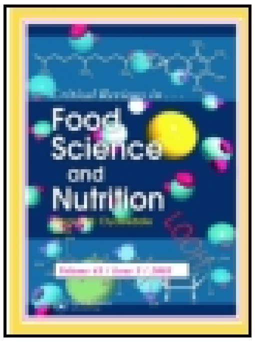

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REVIEW

Fruits, vegetables, and health: A comprehensive narrative, umbrella review of the science and recommendations for enhanced public policy to improve intake

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ABSTRACT
Fruit and vegetables (F&V) have been a cornerstone of healthy dietary recommendations; the 2015–2020 U.S. Dietary Guidelines for Americans recommend that F&V constitute one-half of the plate at each meal. F&V include a diverse collection of plant foods that vary in their energy, nutrient, and dietary bioactive contents. F&V have potential health-promoting effects beyond providing basic nutrition needs in humans, including their role in reducing inflammation and their potential preventive effects on various chronic disease states leading to decreases in years lost due to premature mortality and years lived with disability/morbidity. Current global intakes of F&V are well below recommendations. Given the importance of F&V for health, public policies that promote dietary interventions to help increase F&V intake are warranted. This externally commissioned expert comprehensive narrative, umbrella review summarizes up-to-date clinical and observational evidence on current intakes of F&V, discusses the available evidence on the potential health benefits of F&V, and offers implementation strategies to help ensure that public health messaging is reflective of current science. This review demonstrates that F&V provide benefits beyond helping to achieve basic nutrient requirements in humans. The scientific evidence for providing public health recommendations to increase F&V consumption for prevention of disease is strong. Current evidence suggests that F&V have the strongest effects in relation to prevention of CVDs, noting a nonlinear threshold effect of 800 g per day (i.e., about 5 servings a day). A growing body of clinical evidence (mostly small RCTs) demonstrates effects of specific F&V on certain chronic disease states; however, more research on the role of individual F&V for specific disease prevention strategies is still needed in many areas. Data from the systematic reviews and mostly observational studies cited in this report also support intake of certain types of F&V, particularly cruciferous vegetables, dark-green leafy vegetables, citrus fruits, and dark-colored berries, which have superior effects on biomarkers, surrogate endpoints, and outcomes of chronic disease.

KEYWORDS
Fruit; vegetable; produce; health; nutrition

Introduction

Dietary risk factors associated with poor health in the United States are those considered to be low in fruits, vegetables, whole grains, nuts, and seeds and high in refined carbohydrates, added sugars, sodium, and certain saturated fats. Diets high in fruits and vegetables (F&V) are widely recommended in developed countries for their health-promoting properties; they have historically held a place in dietary guidance because of their vitamin, mineral, dietary fiber, and, more recently, dietary bioactive content. Most nutritional and global recommendations include consumption of at least 2 servings of fruits and 3 servings of vegetables per day for adults (WHO 2002; Nishida et al. 2004; Health Canada 2014; U.K. Government 2018; USDA 2018a). More than 100 countries worldwide have developed food-based dietary guidelines adapted to their nutrition situation, food availability, culinary cultures, and eating habits that encourage increased F&V consumption. However, F&V in their harvested consumed form have been shown to vary widely in nutritional contribution, density, and dietary bioactive content of a standard serving (Song et al. 2010; Hornick and Weiss 2011).

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Eighty-eight percent of countries face a serious burden from two or three forms of malnutrition: acute and/or chronic undernutrition, micronutrient deficiencies, obesity, and diet-related diseases, including type 2 diabetes, cardiovascular diseases (CVDs), and certain types of cancer (FAO 2018). With noncommunicable disease (NCD) conditions accounting for nearly two-thirds of deaths worldwide, the emergence of chronic disease as the predominant challenge to global health is undisputed (Bauer et al. 2014). Twenty-three percent of the total global burden of disease is attributable to disorders in people aged ≥60 years; however, primary prevention in younger populations can significantly improve health in successive cohorts of older people. The leading global contributors to disease burden in older people are CVDs, cancers and malignant neoplasms, chronic respiratory diseases, musculoskeletal diseases, and neurological and mental disorders (Prince et al. 2015).

While dietary recommendations for F&V intake have many similarities between countries, many countries choose different strategies for separating F&V into subgroups based on the needs of their population. This approach makes sense from a menu-planning perspective but does not directly correspond with nutrient content (Slavin and Lloyd 2012). For instance, many F&V are excellent sources of vitamin C (e.g., citrus fruits, strawberries, green peppers, white potatoes) but are spread over many F&V categories (Slavin and Lloyd 2012). F&V categories in the 2015–2020 U.S. Dietary Guidelines for Americans (DGA) (USDA 2018a) are listed in Table 1. These categories are important because the DGA serve as the cornerstone of U.S. nutrition policy and direct the development and implementation of all nutrition education and assistance programs (e.g., MyPlate and the National School Lunch Program). No individual food or food group has all of the nutrients needed to support life. However, consuming a mixture of foods (i.e., dietary diversity) is optimal for achieving nutrient intakes required for growth, development, reproduction, and longevity. Thus, dietary guidance over time has consistently supported the principles of moderation and variety (Slavin and Lloyd 2012).

Table 1. USDA food patterns: food groups and subgroups.

Food group and subgroup	Example
Fruits	
Fruits	All fresh, frozen, canned, and dried fruits and fruit juices (e.g., oranges and orange juice, apples and applesauce, bananas, grapes, melons, berries, and raisins).
Vegetables	
Dark-green vegetables	All fresh, frozen, and canned dark-green leafy vegetables and broccoli, cooked or raw (e.g., broccoli, spinach, romaine, and collard, turnip, and mustard greens).
Red and orange vegetables	All fresh, frozen, and canned red and orange vegetables, cooked or raw (e.g., tomatoes, red peppers, carrots, sweet potatoes, winter squash, and pumpkin).
Beans and peas	All cooked and canned beans and peas (e.g., kidney beans, lentils, chickpeas, and pinto beans). Does not include green beans or peas.
Starchy vegetables	All fresh, frozen, and canned starchy vegetables (e.g., white potatoes, corn, and green peas).
Other vegetables	All fresh, frozen, and canned other vegetables (e.g., lettuce, green beans, and onions).

Adapted from Slavin and Lloyd (2012).

Determinants of food choice

What people eat is influenced by many complex factors that span from individual levels of influence to dimensions of their environment. According to the European Food Information Council (EUFIC), the key driver for eating is hunger; what we choose to eat is not determined solely by physiological or nutritional needs (EUFIC 2006).

Some of the other factors that influence food choice include the following:

- Biological determinants such as hunger, appetite, and taste
- Economic determinants such as cost, income, and availability
- Physical determinants such as access, education, skills (e.g., cooking), and time
- Social determinants such as culture, family, peers, and meal patterns
- Psychological determinants such as mood, stress, and guilt
- Attitudes, beliefs, and knowledge about food

The complexity of food choice is apparent, and the above list is not exhaustive (EUFIC 2006).

Behavioral strategies are needed to motivate and enhance the capacity of individuals to adopt and improve their lifestyle behaviors. Environmental change is also important because environmental context and conditions affect what and how people eat and what food choices are available (Hawkes et al. 2015). Children in particular have been shown to respond positively to an image of a figurehead regularly associated with a public health campaign's message. A recent randomized controlled trial (RCT) of >1200 children aged >3 years found that viewing a photograph of Michelle Obama's face relative to control conditions during Halloween "trick or treating" caused children to be 19% more likely to choose fruit over candy (Aronow, Karlan, and Pinson 2018). However, this study is limited since it did not allow for extrapolation of why Michelle Obama's face influenced children's dietary decision making. Other factors such as socioeconomic status and political leanings of the children's parents may make these findings non-generalizable to the general population (Aronow, Karlan, and Pinson 2018). Use of rewards to encourage healthy eating in children remains controversial; however, a recent cluster-randomized trial (n = 422) of 4- to 6-year-old children found both tangible and social reward to be effective in increasing consumption of "disliked" vegetables, with effects maintained for 3 months (Cooke et al. 2011). On the contrary, most current school-based intervention efforts have not proven to be effective in reversing rates of childhood obesity and additional approaches to the problem are needed (Birch and Ventura 2009).

Emerging evidence suggests that interventions that reduce reward and attention region responsivity in the brain to food cues and increase inhibitory control may reduce overeating and excessive weight gain in adults (Stice and Burger 2019). Initial deficit in inhibitory control and bias for immediate reward have been suggested to contribute to overconsumption of high-calorie foods. A landmark pilot randomized trial in adults demonstrated for the first time a reversal of obesity-related abnormalities as well as mental “reward system” responsivity to food cues with a 6-month behavioral intervention (Deckersbach et al. 2014). Compared to controls, participants ($n = 13$) achieved significant weight loss and had increased activation of the reward system for low-calorie food images, as well as large shifts in relative activation favoring low-calorie vs. high-calorie foods (Deckersbach et al. 2014), providing the first demonstration of a positive shift toward healthy vs. unhealthy food cues in a behavioral intervention.

Because food choice differs according to life stage and the power of one factor may vary between individuals or groups of people, single interventions to modify food choice behavior will not suit all population or subpopulation groups (EUFIC 2006). Recent evidence suggests that the interaction between food preferences and the environment in which those preferences are learned, expressed, and reassessed has a central role in determining food choice (Hawkes et al. 2015). Potential mechanisms to help individuals alter their food choices to include more F&V, among other healthy options, include enabling an environment for learning of healthy preferences, overcoming barriers to the expression of healthy preferences, encouraging people to reassess existing unhealthy preferences at the point of purchase, and stimulating a food-systems response (Hawkes et al. 2015). Unfortunately, in the United States, the ready availability and low cost of energy-dense and nutrient-deplete foods provides an eating environment that fosters food preferences inconsistent with dietary guidelines. Food scientists and the food industry have the ability to play a critical role in shifting individuals toward more healthy dietary patterns through developing new innovative flavorful products and improving both local and global supply chains to increase availability and decrease cost of F&V.

Current gaps in fruit and vegetable intake

According to a report from the Produce for Better Health Foundation (2015), recent F&V consumption losses are tied to two common behaviors: a decline in dinner side dishes for vegetables, and reduced consumption of fruit juice at breakfast (Produce for Better Health Foundation). Staples such as orange juice, lettuce/salad, corn, and green beans have led the declines. Fewer side salad dishes also reduce the consumption of salad-related produce, such as tomatoes and cucumbers. The report shows that vegetable intakes have long been affected by shifts occurring at the dinner table. As Americans look for more convenient dinner occasions (e.g., ready-to-eat or frozen main dishes), vegetable consumption has decreased because there are fewer side dishes at dinner. As public health bodies continue to encourage decreased consumption of “sugar-sweetened” beverages, consumers often include 100% juice in this mix (Produce for Better Health Foundation 2015).

Since publication of the 2010 DGA, adequate fruit intake has remained low or stable and vegetable intake has declined, particularly among children of all ages, adolescents, and adult males (DGAC 2015). Across the U.S. population, only about 15% of individuals meet daily fruit intake recommendations (DGAC 2015; USDA 2018a). Children aged 1–3 years and 4–8 years differ from the rest of the population in that many do meet recommended intakes for total fruit, which is 1 cup and 1–1.5 cups per day, respectively. Among older children, adolescents, and adults of all ages, few consume the recommended daily amounts of fruit, which range from 1.5 to 2 cups for older children and adolescents to 1.5 to 2.5 cups for adults. Almost 90% of all fruit intakes come from single fruits, fruit salads, or fruit juices. The most commonly consumed fruits are apples, bananas, watermelon, grapes, strawberries, oranges, peaches, cantaloupe, pears, blueberries, raisins, and pineapple. Commonly consumed fruit juices are orange juice, apple juice, and grape juice.

The U.S. population also consumes too few vegetables; only 10% and 15% of boys and girls aged 1–3 years, respectively, consume the recommended 1 cup of vegetables per day. For children aged 4–8 years, less than 5% consume the recommended 1.5–2 cups of vegetables per day. Vegetable consumption is lowest among boys aged 9–13 years and girls aged 14–18 years, as less than 1% of this population consumes the recommended 2–2.5 cups per day. Intakes increase slightly with age during the adult years but still remain low. Overall, nearly 90% of the U.S. population does not meet daily vegetable intake recommendations (DGAC 2015; USDA 2018a). White potatoes, the most commonly consumed single discrete vegetable also commonly categorized as “staple foods” instead of as a vegetable, make up about 80% of all starchy vegetable consumption (USDA 2015) and 21% of all vegetable consumption. Mean gram intake of all potatoes and more energy dense French fries by U.S. adults is 110 ± 1.9 g and 72.1 ± 2.5 g, respectively (Freedman and Keast 2012), and potatoes are among the most affordable vegetable options (Drewnowski and Rehm 2013). Tomatoes account for 18% of all vegetable consumption (note: tomatoes are grouped as a vegetable by USDA), while lettuce and onions are the only other vegetables that make up more than 5% each of total vegetable group consumption (USDA 2015).

It is worth noting that consumption patterns for some specific F&V follow a socioeconomic gradient. For example, whereas whole fruit consumption tends to be associated with higher education and incomes, the consumption of 100% fruit juice is higher among groups of lower socioeconomic status. Whereas the consumption of white potatoes is associated with lower incomes, the consumption of salad leafy greens is much higher among higher income groups. A recent paper modeled the frequency of salad consumption using residential property values as a predictor of dietary behavior (Drewnowski, Buszkiewicz, and Aggarwal 2019). These disparities in FV consumption patterns can be explained in part by differences in affordability and cost. Nutrient density profiling methods have been used to assess affordability of different F&V (Drewnowski and Rehm 2013).

Contribution to nutrient intakes

F&V prepared without added fat or sugar have low energy density and are an excellent source of nutrients such as (but not limited to) vitamin C, carotenoids, potassium, and dietary fiber (DGAC 2015; USDA 2018a). Thus, increasing consumption of F&V improves diet quality (DGAC 2015) and can lead to a decrease in total kilocalorie consumption, particularly when F&V are promoted as alternatives for foods higher in saturated fat and added sugar. According to the 2015 DGA, nutrients of concern in the American diet include potassium, dietary fiber, calcium, and vitamin D (USDA 2018a). F&V vary widely in their nutrient content; however, they remain a top contributor to both potassium and dietary fiber intakes. In 2009–2010, the average dietary potassium intake of the U.S. population aged ≥ 2 years was 2640 mg per day. F&V contribute $\sim$20% of total potassium intakes in the United States (Bailey et al. 2016). F&V intake accounts for 28% of the U.S. population's dietary fiber intake (Hoy and Goldman 2014).

On any given day, 20% of Americans consume a salad; this has been shown to contribute to intakes of nutrients that tend to be lower than recommendations, including dietary fiber and vitamins A, C, and E (USDA 2018b). Canned F&V have also been associated with higher intakes of select nutrients such as dietary fiber, total sugar, choline, and potassium, as well as a higher-quality diet in U.S. adults. Child consumers of canned F&V also eat more protein, vitamin A, calcium, and magnesium (Freedman and Fulgoni 2016). Intake of nutrients of concern is significantly higher among those National Health and Nutrition Examination Survey (NHANES) participants aged >1 year who consume frozen F&V, whereas sodium intakes are lower (Storey and Anderson 2018). Vegetable consumption in any form has been shown to increase intakes of potassium, dietary fiber, calcium, magnesium, iron, vitamin C, and folate among most subpopulations, including women of childbearing age (Storey and Anderson 2016). However, geo-localized disparities in food consumption patterns are apparent and a new study demonstrates associations between higher residential property value with higher salad and lower soda intakes (Drewnowski, Buszkiewicz, and Aggarwal 2019).

Dietary bioactive compounds in fruits and vegetables: beyond basic nutrition

Nutrition and health experts around the world recognize the importance of F&V in providing essential micronutrients and fiber to the diet; however, produce is also the primary source of dietary bioactive compounds, endogenous protective substances that often contribute the vibrant colors present in F&V. The U.S. National Institutes of Health (NIH) has defined dietary bioactive compounds as "compounds that are constituents in foods and dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status" (NIH Office of Dietary Supplements 2018). Current public health recommendations to increase the consumption of F&V are largely driven by the need to meet essential nutrient intakes from foods; however, policy recommendations (e.g., the 2015–2020 DGA) and groups (e.g., the National Fruit and Vegetable Alliance) also note the contribution of dietary bioactives to health promotion (DGAC 2015; Wallace et al. 2015; USDA 2018a). Consumers are now choosing F&V not only for their content of vitamins, minerals and fiber, but also for their concentration of dietary bioactives.

Examples of bioactives present in F&V are illustrated in Table 2. Upward of 5000 dietary bioactive compounds have been identified to date (Gonzalez-Gallego, V. Garcia-Mediavilla, S. Sanchez-Campos, and Tunon 2010; Liu 2013; Casas, Estruch, and Sacanella 2018), many of which now have a substantial body of evidence supporting their benefits on human health. Lupton et al. (2014) recognized the importance of dietary bioactives and proposed criteria for establishing recommended dietary intakes based on these putative health outcomes. In a few instances, the dietary reference intake framework for essential nutrients has been applied in using nonessential food components, such as carotenoids, dietary fiber, and certain trace elements, in the United States and Canada (IOM 1998, 2001, 2005a). The Chinese Nutrition Society (2018) has published intake recommendations for at least 19 nonessential bioactives (Table 3). However, the issue that arises when examining mostly observational evidence is the inability to distinguish between the effects of a single bioactive ingredient or class of compounds and other nutritional constituents (Ellwood et al. 2014).

Of the dietary bioactive classes present in F&V, polyphenols and carotenoids have been the most widely studied.

Table 2. Classification of dietary bioactive compounds present in fruits and vegetables.

Class	Compound(s)
Carotenoids	α-carotene, β-carotene, β-cryptoxanthin, Lutein, Zeaxanthin, Lycopene
Phenolics	
Phenolic acids	Hydroxy-benzoic acids, Hydroxy-cinnamic acids
Flavonoids	Flavonols, Flavones, Flavanols, Flavanones, Anthocyanins, Isoflavones
Stilbenes	(*E*)-stilbene, (*Z*)-stilbene
Coumarins	Scopoletin, Aesculetin, Umbelliferone
Tannins	Hydrolysable tannins, Phlorotannins, Condensed Tannins
Alkaloids	True alkaloids, Protoalkaloids, Polyamine alkaloids, Peptide and cyclopeptide alkaloids, Pseudoalkaloids
Nitrogen-containing compounds	Non-protein amino acids, Amines, Cyanogenic glycosides, Glucosinolates, Lectins, Peptides and polypeptides
Organosulfur compounds	Isothiocyanates, Indoles, Allylic sulfur compounds

Adapted and expanded with permission from Liu (2004).

Table 3. Specific proposed levels and upper limits for non-nutrient substances published by the Chinese Nutrition Society.

Non-nutrient substance	Specific proposed level	Upper limit
Dietary fiber (g/d)[a]	25–30	IE
Soy isoflavones (mg/d)	50	80
Lutein (mg/d)	6	60
Lycopene (mg/d)	18	50
Phytosterols (g/d)	0.8	2.4–3.9
Glucosamine (g/d)	1.0–1.5	IE
Anthocyanins (mg/d)	50	NN
Proanthocyanidins (mg/d)	200	800
Curcumin (mg/d)	IE	180
Resveratrol (g/d)	IE	2.5
L-carnitine (mg/d)	IE	2000
Fructooligosaccharides (g/d)	IE	15
R-GABA	IE	NN
Allicin	IE	IE
Chlorogenic acid	IE	IE
Lipoic acid	IE	IE
Catechins	IE	NN
Isothiocyanates	IE	IE
Quercetin	IE	IE

Adapted from the Chinese Nutrition Society (2018). GABA, γ-aminobutyric acid; IE, inadequate evidence; NN, not necessary.
[a]Adequate intake.

There is consistent evidence from prospective cohort studies that high intakes of flavonoids are associated with a reduced risk of CVD and a reduced incidence of CVD, coronary heart disease (CHD), and all-cause mortality in men and women (Kim and Je 2017). Among the flavonoids, anthocyanins appear to have a significant impact on glucose metabolism (Li et al. 2017), as well as total and low-density lipoprotein cholesterol levels, particularly among people with hyperlipidemia (Wallace, Slavin, and Frankenfeld 2016), across RCTs. Although they are often considered a simple biomarker of F&V intake, carotenoids possess important anti-inflammatory and antioxidant properties independent of their pro–vitamin A activity. Interestingly, a dose-response relationship has been found between blood concentrations of α- and β-carotene as well as total carotenoids and risk of lung cancer (Abar et al. 2016). Lutein, a yellow xanthophyll carotenoid found in spinach and other colorful F&V, is strongly correlated with visual performance, a reduced risk of age-related macular degeneration (AMD), and enhanced cognition (Johnson 2014; Renzi-Hammond et al. 2017; Mewborn et al. 2018a; Mewborn et al. 2018b). A recent expert review of the literature demonstrates that lutein meets the criteria outlined by Lupton et al. (2014) and suggests that this evidence is sufficient to propose recommendations for reference intake values (Ranard et al. 2017).

Emerging biomarkers of dietary intake

A biomarker is a measurable substance that is taken to reflect some underlying physiological state, whether normal or pathological. In theory, almost any measurement that reflects a change in biochemical processes, structures or functions can be used as a biomarker (Cross et al. 2017). Biomarkers can be used to assess dietary intakes (exposure), biological responses, or responses to a behavior or nutrition intervention (effect); can serve as predictors of a clinical endpoint or disease outcome (intermediate biomarker); and/or can measure predisposition to a disease or response to treatment (genetic susceptibility) (Cross et al. 2017).

The use of biomarkers to characterize and monitor dietary exposure to F&V is not a new concept. Researchers in the early 1990s first described plasma carotenoids as being useful biomarkers of F&V intake (Campbell, Gross, G. A. Grandits, and Potter 1994). More recently, resonance Raman spectroscopic evaluation of skin carotenoids has been utilized as a biomarker of carotenoid status (Mayne et al. 2013). In addition, the urinary metabolite 3,3′-diindolylmethane (DIM) has been shown to discriminate between volunteers fed high and low doses of *Brassica* vegetables, and DIM has been suggested to be a reliable biomarker of glucobrassicin exposure and indole-3-carbinol uptake (Fujioka et al. 2016).

The current pace of biomarker discovery and its applications is greater than ever before, in part due to the rapid development of "omics" technologies and data collection. Some single-omics analyses have provided valuable data, mostly in the field of nutrigenomics. Thus, several gene-diet interactions in determining both intermediate (plasma lipids, etc.) and final cardiovascular phenotypes (stroke, myocardial infarction, etc.) have been reported (Fitó et al. 2016). In order to support this development, there is a need to develop ontologies for food, nutrition, and diet-related health areas. There is also a need to classify biomarkers in such a way that systematically attempts to validate them and develop them into trusted research and clinical tools according to standardized criteria based on their intended use (Dragsted et al. 2017).

Table 4. Literature search strategy.

PubMed Search
(("fruit"[MeSH Terms] OR "fruit"[All Fields]) OR ("fruit"[MeSH Terms] OR "fruit"[All Fields] OR "fruits"[All Fields])) AND (("vegetables"[MeSH Terms] OR "vegetables"[All Fields] OR "vegetable"[All Fields]) OR ("vegetables"[MeSH Terms] OR "vegetables"[All Fields])) AND systematic[sb]

Limited to studies in the English language.

Methods

Literature search and selection criteria

We followed standardized procedures for performing an umbrella review as previously described by Aromataris et al. (2015). We systematically searched the PubMed database from inception until May 21, 2019 using the search strategy outlined in Table 4. We included all systematic reviews with or without meta-analyses of human studies with a health-related outcome (e.g., CVD, cancer, mortality, etc). English language restrictions were applied. One investigator (DDW) performed the primary title and abstract screening. The full texts of all potentially eligible articles were retrieved, and consensus between two investigators (DDW and TCW) determined the final eligibility of each manuscript.

Data extraction

Two investigators (DDW and TCW) extracted the following information for each article: 1) first-author last name, 2) year of publication, 3) country in which the study was conducted, 4) outcome variable (e.g., bladder cancer), 5) number of studies for F&V and F&V included in the systematic review, 6) outcome comparison (e.g., high vs. low or dose-response), 7) the most-adjusted, study-specific estimates for the health outcome (e.g., relative risk [RR], odds ratio [OR], hazard ratio [HR], or incident risk ratio), along with the 95% confidence interval (CI). We included all systematic reviews, regardless of whether multiple ones were available for the same health outcome. We did not conduct any data analyses due to heterogeneity between systematic reviews and the overall large quantity of available data.

Effect of fruit and vegetable intakes on all-cause mortality

NCDs are the leading cause of death worldwide, primarily from CVD and cancers (GBD 2013 Mortality and Causes of Death Collaborators 2015). In 2016, NCDs were responsible for 41 million (71%) of the 57 million deaths that occurred globally (Riley, Gouda, and Cowan 2017). During the past 50 years, lifestyle factors have been identified as modifiable factors associated with premature death. Despite often unclear direct biological mechanisms, epidemiological risk factors can change the probability of death and can serve as important public health indicators. Several dated meta-analyses have shown that obtaining recommended intakes of F&V, among other food groups such as whole grains, nuts, and fish, is one of the most important factors associated with a lower risk of all-cause mortality (Wang et al. 2014b; Aune et al. 2016; Mayhew et al. 2016; Zhao et al. 2016). The most recent systematic review and meta-analysis found that with increasing intake (for each daily serving), the risk of all-cause mortality decreased for fruits (RR, 0.94; 95% CI, 0.92–0.97), vegetables (RR, 0.96; 95% CI, 0.95–0.98), whole grains (RR, 0.92; 95% CI, 0.89–0.95), nuts (RR, 0.76; 95% CI, 0.69–0.84), and fish (RR, 0.93; 95% CI, 0.88–0.98) (Schwingshackl et al. 2017c). Optimal consumption of risk-decreasing foods (i.e., fruits, vegetables, whole grains, nuts, and fish) resulted in a 56% reduction in all-cause mortality (Schwingshackl et al. 2017c). However, these investigated food groups are often only part of healthy dietary patterns. High adherence to the HEI and Dietary Approaches to Stop Hypertension (DASH) diets has been associated with a 22% lower risk of all-cause mortality (Schwingshackl and Hoffmann 2015). In the United States, morbidity and chronic disability now account for nearly half of the health burden. Diet has been suggested to be a more important factor associated with disease burden in the United States than both physical activity and BMI. Data from the Global Burden of Disease (GDB) database indicate that the most important dietary risks in the U.S. population are diets low in fruits, vegetables, nuts, and seeds and high in sodium, processed meats, and saturated fats (Murray 2013).

Effects of fruit and vegetable intake on health outcomes

The literature search strategy identified 401 articles, of which 96 systematic reviews were identified after completion of the title/abstract screening that assessed F&V intake on various disease outcomes (Tables 5–7). All 96 studies were included for data extraction after full-text review. Most systematic reviews contained meta-analyses that assessed high vs. low intake of F&V on disease outcomes. Fewer systematic reviews assessed whether a dose-response relationship existed between the amount of F&V consumed and specific health outcomes. Various types of cancer and cardiovascular outcomes were the most frequently assessed disease outcome, with other disease states such as type-2 diabetes, AMD and osteoporosis, among others, being less common. As anticipated for assessment of disease outcomes, the majority of systematic reviews included observational data and human interventions studies were scarce. Results of the individual systematic reviews are discussed in the corresponding disease state sections of this manuscript. The review was focused on the major global causes of morbidity and mortality: CVD, cancers, infectious diseases, musculoskeletal diseases, and other important health topics. F&V intakes with regard to contributors to chronic disease including weight status, inflammation, and immunity are also discussed.

Cancer

Cancer is the second leading cause of death in the United States and worldwide. It is responsible for 1.6 million and 8.8 million deaths domestically and globally, respectively, and nearly one in six deaths are attributable to cancer (Siegel, Miller, and Jemal 2016). The occurrence of cancer as a whole is increasing with age and the pathogenesis often takes several decades. Aside from its societal burden and loss of human potential, cancer has a large global economic impact currently estimated at over $1.16 trillion annually, which is expected to increase by 70% within 2 decades, posing serious challenges to health systems across the world (IARC 2014). Approximately 20% of all cancers diagnosed in the United States have been suggested to be attributable to unhealthy diet, excessive alcohol consumption, physical inactivity, and body fatness (Kushi et al. 2012). Nutrition is an important part of both cancer prevention and treatment. Efforts to promote an overall healthy diet plentiful in F&V are well justified but sustained effects on cancer risk are likely to be modest over time (Wallace et al. 2019). The American Cancer Society currently recommends consuming ≥2.5 cups of F&V daily for cancer prevention (Kushi et al. 2012). The most recent systematic review of prospective cohort studies by Aune et al. (2017) assessed F&V intake on risk of total cancer. The dose-response meta-analysis showed a 3% (HR, 0.97; 95% CI, 0.95–0.99), 4% (HR, 0.96; 95% CI, 0.94–0.99) and 4% (HR, 0.96; 95% CI, 0.93–0.99) in total cancer per 200 g/d increase in F&V, fruits and vegetables. An earlier systematic review of prospective cohort studies by Wang et al. (2014b) assessed F&V intake and overall risk of cancer mortality. Two studies reported data between cancer

Table 5. Summary of systematic reviews assessing fruit and vegetable intake on cancer outcomes.

Reference	Country	Cancer Outcome	Number of effects			Outcome comparison	RR/OR (95% CI)		
			FV	F	V		FV	F	V
Al-Zalabani et al. (2016)	Netherlands	Bladder	10	27	29	H vs. L	0.81 (0.67–0.99)	0.77 (0.69–0.87)	0.83 (0.75–0.92)
Aune et al. (2011)	UK	Colorectal	11	14	16	H vs. L	0.92 (0.86–0.99)	0.90 (0.83–0.98)	0.91 (0.86–0.96)
			11	13	12	DR (per 100/g/d)	0.99 (0.98–1.00)	0.98 (0.94–1.01)	0.98 (0.97–0.99)
Aune et al. (2012)	UK	Breast	6	10	10	H vs. L	0.89 (0.80–0.99)	0.92 (0.86–0.98)	0.99 (0.92–1.06)
			6	10	9	DR (per 200g/d)	0.96 (0.93–1.00)	0.94 (0.89–1.00)	1.00 (0.95–1.06)
Aune et al. (2017)	UK	Total Cancer	14	25	19	DR (per 200g/d)	0.97 (0.95–0.99	0.96 (0.94–0.99)	0.96 (0.93–0.99)
Bandera et al. (2007)	UK	Endometrial		14	10	H vs. L		0.90 (0.71–1.12)	0.71 (0.55–0.91)
				10	8	DR (per 100g/d)		0.97 (0.92–1.02)	0.90 (0.86–0.95)
Ben et al. (2015)	China	Colorectal	8	20	17	H vs. L	0.82 (0.75–0.91)	0.79 (0.71–0.88)	0.91 (0.80–1.02)
			6	12	10	DR	0.99 (0.98–0.99)	0.94 (0.92–0.97)	0.98 (0.96–1.01)
Bonequi et al. (2013)[a]	Mexico	Gastric		11	12	H vs. L		0.68 (0.49–0.94)	0.58 (0.43–0.77)
Chen et al. (2013a)	China	Non-Hodgkin lymphoma	4	13	13	H vs. L	0.78 (0.66–0.92)	0.97 (0.87–1.08)	0.81 (0.71–0.92)
			4	12	13	DR (per 1sv/d)	0.95 (0.91–1.00)	0.98 (0.94–1.02)	0.92 (0.87–0.96)
Dessypris et al. (2017)[b]	Greece	Childhood leukemia		2	2	H vs. L		0.81 (0.67–0.99)	0.51 (0.28–0.94)
Fang et al. (2015)	China	Gastric		30	22	H vs. L		0.93 (0.89–0.98)	0.98 (0.91–1.05)
				NR		DR (per 100g/d)		0.95 (0.92–0.99)	
Gandini et al. (2000)	Italy	Breast		12	17	H vs. L		0.94 (0.79–1.11)	0.75 (0.66–0.85)
He, Gu, and Zhang (2017)	China	Breast	3	4	4	H vs. L	1.08 (0.88–1.33)	0.83 (0.67–1.02)	0.96 (0.71–1.30)
			2	3	3	DR (per 1sv/d)	0.98 (0.95–1.01)	0.95 (0.89–1.01)	0.93 (0.79–1.10)
Jin, Ouyang, and Wang (2014)	China	Nasopharyngeal	3	10	11	H vs. L	0.33 (0.25–0.45)	0.63 (0.56–0.70)	0.60 (0.47–0.76)
Johnson et al. (2013)	US	Colorectal		9	8	DR (per 2sv/d)		0.85 (0.78–0.94)	0.94 (0.91–0.98)
Jung et al. (2013)	US	Breast	20	20	20	H vs. L	0.98 (0.93–1.02)	0.99 (0.95–1.03)	0.99 (0.95–1.04)
Koushik et al. (2012)	Canada	Pancreatic	14	14	14	DR (per 100g/d)	1.01 (0.92–1.10)	1.01 (0.99–1.03)	1.02 (0.99–1.06)
Li (2014)	China	Glioma		17	15	H vs. L		0.83 (0.66–1.04)	0.78 (0.69–0.87)
Li et al. (2014a)	China	Esophageal adenocarcinoma	5	9	9	H vs. L	0.68 (0.49–0.93)	0.73 (0.55–0.98)	0.76 (0.59–0.96)
			4	6	6	DR (per 100g/d)	0.88 (0.78–0.98)	0.87 (0.76–0.99)	0.91 (0.83–0.99)
Liu et al. (2013)	China	Esophageal squamous cell carcinoma		29	24	H vs. L		0.53 (0.44–0.64)	0.56 (0.45–0.69)
				19	15	DR (per 100g/d)		0.61 (0.52–0.72)	0.84 (0.79–0.92)
Liu et al. (2015)	China	Bladder	9	27	24	H vs. L	0.83 (0.69–1.01)	0.81 (0.73–0.89)	0.84 (0.72–0.96)
				14	12	DR (per 200g/d)		0.91 (0.83–0.99)	0.92 (0.87–0.97)
Liu and Lin (2014)	China	Thyroid		9	5	H vs. L		0.97 (0.78–1.21)	0.76 (0.58–1.00)
Lunet et al. (2007)	Portugal	Gastric, cardia	13	13	13	H vs. L		0.58 (0.38–0.89)	0.63 (0.50–0.79)
		Gastric, non-cardia	13	13	13	H vs. L		0.61 (0.44–0.84)	0.75 (0.59–0.95)
Marques-Vidal, Ravasco, and Ermelinda Camilo (2006)	Portugal	Colorectal	6	14	15	Summary	NR	NR	NR
Meng et al. (2014)	China	Prostate		14	12	H vs. L		1.02 (0.98–1.07)	0.97 (0.93–1.01)
Michels et al. (2007)	US	Breast	6			Summary	NR	NR	NR
Paluszkiewicz et al. (2012)	Poland	Pancreatic		5	7	H vs. L		0.81 (0.61–1.09)	0.87 (0.75–1.01)
Pavia et al. (2006)	Italy	Oral		16	15	H vs. L		0.51 (0.40–0.65)	0.50 (0.38–0.65)
Schwingshackl et al. (2018)	Germany	Colorectal		19	20	H vs. L		0.93 (0.88–0.98)	0.96 (0.92–1.00)
				16	15	DR (per 100g/d)		0.97 (0.95–0.99)	0.97 (0.96–0.98)
Sergentanis et al. (2018)	Greece	Non-Hodgkin lymphoma	3	5	5	H vs. L	0.79 (0.65–0.96)	1.03 (0.92–1.16)	0.89 (0.79–1.00)
		Acute myeloid leukemia		3	3	H vs. L		1.23 (0.94–1.61)	0.93 (0.68–1.26)
		Multiple myeloma		3	3	H vs. L		1.05 (0.72–1.55)	1.05 (0.84–1.31)
		Hodgkin lymphoma		2	2	H vs. L			
Vieira et al. (2015)	UK	Bladder	9	12	10	H vs. L	0.89 (0.75–1.05)	0.91 (0.82–1.00)	0.92 (0.84–1.01)
			8	12	10	DR (per sv/d)	0.97 (0.95–0.99)	0.98 (0.96–1.00)	0.97 (0.94–1.00)
Vieira et al. (2016)	UK	Lung	18	29	25	H vs. L	0.86 (0.78–0.94)	0.82 (0.76–0.89)	0.92 (0.87–0.97)
			14	23	20	DR (per 100g/d)	0.96 (0.94–0.98)	0.92 (0.89–0.95)	0.94 (0.89–0.98)
Vieira et al. (2017)	UK	Colorectal Colon Rectal		13	11	DR (per 100g/d)		0.96 (0.93–1.00)	0.98 (0.96–0.99)
				12	12	DR (per 100g/d)		0.98 (0.96–1.01)	0.97 (0.95–0.99)
				9	8	DR (per 100g/d)		0.98 (0.93–1.03)	0.99 (0.96–1.02)
Vingeliene et al. (2017)	UK	Esophageal	2	4	5	DR		0.94 (0.89–1.00)	0.98 (0.90–1.06)
		Esophageal squamous cell carcinoma		3	4	DR		1.03 (0.95–1.11)	0.91 (0.81–1.03)
		Esophageal adenocarcinoma		3	3	DR		0.84 (0.75–0.94)	0.89 (0.80–0.99)
Wakai et al. (2011)[c]	Japan	Lung		8	5	H vs. L		0.85 (0.75–0.96)	
				8		DR (per 1sv/d)		0.92 (0.84–1.00)	
Wang et al. (2014b)	China	Mortality	2	7	8	DR (per 1sv/d)	0.97 (0.90–1.03)	0.99 (0.97–1.00)	0.99 (0.97–1.01)
Wang et al. (2014a)	China	Gastric		22	19	H vs. L		0.90 (0.83–0.98)	0.96 (0.88–1.06)
				16	16	DR (per 100g/d)		0.95 (0.91–0.99)	0.96 (0.91–1.01)
Wang et al. (2015a)	China	Lung		38	37	H vs. L		0.80 (0.74–0.88)	0.74 (0.67–0.82)
Wang et al. (2015b)	China	Lung	8	16	19	H vs. L	0.87 (0.79–0.95)	0.84 (0.79–0.90)	0.90 (0.84–0.96)
			4	8	9	DR (per 1sv/d)	0.97 (0.95–0.99)	0.96 (0.94–0.98)	0.96 (0.92–1.00)
Woo et al. (2014)[d]	Korea	Gastric		4	2	H vs. L		0.61 (0.42–0.88)	0.66 (0.37–1.16)
		Colorectal			2	H vs. L			0.51 (0.19–1.32)

(*continued*)

Table 5. Continued.

Reference	Country	Cancer Outcome	Number of effects FV	F	V	Outcome comparison	RR/OR (95% CI) FV	F	V
		Breast		4	2	H vs. L		0.78 (0.60–1.01)	0.41 (0.12–1.39)
Wu et al. (2015a)[e]	China	Breast		11	13	H vs. L		0.68 (0.49–0.93)	0.77 (0.62–0.96)
Xu et al. (2015)	China	Bladder	8	14	13	DR (per 0.2sv/d)	0.99 (0.97–1.01)	0.99 (0.99–1.00)	1.00 (0.99–1.00)
Yang et al. (2014)	China	Hepatocellular	2	12	17	H vs. L		0.93 (0.80–1.09)	0.70 (0.56–0.87)
				8	9	DR (per 100g/d)		0.99 (0.94–1.05)	0.92 (0.88–0.96)
Yao et al. (2014)	China	Bladder	11	27	21	H vs. L	0.83 (0.69–0.99)	0.77 (0.69–0.87)	0.81 (0.7–0.93)
			5	15	11	DR (per 100g/d)	0.97 (0.95–0.99)	0.93 (0.88–0.98)	0.94 (0.89–0.99)
Zhang et al. (2017)	China	Renal cell		18	16	H vs. L		0.86 (0.75–0.98)	0.73 (0.63–0.85)
				10	10	DR (per 1sv/d)		0.97 (0.93–1.01)	0.90 (0.84–0.96)

CI, confidence interval; DR, dose-response; F, fruit; FV, fruit and vegetable; H vs. L, high vs. low; NR, not reported; OR, odds ratio; RR, relative risk; sv, serving; V, vegetable.
[a]Study conducted in the Latin American population.
[b]Study conducted on maternal/child diet.
[c]Study conducted in the Japanese population.
[d]Study conducted in the Korean population.
[e]Study conducted in Chinese women.

Table 6. Summary of systematic reviews assessing fruit and vegetable intake on CVD outcomes.

Reference	Country	Outcome	Number of effects FV	F	V	Outcome comparison	RR/OR (95% CI) FV	F	V
Aune et al. (2017)	UK	CHD	17	26	23	DR (per 200g/d)	0.92 (0.90–0.94)	0.90 (0.86–0.94)	0.90 (0.86–0.94)
		Stroke	10	19	14	DR (per 200g/d)	0.84 (0.76–0.92)	0.82 (0.74–0.90)	0.87 (0.79–0.96)
		CVD	17	25	22	DR (per 200g/d)	0.92 (0.90–0.95)	0.87 (0.82–0.92)	0.90 (0.87–0.93)
Bechthold et al. (2019)	Germany	CHD		17	19	H vs. L		0.89 (0.84–0.93)	0.92 (0.87–0.98)
						DR (per 100g/d)		0.94 (0.90–0.97)	0.97 (0.96–0.99)
		Stroke		17	16	H vs. L		0.83 (0.77–0.89)	0.87 (0.82–0.93)
						DR (per 100g/d)		0.90 (0.84–0.97)	0.92 (0.86–0.98)
		Heart failure		3	3	H vs. L		0.95 (0.88–1.02)	0.99 (0.82–1.18)
						DR (per 100g/d)		0.98 (0.94–1.01)	0.96 (0.94–0.98)
Blanch, Clifton, and Keogh (2015)	Australia	Endothelial vasodilator function	11	11	3	Summary	NR	NR	NR
		Vascular function	1	7	0	Summary	NR	NR	NR
Dauchet, Amouyel, and Dallongeville (2005)	France	Stroke	6	5	4	DR (per sv/d)	0.95 (0.92–0.97)	0.89 (0.85–0.93)	0.97 (0.92–1.02)
Dauchet et al. (2006)	France	CHD	6	6	7	DR (per sv/d)	0.96 (0.93–0.99)	0.93 (0.89–0.96)	0.89 (0.83–0.95)
Gan et al. (2015)	China	CHD	16	26	22	H vs. L	0.84 (0.79–0.90)	0.86 (0.82–0.91)	0.87 (0.81–0.93)
			14	22	18	DR[a]	0.88 (0.85–0.91)	0.84 (0.75–0.93)	0.82 (0.73–0.92)
He, Nowson, and MacGregor (2006)	UK	Stroke	9	6	6	H vs. L	0.74 (0.69–0.79)	0.72 (0.66–0.79)	0.81 (0.72–0.90)
He et al. (2007)	UK	CHD	13	9	9	H vs. L	0.83 (0.77–0.89)	0.87 (0.80–0.95)	0.84 (0.76–0.92)
Hu et al. (2014)	China	Stroke	24	19	16	H vs. L	0.79 (0.75–0.84	0.77 (0.71–0.84)	0.86 (0.79–0.93)
Law and Morris (1998)	UK	Ischemic heart disease		3	2	H vs. L		0.86 (0.71–1.05)	0.82 (0.66–1.02)
Li et al. (2016)	China	Hypertension	16	8	6	H vs. L	0.81 (0.74–0.89)	0.73 (0.62–0.86)	0.97 (0.91–1.02)
Mente et al. (2009)	Canada	CHD	7	10	9	H vs. L	0.79 (0.72–0.87)	0.80 (0.66–0.93)	0.77 (0.68–0.87)
Schoenaker, Soedamah-Muthu, and Mishra (2014)	Australia	Preeclampsia	10			H vs. L	NR	NR	NR
Schwingshackl et al. (2017b)	Germany	Hypertension		7	8	H vs. L		0.93 (0.87–1.00)	0.96 (0.91–1.01)
				6	7	DR (per 100g/d)		0.97 (0.96–0.99)	1.00 (0.98–1.01)
Sherzai et al. (2012)	US	Stroke	6			Summary	NR	NR	NR
Tian et al. (2018)	China	Metabolic syndrome	7	9	9	H vs. L	0.76 (0.62–0.93)	0.87 (0.82–0.92)	0.85 (0.80–0.91)
Wang et al. (2014b)	China	CVD mortality	4	6	6	DR	0.96 (0.92–0.99)	0.95 (0.91–1.00)	0.96 (0.93–0.99)
Wu, Sun, and He (2016)	China	Hypertension	6	8	8	H vs. L	0.90 (0.84–0.98)	0.87 (0.79–0.95)	0.88 (0.79–0.99)
Zhan et al. (2017)	China	CVD	34	41	45	H vs. L	0.83 (0.79–0.86)	0.84 (0.79–0.88)	0.87(0.83–0.91)
			30	34	36	DR (per 100g/d)	0.96 (0.94–0.98)	0.88 (0.86–0.91)	0.90 (0.87–0.93)
Zhang and Zhang (2018)	China	Metabolic syndrome	8	16	16	H vs. L	0.75 (0.63–0.90)	0.81 (0.75–0.88)	0.89 (0.85–0.93)

CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DR, dose-response; F, fruit; FV, fruit and vegetable; H vs. L, high vs. low; NR, not reported; OR, odds ratio; RR, relative risk; V, vegetable.
[a]Per 477 g/d fruits and vegetables; per 300 g/d fruit; per 400 g/d vegetables.

Table 7. Summary of systematic reviews assessing fruit and vegetable intake on other disease outcomes.

Reference	Country	Outcome	Number of effects			Outcome comparison	RR/OR (95% CI)		
			FV	F	V		FV	F	V
Aune et al. (2017)	UK	All-cause mortality	24	37	33	DR (per 200g/d)	0.90 (0.87–0.93)	0.85 (0.80–0.91)	0.87 (0.82–0.92)
Cao et al. (2016)	China	Dementia	2			H vs. L	0.46 (0.16–1.32)		
Carter et al. (2010)	UK	Type 2 diabetes	4	5	5	H vs. L	1.00 (0.92–1.09)	0.93 (0.83–1.01)	0.91 (0.76–1.09)
Dinu et al. (2018)	Italy	AMD		3	4	H vs. L		0.91 (0.82–1.01)	0.92 (0.82–1.03)
Hamer and Chida (2007)	UK	Type 2 diabetes	5			H vs. L	≥5 sv/d: 0.96 (0.79–1.17)	≥3 sv/d: 1.01 (0.88–1.15)	≥3 sv/d: 0.97 (0.86–1.09)
Hamidi et al. (2011)	Canada	Fragility fractures	1		1	Summary	NR	NR	NR
		BMD	7			Summary	NR	NR	NR
		Bone turnover markers	3			Summary	NR	NR	NR
Hosseini et al. (2017)	Australia	Asthma	6	16	17	H vs. L	0.90 (0.80–1.01)	0.98 (0.96–1.00)	0.95 (0.92–0.98)
		Wheezing		17	10	H vs. L		0.94 (0.91–0.97)	0.98 (0.94–1.03)
Hosseini et al. (2018)	Australia	Inflammation: CRP (mg/L)	23			H vs. L	−0.33 (−0.56 to −0.10)a		
		TNF-α (pg/mL)	16			H vs. L	−0.87 (−1.59 to −0.15)a		
		IL-6 (pg/mL)	22			H vs. L	−0.12 (−0.31 to −0.006)a		
Hu, Cheng, and Jiang (2018)	China	Premenopausal osteoporosis		9	9	H vs. L		0.68 (0.56–0.83)	0.87 (0.65–1.16)
Jiang et al. (2017)	China	Dementia	9	3	3	H vs. L	0.8 (0.71–0.89)	0.84 (0.72–0.97)	0.79 (0.54–1.15)
		Cognitive impairment and dementia	4			DR (per 100g/d)	0.87 (0.77–0.99)		
Kaiser et al. (2014)	US	Weight loss	7			H vs. L	0.04 (–0.10 to 0.17)a		
Ledoux, Hingle, and Baranowski (2011)	US	Adiposity	23			Summary	NR	NR	NR
						Summary	NR	NR	NR
						Summary	NR	NR	NR
Li et al. (2014b)	China	Type 2 diabetes	9	11	9	H vs. L	0.94 (0.86–1.03)	0.93 (0.88–0.99)	0.90 (0.8–1.01)
			6	7	5	DR (1 sv/d)	0.96 (0.86–1.07)	0.94 (0.89–1.00)	0.98 (0.89–1.08)
Li et al. (2015)	China	Ulcerative colitis		8	9	H vs. L		0.69 (0.49–0.96)	0.71 (0.58–0.88);
		Crohn's disease		10	8	H vs. L		0.57 (0.44–0.74)	0.66 (0.40–1.09)
Liu et al. (2016)	China	Depression		10	8	H vs. L		0.86 (0.81–0.91)	0.89 (0.83–0.94)
Loef and Walach (2012)	Germany	Dementia				Summary	NR	NR	NR
		MCI				Summary	NR	NR	NR
Luo et al. (2016)	China	Hip fracture	8	6	6	H vs. L	0.83 (0.70–0.98)	0.87 (0.74–1.04)	0.75 (0.61–0.92)
Mottaghi, Amirabdollahian, and Haghighatdoost (2018)	Iran	Cognitive impairment	10	3	3	H vs. L	0.79 (0.67–0.93)	0.84 (0.73–0.97)	0.79 (0.54–1.15)
Murphy et al. (2014)	US	Infant birth weight				Summary	NR	NR	NR
		Small for gestational age birth				Summary	NR	NR	NR
Mytton et al. (2014)	UK	Body weight	8			H vs. L	−0.68 (−1.20 to −0.15)[a]		
		Energy intake	6			H vs. L	367.94 (−27.10 to 762.98)[a]		
Nurmatov, Devereux, and Sheikh (2011)	US	Asthma and allergy	22			Summary	NR	NR	NR
Raghavan et al. (2019a)	US	Gestational age	11			Summary	NR	NR	NR
		Birth weight	21			Summary	NR	NR	NR
Raghavan et al. (2019b)	US	Hypertensive disorders of pregnancy	4			Summary	NR	NR	NR
		Gestational diabetes mellitus	11			Summary	NR	NR	NR

(*continued*)

Table 7. Continued.

Reference	Country	Outcome	Number of effects			Outcome comparison	RR/OR (95% CI)		
			FV	F	V		FV	F	V
Saghafian et al. (2018)	Iran	Depression	6	6	9	H vs. L	0.80 (0.65–0.98)	0.83 (0.71–0.98)	0.86 (0.75–0.98)
				4	4	DR (per 100g/d)		0.97 (0.95–0.99)	0.97 (0.95–0.98)
Schlesinger et al. (2019)	Germany	Obesity		4	3	H vs. L		0.88 (0.80–0.96)	0.93 (0.83–1.03)
				4	2	DR (per 100g/d)		0.93 (0.86–1.00)	0.98 (0.93–1.03)
		Weight gain		3	5	H vs. L		0.86 (0.70–1.05)	0.78 (0.62–0.98)
				3	5	DR (per 100g/d)		0.91 (0.86–0.97)	0.90 (0.91–1.01)
Schwingshackl et al. (2017c)	Germany	All-cause mortality		34	37	H vs. L		0.91 (0.89–0.94)	0.93 (0.90–0.95)
				17	17	DR (per 100g/d)		0.94 (0.92–0.97)	0.96 (0.95–0.98)
Schwingshackl et al. (2017a)	Germany	Type 2 diabetes		15	13	H vs. L		0.96 (0.93–1.00)	0.95 (0.89–1.01)
				13	11	DR (per 100g/d)		0.98 (0.97–1.00)	0.98 (0.96–1.00)
Seyedrezazadeh et al. (2014)	Canada	Wheezing		15	11	H vs. L		0.81 (0.74–0.88)	0.89 (0.81–0.98)
		Asthma	4	23	18	H vs. L	0.64 (0.41–1.01)	0.84 (0.80–0.90)	0.88 (0.82–0.95)
		Atopy		3	3	H vs. L		0.98 (0.95–1.01)	0.99 (0.96–1.01)
Skoczek-Rubinska, Bajerska, and Menclewicz (2018)	Poland	Periodontal diseases	15			Summary	NR	NR	NR
Wang et al. (2014b)	China	All-cause mortality	7	7	7	DR (per 1sv/d)	0.95 (0.92–0.98)	0.94 (0.90–0.98)	0.95 (0.92–0.99)
Wang et al. (2016b)	China	Type 2 diabetes	9	13	10	H vs. L	0.95 (0.90–1.02)	0.91 (0.87–0.91)	0.91 (0.82–1.01)
Wu et al. (2015b)	China	Type 2 diabetes	7	9	7	DR (per 1sv/d)	0.99 (0.98–1.00)	0.99 (0.97–1.00)	0.98 (0.95–1.01)
Wu, Sun, and Tan (2017)	China	Cognitive impairment	9			H vs. L	0.74 (0.62–0.88)		

AMD, age-related macular degeneration; BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DR, dose-response; F, fruit; FV, fruit and vegetable; H vs. L, high vs. low; ND, no data; OR, odds ratio; RR, relative risk; V, vegetable.

[a]Denotes fixed-effect standard mean difference (95% CI).

mortality and consumption of F&V (HR, 0.97; 95% CI, 0.90–1.03), seven studies on fruit (HR, 0.99; 95% CI, 0.97–1.00), and eight studies on vegetables (HR, 0.99; 95% CI, 0.97–1.01) (Wang et al. 2014b). At least 44 systematic reviews have assessed F&V intake and site-specific cancers (discussed below; Table 5). Table 8 summarizes recent findings on whole grains, vegetables, and fruit and risk of cancer from the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) Continuous Update Project *2018 Expert Report* (WCRF and AICR 2018).

Several biological mechanisms have been proposed to elucidate the protective effects of F&V on cancer outcomes. Cancer is a disease characterized by chromosomal changes that can be induced due to variable mechanisms. Anticarcinogenic properties of F&V have been suggested to be attributed to high levels of some micronutrients, fiber, and dietary bioactive compounds. Further, the metabolism of chemical carcinogens has been shown to be influenced by several dietary constituents (Wattenberg 1975). Naturally occurring inducers of the microsomal mixed-function oxidase system are present in plants; cruciferous vegetables containing indoles are particularly potent in this regard. Phenolic antioxidants also seem to affect the microsomal mixed-function oxidase system. Polyphenols have been shown the capacity to block or attenuate initiation or to suppress the stages of promotion and progression of carcinogenesis by controlling proliferation, apoptosis, cell cycle progression, inflammation, angiogenesis, invasion and metastasis (Gonzalez-Vallinas et al. 2013). The relative efficacy of chlorophyl and chlorophyllin has been shown to modify genotoxic effects of various known toxicants (Sarkar, Sharma, and Talukder 1994). The inhibitory activity of isothiocyanates and indoles against tumorigenesis stems from their ability to influence phase I and phase II biotransformation enzymes (Zhang and Talalay 1994; Boone, Kelloff, and Maolone 1990; McDannell and McLean 1988). For example, sulforaphane, which is present in broccoli is a potent inducer of phase II detoxification enzymes quinine reductase and glutathione transferase and an inhibitor of the carcinogen-activating cytochrome P450 2E1 (Zhang, Cooney, and Bertram 1992; Barcelo et al. 1996).

Bladder cancer

The WCRF and AICR (2018) support that a diet high in non-starchy F&V may have (limited-suggestive evidence) beneficial effects on bladder cancer. At least four systematic reviews have assessed the effectiveness of F&V to impact bladder cancer risk, reporting mixed results (Yao et al. 2014; Vieira et al. 2015; Xu et al. 2015; Al-Zalabani et al. 2016). The only systematic review utilizing a dose-response outcome comparison found weak evidence to support a beneficial effect of combined F&V, fruits, vegetables, or citrus intake against bladder cancer. Green leafy vegetables showed a slight beneficial effect (Xu et al. 2015). The most recent systematic review and high vs. low meta-analysis found F&V intake to have a protective effect against bladder cancer (HR, 0.81; 95% CI, 0.67–0.99). Intakes of high vs. low total fruit (HR, 0.77; 95% CI, 0.69–0.87), citrus fruit (HR, 0.85; 95% CI, 0.76–0.94), total vegetables (HR, 0.83; 95% CI, 0.75–0.92), and cruciferous vegetables (HR, 0.84; 95% CI, 0.77–0.91) were also associated with a reduced risk of bladder cancer (Al-Zalabani et al. 2016).

Brain tumor

One systematic review and meta-analysis utilizing a high vs. low outcome comparison of mostly case-controlled studies and two extremely small cohort studies found that risk of glioma was associated with vegetable intake (HR, 0.78; 95% CI, 0.69–0.87) (Li 2014).

Breast cancer

Breast cancer is the most frequent cancer among women (IARC Working Group on the Evaluation of Cancer-Preventive Strategies 2016; Wallace et al. 2019). The number of new cases was estimated to be 14.1 million in 2012 and is expected to reach 22.2 million by 2030 (Ferlay et al. 2015). At least seven systematic reviews have assessed the effectiveness of F&V to impact breast cancer outcomes, reporting mixed results (Gandini et al. 2000; Michels et al. 2007; Aune et al. 2012; Jung et al. 2013; Woo et al. 2014; Wu et al. 2015a; He, Gu, and Zhang 2017). The most recent systematic review found no effect of F&V, fruits or vegetables on breast cancer survival (He, Gu, and Zhang 2017). Wu et al. (2015a) found a significant reduction in risk of breast cancer in Chinese women using a high vs. low outcome comparison model. Jung et al. (2013) found no association between total F&V intake and risk of overall breast cancer; however, vegetable consumption was inversely associated with risk of estrogen receptor–negative breast cancer (HR, 0.82; 95% CI, 0.74–0.90) (Jung et al. 2013).

Childhood leukemia

One systematic review identified two case-controlled studies that both found maternal dietary intake of F&V to decrease the risk of childhood leukemia (Dessypris et al. 2017).

Colorectal cancer

At least seven systematic reviews have assessed the impact of F&V on colorectal cancer risk, all consistently reporting beneficial effects (Marques-Vidal, Ravasco, and Ermelinda Camilo 2006; Aune et al. 2011; Johnson et al. 2013; Woo et al. 2014; Ben et al. 2015; Vieira et al. 2017; Schwingshackl et al. 2018). Consistent with preceding systematic reviews, the most recent analysis found modest effects of both fruit (HR, 0.93; 95% CI, 0.88–0.98) and vegetable (HR, 0.96; 95% CI, 0.92–1.0) intake on colorectal cancer incidence in the high vs. low meta-analysis. Dose-response meta-analysis also showed beneficial effects for each additional daily 100 g increase in fruit (HR, 0.97; 95% CI, 0.95–0.99) and vegetable (HR, 0.97; 95% CI, 0.96–0.98) intake (Schwingshackl et al. 2018). The WCRF and AICR (2018) consider foods rich in dietary fiber to be strongly linked to a reduced risk of colorectal cancers. F&V may exert the most pronounced and consistent effects on colorectal cancers due to their interaction with the colonic mucosa.

Endometrial cancer

One systematic review and meta-analysis utilizing both high vs. low and dose-response outcome comparison of mostly case-controlled studies (n = 16) and one prospective cohort study assessed the effect of F&V on endometrial cancer (Bandera et al. 2007). Random-effects summary estimates comparing high vs. low categories of intake reported HRs of 0.71 (95% CI, 0.55–0.91) for total vegetables, 0.90 (95% CI, 0.74–0.97) for cruciferous vegetables, and 0.90 (95% CI, 0.72–1.12) for total fruit. Dose-response meta-analyses indicate that for every 100-g increase in daily intake, HRs were 0.90 (95% CI, 0.86–0.95) for total vegetables, 0.79 (95% CI, 0.69–0.90) for cruciferous vegetables, and 0.97 (95% CI, 0.92–1.02) for total fruit (Bandera et al. 2007).

Esophageal cancer

At least three systematic reviews have assessed the impact of F&V on esophageal cancer risk, reporting mixed effects (Liu et al. 2013; Li et al. 2014a; Vingeliene et al. 2017). The most recent systematic review, an update by the WCRF/AICR, found that fruit (HR per 100-g daily increase, 0.94; 95% CI, 0.89–1.00) and vegetable (HR per 100-g daily increase, 0.98; 95% CI, 0.90–1.06) intake was not related to the risk of esophageal cancer (all types combined). Fruit (HR, 0.84; 95% CI, 0.75–0.94) and vegetable (HR, 0.89; 95% CI, 0.80–0.99) intake was associated with a reduction in esophageal adenocarcinoma (Vingeliene et al. 2017), consistent with the prior systematic review by Li et al. (2014a).

Gastric cancer

At least five systematic reviews have assessed the impact of F&V on gastric cancer risk (Lunet et al. 2007; Bonequi et al. 2013; Wang et al. 2014a; Woo et al. 2014; Fang et al. 2015).Two of these systematic reviews focused on specific subpopulations, Latin (Bonequi et al. 2013) and Korean (Woo et al. 2014), with high heterogeneity. The most recent systematic review showed that consumption of white vegetables (HR, 0.67; 95% CI, 0.47–0.95), but not total vegetables (HR, 0.98; 95% CI, 0.91–1.05), reduced the risk for gastric cancer. The combined HRs for gastric cancer were 0.93 (95% CI, 0.89–0.98) for total fruit consumption and 0.90 (95% CI, 0.82–1.00) for citrus fruit consumption. Other categories showed no significant association. Dose-response analysis indicated that the risk of gastric cancer was inversely associated with each 100-g increase in daily fruit consumption (HR, 0.95; 95% CI, 0.92–0.99) (Fang et al. 2015).

Hematological malignancies

One systematic review has assessed the impact of F&V on hematological malignancy risk among prospective studies (Sergentanis et al. 2018). Total fruit consumption was not associated with the risk of non-Hodgkin lymphoma, acute myeloid leukemia, multiple myeloma, and Hodgkin lymphoma. However, citrus fruit consumption was associated with reduced non-Hodgkin lymphoma risk (HR, 0.85; 95% CI, 0.73–1.00). Vegetable intake was marginally associated with reduced non-Hodgkin lymphoma risk (HR, 0.89; 95% CI, 0.79–1.00), but not with acute myeloid leukemia, multiple myeloma, and Hodgkin lymphoma risk. Non-Hodgkin lymphoma risk was inversely associated with cruciferous vegetable consumption (HR, 0.84; 95% CI, 0.71–1.00). Combined F&V consumption was associated with decreased non-Hodgkin lymphoma risk (HR, 0.79; 95% CI, 0.65–0.96) (Sergentanis et al. 2018). Chen et al. (2013a) also found similar effects on non-Hodgkin lymphoma risk.

Hepatocellular carcinoma

One systematic review has assessed the impact of F&V on hepatocellular carcinoma risk among 10 prospective cohort and 9 case-controlled studies (Yang et al. 2014). High vs. low intake of vegetables was inversely associated with risk of hepatocellular carcinoma (HR, 0.72; 95% CI, 0.63–0.83). Dose-response meta-analysis showed an HR of 0.92 (95% CI, 0.88–0.95) with a daily increase of 100 g of vegetables (Yang et al. 2014).

Lung cancer

At least four systematic reviews have assessed the impact of F&V on lung cancer risk, all consistently showing beneficial effects (Wakai et al. 2011; Wang et al. 2015a; Wang et al. 2015b; Vieira et al. 2016). The most recent systematic review found high vs. low intakes of F&V (HR, 0.86; 95% CI, 0.78–0.94), vegetables (HR, 0.92; 95% CI, 0.87–0.97), and fruit (HR, 0.82; 95% CI, 0.76–0.89) to be associated with a reduced risk of lung cancer. The association with F&V intake was not significant in current smokers or former smokers. Significant inverse dose-response associations were observed for each daily 100-g increase of F&V (HR, 0.96; 95% CI, 0.94–0.98), vegetables (HR, 0.94; 95% CI, 0.89–0.98), and fruits (HR, 0.92; 95% CI, 0.89–0.95). There was a nonlinear relationship between F&V intake and lung cancer risk, showing that no further benefit is obtained when consumption is increased above approximately 400 g per day (Vieira et al. 2016).

Nasopharyngeal cancer

One systematic review has assessed the impact of F&V on nasopharyngeal cancer risk among 1 prospective cohort and 14 case-controlled studies (Jin, Ouyang, and Wang 2014). The results showed a significant association between high vs. low F&V (HR, 0.33; 95% CI, 0.25–0.45), fruit (HR, 0.63; 95% CI, 0.56–0.70), and vegetable (HR, 0.60; 95% CI, 0.47–0.76) intake and nasopharyngeal cancer risk (Jin, Ouyang, and Wang 2014).

Oral cancer

One older systematic review from 2006 assessed the impact of F&V on oral cancer risk among 1 prospective cohort and 15 case-controlled studies (Pavia et al. 2006). The results showed a significant association between high vs. low F&V (HR, 0.51; 95% CI, 0.40–0.65) and vegetable (HR, 0.50; 95% CI, 0.38–0.65) intake, but not fruit intake and oral cancer risk (Pavia et al. 2006). Black raspberries have been

Table 8. Recent findings on whole grains, vegetables, and fruit and risk of cancer from the 2018 WCRF/AICR Continuous Update Project.

Whole grains, vegetables, and fruit and the risk of cancer

		Decreases risk		Increases risk	
WCRF/AICR grading		Exposure	Cancer site	Exposure	Cancer site
Strong evidence	Convincing			Aflatoxins	Liver
	Probable	Whole grains	Colorectum	Foods preserved by salting (including preserved nonstarchy vegetables)	Stomach
		Foods containing dietary fiber	Colorectum		
		Nonstarchy vegetables and fruit (aggregated)	Aerodigestive cancer and some other cancers (aggregated)		
Limited evidence	Limited-suggestive	Nonstarchy vegetables	Mouth, pharynx, and larynx	Nonstarchy vegetables (low intake)	Colorectum
			Nasopharynx		
			Esophageal (adenocarcinoma)		
			Esophageal (squamous cell carcinoma)		
			Lung (people who smoke or used to smoke tobacco)		
			Breast (estrogen receptor–negative)	Preserved nonstarchy vegetables	Nasopharynx
		Fruit	Esophageal (squamous cell carcinoma)		
			Lung (people who smoke or used to smoke tobacco)		
		Citrus fruit	Stomach (cardia)		
		Nonstarchy vegetables and fruit	Bladder	Fruit (low intake)	Stomach
		Foods containing carotenoids	Lung		colorectum
			Breast		
		Foods containing β-carotene	Lung		
		Foods containing vitamin C	Lung (people who smoke tobacco)		
			Colorectum (colon)		
		Foods containing isoflavones	Lung (people who have never smoked tobacco)		
Strong evidence	Substantial effect on risk unlikely	β-carotene			
		Prostate			

Adapted from the WCRF and AICR (2018). AICR, American Institute for Cancer Research; WCRF, World Cancer Research Fund.

suggested to have chemoprotective and chemotherapeutic properties in the oral cavity (Kresty, Mallery, and Stoner 2016).

Pancreatic cancer

At least two systematic reviews have assessed the impact of F&V on pancreatic cancer risk, neither showing significant effects (Koushik et al. 2012; Paluszkiewicz et al. 2012).

Prostate cancer

Prostate cancer is the most frequent cancer among men (Wallace et al. 2019). One systematic review has assessed the impact of F&V on prostate cancer risk among 16 prospective cohort studies and found no effect (Meng et al. 2014). It has been suggested that higher consumption of tomato products, rich in the carotenoid lycopene, may have modest effects on prostate cancer incidence (Chen, Song, and Zhang 2013b).

Renal cell carcinoma

One systematic review has assessed the impact of F&V on renal cell carcinoma risk among 4 prospective cohorts, 1 pooled study, and 14 case-controlled studies (Zhang et al. 2017). The results showed a significant association between high vs. low intake of fruits (HR, 0.86; 95% CI, 0.75–0.98) and vegetables (HR, 0.73; 95% CI, 0.63–0.85). Linear dose-response analysis showed beneficial effects for each daily serving increase of vegetables (HR, 0.90; 95% CI, 0.84–0.96) but not fruit (Zhang et al. 2017).

Thyroid cancer

One systematic review assessed the impact of F&V on thyroid cancer risk but failed to show any significant effects (Liu and Lin 2014).

Cardiovascular disease

CVD is the leading cause of death in both developed and developing nations, and prevention is a top priority for leading health organizations around the globe (Riley, Gouda, and Cowan 2017). CVDs take the lives of 17.9 million people every year and account for 31% of all global deaths and 48% of deaths from NCDs (Wang et al. 2016a). In the United States, annualized CVD mortality rates have declined since 1980 but still represent approximately 252.7 deaths per 100,000 persons as of 2014 (Roth et al. 2017).

At least 16 systematic reviews to date have assessed the effect of fruits and/or vegetables on cardiovascular outcomes or intermediate outcomes (e.g., hypertension), all finding statistical significance, except two that showed marginal statistical significance (Table 6) (Law and Morris 1998; Dauchet, Amouyel, and Dallongeville 2005; Dauchet et al.

2006; He, Nowson, and MacGregor 2006; He et al. 2007; Mente et al. 2009; Sherzai et al. 2012; Hu et al. 2014; Schoenaker, Soedamah-Muthu, and Mishra 2014; Wang et al. 2014b; Blanch, Clifton, and Keogh 2015; Gan et al. 2015; Li et al. 2016; Wu, Sun, and He 2016; Aune et al. 2017; Bechthold et al. 2019; Schwingshackl et al. 2017b; Zhan et al. 2017). Two systematic reviews showed significant beneficial effects on metabolic syndrome (Tian et al. 2018; Zhang and Zhang 2018). The most comprehensive systematic review conducted by Aune et al. (2017) combined data from 95 studies (142 publications; mostly longitudinal) and found nonlinear dose-response relationships between F&V intake of up to 800 g per day and CHD, stroke, and CVD. Specific inverse associations were observed between CVD and intake of apples/pears, citrus fruits, green leafy vegetables/salads, and cruciferous vegetables (Aune et al. 2017). The authors predict that an estimated 5.6 and 7.8 million premature deaths worldwide in 2013 may be attributed to low fruit and vegetable intake (Aune et al. 2017). Similar nonlinear dose-response relationships have been published in three recent systematic reviews assessing F&V intake and risk of CVD (Zhan et al. 2017), hypertension (Schwingshackl et al. 2017b), and CHD, stroke, and heart failure (Bechthold et al. 2019).

Hundreds of epidemiological analyses have provided consistent longitudinal evidence that F&V exert a protective effect against CVDs. Many of these studies were recently reviewed by Yahia, Maldonado Celis, and Svendsen (2017). F&V have been recognized for their cholesterol-lowering effects largely due to their dietary fiber content (IOM 2005b). A 5-year single-blinded secondary prevention trial of 605 individuals randomized to either a Mediterranean α-linolenic acid–rich treatment diet compared to the usual postinfarct prudent diet control found a large reduction in combined cardiac death and nonfatal myocardial infarction (HR, 0.30; 95% CI, 0.11–0.82) among those in the treatment group (de Lorgeril et al. 1994). A diet rich in fruits, vegetables, and low-fat dairy foods with reduced saturated fat lowered both systolic and diastolic blood pressure by 5.5 and 3.0 mmHg in a 3-week study of 459 individuals enrolled in the DASH trial (Appel et al. 1997). In two smaller RCTs, F&V consumption improved small artery elasticity and dose-dependent microvascular function in hypertensive individuals (McCall et al. 2009; Al-Solaiman et al. 2010). The Flavonoids and Vascular Function at the University of Reading Study (FLAVURS) found high F&V intake of $\geq$6 servings per day to be effective in improving several biomarker measures of cardiovascular health over an 18-week period, with an additional benefit from F&V-containing flavonoids (Macready et al. 2014). Many other short-duration RCTs and controlled human feeding studies have also assessed and illustrated the effect of F&V consumption on validated biomarkers of CVD, such as blood pressure and blood lipids (Adebawo et al. 2006; Slavin and Lloyd 2012; Yahia, Maldonado Celis, and Svendsen 2017). Several small RCTs have assessed the effect of individual fruits (e.g., berries) or vegetables on biomarkers of CVD (Basu, Rhone, and Lyons 2010). Several biological mechanisms have been proposed to elucidate the protective effects of F&V on the cardiovascular system (Table 9). *In vivo* models show inhibition of lipid oxidation, an increase in antioxidant capacity of the serum and plasma (Harasym and Oledzki 2014) reduction of oxidative stress (Thompson 2010) an anti-inflammatory effect (Loke et al. 2008), prevention of platelet aggregation, reduction in vascular tone (Wang et al. 2014c), and induction of glutathione endothelial nitric oxide synthase (eNOS) and inducible NOS (iNOS) (Mukai and Sato 2009) to be potential mechanisms of action.

Immunity, infectious disease, and pulmonary health

Infection and immunity

The immune system is a highly integrated network of cells sensitive to a number of environmental factors, including nutrition. Lymphoid organs have been shown to be directly influenced by the diet and products derived from the gut microbiota (De Rosa et al. 2015), as lymphoid organs are abundant in the gastrointestinal tract. Disruption of the gut microbiota due to suboptimal diet, including low intake of F&V, may be a real driver of inflammatory conditions observed among industrialized societies. Inflammation is the first biological response of the immune system to infection, injury, or irritation and is mediated through the regulation of various inflammatory cytokines such as nitric oxide, interleukins (ILs), tumor necrosis factor (TNF)-α, and interferon-γ (IFN-γ) as well as noncytokine mediator prostaglandin E_2 (Zhu, Du, and Xu 2018). Dietary patterns characterized by a higher portion of F&V have been inversely associated with inflammatory markers such as C-reactive protein (CRP), IL-6, and adhesion factors (Nanri et al. 2008; Salas-Salvadó et al. 2008). A study of adolescent boys found that a diet high in F&V was associated with lower levels with markers of inflammation (Holt et al. 2009). Commercially available F&V juice powder concentrate resulted in increased plasma nutrients and antioxidant capacity. Reductions in DNA strand breaks and increases in circulating $\gamma\delta$-T cells were also noted after the 77-day treatment (Nantz et al. 2006).

F&V contain high levels of dietary bioactive compounds that show anti-inflammatory effects, but their mechanisms of action have not been completely identified. Diets high in fiber promote short-chain fatty acid (SCFA) production—particularly butyrate, which also controls the intestinal immune response through increased production of transforming growth factor-β and reduction of proinflammatory cytokines such as IL-6, IL-17, and IFN-γ (Cox et al. 2009; Maslowski et al. 2009; Maslowski and Mackay 2011). SCFAs are reduced in ulcerative colitis, and treatment with dietary fibers improves the course of the disease (Maslowski et al. 2009). Flavonoids, largely present in F&V, have been suggested to be involved in the role played by plant foods in disease prevention; however, more evidence is needed to clarify their role as a modulator of immune function in humans (Peluso et al. 2015). Anthocyanins from blueberries have been shown to significantly reduce plasma concentrations of nuclear factor-κB (NF-κB)–related proinflammatory cytokines and chemokines in a group of 120 men and women aged 40–74 years (Karlsen et al. 2007). Cross-sectional data show an association between flavonoid intakes and plasma CRP concentrations (Chun et al. 2008). Vitamin A, present in plants as β-carotene, is converted to retinoic acid by intestinal CD103+ dendritic cells or intestinal epithelial cells and consequent production of IL-22 by γ/δT cells and type 3 innate lymphoid cells, thus contributing to maintenance of immune homeostasis (Kunisawa and Kiyono 2013). Deficiency or insufficiency of other vitamins has also been thought to influence immune cell function (De Rosa et al. 2015).

Pulmonary health

Lung tissues are particularly vulnerable to oxidative damage due to high and continuous exposure to oxygen. The rise in prevalence and related medical and economic costs of pulmonary disorders across all age and gender groups is of public health concern (Okoko et al. 2007). Chronic obstructive pulmonary disease (COPD) was the fourth leading disease contributing to years of life lost due to premature mortality in the United States in 2010. Of the leading diseases and injuries contributing to disability-adjusted life-years, COPD and asthma increased by >34% and 14% from 1990 to 2010 in the United States (Murray 2013).

Asthma and allergic response. It has been estimated that >300 million people worldwide suffer from asthma alone, with 250,000 annual deaths related to the disease (Misso et al. 2005). Environmental factors such as cigarette smoke, allergen exposure, pollen, mites, air pollution, chemical sprays, high ozone levels, small birth size, respiratory infections (e.g., rhinovirus), and broad-spectrum antibiotic use during the first few years of life play a major role in the development of asthma exacerbations. Both F&V have been illustrated to have a protective effect against either systemic or airway inflammation in both children and adults (Hosseini et al. 2017). The prevalence of asthma in recent decades may be associated with changes in dietary habits since the 1950s, particularly lower intakes of antioxidants. There is ample evidence that associates oxidative stress with various deleterious effects on airway function, including airway smooth muscle contraction, induction of bronchial hyperreactivity, mucus secretion, epithelial shedding, and vascular exudation (Greene 1999; Bowler 2004). Dietary antioxidants present in F&V have the capacity to scavenge reactive oxygen species (ROS) and inhibit NF-κB–mediated inflammation, whereas diets low in antioxidants have a reduced capacity to respond to enhanced oxidative stress (Wood and Gibson 2009). A recent systematic review of cross-sectional, cohort, case-controlled, and intervention studies found inverse associations between fruit intake and risk of prevalent wheeze and asthma severity. Overall risk of asthma was reported to be correlated with decreasing intakes of vitamin C among 10 observational studies (Allen, Britton, and Leonardi-Bee 2009). Consistent with these findings, previous observational reports indicate that citrus fruit consumption may be inversely associated with incidence of asthma, suggesting that the anti-inflammatory effect of citrus fruits may be due to their high levels of vitamin C (Patel 2006).

Table 9. Proposed mechanisms for the cardioprotective effects of fruits and vegetables.

Reference	Proposed Mechanism(s)
Harasym and Oledzki (2014)	Inhibition of lipid oxidation
John et al. (2002), Harasym and Oledzki (2014)	Increase in antioxidant capacity of the serum and plasma
da Silva Pereira et al. (2014)	Protection against oxidation of cholesterol and other lipids in the arteries
Mayne (2003), Wallace (2011), Harasym and Oledzki (2014)	Reduction in overall oxidative stress
Loke et al. (2008)	Anti-inflammatory effect
Lefer (1990), Wang et al. (2014c)	Increase formation of endothelial prostacyclin that inhibits platelet aggregation and reduces vascular tone
Mukai and Sato (2009)	Induction of glutathione, eNOS, and iNOS
Hwang et al. (2003), Angeloni et al. (2007), La, Howell, and Grenier (2009), Park et al. (2009), Gong et al. (2010)	Antiapoptotic effects evidenced by inhibition of cytochrome C release into the cytoplasm and inactivation of H_2O_2-induced caspases-3, increase in the bioavailability of nitric oxide, and reduction in matrix metalloprotein production
Appel et al. (1997), John et al. (2002)	Slight decrease in blood pressure

eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; VEGF, vascular endothelial growth factor.

A systematic review of 42 studies (>42,000 children) showed that maternal diets rich in F&V during pregnancy and lactation were among the few consistent associations with a lower risk of developing allergic disease in children. High maternal consumption of apples (>4 per week) appeared to have a protective effect on the development of asthma in 5-year-old children when assessed as physician-diagnosed asthma (Netting, Middleton, and Makrides 2014). It should be noted that several proteins from F&V are analogous to pollen allergens and may play a significant role in pollen–fruit/vegetable cross-reactivity. For example, some allergens from apples, pears, carrots, and peanuts are homologous to the major birch pollen allergen and can cause symptoms when ingested (Rosenlund et al. 2011). This could explain the increased risk of asthma in children with higher intakes of apple juice but not orange juice in recent cross-sectional studies (to note, excess free fructose has also been hypothesized to be related to asthma development) (DeChristopher, Uribarri, and Tucker 2016; DeChristopher and Tucker 2018). However, it could also be speculated that early introduction to these types of allergens through high intake during pregnancy and lactation (e.g., >4 apples per week) may help protect offspring from future allergy development.

Chronic obstructive pulmonary disorder. COPD is characterized by airflow limitation that is not fully reversible (Kim and Criner 2013), and it can include a combination of emphysema, chronic bronchitis, and small airway obstruction (Hogg et al. 2004; McDonough et al. 2011). Cigarette smoking serves as the major risk factor for developing COPD and is also the major source of oxidants and ROS to the lungs. Increased F&V intake may be protective against COPD development due to their high vitamin, mineral, and polyphenol content. Two RCTs manipulating F&V intake have been conducted in patients with COPD. A 12-week study showed no effect of a high F&V intake on forced expiratory volume (FEV1), systemic inflammation, or airway oxidative stress (Baldrick et al. 2012). However, a 3-year study in 120 patients with COPD revealed improvement in lung function in the high F&V group compared to the control (Keranis et al. 2010), suggesting that longer-term intervention may be needed to provide a therapeutic effect. Along those lines, for each 1-serving-per-day incremental increase in total F&V intake, the risk of COPD decreased by 8% (95% CI, 4%–11%) in smokers and 4% (95% CI, 0%–7%) in former smokers in a prospective investigation of 1918 cases of COPD over an average of 13.2 years (Kaluza et al. 2017). A case control study in Taiwan reported subjects with COPD to have lower intake and serum levels of vitamin C compared to healthy controls (Lin et al. 2010). A prospective investigation in the United Kingdom found increased plasma vitamin C concentrations to be associated with a decreased risk of obstructive airway disease in 7000 adults aged 45–74 years, suggesting a protective effect (Sargeant, Jaeckel, and Wareham 2000). However, much like the asthma data, trials demonstrating efficacy of vitamin C in regard to COPD are currently lacking.

Mental health and cognition

Cognition represents a complex set of higher mental functions sub-served by the brain and includes attention, memory, thinking, learning, and perception (Bhatnagar and Taneja 2001). Many studies report that the elderly population is growing; as the number of elderly persons increases, an increase in the number of people showing cognitive decline is to be expected. By 2030, one in five Americans will be aged >65 years (U.S. Federal Interagency Forum on Aging-Related Statistics 2010), and age represents the single most important predictor of cognitive decline in the developed world (Daviglus et al. 2010). Loss of cognitive capacity is one of the major factors affecting quality of life in elderly individuals and their family members and is one of the main reasons people enter nursing homes (Thom, Haan, and Van Den Eeden 1997; Black, Rabins, and German 1999). At the same time, there is an increasing body of evidence that suggests nutrition can play an important role in mental health and cognition across the lifespan. Maternal prenatal nutrition and the child's nutrition in the first 2 years of life (1000 days) are crucial factors in a child's neurodevelopment and lifelong mental health (Schwarzenberg et al. 2018).

Cognitive impairment

It has been estimated that approximately 8.3% of individuals aged ≥65 years exhibit age-related cognitive impairment (Matthews et al. 2013). A number of observational studies and animal models have found associations between dietary components and age-related cognitive impairment. At least five systematic reviews have assessed the role of F&V on the incidence of age-related cognitive impairment but show inconsistent effects (Loef and Walach 2012; Cao et al. 2016; Jiang et al. 2017; Mottaghi, Amirabdollahian, and Haghighatdoost 2018; Wu, Sun, and Tan 2017). The most recent systematic review by Mottaghi, Amirabdollahian, and Haghighatdoost (2018) showed that high vs. low intake of F&V was associated with a reduced risk of cognitive impairment (HR, 0.79; 95% CI, 0.67–0.93). The authors suggest that the association may be dependent on the geographical region, as subgroup analyses showed significant effects among studies conducted in China but not Western countries (Mottaghi, Amirabdollahian, and Haghighatdoost 2018). The only dose-response meta-analysis showed that an increment of an 100-g per day increase in F&V consumption was related to a 13% decrease (HR, 0.87; 95% CI, 0.77–0.99) in cognitive impairment and dementia risk (Jiang et al. 2017).

F&V are important components of the Mediterranean diet pattern, which has been associated with slower cognitive decline and a reduced risk for Alzheimer's disease in elderly individuals (DGAC 2015). Evidence indicates that F&V consumption may have a protective effect on global cognitive performance (Nurk et al. 2010) and memory and executive function (Sabia et al. 2009) and that people with high intakes perform better on cognitive tests and are less likely to exhibit cognitive decline (Gillette Guyonnet et al. 2007). By contrast, other studies suggest nonsignificant effects of intake on the following: cognitive flexibility, memory, and information processing speed (Nooyens et al. 2011); perceptual speed and attention (Morris et al. 2006); or verbal memory, general cognition, working memory, and category fluency (Kang, Ascherio, and Grodstein 2005).

Depression and mental health

The role of habitual diet in the development of depressive disorders and symptoms has become a recent research focus over the past decade. At least three systematic reviews have assessed the role of F&V among observational studies, all showing beneficial effects on the incidence of depression (Liu et al. 2016; Wu, Sun, and Tan 2017; Saghafian et al. 2018). The most recent systematic review by Saghafian et al. (2018) found beneficial effects of high vs. low fruit (HR, 0.83; 95% CI, 0.71–0.98) and vegetable (HR, 0.86; 95% CI, 0.75–0.98) consumption on the incidence of depression. Higher F&V intakes have also been associated with reduced suffering from depression (HR, 0.85; 95% CI, 0.78–0.92) and distress (HR, 0.87; 95% CI, 0.78–0.98) among individuals aged ≥12 years enrolled in the Canadian Community Health Survey. Perceived poor mental health status and previous diagnosis of a mood or anxiety disorder was also inversely associated with F&V intake (McMartin, Jacka, and Colman 2013). Cross-sectional examination of the European Prospective Investigation Into Cancer (EPIC)–Norfolk Study reported similar findings, as participants who reported higher F&V intake were more likely to exhibit better mental health (Myint et al. 2007). Likewise, raw F&V intake, but not processed F&V intake, significantly predicted higher mental health outcomes when controlling for covariates in a cross-sectional study of 422 young adults aged 18–25 years (Brookie, Best, and Conner 2018).

Aside from data on F&V consumption, several studies indicate that better diet quality (e.g., Mediterranean diet) is associated with better mental health outcomes (Akbaraly et al. 2009; Sánchez-Villegas et al. 2009; Psaltopoulou et al. 2013; Lai et al. 2014). Two recent meta-analyses illustrated an inverse relationship between better diet quality and depression (Psaltopoulou et al. 2013; Lai et al. 2014). A habitually poor-quality diet has also been independently associated with a greater likelihood of or risk for depression and anxiety (Jacka et al. 2010; Sánchez-Villegas et al. 2011; Sánchez-Villegas et al. 2012). Even though stress and depression may promote unhealthy eating, a recent longitudinal study with 10 years of follow-up suggested that reverse causality is a less likely explanation for longer-term associations (Le Port et al. 2012). Given that the average age of onset for anxiety and mood disorders is 6 and 13 years, respectively (Merikangas et al. 2010), the potential for early intervention using strategies targeted at improving diet quality through consumption of F&V may be of substantial public health benefit. A recent cross-sectional analysis reported poor nutritional quality of the diet to be associated with symptoms of attention deficit hyperactivity disorder in children aged 6–17 years (van Egmond-Fröhlich, Weghuber, and de Zwaan 2012).

Migraine

Migraines are a neurovascular disorder characterized by recurrent attacks and debilitating pain associated with photophobia, phonophobia, nausea, vomiting, and sensitivity to movement. Migraines are prevalent in 17% of women and 6% of men (Stewart, Roy, and Lipton 2013) and cause 112 million bedridden days per year (Hu et al. 1999). It has been hypothesized that obesity, a low-grade chronic inflammatory state, may exacerbate the neurovascular inflammatory response in migraine (Chai et al. 2014). There are currently no studies that unequivocally support the role of specific foods in migraine headaches, yet elimination diets are commonly prescribed to mitigate migraine attacks. F&V consumption did not differ among normal-weight women with or without migraines enrolled in the 1999–2004 NHANES data sets (Evans et al. 2015). Null findings were also present among participants enrolled in the cross-sectional Women's Health Study (Rist, Buring, and Kurth 2015). Longstanding speculation suggests that magnesium loss may be enhanced during migraine (Sun-Edelstein and Mauskop 2009; Rybicka et al. 2012), but it remains to be studied whether migraineurs have outright higher magnesium demands than the general population. Furthermore, even though many F&V are a source of magnesium, human studies on migraines have been conducted using high-dose supplementation.

Musculoskeletal outcomes

Bone health and osteoporosis

Osteoporosis is a debilitating disease that is characterized by low bone mass, deterioration of bone tissue, and disruption of bone microarchitecture and can lead to compromised bone strength and an increase in the risk of fractures (NIH Consensus Development Panel on Osteoporosis Prevention 2001). The National Osteoporosis Foundation estimates the recent prevalence of osteoporosis and low bone mass (i.e., osteopenia) to be approximately 10.3% and 43.9%, respectively, of U.S. adults aged $\geq$50 years (Wright et al. 2014). Although more women than men are affected, the disease burden in men is considerable: approximately one-third of hip fractures occur in men (Seeman et al. 2006), and their mortality is higher than women, with about 37.5% dying within the first 12 months compared with 28.2% of affected women (Center et al. 1999). Since lifestyle choices influence 20%–40% of adult bone mass, optimization of lifestyle factors that are known to influence peak bone mass and strength early in life, is an important strategy aimed at reducing osteoporosis or low bone mass later in life (Weaver et al. 2016b). The ability of lifestyle interventions during childhood to impact bone mass and fracture risk in adults, assumes that BMD tracks from youth into adulthood. There is good evidence to support BMD tracking from childhood into adolescence (Kalkwarf et al. 2010) and into early adulthood (Wren et al. 2014; Yang et al. 2018) and that lifestyle factors can contribute deviations in BMD tracking both positively and negatively (Weaver et al. 2016b; Yang et al. 2018).

Historically, nutritional strategies aimed at maximizing bone strength in youth and slowing bone loss in older adults have targeted individual nutrients such as calcium and vitamin D (Weaver et al. 2016a). More recently, however, there has been considerable interest on the impact of whole foods and certain dietary patterns on bone outcomes. The most recent dietary recommendations worldwide promote diets rich in fruits and vegetables, and these recommendations coincide with studies aimed at examining the effects of these diets on bone.

In youth, At least five cross-sectional studies have reported benefits to bone development with higher intakes of F&V (Weaver et al. 2016b). The beneficial effects on bone in children and adolescence may be sex dependent, as more positive outcomes were observed in females. Higher F&V intake may also have beneficial effects on bone maintenance later in life. A recent systematic review of 18 observational studies involving 12,543 women found that higher consumption of F&V led to a 32% and 13%, respectively, decreased rates of postmenopausal osteoporosis, respectively (Hu, Cheng, and Jiang 2018). Similarly, daily intakes of $\leq$1 serving of F&V was associated with a 39% increased hip fracture risk in relation to moderate daily intakes (e.g., >5 servings per day) among men and women enrolled in the CHANCES (Consortium on Health and Ageing: Network of Cohorts in Europe and the United States) project, a meta-analysis of five cohorts representing 142,018 men and women from Europe or the United States (Benetou et al.

2016). These associations were shown to be more evident among women (Benetou et al. 2016). Participants in the Women's Health Initiative (WHI) Modification Trial showed a slightly reduced risk of falling and in bone mineral density (BMD) related to F&V intake, but no influence on osteoporotic fractures after 8 years of follow-up (McTiernan et al. 2009). The Scarborough Fair Study, a multicenter clinical trial, found that increasing intake of F&V to >9 servings per day (vs. <5 servings per day) for 3 months showed improvements in numerous markers of bone turnover (Gunn et al. 2015). On the contrary, a smaller RCT of participants aged 65–85 years who habitually consumed ≤2 servings of F&V per day at baseline showed no effects on bone turnover markers after they consumed 5 servings per day for 4 months (Neville et al. 2014). A prospective study of older women aged ≥70 years found that higher intakes of vegetables were associated with a lower fracture risk. In multivariable-adjusted models for vegetable types, cruciferous and allium vegetables were inversely associated with all fractures by 28% and 34%, respectively (Aune et al. 2017). A prospective analysis of 40,644 men in the Cohort of Swedish Men and 34,947 women in the Swedish Mammography Cohort found that those who did not consume F&V had an 88% higher hip fracture rate compared to those who consumed 5 servings per day. The fracture rate was gradually lower with higher intakes and similar results were observed when men and women were analyzed separately (Byberg et al. 2015). Using retrospective analyses of the Canadian Multicenter Osteoporosis Study, associations between two dietary patterns ("nutrient dense" and "high consumption of vegetables and fruit") were shown to reduce fracture risk in postmenopausal women, but not men (Langsetmo et al. 2011). Comparable dose-dependent associations were observed between total F&V intake and BMD and osteoporosis risk in Chinese men and women aged 40–75 years (Qiu et al. 2017). Dried plums, in particular, have been suggested to have significant effects on BMD and markers of bone turnover in both animal models and human intervention studies of postmenopausal osteoporosis (Hooshmand et al. 2011; Hooshmand et al. 2016; Arjmandi et al. 2017; Wallace 2017).

A recent scoping review illustrates current evidence on the association of dietary patterns and bone health and concludes that a dietary pattern emphasizing intake of fruit, vegetables, whole grains, poultry, fish, nuts, legumes, and low-fat dairy shows a beneficial effect on bone health (Movassagh and Vatanparast 2017). A healthy dietary pattern with high intakes of F&V may lead to less bone resorption (Hardcastle et al. 2011a) by providing micronutrients essential for bone formation (Macdonald et al. 2009) and dietary bioactive compounds, such as flavonoids, known to modulate inflammation and oxidative stress (Hardcastle et al. 2011b). Contrary to the "acid-alkali" hypothesis, an RCT of 276 postmenopausal women found no effect of potassium citrate supplementation on markers of bone turnover or BMD, suggesting that alkali provision does not explain any long-term benefits of F&V intake on bone (Macdonald et al. 2008).

Arthritis

Arthritis, a chronic condition referring to joint pain or joint disease, is the leading cause of disability in the United States and other global populations (Kuo et al. 2013; Murphy et al. 2017). Osteoarthritis, the most common form of arthritis, is a progressive and degenerative joint disease characterized by inflammation, chronic pain, functional limitation, and reduced quality of life (Wallace et al. 2017; Wirth et al. 2017). Rheumatoid arthritis is similar in its symptoms but is an autoimmune disorder (Myasoedova et al. 2010). Both conditions have been suggested to be primarily driven by an increase in oxidative stress and inflammation (Mateen et al. 2016; Geyer and Schönfeld 2018). A recent review examined the role of fruits and associated polyphenols in the management of arthritis (Basu, Schell, and Scofield 2018). F&V provide many dietary bioactive compounds, especially phenolics with anti-inflammatory properties that are thought to be important for reducing the risk of or improving the course of arthritis. Clinical research demonstrates a protective role of strawberries, pomegranate juice, figs, and olives in reducing arthritic pain and/or related inflammatory markers in short-duration trials (Bahadori et al. 2016; Ghavipour et al. 2017; Schell et al. 2017); however, these data merit further exploration to determine mechanisms and dosing. Cross-sectional reports from the Korean National Health and Nutrition Examination Survey (KNHANES) suggest that higher intakes of F&V are associated with a lower prevalence of knee pain in adults with knee osteoarthritis (Han et al. 2017). A prospective study of 29,368 women, average age 61 years, found that total fruit (>83 servings per month) but not vegetable intake was associated with a reduced risk of rheumatoid arthritis (Cerhan et al. 2003). Cruciferous vegetable intake (>11 servings per month), particularly of broccoli (>3 servings per month), was moderately associated with a reduced risk of rheumatoid arthritis (Cerhan et al. 2003). A case-controlled study of men and women, average age 60 years, did not find lower intake of F&V to be associated with a higher incidence of inflammatory polyarthritis; however, subjects with the lowest intake (<55.7 mg per day) of vitamin C were three times more likely to develop inflammatory polyarthritis compared with those with the highest intake (94.9 mg per day) (Pattison et al. 2004). Both vitamin C and dietary carotenoids, particularly β-cryptoxanthin and zeaxanthin, have been suggested to be associated with a reduced risk of inflammatory polyarthritis (Pattison et al. 2005).

Other important health topics

Chronic kidney disease

Chronic kidney disease (CKD) is a disorder resulting from structural changes to the kidney (e.g., cysts, loss of tissue, or masses) and/or urinary tract, leading to changes in the composition of the urine, reduced kidney function, or both (Palmer et al. 2017). The kidney is injured in diseases primary to the kidney or secondary diseases (e.g., CVDs, metabolic syndrome, diabetes, etc.). Diabetes and hypertension are the leading causes of CKD in middle- and higher-income countries, accounting for approximately 35% and 25% of kidney disease, respectively (Jha et al. 2013). Overall, CKD affects an estimated 10%–15% of the population (Chadban et al. 2003; Singh et al. 2009; Zhang et al. 2012). Two clinical studies (181 people total) have evaluated the effect of increased F&V intake on CKD (Goraya et al. 2013; Goraya et al. 2014). The first study compared treating metabolic acidosis in hypertensive patients with stage 4 CKD with F&V or sodium bicarbonate for 1 year (Goraya et al. 2013). Both treatments offered showed similar decreases in lower-than-baseline urine indices of kidney injury (Goraya et al. 2013). The second study found that 3 years of dietary acid reduction with sodium bicarbonate or base-containing F&V preserved the estimated glomerular filtration rate (GFR) and reduced urine excretion of angiotensin, an index of angiotensin II levels, in patients with stage 3 CKD (Goraya et al. 2014). Collectively, these two studies support that oral alkali treatment of metabolic acidosis of CKD appears to slow the rate of GFR decline. Dietary acid reduction with F&V or bicarbonate has been suggested to attenuate kidney injury in patients with stage 2 CKD with a moderately reduced GFR, in part due to reductions in systolic blood pressure. These effects may be due to the potassium content of F&V, which seems to have an inverse association with blood pressure (Goraya et al. 2012). Data from NHANES III ($n = 14{,}543$) showed that for each 10-g increase in total dietary fiber, the odds of elevated serum CRP levels were decreased by 11% and 38% in those without and with CKD, respectively. Total dietary fiber was not associated with mortality in individuals without CKD but was inversely related to mortality in those with CKD (Raj Krishnamurthy et al. 2012). A recent systematic review of longitudinal studies found no association between healthy dietary patterns, characterized by higher intakes of fruits, vegetables, fish, legumes, cereals, whole grains, and fiber and lower intakes of red meat, salt, and refined sugars, on end-stage renal disease but a lower rate of mortality (HR, 0.73; 95% CI, 0.63–0.83) was noted in patients with CKD (Kelly et al. 2017).

Eye health

The prevalence of visual impairment and blindness among individuals in six World Health Organization (WHO) regions is estimated to be 285 million, 39 million of whom are blind. People aged ≥50 years represent 65% and 82% of those who are visually impaired and blind, respectively. The major causes of visual impairment are uncorrected refractive errors (43%), followed by cataracts (33%); the first cause of blindness is cataracts (51%) (Pascolini and Mariotti 2012). AMD is the leading cause of severe visual loss and blindness, affecting about 30–50 million people worldwide (Wong et al. 2014).

Age-related macular degeneration. The prevalence of AMD is likely to increase over the next decades, due to increasing life expectancy (Colijn et al. 2017). Despite recent progress in the discovery of underlying risk factors, the exact pathogenesis of AMD remains unknown and primary prevention is therefore an increasingly important public health strategy. A recent systematic review and meta-analysis found no significant association between fruit or vegetable intake and AMD; however, the limited number of prospective studies evaluating such groups reduced the statistical power for the analyses (Dinu et al. 2018). It has been postulated that high intake of F&V has a protective effect against the onset and development of AMD, but the majority of evidence is cross-sectional (Goldberg et al. 1988; Age-Related Eye Disease Study Research Group 2000; Ersoy et al. 2014; Kim et al. 2018). Cross-sectional evaluation of elderly men (≥65 years) enrolled in the KNHANES 2010–2012 data sets showed higher F&V intake to have an inverse association with AMD only among smokers (HR, 0.22; 95% CI, 0.05–0.93) (Kim et al. 2017). Future RCTs and cohort studies are needed to increase the strength of the evidence. Adherence to dietary recommended amounts of vegetables (≥200 g per day), fruit (2 servings per day), and fish (2 servings per week) showed an inverse relationship with incidence of AMD among participants in the Rotterdam Study cohort (HR, 0.58; 95% CI, 0.36–0.93) (de Koning-Backus et al. 2019). F&V that contain carotenoids such as lutein and zeaxanthin have the potential to decrease the risk of AMD (Seddon et al. 1994). These carotenoids selectively accumulate in the macula lutea (point of high-resolution vision) and protect pigment epithelial cells from blue light and damage caused by short-wave rays (Krinsky, Landrum, and Bone 2003; Johnson 2014; Mares 2016).

Cataracts. A cataract is a clouding of the lens, which results in impaired vision or visual acuity. Two hundred and fifty-three participants enrolled in the WHI showed a slightly reduced 10%–15% risk in the development of cataracts over a 10-year follow-up period among those with the highest intake of F&V (10 servings per day) (Christen et al. 2005). A larger analysis of the Carotenoids in Age-Related Eye Disease Study (subjects recruited from the WHI Observational Study 7 years later) found women in the high lutein and zeaxanthin group to have a 23% (OR, 0.77; 95% CI, 0.62–0.96) lower prevalence of nuclear cataracts (Moeller et al. 2008). Likewise, the Nurses' Health Study suggested that the highest fruit consumption (3.9 servings per day) was associated with a decreased prevalence odds of nuclear opacities (OR, 0.58; 95% CI, 0.32–1.05) (Moeller et al. 2004). The Health Professionals Follow-up Study showed men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (RR, 0.81; 95% CI, 0.65–1.01). Among specific food high in carotenoids, broccoli and cooked spinach consumption among men reduced the risk of cataracts by 23% (RR, 0.77; 95% CI, 0.61–0.97) and 49% (RR, 0.51; 95% CI, 0.32–0.82), respectively (Brown et al. 1999).

Glaucoma. Glaucoma is an optic neuropathy characterized by a progressive typical pattern of optic neurodegeneration and visual field loss. Combined analyses from the Nurses' Health Study and Health Professionals Follow-up Study showed higher green leafy vegetable intake to be associated with a lower risk of primary open-angle glaucoma (POAG), particularly POAG with early paracentral visual field loss at diagnosis (Kang et al. 2016). Higher intake of certain F&V high in vitamins A and C and carotenoids has been associated with a decreased likelihood of glaucoma in older African-American women (Giaconi et al. 2012). In a cross-sectional sample of older women, high intake of certain carotenoid-containing F&V such as peaches, green collards, kale, and carrots was associated with a decreased risk of diagnosed glaucoma (Coleman et al. 2008).

Gastrointestinal health and the microbiome

The gut harbors trillions of microbes constituting a complex community of microbiota that interact with each other and with the host to modulate biological processes essential for health. Understanding of the biological role that the gut microbiota plays in human health has increased dramatically over the past decade (Makki et al. 2018). Because of their metabolic activities and fermentation end products, gut bacteria can be categorized as either beneficial or potentially pathogenic (Wallace et al. 2011). There is a clear association between the gut microbiome and development of chronic NCD, providing a rationale for the development of strategies to target the gut microbiota to improve long-term human health (Deehan et al. 2017). Diet has a major impact on gut microbiota composition, diversty and metabolic capacity in a time-dependent manner (Wallace et al. 2011; Makki et al. 2018).

The importance of fiber from foods such as F&V for normal function of the digestive system has long been appreciated; however, recent evidence suggests that additional properties such as viscosity and fermentability are important characteristics in terms of the physiological benefits of fiber. Dietary fiber intake alters the niche environment in the gut by providing substrates for microbial growth, allowing microbial species that are able to utilize these substrates to expand their populations (Deehan et al. 2017). There are hundreds, if not thousands, of discrete fiber structures in F&V that align with bacterial populations and functions. For example, only some *Bacteroides* ferment complex arabinoxylans, whereas most do not (Klurfeld et al. 2018). F&V range in their dietary fiber concentration: fruits, 2.0–14.8 g/100 g; legumes, 4.5–4.7 g/100 g; leafy vegetables, 1.2–4.0 g/100 g; and roots and tubers, 1.1–9.5 g/100 g (Slavin and Lloyd 2012). Soluble and insoluble fibers are found in F&V in different portions. Soluble fibers are complex carbohydrate polymers that are not digested and absorbed in the upper gastrointestinal tract; most undergo complete or partial fermentation in the colon and exert varying beneficial physiological effects depending on the type of fiber (Howlett et al. 2010; Jones 2014). In the last decade, certain prebiotic fibers have been shown to be fermented by and modulate the human microbiota toward a more healthful community. Cross-sectional assessments show that long-term intake of F&V is associated with improved microbial gene richness and diversity (Cotillard et al. 2013; Kong et al. 2014). Fermentation of prebiotic fibers results in production of SCFAs and other functional benefits beyond the gastrointestinal tract (IOM 2005b). For example, SCFAs and bile acids are tightly involved in energy homeostasis, insulin signaling, fat accumulation, and inflammatory signaling, as previously reviewed (Kootte et al. 2012; Canfora, Jocken, and Blaak 2015; Delzenne et al. 2015; Gomes, Costa, and Alfenas 2017; Holscher 2017).

Aside from the gut microbiome, dietary fibers may affect the gastrointestinal transit of nutrients via various mechanisms depending on their physical-chemical properties. Colonic transit time is an important host factor in shaping the microbiota ecosystem because it regulates water and nutrient availability as well as the rate of luminal washout (Lewis and Heaton 1997; Cremer et al. 2016). With regard to gastrointestinal transit, it is generally accepted that laxation is one of the major health benefits of insoluble fiber intake. Insoluble fibers increase fecal bulking and stool water content due to their high water-binding capacity, which in turn stimulates mucus secretion and peristalsis (IOM 2005b). However, contrary to popular thought, the current scientific literature on the role of dietary patterns, including fruit, vegetable, and dietary fiber intake, and the occurrence of colonic diverticulosis, diverticular disease, and acute diverticulitis is still conflicting (Tursi 2017).

Inflammation

Aging of the immune system, termed "immunosenescence," has been suggested to be a consequence of continuous chronic antigenic overload and suboptimal immune cell output (Palmer 2013; Pera et al. 2015; Calder et al. 2017a). Inflammation is a central component of innate (nonspecific) immunity. The inflammatory response is beneficial as an acute, transient reaction to harmful conditions, facilitating the defense, repair, turnover, and adaptation of many tissues to insult. However, chronic low-grade inflammation is likely to be detrimental for many tissues and for normal body functions. The term "inflamm-aging" has recently been conceptualized as a consequence of a global reduction in the ability to cope with antigenic, chemical, physical, and nutritional stressors and of a gradual increase in proinflammatory markers (Cevenini, Monti, and Franceschi 2013; Calder et al. 2017b). Interestingly, centenarians show a complex and peculiar balance between proinflammatory and anti-inflammatory characteristics, whether phenotypically or genetically (Franceschi et al. 2007), whose net result is a slower, more limited, and balanced development of inflamm-aging compared with older adults who do not achieve noncentenarian status, who are characterized by either faster or inadequately counteracted anti-inflammatory responses (Cevenini, Monti, and Franceschi 2013). Centenarians also stand out as their gut microbiota has been suggested to be of high diversity in regard to species composition (Kong et al. 2016; Santoro et al. 2018). Obesity and its comorbidities are associated with increased inflammation. Several mechanisms trigger inflammation in adipose tissue, including excess fatty acids, hypoxia, and activation of the inflammasome. The microbiota is involved in age- and obesity-induced inflammation via lipopolysaccharide (LPS)–related endotoxemia, which in turn promotes cytokine secretion and insulin resistance (Pereira and Alvarez-Leite 2014). LPSs are found on the outer membrane of gram-negative bacteria such as Proteobacteria (e.g., *Escherichia coli*) and serve as an endotoxin (Minihane et al. 2015).

The importance of chronic low-grade inflammation in the pathology of numerous age-related chronic conditions is clear. An elevated inflammatory state can potentially trigger or facilitate onset of the most prevalent age-related diseases such as atherosclerosis and other CVDs, metabolic syndrome, type 2 diabetes, sarcopenia, osteoporosis, neurodegeneration, and cancer, among others (Minihane et al. 2015; Calder et al. 2017b). Inflammation plays a direct role in the progression of nonalcoholic fatty liver disease (NAFLD), the most common liver disorder in Western countries (Minihane et al. 2015). There is a substantial amount of evidence to suggest that many foods, nutrients, and dietary bioactive compounds modulate the inflammation both acutely and chronically (Calder et al. 2011; Calder et al. 2013). However, most dietary studies have been limited to measuring a small number of inflammation (i.e., CRP and TNF-α) blood markers and therefore may not reflect inflammation in tissue compartments or response to inflammatory challenges (Minihane et al. 2015). Joseph, Edirisinghe, and Burton-Freeman (2016) provide a comprehensive overview of human clinical trials investigating the acute and chronic feeding effect of polyphenols from commonly consumed fruits or their derived products on inflammation.

Recent observational data suggest that the reduced risk of neurodegenerative diseases associated with F&V intake is at least somewhat driven by a higher intake of flavonoids (Barberger-Gateau et al. 2007; Spagnuolo, Moccia, and Russo 2018). A number of RCTs have provided evidence that flavonoids are capable of modulating inflammatory cytokines such as TNF-α and CRP (Ueda, Yamazaki, and Yamazaki 2004; Chun et al. 2008). Evidence indicates that flavonoids are not high enough in concentration to provide sufficient antioxidant activity in the bodily tissues; however, they are capable of modulating intracellular signaling pathways and gene expression, and interacting with the mitochondria (Meyer et al. 2000; Ford and Mokdad 2001; Knekt et al. 2002; Hodge et al. 2004; Liu et al. 2004; Montonen et al. 2005; Bazzano et al. 2008; Harding et al. 2008; Villegas et al. 2008; Cooper et al. 2012; Wedick et al. 2012; Kurotani et al. 2013; Muraki et al. 2013; Mursu et al. 2014). The first systematic review in this area identified F&V intake to be inversely related to inflammatory biomarkers; this was particularly well supported by intervention studies investigating the Mediterranean diet pattern (Barbaresko et al. 2013). Nearly three-quarters of studies using dietary pattern scores found the Mediterranean diet pattern is more strongly inversely associated with CRP concentrations compared to the Healthy Eating Index (HEI), a marker of adherence to the Dietary Guidelines (Barbaresko et al. 2013). The Moli-Sani study followed >7000 men and women aged $\geq$ 35 years, and the results support that adherence to the Mediterranean diet pattern is associated with a lower inflammation index and increase in adiponectin concentrations. Additionally, adults who reported consuming nuts were also found to have lower inflammatory markers independently from adherence to the Mediterranean diet pattern (Bonaccio et al. 2017).

Nonalcoholic fatty liver

NAFLD has become a major global health burden in both developed and developing countries (Loomba and Sanyal 2013), leading to increased risk for cirrhosis, hepatocellular carcinoma, type 2 diabetes, and CVD (Anstee, Targher, and Day 2013). Lifestyle intervention aimed at weight reduction is the most established treatment for NAFLD (EASL-EASD-EASO 2016). In a cross-sectional study of 175 overweight Latino youth, consumption of nonstarchy vegetables was associated with lower liver fat deposition (Cook et al. 2014). Other observational studies support the notion that patients with NAFLD consume lower amounts of vegetables and dietary fibers compared to controls (Musso 2003; Shi et al. 2012; Han et al. 2014). A significant body of evidence in experimental models of NAFLD has drawn attention to polyphenols contained in F&V because these compounds seem to inhibit de novo lipogenesis, stimulate β-oxidation in the liver, and suppress activation of hepatic stellate cells (Salomone, Godos, and Zelber-Sagi 2016). A comprehensive review by Charytoniuk et al. (2017) describes the precise metabolism, pharmacology, and clinical trials of resveratrol, a common polyphenol in fruits, and provides a brief summary of alternative treatment methods for NAFLD (Charytoniuk et al. 2017).

Satiety, weight loss, weight maintenance, and obesity

Obesity is characterized by the accumulation of excess weight and body fat in adipose tissues and is of major public health concern because of its link to chronic disease. Age-standardized prevalence of obesity (body mass index [BMI] $\geq$ 30) and severe obesity (BMI $\geq$ 40) among adults in the United States increased from 33.7% and 5.7% in 2007–2008 to 39.6% and 7.7% in 2015–2016 (Hales et al. 2018), respectively. Obesity and severe obesity prevalence in youth age 2–19 y seems to have plateaued between 2003–2004 (17%) and 2013–2014 (17%), even though specific trends for age groups somewhat differ (Ogden et al. 2016). Very few studies in the peer-reviewed literature have investigated whether there is a direct relationship between consuming F&V and losing weight. A handful of systematic reviews have attempted to assess the effect of F&V on body weight and energy intake (Ledoux, Hingle, and Baranowski 2011; Mytton et al. 2014), metabolic syndrome (Shin et al. 2015; Tian et al. 2018; Zhang and Zhang 2018), or weight loss (Kaiser et al. 2014). Despite the alarming increase in the prevalence of obesity across the globe, observational studies and small RCTs do not provide convincing evidence that increasing F&V intake without explicitly combining this approach with efforts to reduce intake of overall energy results in weight loss (Ledoux, Hingle, and Baranowski 2011; Kaiser et al. 2014). Promoting increased F&V consumption, in the absence of specific advice to decrease consumption energy-rich foods, is unlikely to lead to weight gain and may have a role in weight maintenance (Mytton et al. 2014).

It has been proposed that the soluble dietary fibers present in F&V delay gastric emptying of ingested food by forming a gel-like environment in the small intestine that partially diminishes the activity of digestive enzymes essential for macronutrient absorption. This in turn prolongs the contact of the nutrients with receptors in the small intestine, causing the release of putative satiety peptides and creating a hyperosmolar environment in the colon, which leads to a decrease in insulin secretion and improvement in glucose control, and attraction of fluids into the gut lumen, and increased satiety (Watson and Preedy 2013). Along these lines, two recent systematic reviews suggest that the addition of dietary fiber to the diet theoretically improves satiety by slowing the absorption of various nutrients, including fat; however, meta-analyses are currently unable to demonstrate significant effects, likely due to heterogeneity in study design and insufficient standards for characterizing and reporting dietary fiber in foods (Poutanen et al. 2017; Warrilow et al. 2019).

Skin health

The skin is the largest organ in the human body and is constantly exposed to environmental factors that induce oxidative stress (e.g., ultraviolet [UV] radiation and chemical oxidants) that favors skin aging. Premature skin aging is demonstrated to be associated with nonhealthy lifestyle habits such as smoking, stress, excessive calorie restriction, and low diet quality (Biesalski et al. 2003). Multiple mechanisms within skin biology have been linked with the onset and clinical course of various skin diseases such as acne, atopic dermatitis, aging, and even cancer. UV exposure seems to be the most generally recognized environmental factor associated with the development of skin aging, which leads to generation of free radicals that may cause damage to cellular lipids, proteins, and DNA (Pappas, Liakou, and Zouboulis 2016). Thus, optimal supply of antioxidants in the skin increases dermal defense against UV irradiation, supports long-term protection, and contributes to the maintenance of skin health and appearance. Furthermore, deficiencies of vitamin A, vitamin C, riboflavin, niacin, pyridoxine, vitamin E, zinc, selenium, and certain essential fatty acids and amino acids have all been shown to cause skin and hair abnormalities (Pappas, Liakou, and Zouboulis 2016). Consequently, a diet rich in F&V and other sources of these antioxidants may be fundamental for healthy skin. For example, human intervention studies of mixed carotenoids also illustrate their photoprotective effect (Stahl and Sies 2012). Optimal supply of antioxidants in the skin increases dermal defense against UV irradiation, supports long-term protection, and contributes to the maintenance of skin health and appearance.

High fruit intake was associated with a lower risk of seborrheic dermatitis (HR, 0.76; 95% CI, 0.58–0.97) in women enrolled in the Rotterdam Study (Sanders et al. 2019). A recent case-controlled study showed that among women with a recent diagnosis of acne, low weekly intake of F&V was associated with an increased risk of acne (HR, 2.33; 95% CI, 1.20–4.53) (Di Landro et al. 2016). A study of 763 maternal-child pairs showed that higher maternal intake of green and yellow vegetables (HR, 0.41; 95% CI, 0.24–0.71), citrus fruit (HR, 0.53; 95% CI, 0.30–0.93), and β-carotene (HR, 0.52; 95% CI, 0.30–0.89) during pregnancy was significantly associated with a reduced risk of eczema (Miyake et al. 2010).

Type 2 diabetes mellitus

Type 2 diabetes makes up >90% of all diabetes cases. The prevalence of type 2 diabetes is increasing worldwide and is expected to grow from 382 million reported in 2013 to an estimated 592 million by 2035 (Guariguata et al. 2014). The disease is characterized by either a resistance to insulin or its relative deficiency. F&V contain considerable protective constituents, including potassium, folate, vitamins, fiber, and phenolic compounds. Furthermore, it is widely accepted that antioxidants and other components of F&V may play a role in modulating insulin sensitivity (Wallace et al. 2013). Findings from observational studies have been inconsistent. Several studies suggest that higher intake of F&V (particularly intake of berries and green leafy vegetables) has an inverse relationship, whereas others show no effect (Meyer et al. 2000; Ford and Mokdad 2001; Knekt et al. 2002; Hodge et al. 2004; Liu et al. 2004; Montonen et al. 2005; Bazzano et al. 2008; Harding et al. 2008; Villegas et al. 2008; Cooper et al. 2012; Wedick et al. 2012; Kurotani et al. 2013; Muraki et al. 2013; Mursu et al. 2014). Some flavonoids such as grape seed procyanidins have been shown to have antidiabetic properties because they improve altered glucose and oxidative metabolism (Pinent et al. 2004).

Six systematic reviews have assessed the effect of total F&V intake on type 2 diabetes (Hamer and Chida 2007; Carter et al. 2010; Li et al. 2014b; Wu et al. 2015b; Wang et al. 2016b; Schwingshackl et al. 2017a). The most recent systematic review by Schwingshackl et al. (2017a) reported a borderline inverse association for the high vs. low (OR, 0.95; 95% CI, 0.89–1.01) and dose-response (OR, 0.98; 95% CI, 0.96–1.00) analysis. The inverse association between vegetables and type 2 diabetes was only observed in Asian and Australian studies, but not American and European studies, and in studies with a lower number of cases. The inverse association of fruit with type 2 diabetes was only observed in those studies with a duration longer than 10 years and those that included younger participants (aged <50 years) (Schwingshackl et al. 2017a). A similar systematic review by Wu et al. (2015b) found that there was a threshold of around 2–3 servings of vegetables per day and 2 servings of fruit per day, after which the risk of type 2 diabetes did not reduce further. These findings are consistent with the general recommendation to consume 5 servings of F&V per day (3 of vegetables and 2 of fruit) (DGAC 2015; DGAC and OverDrive Inc 2016), but the effect of specific F&V on type 2 diabetes risk is unknown (Wu et al. 2015b). RCTs of patients with type 2 diabetes are rare, but at least one adequately powered intervention confirmed the beneficial effect of nuts on blood lipids, which was also seen in patients without diabetes (Jenkins et al. 2008). This study did not find improvements in A1c or other glycated proteins (Jenkins et al. 2008).

Increasing fruit and vegetable consumption

F&V are colorful, flavorful, and nutritious components of the diet and are often most attractive when harvested at their peak maturity. However, most F&V grow only in certain parts of the world, under specific environmental conditions, and at particular times throughout the year. They also typically contain >90% water and once harvested begin to undergo higher rates of respiration that results in moisture loss, quality deterioration, and potential microbial spoilage. Storage and processing technologies, such as freezing, canning, drying, and juicing, all serve to transform perishable produce into products that can be consumed year-round. A substantial amount of peer-reviewed research highlighting the effects of processing, storage, and cooking on the nutritional quality of F&V has been published over the last century (Rickman, Barrett, and Bruhn 2007a; Rickman, Bruhn, and Barrett 2007b). Washing, peeling, and blanching prior to processing are responsible for some loss of water-soluble nutrients, whereas thermal processing (e.g., canning and pre-freeze blanching treatments) can be detrimental to heat-sensitive nutrients. Since both unprocessed and processed F&V must undergo some form of transport and storage, degradation of nutrients prior to consumption is to be anticipated. The retention of vitamin C (i.e., ascorbic acid) is often used as an estimate for the overall nutrient retention of food products; however, ascorbic acid is by far the least stable nutrient during processing, as it is highly water soluble and sensitive to both oxidation and heat treatment (Rickman, Barrett, and Bruhn 2007a). Other vitamins, minerals, and dietary bioactive compounds are significantly more stable during processing and cooking.

Nutritional quality of processed products is highly dependent on the cultivar, and different cultivars are often used for canned and frozen F&V compared to those intended for fresh consumption. For instance, nearly 80% of all tomatoes consumed in the United States are canned; these tomato cultivars contain significantly higher levels of vitamin E (α-tocopherol) and carotenoids (e.g., lycopene) compared to fresh tomato cultivars (Abushita, Daood, and Biacs 2000). Studies examining the effects of processing on a food may not subsequently study the effects of storage and cooking on the same food. By the time an individual consumes fresh purchased produce, the canned or frozen equivalent may be nutritionally similar owing to oxidative degradation of the nutrients during handling and storage of the fresh product. Nutritional quality also varies according to the season, harvest location, and environmental conditions (e.g., drought). Therefore, individual results may not be representative of yearly averages or regional availability (Rickman, Barrett, and Bruhn 2007a; Rickman, Bruhn, and Barrett 2007b). Processed products such as canned goods may contribute to increased sodium intakes; however, draining brine and/or rinsing vegetables and legumes reduces their sodium content (Rickman, Bruhn, and Barrett 2007b) in addition to other water soluble nutrients like vitamin C.

Considerable attention has been given to the role of 100% fruit juice in relation to both childhood weight gain and development of type 2 diabetes during adulthood (Byrd-Bredbenner et al. 2017). Several reviews of the peer-reviewed literature, as well as a recent systematic review, indicate that 100% fruit juice consumption does not contribute to clinically relevant weight gain in children, although a small number of studies do show an increased risk (Clemens et al. 2015; Hyson 2015; Crowe-White et al. 2016; Byrd-Bredbenner et al. 2017). Children who consume 100% fruit juice have been shown to have better diet quality and likelihood of meeting daily fruit goals (Clemens et al. 2015; Byrd-Bredbenner et al. 2017; USDA 2018a). They also exhibit higher intakes of vitamin C, folate, and potassium (Clemens et al. 2015; Byrd-Bredbenner et al. 2017; USDA 2018a) as well as a 60% reduced likelihood of consuming sugar-sweetened beverages (Byrd-Bredbenner et al. 2017). Limited evidence from clinical trials suggests potential improvements in a variety of antioxidant biomarkers after consumption of 100% fruit juice (Crowe-White et al. 2017); however, the antioxidant content of most 100% juices has been shown to be less compared to whole fruits (Crowe and Murray 2013). Weak evidence suggests that one or more blood lipid measures may be positively influenced by consumption of 100% fruit juice (Crowe-White et al. 2017). The collective scientific literature fails to show any association between 100% fruit juice and type 2 diabetes (Xi et al. 2014). There are many plausible mechanisms by which 100% fruit juice might be protective against a number of chronic diseases, and investigation of its effects on human health and disease prevention or promotion must remain an active area of research (Hyson 2015). Preliminary data suggest that polyphenols present in 100% fruit juices may inhibit the absorption of naturally occurring sugars (Johnston, Clifford, and Morgan 2002; Byrd-Bredbenner et al. 2017). Consumption of 100% fruit juice should be within limits set by the DGA (USDA 2018a) and the American Academy of Pediatrics (Heyman and Abrams 2017). Heterogeneity in study methodology, including biomarkers, 100% fruit juice type, dosage, and intervention duration, precludes the ability to make evidence-based recommendations regarding a specific dose-duration–100% fruit juice effect (Crowe-White et al. 2017).

Future research needs and key questions

Although F&V provide an array of healthful nutrients to the diet, their illustrated protective and therapeutic effects in relation to certain chronic disease states is largely observational. Future RCTs with large sample sizes and adequate study designs are needed to affirm the collective and individual effects seen from observational studies. Use of large, long-term clinical databases on populations and their health outcomes may help determine the contributions of individual or collective F&V intake on the quality of an individual's dietary pattern and therefore the prevention and management of disease for that individual. It is likely that individuals who consume higher amounts of F&V also exhibit other lifestyle habits that contribute to long-term health maintenance, leaving room for significant amounts of confounding among observational studies. Higher-quality systematic reviews utilizing dose-response meta-analysis methodologies customized to the nutrition field are necessary for future public health messaging and policy formulation. Biomarkers not only help indicate health status from a prevention standpoint, but they are useful tools to ascertain compliance among intervention studies. However, limited biomarkers are available, and some that are available are difficult to interpret due to other factors contributing to the biomarker exposure. Biomarkers not only help indicate health status from a prevention standpoint, but they are useful tools to ascertain compliance among intervention studies. Gene-nutrient interaction studies that measure genetic variants in relevant genes will enable future individualized nutrition recommendations. Defining intake without using "servings" of F&V but rather more precise measures (e.g., grams) will help scientists better compare outcomes among various studies. Additional research is needed on the effect of F&V processing in regard to health promotion and disease prevention, as processed food products may help increase consumer options and availability while decreasing costs and food waste. The food industry should continue to invest in product development as a means of inserting F&V into processed products. Continuing to improve food composition databases to include processed foods, mixed dishes, and other branded products will allow researchers to better monitor intakes of F&V products and assess exposures and effects of new product innovations (e.g., foods with natural colors). Updating databases that emphasize whole foods vs. single macro- or micronutrients alone is important in advancing the field.

Conclusions

Strong accumulating evidence demonstrates that habitual consumption of F&V, primarily of the non-starchy variety, has health-promoting properties that extend beyond helping individuals obtain essential nutrient requirements. Authoritative bodies have long recommended consumption of F&V because of their low energy density, high nutrient density, and dietary fiber content. In addition to essential nutrients, it is well established that F&V contain a diverse array of dietary bioactive compounds that provide human health benefits beyond basic nutrition in addition to their essential nutrients. The majority of evidence linking F&V intake to health promotion and chronic disease prevention is observational and cannot be used to establish causality. RCTs that are strong in their design and execution have the ability to establish causality but will likely always have the caveat of an insufficient duration to capture disease outcomes (Blumberg et al. 2010). Moreover, many health benefits chronic conditions are interrelated (e.g., microbiota, inflammation and immune function) giving precedent to conducting research on F&V using a more systems-based approach. New technologies such as administration of rare, long-lived radiotracer ^{41}Ca to monitor changes in bone calcium balance in response to a nutrition intervention (Weaver et al. 2017) will likely facilitate overcoming many of these hurdles as their costs decrease, allowing widespread clinical and research use. These types of studies are needed to confirm the effects of F&V shown across observational studies, which in many instances are confounded and contradictory. The scientific evidence for providing public health recommendations to increase F&V consumption for prevention of disease is strong. Current evidence suggests that F&V have the strongest effects in relation to prevention of CVDs, noting a nonlinear threshold effect of 800 g per day (i.e., about 5 servings a day). A growing body of clinical evidence (mostly small RCTs) demonstrates effects of specific F&V on certain chronic disease states; however, more research on the role of individual F&V for specific disease prevention strategies is still needed in many areas. Data from the systematic reviews and mostly observational studies cited in this report also support intake of certain types of F&V, particularly cruciferous vegetables, dark-green leafy vegetables, citrus fruits, and dark-colored berries, which have superior effects on biomarkers, surrogate endpoints, and outcomes of chronic disease.

Abbreviations

AICR	American Institute for Cancer Research
AMD	age-related macular degeneration
BMD	bone mineral density
BMI	body mass index
CHANCES	Consortium on Health and Ageing: Network of Cohorts in Europe and the United States
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DGA	U.S. Dietary Guidelines for Americans
DGAC	Dietary Guidelines Advisory Committee
DIM	3,3′-diindolylmethane
EPIC	European Prospective Investigation Into Cancer
EUFIC	European Food Information Council
F&V	fruit and vegetable
FAO	Food and Agriculture Organization of the United Nations
FLAVURS	Flavonoids and Vascular Function at the University of Reading Study
GBD	Global Burden of Disease
GFR	estimated glomerular filtration rate
HEI	Healthy Eating Index
HR	hazard ratio
IARC	International Agency for Research on Cancer
IFN	interferon
IL	interleukin
IOM	Institute of Medicine
KNHANES	Korean National Health and Nutrition Examination Survey
LPS	lipopolysaccharide
NAFLPD	nonalcoholic fatty liver disease

NCD	noncommunicable disease
NF-κB	nuclear factor-κB
NHANES	National Health and Nutrition Examination Survey
NIH	U.S. National Institutes of Health
OR	odds ratio
POAG	primary open-angle glaucoma
RCT	randomized controlled trial
ROS	reactive oxygen species
RR	relative risk
SCFA	short-chain fatty acid
TNF	tumor necrosis factor
USDA	U.S. Department of Agriculture
UV	ultraviolet
WCRF	World Cancer Research Fund
WHI	Women's Health Initiative
WHO	World Health Organization

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