.

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Reproductive Health

Section Editor:

Prabhudas Palan
Department of Obstetrics and Gynecology, Bronx-Lebanon Hospital Center, Bronx, New York

Birth Defects

Neural tube defects (NTDs) occur when the spinal cord fails to develop properly within three to four weeks of conception. When the neural tube fails to close toward the bottom, the child is born with spina bifida. If the neural tube fails to close toward the top, the child is born without a brain (anencephaly), and usually dies soon after birth. NTDs are among the most common birth defects, with an incidence of 1 to over 6 per 1,000 births.[1,2]

Studies have shown that inadequate maternal folic acid intake is associated with a higher incidence of NTDs.[3,4] Folic acid, a water soluble B vitamin, is an essential nutrient that should be obtained daily from the diet. Fruits and vegetables, including dark green leafy vegetables, oranges, orange juice, and dried beans, are major dietary sources of folic acid.

Intervention trials have demonstrated a strong protective effect of folic acid against NTDs.[5,6] The Medical Research Council (MRC) Vitamin Study, a randomized, double-blind prevention trial, found a 72% overall reduction in risk associated with the use of folic acid in 1,817 women at high risk for NTDs.[7] In another nonrandomized, large-scale intervention study in China, it was demonstrated that women who used a daily folic acid supplement (400 micrograms) early in their pregnancy had a 79% reduction in NTD risk in northern China (area with higher baseline rates of 4.8 per 1,000 births) and a 41% reduction in the southern region (area with lower baseline rates of 1 per 1,000 births) compared to those who did not take supplements.[8]

The protective effect of folate against NTDs is supported by a number of epidemiological investigations. In a large prospective study, Milunsky and colleagues[9] found that the offspring of women who took multivitamin supplements containing folic acid during the first 6 weeks of pregnancy had a 73% lower risk for NTDs. Another prospective study between 1984 and 1987 (before fortification of grain products) of 23,228 U.S. women assessed folic acid intake from foods and supplements early during pregnancy. Results indicate that women with the lowest intakes of folic acid from foods had the highest risk of NTD (4 cases per 1,000 births). When intakes from foods and supplements were combined, women in the highest intake category had a 77% reduction in risk compared to those in the lowest intake category.[10] These findings suggest that dietary sources of folic acid play an important role in preventing NTDs.

The mechanism by which folic acid protects against NTDs is not yet known. It is hypothesized that since folic acid is essential to the synthesis of DNA, it may affect cell proliferation and normal fetal growth. During fetal development, nucleic acid and protein synthesis are at their peak and maternal folate requirements increase rapidly during this time. When folate is insufficient, nucleic acid is inhibited and cells are unable to manufacture enough DNA. Folate must be present in required amounts prior to pregnancy and during the first few weeks of gestation, until the stage of closure of the neural tube is completed. Thus, adequate folic acid intake before pregnancy is of particular importance, since approximately 50% of

pregnancies in the U.S. are unplanned and the majority of women do not know they are pregnant during the first few critical weeks of fetal development.[11]

The strong scientific evidence related to the protective effect of folic acid has been translated into public health policy. In 1992, the U.S. Public Health Service issued the recommendation that all women capable of becoming pregnant should consume 400 micrograms of folic acid daily. More recently, mandatory folic acid fortification of grain products has been instituted in many countries, including the U.S., Canada, and Chile. Studies show that folic acid fortification has clearly improved folate status for women of reproductive age,[12,13] and has lowered the incidence of NTDs by about 15% to 50%.[14,15,16] However, to achieve the maximal possible NTD protective effect of about 70%, the intake of folate from folate-rich foods or supplements is necessary.[17] In 1997, a survey by the CDC found that only 32% of women of childbearing age consume a daily supplement containing folic acid. Efforts to increase the use of folate supplements in women of childbearing age have been met with limited success,[18,19,20] emphasizing the important role dietary sources of folic acid, such as fruits and vegetables, can play to better insure adequate folate intake and help to further reduce the prevalence of NTDs.

Preeclampsia

Preeclampsia is a disorder that occurs during pregnancy and affects both the mother and the unborn baby. It is characterized by high blood pressure, edema, and protein in the urine. Preeclampsia complicates between 2 and 10 percent of pregnancies and is the cause of about 200,000 deaths every year worldwide.[21,22] The causes of preeclampsia are still poorly understood. It has been suggested that an increase in lipid peroxidation caused by free radicals might be involved in its pathophysiology.[23,24,25] Antioxidants, such as carotenoids and vitamin C, may prevent against lipid peroxidation and free radical damage.[26] Increasing the intake of various fruits and vegetables can markedly improve antioxidant status in humans.

Few epidemiologic studies have examined the association between antioxidant intake and incidence of preeclampsia. One recent retrospective case-control study assessed the diet of 109 women with preeclampsia and 259 controls.[27] Findings indicate that women consuming less than five servings of fruits and vegetables daily were almost twice as likely to develop preeclampsia as compared with those who consumed five or more servings of fruits and vegetables daily. Higher intake of dietary vitamin C was found to lower the risk of preeclampsia.

The limited epidemiological evidence is strengthened by a number of clinical studies. Supplementation studies with women at risk for preeclampsia have shown improvement in biochemical indices of the disease with increased vitamin C intake.[28,29] In addition, women with preeclampsia have been found to have lower plasma antioxidants levels, especially lower vitamin C levels, than normotensive women.[30,31,32] Finally, a protective effect of vitamin C against developing preeclampsia has been demonstrated in vivo[33] and in vitro.[34]

Results are intriguing; however, it is too early to say anything definitive about the potential role fruits and vegetables may play in the prevention of preeclampsia. Further investigations are needed to determine the relationship between diet and preeclampsia.

Summary of Evidence

Based on a review of literature emphasizing articles published 2001-2003, there is strong evidence to indicate that adequate folate consumption before conception and during early pregnancy can reduce the first occurrence of NTDs by at least 50% and the re-occurrence of NTDs by 70-74%. Folic acid containing fruits and vegetables, along with fortified grain products, can play a vital role in meeting folic acid recommendations for women of childbearing age.

There is a limited, but growing, amount of evidence to suggest that daily intake of antioxidant-rich fruits and vegetables may possibly protect against the development of preeclampsia. Further research is needed to ascertain the effect of dietary antioxidants, especially vitamin C-rich foods, on prevention of the disease.

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Bone Health

Section Editor:

Sarah Booth
Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111

An estimated 34 million Americans have reduced bone mass, and the majority of bone diseases are often undiagnosed or untreated.[1] The most common bone disease, osteoporosis, is responsible for approximately 1.5 million fractures each year.[1] Although 80% of those with osteoporosis are women, men also suffer from this disease.[1] The prevalence of bone disease is a great public health concern, particularly as the elderly segment of the population increases. Approximately 50% of women and 25% of men over the age of 50 will suffer an osteoporosis-related fracture during their lifetime.[1] The estimated direct health care costs of osteoporosis in 2001 were between $11.6 and $17.1 billion.[1]

Bone makes up the skeleton and provides shape and support for the body, protects some organs, serves as a storage site for minerals, and provides marrow for the development and storage of blood cells. Another role of bone is to act as a buffer, aiding the body's defense system against acid-base disorders and preserving the body's pH.[2] Bone turnover (also known as bone remodeling) consists of bone formation and bone resorption.[3] This remodeling process provides a mechanism for the maintenance of healthy bone, whereby old bone is removed and replaced with new bone.[4] When an imbalance in bone remodeling ensues, bone is lost at a rate greater than it is replaced and bone loss occurs.[4] The consequence of this imbalance (occurring in menopause and with advancing age), is a reduction in bone mass which increases fracture risk.[4] It appears that bone resorption cells (osteoclasts) and bone forming cells (osteoblasts) respond independently to changes in body pH, with a small reduction in pH stimulating bone resorption while inhibiting bone formation.[2]

An important determinant of bone health is the maintenance of optimal levels of bone mass,[1] frequently measured by assessing bone mineral density (BMD) at various sites of the skeleton. Increased risk of fracture is associated with low BMD. The main determinants of attainment of maximum BMD and the rate of age-related bone loss are genetics, nutritional factors (e.g., early-life nutrition, vitamin D intake, calcium intake, vitamin K intake, protein intake, fruit and vegetable consumption), exercise, and other factors (e.g., weight, estrogen levels, alcohol use, smoking, and use of certain drugs).[5,6] The World Health Organization categorizes the strength of evidence that fruits and vegetables may play a role in decreasing risk for osteoporotic fractures as 'possible'.[7] This categorization is based on data indicating that "several components of fruits and vegetables are associated with a decreased risk at levels of intake within the normal range of consumption..."[7]

Dietary Patterns High in Fruits and Vegetables May Aid in Conservation of Calcium and Bone Mineral Density and Promote Overall Bone Health

It is recognized that calcium and vitamin D are important nutrients for bone health.[8,9] Recent studies indicate that intakes of zinc, magnesium, potassium, fiber and vitamin C appear to be associated with higher bone mass, suggesting that fruit and vegetable consumption may play a role in bone health.[3,8,9,10] There has been interest in diets that promote 'alkaline ash', an environment that is associated with a reduced rate of bone breakdown.[11,12,13] Dietary potassium and magnesium, two minerals found in fruits and vegetables, are involved in the modulation of the body's pH.[11, 14] By contributing to an alkaline environment, these minerals may help to reduce bone breakdown.[11,14] A randomized, double blind, placebo-controlled trial found that alkaline salts of potassium that occur naturally in fruits and vegetables reduce the rise in urinary calcium excretion and markers of bone turnover associated with high salt diets.[15] It is estimated that this compensatory effect for diets high in table salt could be achieved by daily consumption of 7-8 servings of potassium-rich fruits and vegetables.

A recent study of 907 Framingham Heart Study subjects aged 69-97 years found that a dietary pattern high in fruits and vegetables was associated with higher BMD in men and women.[16] Population-based intervention trials, including the Dietary Approaches to Stop Hypertension (DASH) trial have found that an increase in fruit and vegetable consumption from 3.6 to 9.5 daily servings decreased urinary calcium excretion from 157 mg per day to 110 mg per day.[17] This effect may be related to the reduced acid load of the fruit and vegetable diet compared to the control diet.[2] A cross-sectional study of 62 healthy women aged 45-55 years supports the hypothesis of a positive influence of alkaline-forming foods on bone health.[3] This study found that intakes of potassium beta-carotene, vitamin C, magnesium, and fiber, as well as a high intake of fruit (1-4 times per day $\geq$ 5 days per week) during childhood ($\leq$12 years of age) were positively associated with a higher bone mineral density (BMD). Average bone resorption was lower with higher intakes of potassium, magnesium, beta-cartotene, and vitamin C. The relationships identified between dietary intake and markers of bone turnover warrant further study.[3] Greater intakes of fruit and vegetables, and certain micronutrients in these foods (i.e., dietary potassium and magnesium), were also associated with a reduced rate of decline in BMD in a cross-sectional and 4-year longitudinal study of individuals who were part of the original cohort of the Framingham Heart Study.[11]

Following up on observations in a rat model, an intervention study was designed involving 58 women assigned to consume either 100 grams of dried plums or 75 grams of dried apples (amounts determined to provide similar calories, fat, carbohydrate, and fiber).[18] When compared to baseline values, only dried plums increased serum levels of compounds (i.e., insulin-like growth factor and bone-specific alkaline phosphatase) that are associated with enhanced bone formation.[18]

Vitamin K May Promote Bone Mineral Density in Women

Phylloquinone, the primary dietary form of vitamin K found in green leafy vegetables, may protect against age-related bone loss through its role in gamma-

carboxylation of certain proteins in bone (e.g., osteocalcin).[19] A cross-sectional study of participants in the Framingham Heart Study (1,112 males, 1,479 females) found higher dietary vitamin K intakes (independent of potassium intakes) were associated with higher BMD measures at the hip and spine in women.[19] Women in the lowest quintile of vitamin K intake (mean 70.2 mcg per day; equivalent to less than ¼ cup of broccoli per day) had significantly lower BMD at the femoral neck and spine than did those in the highest quintile of vitamin K intake (mean 309 mcg per day; equivalent to 1.5 cups of broccoli per day).[19] While the BMD changes across quartiles of intake were modest, these small differences may be important for the prevention of hip fracture.[20,21,22] It is estimated that for each standard deviation decrease in BMD of the femoral neck, there is a 2.6-fold increase in the age-adjusted risk of hip fracture,[20] approximately equivalent to effects of 13-14 years of aging on the risk of hip fracture. In the Nurses' Health Study cohort (n=72,327 females aged 38-63 years) it was found that women in the highest quintiles of vitamin K intake had a lower risk of hip fracture than women in the lowest quintile (<109 mcg per day).[23] Those consuming one or more servings per day of iceberg and romaine lettuce had a 45% lower risk of hip fracture compared to those consuming ≤ 1 serving per week.[23]

Preliminary Studies Suggest Flavonoids May Play a Role in Bone Health

Preliminary data suggest a potential role of flavonoids in bone health.[24, 25] Hesperidin, a citrus flavonoid, was shown to be associated with higher BMD in a mouse model, suggesting a beneficial effect on bone health.[25] In another study using rabbit osteoclasts, intracellular reactive oxygen species were decreased significantly by the flavonoids quercetin (75% reduction) and kaempferol (25% reduction). The antioxidant properties of the flavonoids were also associated with an inhibition of bone resorption in these cells.[24] Quercetin and kaemferol are found in vegetables including onions, hot peppers, broccoli, kale, spinach, and rutabagas. Therefore, there may be multiple mechanisms by which these fruits and vegetables have a potential protective role in bone health.

Summary of Evidence

Based on a review of literature emphasizing articles published 2001-2003, available data support a healthy lifestyle and diet emphasizing fruits and vegetables for promotion of bone health. More research is needed to better understand the relationship between various micronutrients and bone health. Several observational studies support an association between micronutrient intake and BMD, possibly through modifying body pH. Mechanisms suggested for the involvement of micronutrients other than calcium and vitamin D are plausible but require clinical trials to more clearly define their roles in bone health.

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FRUIT AND VEGETABLE INTAKES IN CHILDREN: THE CRITICAL INFLUENCE OF FAMILY AND ADVERTISING

SUMMARY

Accumulated evidence shows that parents have strong influence on children's diet choices. Parents influence their children's fruit and vegetable choices in particular through several mechanisms. These include modeling of intake, making changes in the availability of these foods, frequency of family dining, and family connectedness. Television advertising also negatively impacts diet quality in children, and may influence obesity by increasing the intake of foods high in fat, sugar, and salt.

Effects of Caregivers and Modeling Behaviors

- Parent's eating behavior is a significant determinant of children's food choices (Kratt et al, 2000; Fisher et al, 2002; Fitzgibbon et al, 2002; Skinner et al, 2002a; Skinner et al, 2002b; Hannon et al, 2003). Direct associations have been found between women's fruit intake and that of their children (Fisher et al, 2002). Vegetable variety in school-aged children was predicted by maternal vegetable preferences, and the variety of fruits eaten by these children was predicted by both the variety of fruits offered and fruit exposure in infancy (Skinner et al, 2002b).
- Family food providers' fruit and vegetable intake successfully predicted that of children and adolescents (Hannon et al, 2003).
- **Modeling** of desired food intake by parents has been found to be a key factor in what children eat (Tibbs et al, 2001; Fisher et al, 2002; Fitzgibbon et al, 2002; Webber Cullen et al, 2002).
- **Modeling** can be effective for getting children to try new foods or disliked foods (Fisher et al, 2002) and is a component of the 'High 5' program, which successfully increased fruit and vegetable intakes in both parents and children (Reynolds et al, 2000).
- **Models** can have substantial impacts on food selection if the model is an authority figure or is similar to the observer. For example, parents who more frequently model healthful diet behaviors report an increased overall performance of low fat dietary patterns (Tibbs et al, 2001), and modeling by preschoolers also can result in an increase of formerly-disliked foods by their peers (Fitzgibbon et al, 2002).
- A strong correlate of fruit and vegetable intake is home availability of these foods (Neumark-Sztainer et al, 2003), accessibility to these foods, (Fisher et al, 2002) or both (Webber Cullen et al, 2002).

Family dynamics

A strong association has been noted between 'family connectedness' and fruit and vegetable consumption (Neumark-Sztainer et al, 2003). Adolescents who reported low compared to high levels of family connectedness had lower fruit and

vegetable intakes, and shared family meals resulted in higher adolescent fruit and vegetable intake (Hannon et al, 2003).

- **Family-style dinners** (daily) were associated with a higher fruit and vegetable intake (0.8 more servings per day) in kids when compared to children who ate with their family only on certain days or never. Family-style dinners raised intakes of fiber, calcium, iron, and vitamins C, E, B6 and B12, while reducing saturated and *trans* fats, soda, fried foods, and dietary glycemic load (Gillman et al, 2000).

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