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Dietary fruits and vegetables and cardiovascular diseases risk

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ABSTRACT

Diet is likely to be an important determinant of cardiovascular disease (CVD) risk. In this article, we will review the evidence linking the consumption of fruit and vegetables and CVD risk.

The initial evidence that fruit and vegetable consumption has a protective effect against CVD came from observational studies. However, uncertainty remains about the magnitude of the benefit of fruit and vegetable intake on the occurrence of CVD and whether the optimal intake is five portions or greater. Results from randomized controlled trials do not show conclusively that fruit and vegetable intake protects against CVD, in part because the dietary interventions have been of limited intensity to enable optimal analysis of their putative effects.

The protective mechanisms of fruit and vegetables may not only include some of the known bioactive nutrient effects dependent on their antioxidant, anti-inflammatory, and electrolyte properties, but also include their functional properties, such as low glycemic load and energy density. Taken together, the totality of the evidence accumulated so far does appear to support the notion that increased intake of fruits and vegetables may reduce cardiovascular risk. It is clear that fruit and vegetables should be eaten as part of a balanced diet, as a source of vitamins, fiber, minerals, and phytochemicals.

The evidence now suggests that a complicated set of several nutrients may interact with genetic factors to influence CVD risk. Therefore, it may be more important to focus on whole foods and dietary patterns rather than individual nutrients to successfully impact on CVD risk reduction.

A clearer understanding of the relationship between fruit and vegetable intake and cardiovascular risk would provide health professionals with significant information in terms of public health and clinical practice.

KEYWORDS

Fruits; vegetables;
cardiovascular diseases;
hypertension; diabetes;
hyperlipidemia; obesity;
bioactive components

Introduction

Dietary factors play an important role in the development and progression of cardiovascular disease (CVD) (Din, 2002), and dietary optimization must be considered an important lifestyle intervention for the management of existing CVD and its prevention (Ferrari et al., 2004).

The importance of diet in maintaining optimal health has emerged from several lines of evidence including observations that the rates of particular diseases differ significantly between cultures; with dietary variation being an obvious factor contributing to these differences (Key et al., 1996; Ness and Powles, 1997). In contrast to the literature on cancer risk (Steinmetz and Potter, 1991), most studies of diet and CVD have reported associations of risk with specific nutrients rather than with entire foods (Willett, 1990). Nonetheless, several studies have reported on the role of overall dietary patterns in predicting cardiovascular risk (Hu, 2002). In these studies, high intakes of fruits, vegetables, legumes, whole grains, poultry, and fish were associated with lower cardiovascular risk whereas a western pattern diet, characterized by high intakes of red and processed meat, sweets, fried food, and refined grains were associated with higher cardiovascular risk independent of lifestyle factors (Hu et al., 2000; Fung et al., 2001). The utility of adopting a

whole diet approach (e.g., the Dietary Approaches to Stop Hypertension (DASH), Mediterranean, and Portfolio diets), with emphasis on antioxidant-rich fruits and vegetables and whole grains, in CVD prevention has been widely supported (Witztum, 1994; De Waart et al., 2001; Sacks et al., 2001; Trichopoulou et al., 2003).

Diets rich in antioxidants derived from fruits and vegetables are thought to be protective against reactive oxygen species, and this, provides a potential mechanism through which they may prevent cancer and CVD. This has, in part, been the rationale for the WHO and other health authorities to recommend the consumption of these foods (Committee on Diet and Health, National Research Council, 1989; WHO, 2003). Dietary advice for CVD prevention is complex for a number of reasons. Fruit and vegetables differ qualitatively and quantitatively in their content of specific antioxidants; particularly, the relative balance between these antioxidants and their bioavailability. Furthermore, it is unclear what the optimal number of portions should be consumed per day and how many portions should be taken as fresh, processed, or dried fruit. It is also unclear whether the benefits of a diet rich in fruit and vegetables would be more evident in primary versus secondary prevention (WHO, 2003). A clear understanding of the relationship

between fruit and vegetable intake and cardiovascular risk would provide health professionals with significant information in terms of public health and clinical practice (Steptoe et al., 2003). The American Heart Association has had a longstanding commitment to provide information about the role of nutrition in CVD risk reduction (Krauss et al., 2000). Nutritional advice is often easier to understand in the context of foods rather than the individual nutrients they contain.

Nevertheless, there remains a low intake of fruits and vegetables worldwide (Hall et al., 2009). An ecological study examined associations between fruits and vegetables consumption in the population and six health outcomes (ischemic heart diseases, stroke and cancers of the stomach, esophagus, colon, rectum, and lung) using global data. Data were obtained from national representative dietary surveys and the Food and Agriculture Organization of the United Nations, with analyses being stratified by 14 geographical regions. The analysis suggested that 2.6 million deaths worldwide and 31% of coronary heart disease and 19% of ischemic stroke may be due to a suboptimal consumption of fruits and vegetables (Lock et al., 2005). More recently, dietary guidelines for Americans recommend that most people should eat at least 9 servings (41/2 cups) of fruits and vegetables a day, 4 servings (2 cups) of fruits, and 5 servings (2.5 cups) of vegetables, based on a 2000 kcal diet (United States Department of Agriculture, 2010).

Often, dietary guidance emphasizes the importance of eating whole fruit and vegetables whilst reducing the consumption of foods high in fat and sodium, that is, French fries. Indeed fruits and vegetables are generally have a low-energy density, but the nutritional contribution of standard servings of fruits and vegetables varies widely (Hornick and Weiss, 2011). Moreover, the content of phytochemicals also varies greatly and is often not listed in nutrient databases (Song et al., 2010).

Many constituents of fruits and vegetables (fiber, fat and water soluble vitamins, sterols, and phytochemicals) have also been associated with reduced risk for CVD, which supports the notion that a high fruit and vegetable consumption might protect against cardiovascular events via a number of different mechanisms (Knekt et al., 1996; Rimm et al., 1996; Liu et al., 2001; Padayatty et al., 2003; Genkinger et al., 2004; Pereira et al., 2004). These nutrients act through a variety of mechanisms, such as reducing antioxidant stress, improving the plasma lipoprotein profile, lowering blood pressure, improving insulin sensitivity, and hemostasis regulation (Van Duyn and Pivonka, 2000; Bazzano et al., 2003; Wannamethee et al., 2006). The benefit of a diet rich in fruits, vegetables, and grains is attributed to the complex mixture of micronutrients, phytochemicals, and fiber (Samman et al., 2003). Therefore, the additive and synergistic effects of these nutrients in fruits and vegetables may be responsible for their potent antioxidant and anticancer activities (Wolfe et al., 2008; Song et al., 2010). This may partially explains why no single antioxidant can replace the combination of nutrients in fruits and vegetables in achieving the observed health benefits.

Overall, several reviews and meta-analyses examining intakes of fruits and vegetables have reported an inverse association between intake of fruit and vegetables and CVD occurrence, although epidemiological evidence for causality is controversial (Dauchet et al., 2005; Dauchet et al., 2006; He

et al., 2006; Agudo et al., 2007; He et al., 2007; Wang et al., 2014). The magnitude of the favorable association remains uncertain because of differences in methodological approaches, analytical techniques, and the definition of outcomes.

In this article, we will review the evidence from primary and secondary prevention trials concerning the link between fruits and vegetables consumption and the risk of CVD.

Health effects of fruits and vegetables

The protective effects of fruits, vegetables, and whole grains against several chronic diseases are well documented; however, the evidence is linked to whole foods, rather than supplements of individual dietary constituents, hence the actions of individual dietary constituents do not fully explain the observed health benefits of diets rich in fruits and vegetables. Supplementation with individual antioxidants has been investigated in randomized clinical intervention trials, but have not consistently shown a benefit (Ommen et al., 1996; Stephens et al., 1996; Yusuf et al., 2000). Isolated components of the diet may either lose their bioactivity, may not behave the same way as they do in whole foods, or may require other constituents of the whole food for their full functional activity (Hennekens et al., 1996).

Fruit and vegetables differ in their nutrient content, the manner in which they are prepared and eaten, and the amounts in which they are eaten daily. Such differences have important implications for the analysis of fruit and vegetable intake and their consequential impact on chronic disease risk. Other factors, potentially confounding the interpretation of fruit and vegetable intake on cardiovascular risk, include the wide variety of fruit and vegetables consumed globally, each with very different micro- and macronutrient, contents, and their potential interactions with other dietary components. These make the interpretation of studies of fruit and vegetable consumption on human health in prospective cohort studies or randomized controlled trials. Few studies have investigated the intake of fruits and vegetables separately as in the European Prospective Investigation into Cancer and Nutrition study (Sargeant et al., 2001). Furthermore, the inclusion of legumes and potatoes in the vegetable category as in the Atherosclerosis Risk in Communities (ARIC) study (Steffen et al., 2003) has not been consistently applied.

The role of fruit or vegetable juices as distinct from that of the whole fruit and vegetable has not been well studied. Fruit and vegetable juices are obviously different in form from whole fruit or vegetables, and often lack much of fiber of the latter. In addition, they are often sweetened with a variety of substances or added sugar, which contribute to their energy density, but not necessarily to their protective function against chronic diseases. However, the beneficial health effects of consuming fruits are partially attributable to their antioxidant activity, which is present in fruit juices. For example, the vitamin C content of citrus juices and polyphenols content of pomegranate juice are considered protective against oxidative stress and atherogenesis (Aviram et al., 2002; Vinson et al., 2002). Nevertheless, it is worth noting that the antioxidant content of juices, measured in vitro, does not necessarily translate into bioavailable antioxidant activity, as the absorption of some antioxidants is poor (Vinson et al., 1995).

Whilst fresh, cooked, and processed fruits and vegetables including frozen and canned, 100% fruit juices, 100% vegetable juices, and dry fruits are all considered as servings of fruits and vegetables a day, processing of fruit and vegetables alters their structure and induces significant changes in chemical composition, nutritional value, and bioavailability of bioactive compounds. These may all have an impact on their potential protective effects. Fruit juices, for example, while containing less fiber than whole fruit, may be a good source of phytochemicals (Ruxton et al., 2006). Vegetables are often cooked before consumption, which causes a significant loss of water-soluble and heat-sensitive bioactive compounds (Ruiz-Rodriguez et al., 2008). In contrast, processing can enhance the availability of some bioactive compounds. It has been shown, for example, that heat treatment improves the bioavailability of lycopene from tomatoes (Rao and Agarwal, 1999) and carotenoids from carrots (Hornero-Méndez and Mínguez-Mosquera, 2007). Furthermore, processing could convert folate polyglutamate in vegetables into monoglutamate, which has better bioavailability (Melse-Boonstra et al., 2004).

Much attention has been paid to antioxidant vitamins found in fruits and vegetables, yet these foods are also rich in fiber (Smith and Tucker, 2011) and nitrate (Lidder and Webb, 2013) and, therefore, a diet rich in fruits and vegetables will also be rich in a complex mixture of micronutrients, phytochemicals, and fiber, with the exact combination dependent on the range of fruits and vegetables consumed.

The protective effect of dietary fiber on cardiovascular risk is biologically plausible, and there are many potential mechanisms through which fiber may act on individual coronary risk factors. Soluble, viscous fiber types can affect absorption from the small intestine because of the formation of gels that attenuate postprandial changes in blood glucose and lipoproteins (Lunn and Buttriss, 2007). The formation of gels also slows gastric emptying, maintaining levels of satiety, and contributing toward less weight gain (Lunn and Buttriss, 2007). Soluble fiber and resistant starch molecules are additionally fermented by bacteria in the large intestine, producing short chain fatty acids, which help reduce circulating cholesterol levels (Slavin et al., 1999).

It has been suggested that an increased intake of salicylate from foods might have contributed to the decline in CVD (Ingester and Feinleib, 1997). However, the impact of salicylate content of foods remains controversial. Salicylates per se do not affect thromboxane B₂ formation or platelet aggregation. It is acetylsalicylate that is able to inactivate cyclo-oxygenase and subsequently affect cardiovascular risk (Janssen et al., 1996).

Other nutrients in fruits and vegetables, for example fructose, are thought to be dietary risk factors for CVD. Because of its low glycemic index, fructose was suggested as an alternative sweetener for diabetic patients (Henry et al., 1991). However, in patients with overt hyperglycemia and insulin deficiency, fructose may be associated with a greater increase in blood glucose concentrations than in diabetic patients with less elevated blood glucose concentrations (Swanson et al., 1992). Moreover, fructose-induced hypertriglyceridemia in nondiabetic subjects susceptible to elevated serum triglycerides has also been a matter of concern (Henry et al., 1991). This is particularly relevant in patients with diabetes, among whom hypertriglyceridemia is

the most common lipid abnormality and may increase the risk of CVD.

Bioactive components of fruits and vegetables

A number of mechanistic hypotheses involving specific constituents of fruits and vegetables have been proposed. The antioxidant hypothesis suggests antioxidant vitamins such as C and E, β -carotene, and other carotenoids; antioxidant minerals, such as selenium and zinc and other antioxidant compounds such as flavonoids are protective (Witztum, 1994). The lipid oxidation hypothesis, proposes that low density lipoprotein (LDL) cholesterol is modified to oxidized LDL by free radicals, and this is a potentially proatherogenic lipoprotein particle (Witztum and Berliner 1998). When circulating LDL molecules are present at high levels in blood, they infiltrate the artery wall and increase intimal LDL, which can then be oxidized by free radicals. This oxidized LDL is more atherogenic than native LDL and serves as a chemotactic factor in the recruitment of circulating monocytes and macrophages. Since oxidized LDL plays a key role in the initiation and progression of atherosclerosis, giving dietary items with antioxidant activity capable of preventing LDL oxidation has been a putative therapeutic approach. Dietary micronutrients provided as antioxidants may be incorporated into LDL and may then be preferentially oxidized when the LDL is exposed to free radicals; this may occur before any extensive oxidation of the sterol or polyunsaturated fatty acids can occur (Sanchez-Moreno et al., 2000). Therefore, dietary micronutrients might retard the progression of atherosclerotic lesions by reducing the formation of oxidized LDL.

Inflammation is thought to promote the initiation and progression of atherosclerosis, and is also involved in the acute thrombotic complications of atherosclerosis (Libby et al., 2002). The relationship between high-sensitivity C-reactive protein (hs-CRP), a marker of systemic inflammation, and the total antioxidant capacity (TAC) of the diet has reported that dietary TAC is independently and inversely correlated with hs-CRP (Brighenti et al., 2005). The authors suggest that this could be one of the mechanisms behind the protective effects of fruits and vegetables.

The relationship between dietary fruit and vegetables and atheroma formation has been explored in animal models and in vitro cell culture systems. However, the relevance of these models to human disease remains contentious (Wolfe et al., 2008; Song et al., 2010; Wang et al., 2014).

The benefits of a diet rich in fruits and vegetables are not only usually attributed to being low in calories and have a high water content, but may also be due to the displacement of other less healthy foods. The presumptive protection afforded by antioxidants present in fruits and vegetables (Kok et al., 1987; Knekt et al., 1994; Losonczy et al., 1996; Yochum et al., 2000) was originally based on the measurement of several biochemical markers as an index of fruit and vegetable intake (vitamin E, carotenoids, vitamin C, and phytochemicals). However, dietary phytochemicals have been shown to have roles in the regulation of prostaglandin synthesis, reduction of vascular tone, inhibition of platelet aggregation, regulation of cholesterol synthesis and absorption, and reduction of blood pressure and

these may not be reflected by the measurements of the biomarkers that have been used previously.

Of the many nutrients present in fruit and vegetables, dietary vitamins have been evaluated most extensively in literature. Despite the abundance of observational epidemiological data supporting their role in CVD prevention (Marchioli et al., 2001; Knekt et al., 2004; Ye and Song, 2008), intervention trials with folate, carotenoids, and vitamin C have failed to demonstrate convincingly that these vitamins have a role in preventing CVD and cardiovascular mortality (Vivekananthan et al., 2003; Cook et al., 2007; Albert et al., 2008; Sesso et al., 2008). In this context, the U.S. Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of the use of single- or paired-nutrient supplements (except β -carotene and vitamin E that have proven to be harmful) for the prevention of CVD and cancer (Moyer, 2014).

Moreover, a meta-analysis evaluating the effects of combinations of multivitamin and mineral supplements on prevention of CVD found no evidence of a protective effect (Huang et al., 2006). Factors that might have affected the results include inappropriate dosing, insufficient duration of intake, or the stage of disease at which the intervention was introduced. A further possibility is that CVD prevention trials might have recruited participants not likely to benefit from treatment, such as those with a satisfactory vitamin status. In order to translate the knowledge of molecular and cellular mechanisms of atherosclerosis more effectively into clinical benefit, the methodological issues of the current clinical trials must be interpreted with caution.

The tendency of researchers to pursue hypotheses based on single nutrients, may underestimate the potential benefits of chemically complex as foods. The outcomes of the β -carotene and α -tocopherol trials may be particularly instructive in this regard (Greenberg and Sporn, 1996; Rowe, 1996).

Observational studies

Table 1 shows a summary of observational studies on the relationship between fruit and vegetable consumption and prevention of CVD, which had ecological, case-control, or prospective cohort designs. Given the extreme variability of observational studies design, trend analyses of dose-response relationships do not often reveal statistically significant associations, as shown in Table 2. These studies have varied considerably in their inclusion criteria, recruitment methods, sample size, duration of follow-up, definition of events and adjustment factors, and presentation of results. More attention will be required on the design of appropriate long-term prospective studies because they offer the most useful methodological compromise for studying associations between nutritional factors and CVD, particularly for primary prevention.

Methodological differences among observational studies include dietary assessment methods, the variety of fruit or vegetables being investigated, the definition of the reference group, and the choice of exposure categories. Measurement error in dietary assessment is a persistent problem when assessing associations between diet and diseases (Horner et al., 2002). The bias can be large and in either direction. In addition, where errors exist in the measurement of confounders, the bias would

work in the direction of confounding, which may either exaggerate or dilute the estimated association (Willett, 1990). Other potential biases cannot be ruled out, such as those due to misclassification of fruit and vegetable intake by the dietary assessment method, the number of groups of fruit and vegetable consumed, and various reference categories between individual studies (Lee and Nieman, 2003). Findings from validation studies using biomarkers suggest that measurement error in dietary exposures will often result in attenuated estimates, which may often be quite severe (Willett, 1990).

Therefore, more objective and accurate indices of fruit and vegetable intake, such as nutritional biomarkers, are becoming popular. Such biomarkers of intake need to be able to discriminate between differences in intakes should be noninvasive or minimally invasive, reproducible, easily measured, and highly responsive to the intervention being carried out (Crews et al., 2001).

Data from dietary assessments in prospective studies were often unadjusted for total calorie intake and only assessed at a single time-point (baseline). Moreover, the reliability and accuracy of these methods to assess long-term nutritional habits are limited and have not always been robustly validated. Therefore, heterogeneity complicates estimation of the magnitude of effects, and the comparison of results between studies (Dauchet et al., 2009).

It is possible that variation between study populations on the types of fruits and vegetables, and whether cooked or raw vegetables are most commonly consumed, may introduce heterogeneity. Sometimes heterogeneity is introduced by including vegetables that contain more protective nutrients, which yield a stronger association in comparison with weaker association resulting from including heavily processed vegetables. Stratified analysis for fruits and vegetables separately may reduce the heterogeneity. Moreover, adjustment for major confounding factors in the studies that have been included should reduce the potential bias due to these other dietary and lifestyle factors.

Limitations of observational studies include the problem of residual confounding, which also remains when meta-analyses of these studies are undertaken. Exploration of confounding factors, through meta-regression, has not yet confirmed that adjustment for such confounders sufficiently explained the strength or direction of associations observed (Lawlor et al., 2004).

Risk reduction estimates from cohort studies have generally been less impressive than initially observed in ecological or case-control studies. Several reasons for this are possible including an improvement of the dietary habits in the comparator population over the duration of these studies, which could affect the outcomes of prospective follow-up. Also, the lack of comparability of dietary assessment methods combined with inaccurate measurements makes it difficult to detect associations or weaken these associations. Indeed meta-analyses of observational studies report relative risks indicative of a protective effect of fruit and vegetables, but they also show substantial interstudy heterogeneity, which might be explained by methodological issues or publication bias (Dauchet et al., 2006; He et al., 2007).

The observation of a favorable association between fruit and vegetable consumption and cardiovascular risk does not

Table 1. Summary of prospective studies on the association between fruits and vegetables consumption and CVD.

Study	Study cohort	Exposure measure	Follow-up period	Main findings	Reference
The Adventist Health Study	Prospective cohort investigation of 31,208 non-Hispanic white California Seventh-Day Adventists	65 item FFQ	6 years	No associations between CVD risk with fruit index or legumes	Fraser et al. (1992)
The Caerphilly Study	Prospective Ischaemic Heart Disease Study of a sample of 2512 men aged 45–59 years	FFQ	5 years	There was a trend of increasing IHD risk with decreasing vitamin C intake, the relative odds of an IHD event being 1.6 among men in the lowest one-fifth of the vitamin C distribution, but this was not statistically significant	Fehily et al. (1993)
Health Professional Follow Up Study	39,910 U.S. male health professionals 40–75 years of age	131 item FFQ	4 years	Evidence of an association between a high intake of vitamin E and a lower risk of coronary heart disease in men	Rimm et al. (1993)
The Zutphen Elderly Study	805 men aged 65–84 years	Cross-check dietary history	5 years	<ul style="list-style-type: none"> • Flavonoids in regularly consumed foods may reduce the risk of death from CHD in elderly men • Intakes of tea, onions, and apples were also inversely related to coronary heart disease mortality, but these associations were weaker 	Hertog et al. (1993)
Longitudinal population study in Finland	A cohort of 5133 Finnish men and women aged 30–69 years and free from heart disease at baseline	Dietary history	14 years	Antioxidant vitamins protect against CHD, but it could not exclude possibility that foods rich in these micronutrients also contain other constituents that provide the protection	Knekt et al. (1994)
The Massachusetts Health Care Panel Study	1299 elderly living in Massachusetts residents	43 category FFQ	4.75 years	Increased dietary intake of carotenoids decreases the risks of CVD mortality; however, confounding cannot be ruled out	Gaziano et al. (1995)
The Department of Health and Social Security nutritional survey	Elderly people living in the community who had taken part in eight areas in Britain	7 day weighed record	20 years	Vitamin C concentration in elderly people is strongly related to subsequent risk of death from stroke but not from CHD	Gale et al. (1995)
Framingham Study	832 men, aged 45 through 65 years, who were free of cardiovascular disease at baseline	24 h recall	20 years	Intake of fruits and vegetables may protect against development of stroke in men	Gillman et al. (1995)
The Western Electric study	1,556 employed, middle-aged men, aged 40–55 years	Diet history	24 year	Consumption of foods rich in vitamin C and beta-carotene reduces risk of death in middle-aged men	Pandey et al. (1995)
Postmenopausal women	34,486 postmenopausal women with no cardiovascular disease	127 item FFQ	7 year	<ul style="list-style-type: none"> • In postmenopausal women the intake of vitamin E from food is inversely associated with CHD mortality and that such women can lower their risk without using vitamin supplements • The intake of vitamins A and C was not associated with lower risks of CHD mortality 	Kushi et al. (1996)
Longitudinal population study in Finland	A cohort of 5,133 Finnish men and women aged 30–69 years and free from heart disease at baseline	dietary history	14 years	People with very low intakes of flavonoids have higher risks of CHD	Knekt et al. (1996)
Prospective observation of vegetarians, semivegetarians, and meat eaters in United Kingdom	10,802 men and women in the United Kingdom aged between 16 and 79		13.3 years	<ul style="list-style-type: none"> • Deleterious effects of saturated animal fat and dietary cholesterol are more important in the etiology of IHD than the protective effect of dietary fiber. • Reduced intakes of saturated animal fat and cholesterol may explain lower rates of IHD among vegetarians compared with meat eaters. 	Mann et al. (1997)
The Women's Health Study	39,876 female health professionals with no previous history of CVD or cancer	FFQ	5 years	Higher intake of fruit and vegetables may be protective against CVD and support current dietary guidelines to increase fruit and vegetable intake.	Liu et al. (2000a)

(continued on next page)

A combined analysis of the Nurses' Health Study and the Health Professionals' Follow-Up Study	<ul style="list-style-type: none"> • Nurses' Health Study: 84,251 women 34–59 years of age. All were free of diagnosed CVD, cancer, and diabetes at baseline. 	FFQ	NHS: 14 years	Consumption of fruits and vegetables, particularly green leafy vegetables and vitamin C-rich fruits and vegetables, appears to have a protective effect against CHD	Joshipura et al. (2001)
	<ul style="list-style-type: none"> • Health Professionals' Follow-Up Study: 42,148 men 40–75 years. All were free of diagnosed CVD, cancer, and diabetes at baseline. 	FFQ	HPFS: 8 years		
The Physicians' Health Study	22,071 US male physicians aged 40–84 years	FFQ	12 years	An inverse association between vegetable intake and risk of CHD	Liu et al. (2001)
Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study in Finland	27,110 male smokers, aged 50–69 years, without history of cancer	FFQ	6.1 years	Intake of flavonols and flavones seemed to be inversely associated with the risk of lung cancer, but not with that of other cancers	Hirvonen et al. (2001)
The first national health and nutrition examination survey (NHANES-I) follow-up study	9608 adults aged 25–74 years participating free of CVD at the time of their baseline	FFQ	19 years	An inverse association of fruit and vegetable intake with the risk of CVD and all-cause mortality in the general US population	Bazzano et al. (2002)
The ARIC study	15,792 adults aged 45–64 years participating free of CAD at the time of their baseline	FFQ	11 years	A beneficial effect of whole-grain and fruit and vegetable consumption on the risks of total mortality and incident CAD was suggested but not on the risk of ischemic stroke	Steffen et al. (2003)
The Prospective Epidemiological Study of Myocardial Infarction (PRIME) study	Men aged 50–59 years, free of CHD, who were recruited in France ($n = 5982$) and Northern Ireland ($n = 2105$)	FFQ	5 years	Frequency of citrus fruit, but not other fruits, intake is associated with lower rates of acute coronary events in both France and Northern Ireland, suggesting that geographical or related factors might affect the relationship between fruit consumption and CHD risk.	Dauchet et al. (2004)
The Odyssey Cohort	8394 residents in Washington County, Maryland	61 item FFQ	15 years	Participants with the highest quintile of fruit and vegetable intake had a lower risk of all-cause mortality and CVD mortality than those in the lowest quintile	Genkinger et al. (2004)
A combined analysis of the Nurses' Health Study and the Health Professionals' Follow-up Study	Over 100,000 participants in the Nurses' Health Study and the Health Professionals' Follow-up Study	FFQ		Fruit and vegetable intake was inversely associated with risk of CVD, with relative risk for an increment of five servings daily of 0.88 (95% CI = 0.81–0.95), and green leafy vegetables showed the strongest inverse association	Hung et al. (2004)
The Baltimore longitudinal study of aging	501 healthy men at baseline	7-day diet records	18 years	<ul style="list-style-type: none"> • Protective effects of low saturated fat and high fruits and vegetables intake against CHD mortality • The combination of both behaviors is more protective than either alone, suggesting that their beneficial effects are mediated by different mechanisms. 	Tucker et al. (2005)
Nurses' Health Study	72,113 women who were free of CVD and cancer at baseline	FFQ	18 years	A more prudent diet containing high intakes of fruits and vegetables was associated with a reduced risk of cardiovascular mortality and a reduced risk of all-cause mortality when comparing individuals in the highest to the lowest quintile of diet prudence.	Heidemann et al. (2008)
The Jichi Medical School cohort study	10,623 participants (4147 men, 6476 women) who had no history of CVD or carcinoma at baseline	Five category FFQ	10.7 years	Frequent intake of citrus fruit may reduce the incidence of CVD, especially cerebral infarction, in men and women	Yamada et al. (2011)

CAD, coronary artery disease, CHD, coronary heart disease, IHD, ischemic heart disease, CVD, cardiovascular disease, FFQ, food frequency questionnaire.

Table 2. Shortcomings of epidemiological studies.

Study design	Description	Limitation
Ecological studies	To explore relationships between environmental factors and diseases at a population level	<ul style="list-style-type: none">• Do not provide precise information about individuals in a population
Case–control studies	Individuals diagnosed with disease are compared with disease-free individuals	<ul style="list-style-type: none">• Subject to many uncontrolled biases• Rely on retrospective assessment of dietary intake by questionnaire
Cohort studies	The exposure of people who are initially assumed to be healthy are assessed and the group is followed over a period of time. During the follow-up period, some individuals will develop disease	<ul style="list-style-type: none">• Subject to selection and recall bias and potential bias due to the changes in diet and lifestyle following CVD events• Measurements are made at baseline before disease is diagnosed, but diet may change with time
Randomized controlled trials	The participants are allocated to treatment/intervention or control/placebo groups using a random mechanism. Best for studying the effect of an intervention	<ul style="list-style-type: none">• Cohort studies are less subject to recall bias• Expensive in terms of time and money• Often short duration with less power to detect clinical outcomes• Subject to volunteer bias• Ethically problematic

necessarily indicate causality; hence, fruit and vegetable intake might simply indicate a reduced intake of unhealthy nutrients, such as saturated fats and salt. Furthermore, social and behavioral factors may often be associated with a health-conscious lifestyle, and the impact of these cannot always be measured precisely or might not be appropriately considered in statistical analyses. Therefore, the confounding effects in observational studies might not be fully appreciated.

Interventional studies

Because observational studies do not control for unmeasured confounders, the causal relationship remains to be established using randomized controlled trials. Although nutritional prevention trials provide the most robust estimate of causal effects, they also have some limitations that may make their interpretation difficult. The success of these studies relies on compliance of the participants for the duration of the study, which can be over several years. Obviously, a double-blind controlled trial is not feasible in the context of interventions with food items, leaving the possibility for biases in the assessment of end-points. Secondly, increased consumption of fruit and vegetables might induce changes in other components of the diet. For instance, in the DASH trial, fruit and vegetables were substituted by snacks to achieve equivalence of energy intake in the control and experimental diet. Thirdly, results of tightly controlled intervention trials cannot easily be extrapolated to a free-living general population, or to public health policies. Finally, the difficulty of achieving a substantial modification of diet in long-term studies hampers the interpretation of the results.

Not surprisingly, given their methodological difficulties, few randomized nutritional trials have been conducted to evaluate the effect of high fruit and vegetable intake on the incidence or recurrence of CVD (reviewed by Brunner et al., 2006). It must also be emphasized that changes in fruit and vegetable intake achieved in these studies have been generally modest in these clinical studies.

In the Indian heart study, a semivegetarian diet enriched with fruits, vegetables, whole grains, and nuts reduced

coronary death and nonfatal myocardial infarction (Singh et al., 1992). A vegetarian diet is associated with a lower blood cholesterol concentration, a lower incidence of stroke, and a lower risk of mortality from stroke or ischemic heart disease (Bazzano et al., 2002; Bazzano et al., 2003) when compared to a mixed diet. However, vegetarians often have a higher consumption of whole grains, soy, and nuts, all of which have significant cardioprotective effects (Kelly and Sabate, 2006; Mellen et al., 2008).

In the Diet and Reinfarction Trial II, recommendations aimed at promoting increased consumption of fruit, vegetables, fiber, and orange juice had no effect on cardiac death in patients with angina pectoris (Burr et al., 2003). However, the small difference in fruit and vegetable intake between study and control participants (~20 g/day) may have contributed to the lack of significant benefit (Ness et al., 2004; Burr, 2007).

In the Women’s Health Initiative Randomized Controlled Dietary Modification Trial, fruit and vegetable intake in the group that received nutritional advice had increased only slightly (by 1.2 servings per day), compared with the control group and the two groups did not differ significantly in the rate of major CVD events (Howard et al., 2006a).

The Lyon study showed major benefits of a Mediterranean Diet, but given the complexity of this diet and the use of margarines rich in α -linolenic fatty acid, these benefits cannot be attributed to fruit and vegetable consumption alone (de Lorgeril et al., 1999).

Similarly, the Prevención con Dieta Mediterránea study has demonstrated that adherence to the Mediterranean Diet is associated with an increase in serum markers of atheroma plaque stability which may partly explain the cardioprotective role of Mediterranean Diet (Casas et al., 2014).

Nevertheless, when the short-term effects of Mediterranean diets versus those of a low-fat diet were investigated on intermediate markers of cardiovascular risk, significant dietary changes were only seen in olive oil, nuts and red meat within the intervention groups (Estruch et al., 2006). Therefore, any clinical benefit of the Mediterranean Diet cannot be attributed to a change in fruits and vegetables intake.

Fruits and vegetables and cardiovascular risk factors

Investigating the effects of fruit and vegetable intake on classical cardiovascular risk factors is crucial in determining biological plausibility of a causal relationship between fruit and vegetable consumption and CVD.

Hypertension

Fruit and vegetables are good sources of magnesium and potassium, which have been inversely associated with hypertension in previous studies (Zhang et al., 2012). One of the main results of the DASH study is that fruit and vegetable consumption was associated with a significant decrease in blood pressure, in which the effect was more pronounced in hypertensive patients than in normotensive participants (Broekmans et al., 2001; Sacks et al., 2001). This might be attributed to an increase in the intake of potassium, magnesium, or some other component in fruits and vegetables, or alternatively a reduced intake of sodium (Hord et al., 2009). A number of intervention studies have given conflicting results on the beneficiary effect of increased fruits and vegetables intake on blood pressure (Appel et al., 1997; McCall et al., 2009; Berry et al., 2010). This is a consequence of the potential differences in study designs, participant characteristics (in terms of degree of hypertension at baseline) and methods used to achieve an increase in fruits and vegetables intake.

Results from a large randomized controlled trial, to increase daily consumption of fruit and vegetables to at least five portions among healthy study participants randomly selected from primary health care centers, have shown that increased consumption of fruit and vegetables can contribute to a small decrease in blood pressure (John et al., 2002).

Hyperlipidemia

Evidence for the effects of increased fruits and vegetables intake on hypercholesterolemia is limited to date, with many studies either not being specifically designed to test the effects on hypercholesterolemia, or where increased fruits and vegetables was combined with some other dietary intervention, such as reduced fat intake. The large randomized controlled trial, which demonstrated a positive effect of increased fruits and vegetables intake on blood pressure, showed no effect on blood levels of total cholesterol (John et al., 2002).

Several components of fruit and vegetables have cholesterol-lowering properties, particularly dietary fiber (Satija and Hu, 2012). Similarly, ingestion of large quantities of phytosterols (>2 g per day) lowers plasma LDL-cholesterol levels (Thompson and Grundy, 2005). Since the available evidence demonstrates that viscous fibers, plant sterols, vegetable proteins, and nuts can each independently lower serum cholesterol by 5–10% (Anderson et al., 2000). The Portfolio Diet was introduced as a dietary approach based on current dietary recommendations that is feasible, accessible, and has maximized the metabolic advantages of plant-based foods. It is in compliance with the dietary recommendations of the Adult Treatment Panel III of the National Cholesterol Education Program. The major recommendations are that <7% energy

should come from saturated fat, dietary cholesterol intake should be <200 mg/d, dietary fiber intake should be 20–30 g/d, and 50–60% energy should come from carbohydrate, 15% energy from protein and 25–35% energy from fat (NCEP, 2001). It is assumed that the effect of combining these components may be additive and as such leads to clinically significant reductions in serum cholesterol and consequently lower the risk of developing CVD (Jenkins et al., 2002).

Diabetes

The relationship between fruit and vegetable intake and the risk of type II diabetes has not been established and cohort studies have produced conflicting results (Bazzano et al., 2008; Villegas et al., 2008). The discrepancies between studies could be explained by confounding factors and by the possible antagonistic effects of the sugars, fiber, and antioxidants in fruit and vegetables. The results from a few prospective studies regarding fruit and vegetable intake and risk of type 2 diabetes mellitus are not entirely consistent. For instance, an inverse relation between intake of vegetables, but not of fruits, and risk of type 2 diabetes mellitus was observed in the Nurses' Health Study (Colditz et al., 1992). An inverse relation between intake of fruit and vegetables and diabetes mellitus risk in women, but not for men in the National Health and Nutrition Examination I Follow-up Study (Ford and Mokdad, 2001). The Iowa Women's Health Study did not show an association between fruit and vegetable consumption and incident diabetes (Meyer et al., 2000). Also, none of these studies examined different types of fruits and vegetables in relation to the risk of type 2 diabetes mellitus.

Compared with carbohydrate-dense foods, fruits and vegetables (with the exception of potato) generally contribute to a lower glycemic load (a measure of the postprandial glucose-raising potential of dietary carbohydrates). In prospective studies, a diet low in glycemic load has been associated with lower risks of type 2 diabetes mellitus and CVD (Liu et al., 2001; Liu et al., 2000b). The rich fiber content of whole fruits and vegetables may be partly responsible for this response, but other factors, such as the physical structure of fruits and vegetables, antioxidants, carotenoids, flavonoids, and many enzyme inhibitors may play important roles as well (Liu et al., 2001; Ylonen et al., 2003).

A link has been proposed between increased consumption of green leafy vegetables and reduced incidence of diabetes, albeit is based on a limited number of studies (Carter et al., 2010; Cooper et al., 2012), with other classes of fruits and vegetables, such as root vegetables, also potentially playing a role.

Randomized prevention trials have demonstrated the effectiveness of complex lifestyle interventions (including physical activity and body weight reduction) on reducing the risk of diabetes, but the contribution of fruit and vegetables per se in these studies is difficult to estimate given the complexity of the interventions (Pan et al., 1997; Tuomilehto et al., 2001).

Obesity

It has been reported that replacing energy-dense foods with fruit and vegetables could help to decrease calorie intake and,

therefore, body weight (Epstein et al., 2001). Accumulating evidence indicates that the combination of increased fruit and vegetable intake, together with other dietary recommendations, might promote satiety and weight loss in overweight individuals (Tohill, 2005). Although the effect of fruit and vegetable consumption on weight control has been scarcely investigated in clinical settings, it has been found that decreased fat intake combined with increased fruit and vegetable intake results in greater weight loss when compared with low-fat diets alone (Howard et al., 2006b).

Multiple pathways are expected to be involved, high water and fiber content and low-energy density of whole fruits and vegetables may promote weight control by reducing total energy intake through increasing satiety or by substituting for foods with high-energy densities (Pereira and Ludwig, 2001). Multiple enzymatic inhibitors in fruits and vegetables may also affect body weight through other pathways, including the modulation of metabolic efficiency and/or insulin secretion or action (Liu et al., 2003).

Epidemiological studies and their limitations

There is still considerable scientific uncertainty about the relationship between specific dietary components and cardiovascular risk. Reasons for this uncertainty include the high doses of nutrients used in intervention trials that may have resulted in unexpected effects including pro-oxidant activity of excessive doses of a single antioxidant, and residual confounding in cohort studies due to imperfect classification of factors, such as smoking that may have biased the results. Since the effect of antioxidants on mortality may vary by oxidative burden, associations between fruits and vegetables and CVD may be affected by cigarette smoking and body mass index, both sources of oxidative stress.

Interactions between the numerous nutrients found in fruit and vegetables are difficult to evaluate in biological experiments. Moreover, different varieties of fruit and vegetables, growing techniques, industrial processing, and storage and cooking methods can strongly affect the composition and properties of the nutrients. Perhaps the most effective combination of vitamins or the optimal biochemical structure for synthetic molecules used for CVD prevention has not been identified.

Responsiveness of biomarkers may be altered by lifestyle and other factors, such as age, smoking behavior, physical activity, and the presence of low-grade inflammation. Such factors may have affected the response of biomarkers in intervention studies, but the studies are too heterogeneous in terms of design, level of control of overall dietary intake, duration, and the nature of the control group to allow exploration of these issues. The level of nutrients in food will directly affect biomarker response and may vary by individual variety of fruit or vegetable (Kurilich and Juvik, 1999), production conditions (Kopsell and Lefsrud, 2006), and processing, storage, and cooking methods, particularly for vitamin C (Castenmiller et al., 1999).

The current literature does not allow us to examine the association of cardiovascular risk with specific fruits and vegetables or with fruit and vegetable groups, or to examine the effect of seasonal deficits in intake; nor could we examine the effects of secular changes in diet. International collaboration for

food-based analyses of existing cohort studies, where the data are available, could help refine the current state of knowledge. It will be important to address this in future studies to provide clarification regarding the optimum protective level of fruits and vegetables intake, and therefore, be as directly relevant to dietary recommendations and policy as possible.

Conclusions

Many cardiovascular risk factors, including hyperlipidemia, hypertension, obesity, and diabetes are substantially influenced by dietary factors. There is good evidence that a high consumption of vegetables and fruit is associated with a reduced levels of adiposity and consequently a lower risk of hypertension, and type 2 diabetes mellitus. Understanding the relation between fruit and vegetable consumption and CVD is important for guiding consumer education and informing dietary guidelines to reduce cardiovascular risk. The key is to increase the total up to above five daily servings of fruits and vegetables in all forms. Fruit and vegetables should be eaten as part of a balanced diet, as a source of vitamins, fiber, phytochemicals, and water. People should obtain bioactive micronutrients from a wide variety of whole foods for optimal nutrition and health well being, not from dietary supplements, or from foods enriched in cereal or vegetable derived fiber.

Early efforts focused on identifying protective nutrients, for example, vitamin E, vitamin C, and β -carotene, have proven to be disappointing when tested in clinical trials. This is almost certainly owing to the complexity of fruit or vegetables and the large number of bioactive compounds present, and also because of other dietary sources containing these bioactive compounds. Rather, the evidence now suggests that a complicated set of many nutrients interact to influence CVD risk. Therefore, it is important to focus on whole foods and dietary patterns to impact on CVD risk reduction.

Evidence that fruit and vegetable consumption has a protective effect against CVD comes mainly from observational studies. Uncertainty remains about the real magnitude of the relationship between fruit and vegetable intake and the occurrence of CVD. Results from randomized controlled trials do not show conclusively that fruit and vegetable intake protects against CVD, in part because the dietary interventions have not been intensive enough to enable optimal analysis of their putative effects.

Protective mechanisms may involve not only known bioactive nutrients, such as fiber and potassium, but also functional aspects of fruit and vegetable intake, such as low glycemic load and energy density. Taken together, the totality of the evidence accumulated so far does appear to support the notion that increased intake of fruits and vegetables may reduce cardiovascular risk.

The effect of specific classes of fruits and vegetables combined, fruit or vegetables alone, the effect of quantity versus variety of fruits and vegetables consumed and the degree of processing on demonstrated associations remains uncertain. Some of these uncertainties could be answered in future pooling projects.

Future prospects

Because of the physical and biochemical complexity of whole foods, much uncertainty remains regarding the direct relation between fruit and vegetable intake and CVD risk. As fruits and

vegetables are a complex food group, judging biological plausibility of the association demonstrated in observational studies is extremely challenging, so is defining their exact protective mechanism in interventional trials.

Results from the WHO MONICA study show that interpopulation differences are very inadequately explained by the classical cardiovascular risk factors, suggesting that the search for new determinants of vascular risk should be explored further (WHO MONICA project, 1994). A recent randomized clinical trial shows that fruit and vegetable intake in hypertensive patients resulted in a dose-dependent improvement in endothelium dependent forearm blood flow (McCall et al., 2009). Thus, increasing fruit and vegetable consumption is likely to have beneficial effects due to synergistic effects of bioactive compounds that improve the vascular phenotype but may not be readily detected by routine clinical or biochemical examination. Endothelial function is known to be a surrogate measure of vascular function with known diagnostic and prognostic values.

As we continue to identify the roles of nutrients in foods in the complex pathways that contribute to CVD risk and/or prevention, scientists are focusing on genetic modulation of these pathways so that better guidance may be developed for subsets of the population at differential risk. Thus, the use of biological and genetic markers in future studies may help to clarify whether a causal relationship exists between fruit and vegetable intake and CVD risk and/or prevention in a subset of the population in whom interventions would be best targeted. It has recently been shown that there may be genetic variation in the metabolic response to intake of compounds found in fruits and vegetables, such as vitamin C (Timpson et al., 2010) and carotenoids (Borel, 2012).

A recent human nutrigenomics study also confirmed the importance of whole food instead of a single phytochemical (Milenkovic et al., 2011). The effects of orange juice and pure citric phytochemical hesperidin were investigated on the expression of genes in leukocytes in healthy volunteers after consumption of orange juice, hesperidin, or placebo for 4 weeks. Global gene expression profiles were determined using human whole genome cDNA microarrays. Both orange juice and hesperidin consumption significantly affected leukocyte gene expression. Orange juice consumption induced changes in the expression of 3422 genes, hesperidin intake modulated the expression of 1819 genes, and 1582 genes were in common in both groups. Many of the protein products of these affected genes were involved in chemotaxis, adhesion, infiltration, and lipid transport, suggesting lower recruitment and infiltration of circulating cells to vascular wall, lower lipid accumulation, and formation of the atherosclerotic plaque.

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