

# Dietary intake of fruit and vegetables and risk of diabetes mellitus and cardiovascular diseases

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# Dietary intake of fruit and vegetables and risk of diabetes mellitus and cardiovascular diseases

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## 1. Introduction

Despite recent advances in prevention and treatment, cardiovascular disease (CVD) remains a major public health problem in both developed and developing countries. Once considered a disease of the industrialized world, it is now apparent that CVD is a public health menace worldwide. Twice as many deaths from CVDs now occur in developing countries as in developed countries (1). Currently CVDs account for 10.3% of the global burden of disease and 30.9% of mortality (2). Worldwide, approximately 200 million people suffer from CVDs, and diabetes, heart disease and stroke are responsible for nearly 17 million deaths each year, compared to a death rate from HIV/AIDS of 3 million (2-4). Furthermore, five of the top 10 risk factors for noncommunicable disease worldwide are elevated blood pressure, tobacco use, alcohol consumption, cholesterol, and obesity (1). With the exception of moderate alcohol consumption, these factors all act to increase the risk of CVDs.

The worldwide burden of diabetes mellitus has also been increasing rapidly along with increases in obesity and CVDs. In 1985, it was estimated that approximately 30 million people worldwide had diabetes (5); a decade later this estimate had risen to 135 million (6). In 2000, the global burden of diabetes was estimated to be 171 million and this is projected to increase to at least 366 million by the year 2030 (7). A large proportion of this increase is expected to occur in developing countries due to population growth, ageing, lack of physical activity, and obesity. The impact is expected to be greatest in China and India. In addition, rates of type 2 diabetes, associated with insulin resistance and accounting for more than 90% of all cases, are increasing in younger age-groups. Given the increase in diabetes in developing countries and the younger age of incidence, it is predicted that by 2030, the majority of persons with diabetes in developing countries will be aged 45-64 years, hence losing some of their most productive years to disease, disability

or death (6). The feasibility of prevention of diabetes by lifestyle interventions has been demonstrated by studies in China, Canada, the USA, and several European countries in recent years (8-10). Given the prevalence of diabetes and CVDs, preventing even a small proportion of cases would save hundreds of thousands of lives and years of lost productivity, and avoid vast amounts of health-care expenditure.

Diet has long been linked to the development of obesity, diabetes, and CVDs, and dietary modification is one of the cornerstones of chronic disease prevention. The health benefits of a diet rich in fruit, vegetables, and legumes (e.g. beans, peas and lentils, also commonly called pulses and sometimes included as vegetables) have been recognized for some time. There is a substantial amount of evidence that nutrients contained in fruit and vegetables such as dietary fibre, folate, antioxidant vitamins, and potassium, are associated with lower risk of CVDs. However, the precise mechanisms responsible for the effects of these individual nutrients remain poorly understood. Moreover, the examination of single nutrients in relation to CVD-risk may ignore the biochemical complexity of whole foods. Given that dietary advice is easier to understand and implement if provided in terms of whole foods, it is important to examine the direct relationship between whole food intake and the development CVDs and diabetes (11). Research is beginning in this direction with intriguing results which are summarized in this review.

## **2. Issues related to analysis of fruit and vegetable intake**

### **2.1 Dietary assessment of fruit and vegetable intake**

Several different approaches to measuring an individual's dietary intake have been used in prospective epidemiologic studies. Each approach has its advantages and limitations. Methods of dietary assessment generally involve obtaining observations of a participant's food intake, as with the 24-h dietary recall or food record methods, or attempts to get at average or usual food intake by inquiring about the frequency of consumption of different foods (12). Many cohort studies have adopted the food frequency questionnaire (FFQ) to minimize day-to-day variation by assessing average long-term dietary intake and, most importantly, to discriminate individuals' dietary patterns and rank them accordingly (13).

The validity and reliability of FFQs have been assessed using detailed dietary records and suitable biochemical markers and have been reported to be high in cohorts of cooperative participants (13, 14). However, the construction of the food list is a critical element of this method and may affect the validity of results obtained (15). Food lists must be culture-specific in order to provide useful information (16). While the 24-h dietary recall and FFQ are among the most commonly-used methods of dietary assessment in large-scale epidemiologic studies, others include the food record and diet history methods. The food record method involves participants recording a detailed description of all foods consumed within a specified period of time, usually several days. The diet history method involves collecting three forms of dietary information: a detailed interview to assess participants' usual consumption of specific foods, a cross-check food frequency list, and a 3-day dietary record. These methods are described in greater detail on page.

## **2.2 Classification of fruit and vegetables**

The definitions of “fruit” and “vegetables” are not universally agreed upon, but generally include the edible parts of plants. Different types of fruit and vegetables differ widely in their nutrient content and, in recognition of this, national and international agencies recommend fruit and vegetable consumption from diverse groups, frequently based on nutrient content and form. In addition, preparation—frying, peeling, using baking soda in cooking water, and storage conditions—heat, air, light, and humidity, affect the nutrient content of fruit and vegetables. These issues are considered in greater detail on page.

Fruit and vegetables differ in their nutrient content as groups, the manner in which they are prepared and eaten, and the amounts in which they are eaten daily. Such differences have important implications for analysis of fruit and vegetable intake and chronic disease risks. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study of fruit and vegetable intake and cancer risk, fruit and vegetables were analysed separately. It was found that fruit appeared to have more protective associations than vegetables in case-control and cohort studies for several types of cancers. It is possible that the amount and manner in which fruits were consumed across Europe, in contrast to vegetables, may have impacted these results. These aspects of fruit

and vegetable consumption are important considerations in any analysis or review of their effects on chronic disease.

In this review, fruits and vegetables are treated as a combined entity. Many of the studies which provide the basis of this review have combined these two groups of food, although several also provide separate analyses for each. For example, in their investigation of fruit and vegetable intake and glycosylated haemoglobin levels in the population, Sargeant and colleagues included weekly intake of specific types of fresh fruit—apples, oranges, pears, and green leafy vegetables—cabbage and broccoli, and other vegetables—peas, carrots, beans, and tomatoes (17). The atherosclerosis risk in communities (ARIC) study included legumes such as beans, peas and lentils, as well as potatoes (but not fried potatoes) in their vegetable category (18). Similarly, Gillman et al. included legumes, potatoes, and potato chips (fries; frites) in their classification of vegetables (19). Potato differs from all other commonly-consumed vegetables in its energy density (much higher), nutrient density (much lower as a ratio to total energy), glycaemic index and load (much higher), and the likelihood of its presence in fast food (fries or chips). In addition, energy consumed in the form of potato probably exceeds that from all other vegetables in some developed countries. For these reasons, the above studies may seriously underestimate the protective effect of fruit and vegetables, as the potato was not examined separately.

### **2.3 The role of juices**

While juices are frequently included as part of the classification of fruit and vegetables, they are clearly different in form and lack much of the fibre of the whole fruit or vegetable. In addition, they are often sweetened with a variety of substances which contribute to their energy density but not to any protective role in the development of chronic diseases. The role of fruit or vegetable juices as distinct from that of the whole fruit and vegetables has not been well studied. However, the beneficial health effects of consuming fruit and vegetables are attributed, at least in part, to their antioxidant activity which is also present in many fruit juices (20). For example, several studies point to pomegranate juice as a source of protective antioxidant compounds (21). With citrus juices, the vitamin C content has long been considered to protect against oxidative stress and atherosclerotic processes. Other polyphenolic compounds in citrus juices are also being investigated for their potential roles in the prevention of lipid peroxidation and atherosclerosis (22). A recent intervention study supplemented 38 healthy human volunteers with a powdered fruit and vegetable juice concentrate and tested their vasomotor responses after a high-fat meal. After consumption of juice concentrate daily for four weeks prior to testing, the detrimental effect of the high-fat meal was blunted whereas there was no effect of placebo (23). In addition, many juices are rich in potassium which has been shown to reduce blood pressure and may be related a lower risk of stroke. Hence, while juice consumption is less ideal than whole food consumption for the prevention of chronic diseases and obesity, there are many beneficial effects which must also be considered.

### **2.4 Statistical analysis of nutritional data**

Day-to-day variation in an individual's dietary intake about their true mean intake is termed intra-individual variation. Variation between the true mean intakes of individuals within a population is termed inter-individual variation (24). Intra-individual variation in diet has important consequences for the statistical analysis of nutritional data. Using 24-h dietary recall and food record methods, Liu and colleagues demonstrated that reductions in the magnitude of correlation coefficients may occur due to large intra-individual variations in

nutrient intake, which in turn reduces the statistical power of a study to test hypotheses when measurement error due to intra-individual variation is considerable (24). Sempos et al. demonstrated that several days of dietary measurement are generally required to avoid major dilution of the correlation coefficient i.e., biasing the correlation coefficient describing the relationship between a food or nutrient of interest and an outcome of null value (25).

Because of this inherent difficulty with dietary data, the usual criteria for causality must be adjusted in studies of nutritional epidemiology. The magnitude of associations between diet and disease is often small compared to associations in other epidemiologic fields, perhaps because everyone is exposed to food from birth and accurate measurement of the exposure is extremely difficult. It is far more common to find risk estimates of 0.8 to 1.2 rather than twofold or greater. Very strong risk estimates are so uncommon that they may be considered suspicious, but weak associations are also often viewed with caution because they may be explained by bias. However, in nutritional studies, weak associations may have important public health implications because exposures to dietary factors are so common. There is a considerable range of opinion concerning a guideline for judging the strength of association in nutritional studies. Potischman and Weed suggest a statistically-significant risk estimate of at least 20% higher or lower risk to be a positive finding, while a risk estimate of 40-50% higher or lower may be considered a strong finding (26).

## **2.5 Confounding by correlated lifestyles and health habits**

Persons who consume large amounts of fruit, vegetables, legumes, and nutrients such as folate and potassium (much of which is provided by these food items), may have other lifestyle factors which could reduce their risk of CVDs. For instance, persons with high intakes of these foods and nutrients may be more physically active, educated, and less likely to smoke or consume high levels of saturated fat, than their counterparts with lower intakes (13, 27). Most studies of nutritional exposures and disease outcomes adjust for potential confounders such as age, race, sex, level of education, physical activity, cigarette smoking, regular alcohol consumption, and total energy intake. Many studies also adjust for other components of diet, given that other foods or nutrients may also be confounding



factors. For example in the Diet and Nutritional Survey of British Adults, a principal components analysis revealed that people who ate whole-meal bread were more likely to drink low-fat milk and eat more fruit and vegetables, whereas those who ate more white bread were more likely to drink more whole-fat milk and eat more fried foods and less fruit and vegetables (28, 29). Despite these adjustments, as in all observational studies, imperfect measurement of confounding variables and unmeasured potential confounders may still bias study findings.

## **2.6 Intake of nutrients versus whole foods**

While all dietary assessment methods collect information in terms of foods, for a variety of reasons this information is often converted into data on nutrients. The main reason is that the use of data on nutrients relates directly to biological, chemical and metabolic studies (30). In addition, if a particular nutrient is related to disease, as for example, dietary fatty acid composition to coronary disease, analysis of a single food or food group which contributes only modestly to total dietary intake of cholesterol may not demonstrate a relationship to disease (31). One drawback of using nutrients to represent dietary exposure is that the demonstration of a lack of association for a particular nutrient may lead to the incorrect assumption that diet does not contribute to the etiology of a particular disease. Another limitation of the use of nutrient data in analysis is that foods may not be completely represented by their nutrient content values (32).

Representing dietary intake in terms of foods has its own advantages and limitations. Using foods as the exposure of interest is most directly related to dietary recommendations. Because individuals manipulate their diet through food choices, dietary advice phrased in terms of foods is easier for the lay public to understand than the same advice phrased in terms of nutrient intake (11). In addition, recommendations may be made concerning the consumption of particular foods even when the specific beneficial component chemicals remain unknown, as in the case of fruit and vegetable consumption and lung cancer. Epidemiologic studies have shown that a high intake of carotenoids, primarily from yellow-range fruit and green leafy vegetables, is associated with lower rates of lung cancer (33-37). On the other hand, to date, randomized clinical trials of carotene

supplementation have shown either no effect or slightly increased rates of cancer (38-40). Dietary recommendations from government bodies to increase fruit and vegetable consumption are based primarily on observational evidence regarding food intake (30, 41).

Foods are extremely biochemically complex and contain compounds which may interact with one another. Thus although a food or food group contains large amounts of a certain nutrient, the presence of other compounds may decrease the bioavailability of that nutrient. For example, legumes, and in particular dry beans, contain high concentrations of minerals such as iron, but the bioavailability of iron from legumes is poor (42). Therefore, the effect of a particular food in the human body cannot be completely described by the effects of nutrients singly. Although two foods, such as yogurt and milk, may have very similar nutrient values, they can produce different physiological effects (32). Thus ideally, epidemiologic studies of both foods and nutrients should be conducted.

National and international health agencies have developed food-based nutritional guidelines (FBDGs) for many of the reasons noted above. The report of a recent World Health Organization meeting for the purposes of developing dietary guidelines summarizes this reasoning, stating, "There are a number of reasons for developing FBDGs. First, diets are made of foods which are more than mere collections of nutrients. Unlike nutrients, foods and diets have cultural, ethnic, social and family meanings, which can be incorporated into the FBDG. Second, all the biological functions of food components and their health effects have not been identified. If the focus is on a single nutrient, the benefits of the consuming these compounds in foods may not be realized. Third, the combinations of nutrients in various foods can have different metabolic effects. Fourth, methods of food processing and preparation also influence the nutritional value of foods. Finally, there is good evidence from animal, clinical and epidemiological studies which indicates that specific dietary patterns are associated with reduced risk of specific diseases and FBDGs can encourage such practices" (43).

### **3. Potential mechanisms by which fruit and vegetables may protect against CVDs and diabetes**

Many constituents and functional aspects of fruits and vegetables may be responsible for their apparent protective effects on the development of diabetes and CVDs. Among these, the fibre, potassium, folate, and antioxidant content of fruits and vegetables, along with their low glycaemic load and potential to aid in weight management, are likely to contribute most to their effects on risk of diabetes and CVDs. Other components of fruit and vegetables, such as minerals and phytochemicals, may also play a role in the prevention of chronic diseases. The mechanisms by which these constituents may contribute to reducing the risk of CVDs and diabetes are reviewed in this section.

### 3.1 Fibre

Fruit, vegetables, and cereals are the major sources of dietary fibre. Dietary fibre has been shown to delay the absorption of carbohydrates after a meal and thereby decrease the insulinemic response to dietary carbohydrates (44). In one multicentre study of 2909 healthy young adults aged 18–30 years, after adjustment for confounding factors, dietary fibre intake was strongly and inversely associated with body weight, waist-to-hip ratio, fasting insulin levels, and 2-h post-glucose insulin levels (45). In addition, several large prospective cohort studies have shown inverse associations between dietary fibre and risk of developing type 2 diabetes (46–51). Data from the Health Professionals Follow-up Study and from the Nurses Health Study support an inverse association between dietary fibre and the development of diabetes (46, 47). In these two studies, investigators found a stronger association for cereal fibre than for fibre from fruit and vegetables. Meyer et al. found a similar inverse association in the Iowa Women's Health Study (50). In this prospective cohort study of 35 988 older women in Iowa, USA, initially free of diabetes, who were followed for six years, multivariate-adjusted relative risks (RR) of diabetes were 1.0, 1.09, 1.00, 0.94, and 0.78 across quintiles of total dietary fibre intake ( $p$ -value for trend < 0.01). Stronger associations for cereal fibre as compared to fruit and vegetable fibre sources were also found. More recently, two large prospective cohort studies have also reported inverse associations between dietary cereal fibre intake and risk of developing type 2 diabetes (51, 52). Using data from the Atherosclerosis Risk in Communities study, Stevens and colleagues failed to find an association between fibre from fruit and vegetable sources and

diabetes risk among 12 251 American adults aged 45-64 years; only fibre from cereal grains was associated with lower risk of diabetes (51). Researchers in Finland found an association between intake of dietary fibre from cereal grains and development of type 2 diabetes among 2286 men and 2030 women followed for 10 years but they did not examine the relationship of dietary fibre from fruit or vegetable sources and type 2 diabetes (52). It is important to note that most if not all of these studies adjusted for the effects of body mass index (BMI) and other factors which might have obscured an independent effect of dietary fibre on the development of type 2 diabetes. Nevertheless, fibre increases satiety, reduces hunger, and decreases energy intake and hence contributes to weight control and avoidance of obesity (53). Given that obesity is arguably the most potent risk factor in the development of type 2 diabetes, the effects of dietary fibre due to its role in weight management were overlooked in most if not all of these investigations.

Several prospective studies have identified a significant inverse association between dietary fibre intake and risk of coronary heart disease (54-59). As mentioned above, dietary fibre blunts the body's insulinemic response to carbohydrates (44). Experimental studies have also shown that higher levels of insulin may promote dyslipidemia, hypertension, abnormalities in blood-clotting factors, and atherosclerosis (60). In addition, water-soluble dietary fibre has been shown to decrease both total and low-density lipoprotein (LDL) cholesterol while not affecting levels of high-density lipoprotein cholesterol (61). While the cholesterol-lowering effects of dietary fibre are usually thought to be modest, they may play a role in the inverse association between intake of fibre and risk of CVDs. Moreover, recent studies have suggested inverse associations between dietary fibre and other CVD risk factors such as blood pressure, waist-to-hip ratio, fasting blood insulin concentration, 2-h post-glucose blood insulin concentration, concentrations of triglycerides and of fibrinogen (45). Dietary fibre is also associated with lower blood pressure in observational studies (62). In randomized controlled trials, dietary fibre supplementation has been shown to reduce blood pressure by small but significant amounts (63).

### **3.2 Glycaemic Load**

Another important functional aspect of whole fruits and vegetables is their low glycaemic index and glycaemic load (64). The glycaemic index of a food compares the glucose-raising potential of equal amounts of carbohydrate but it does not capture the quantity of carbohydrate in a food serving. The glycaemic load, the product of the glycaemic index value of a food and its total carbohydrate content, captures both aspects of the glucogenic potential of a food (65). Since the introduction of the glycaemic index in 1981, the role of carbohydrates in the development of type 2 diabetes has been thought to depend less on the size and structure of the molecules and more on the body's glycaemic response to different carbohydrates (66). For example, while the carbohydrate in carrots has a high glycaemic index, a carrot contains a relatively small amount of carbohydrate, so the food as a whole, has a moderate glycaemic load.

A diet with a low glycaemic index has been associated with lower risks of type 2 diabetes and coronary heart disease in prospective studies (65, 67). In feeding trials of humans, a low glycaemic index diet has also been associated with prolonged satiety responses (68, 69) which may further aid in weight control. A recent review identified at least 15 studies demonstrating increased satiety, delayed return of hunger, or decreased food intake after consumption of foods with a low, rather than high, glycaemic index (68). The rich fibre 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 and their content of enzyme inhibitors may also play an important role.

Few epidemiologic studies have examined directly the role of type and amount of carbohydrate in relationship to the development of hyperglycaemia or type 2 diabetes. Those which have, generally found little association between total carbohydrate intake or intake of simple sugars and the development of diabetes (46, 50, 70-73). One exception, the Iowa Women's Health Study, found that intake of glucose or fructose was significantly and positively related to the risk of developing type 2 diabetes (50).

Several large prospective cohort studies have examined the relationship between glycaemic index or load and risk of developing type 2 diabetes (46, 47, 50, 74). On the whole, people with diets in the highest range of glycaemic index or load were significantly more likely to develop type 2 diabetes than those with diets in the lowest ranges. For example, in the Nurses Health Study (47), the RR of developing type 2 diabetes was 1.47

(95% confidence interval (CI), 1.16–1.86) comparing the highest and the lowest quintile of dietary glycaemic load. Similarly, in the Health Professionals Follow-up Study (46), the RR of developing type 2 diabetes was 1.37 (95% CI, 1.02–1.83) comparing the extreme quintiles of dietary glycaemic load. However, two large prospective studies found no relationship between dietary glycaemic index or glycaemic load and risk of developing type 2 diabetes (50, 51). This lack of association may have been related to the methods of diet assessment used. On the whole, the evidence suggests that the replacement of high glycaemic index foods in the diet by fruit and vegetables may have a wide range of beneficial public health consequences, including reduced risks of obesity, coronary heart disease and development of type 2 diabetes.

### 3.3 Fructose

Fructose is unlikely to be one of the nutrients in fruit and vegetables that contributes significantly to their protective effects; however it does bear discussion given recent studies of its relationship to chronic disease. In the 1970s fructose, particularly in the form of high-fructose syrup manufactured from starch, began to be used as a replacement for sucrose in beverages and baked goods. Today the majority of fructose consumed is in the form of high-fructose corn syrup (75). Sorbitol and mannitol are used in a variety of food products because they have fewer calories per gram than do either sucrose or fructose; in the liver they are readily converted to fructose. Fructose bypasses the phosphofructokinase regulatory step of glycolysis, in which glucose can be converted to glycogen rather than entering the glycolytic pathway. As a result, fructose increases hepatic pyruvate and lactic acid production, activates pyruvate dehydrogenase, and shifts the balance from oxidation to esterification of fatty acids, which can increase very-low-density lipoprotein synthesis (76). In addition, fructose stimulates less insulin secretion from pancreatic beta cells and causes a lesser rise in postprandial insulin concentrations than glucose-containing carbohydrates. Leptin is regulated by insulin responses to meals, hence lowering circulating leptin and insulin in individuals who consume high fructose diets could increase the likelihood of weight gain and its associated metabolic sequelae (77). In feeding studies, the effects of fructose on plasma triglyceride levels have been found to be inconsistent. This may be due

to factors such as the amount of fructose consumed, energy balance, and baseline triglyceride, insulin, and glucose levels (78). The postprandial rise in triglyceride levels after fat intake may be augmented with the addition of fructose to a test meal (79). However, a study in individuals with type 2 diabetes showed a lack of significant variation in glucose, lipid, and insulin responses to three 28-day isocaloric feeding periods when 20% of calories were either fructose, sucrose, or starch (80).

Fructose in fruit and vegetables is unlikely to cause any of the disturbances in lipid or blood glucose described above. This is because accompanying nutrients such as fibre, phytochemicals and antioxidants are delivered in conjunction with fructose in the form of a whole fruit or vegetable. For most individuals consuming fructose in whole fruits and vegetables rather than fructose-sweetened baked goods and beverages, postprandial rises in glucose may be blunted, and insulin levels may remain more constant than after consumption of other sugars.

### **3.4 Folate**

Folic acid and vitamin B<sub>12</sub> are important for the metabolism of homocysteine. Dietary intake of folate has been shown to be inversely associated with plasma concentrations of homocysteine (81) and elevated homocysteine concentrations have been related to an increased CVD risk (82, 83). Moreover, folate itself may have vasculo-protective effects (84). In a randomized trial, supplementation of the diet with folic acid and vitamin B<sub>6</sub> was shown to reduce markers of endothelial dysfunction and the progression of subclinical atherosclerosis (85). Both dietary and serum folate concentrations have been inversely associated with mortality from CVD (86-89). More recently, an inverse association between dietary folate intake and stroke incidence was demonstrated in a representative sample of the adult population in the USA (90). Thus, increased folic acid intake may be an important aspect of the apparent protective effect against CVDs of a high intake of fruits and vegetables.

### **3.5 Antioxidants**

Antioxidants are substances that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative damage. Atherosclerosis is thought to proceed in part due to the oxidation of lipids in plaque formation. Fruits, including berries, and vegetables are rich sources of antioxidants such as vitamin E, vitamin C, polyphenols, flavonoids, and carotenoids which may help prevent atherosclerosis and subsequent ischaemic heart diseases. However, dietary supplements of specific antioxidants, including vitamins C, E, and beta-carotene, when tested in randomized controlled trials did not on the whole show significant benefit in secondary prevention of CVDs (91).

Recently, other antioxidant compounds such as lycopene and flavonoids have received further attention (21, 92, 93). Dietary lycopene, which is derived in large part from tomato products, was significantly and inversely associated with RR of CVDs in a cohort of 39 876 middle-aged women (94). Flavonoid intake was measured by Yochum and colleagues in 34 492 postmenopausal women in Iowa, USA. After 10 years of follow-up, participants in the highest quintile of flavonoid intake had the lowest risk of death from ischaemic heart disease (93).

Berries are particularly rich in phenolic compounds, and play an important role in fruit consumption in many countries. Polyphenolic compounds from pomegranate juice have been shown to inhibit LDL cholesterol peroxidation, and addition of pomegranate juice to the diet fed to atherosclerotic mice has been shown to inhibit significantly the development of plaques and streaks in these animals (21).

Some research suggests that antioxidants may protect against diabetes mellitus (95-99). Vitamin C intake has been inversely related to the incidence of diabetes and impaired glucose tolerance in a cohort study (100). One study showed that intake of vitamin E, commonly found in vegetable and seed oils, was inversely related to the incidence of diabetes mellitus (101) but another study failed to find a significant association after adjustment for various risk factors (102). Antioxidants ingested in whole foods such as fruit and vegetables and in juices may act in combination with each other and/or other phytochemicals within the foods to provide their protective effects.

### **3.6 Potassium**



Potassium may play an important role in the effect that fruit and vegetable consumption has on the incidence of, and mortality from, CVDs. Epidemiological studies have identified an inverse association between dietary intake of potassium and blood pressure within and across populations (103). In addition, randomized controlled trials have shown that potassium supplementation lowers blood pressure in both hypertensive and normotensive persons (104). Conversely, a low dietary potassium intake has been associated with elevated blood pressure. In a randomized, cross-over trial of potassium depletion in 10 normotensive men, those fed a low potassium diet (10 mmol/day) had significantly increased mean arterial blood pressure (4 mmHg increase,  $p < 0.05$ ) (105). In a second randomized, cross-over trial of dietary potassium depletion (potassium consumption from 96 mmol/day to 16 mmol/day) in 12 hypertensive subjects, the same research group reported significant increases in blood pressure, both systolic (7 mmHg increase,  $p = 0.01$ ) and diastolic (6 mmHg increase,  $p = 0.04$ ), after the low potassium diet (106). Such evidence suggests that a diet rich in fruit and vegetables and hence high in potassium may protect against increased risk of stroke through lowering blood pressure.

Several studies have reported an inverse relationship between potassium intake in the diet and risk of stroke or CVDs. Xie and colleagues conducted an ecologic analysis which indicated an inverse relationship between 24-h urinary excretion of potassium and stroke mortality among 27 population groups (107). In a population of 859 male and female retirees in southern California, USA, Khaw and Barrett-Conner identified a strong inverse association between potassium intake and stroke mortality (108). Ascherio and colleagues also documented an inverse relationship between the risk of stroke and dietary potassium intake in a cohort of 43 738 male health professionals (109). In the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study (NHEFS), dietary potassium was inversely associated with risk of stroke after adjustment for established CVD risk factors (110).

### **3.7 Magnesium**

Fruit and vegetables are also rich in micronutrients and minerals such as magnesium, which may lower the risk of developing diabetes mellitus (46, 71). Magnesium plays an important

role in insulin action, and hypomagnesaemia is well recognized in persons with diabetes (111). Hypomagnesaemia may impair insulin secretion and promote insulin resistance in the diabetic patient (112). In addition, magnesium intake and blood concentrations of magnesium have been found to be inversely related to insulin concentrations in population-based studies (50, 113, 114).

### **3.8 Summary of potential mechanisms**

In summary, while each of the components described in the sections above may play a role in protecting against CVDs, it is their combined effects that are seen in a diet rich in whole fruits and vegetables. The biochemical complexity of fruit and vegetables as delivery systems for protective nutrients and functional components should not be underestimated. Hence, in any dietary recommendation to prevent CVDs and type 2 diabetes it is important to emphasize the consumption of whole fruits and vegetables rather than specific nutrients or supplements.

## **4. Effects of fruit and vegetable intake on risk factors for CVD and diabetes**

### **4.1 Obesity**

The potential role of fruit and vegetables in the management of obesity has been reviewed briefly above and more thoroughly in a companion manuscript. Obesity has increased to epidemic proportions worldwide with more than 1 billion adults classified as overweight, and at least 300 million of these obese as defined by a BMI score of 30 or more (115). Obesity is one of the most prevalent risk factors for chronic diseases such as CVDs (including both stroke and ischaemic heart disease) and diabetes, and has long been recognized as one of the strongest risk factors for the development of type 2 diabetes. It has been estimated to account for 60 to 90% of the variance (116, 117).

Several prospective studies in widely different populations have demonstrated a strongly positive association between BMI, weight gain and the subsequent development of type 2 diabetes (118). Colditz and colleagues found that the risk of type 2 diabetes was increased nearly 90-fold among female nurses who were morbidly obese (BMI  $\geq$  35) at 30 to 55 years of age but of normal weight (BMI  $<$  22) at 18 years of age (118). In addition, many studies have demonstrated that weight loss improves glycaemic control in diabetic individuals and can lead to a remission of diabetes in a few (119-121). Studies examining the effects of energy-restricted diets in people with type 2 diabetes have shown that fasting

hyperglycaemia declines rapidly within the first week and is accompanied by reductions in hepatic glucose production, even before significant weight loss occurs (122, 123). Anderson and colleagues combined the results of 10 studies of obese type 2 diabetics who were treated for four to six weeks with very low-energy diets (121). Over the course of these studies, subjects lost approximately 10% of their body weight and their fasting plasma glucose values decreased by about half after two weeks and remained there for the remainder of the observation period. However, weight loss on these diets was often not sustained and the quality of glycaemic control decreased as weight was regained.

More recent prospective studies of sustained weight loss and development of type 2 diabetes suggest that even modest weight loss is associated with a significantly reduced diabetes risk (124, 125). This type of evidence suggests that obesity and excess energy consumption are perhaps the most important contributing factors to the risk of developing type 2 diabetes. Thus, even minor weight reductions may have major beneficial effects on subsequent diabetes risk in overweight individuals.

## **4.2 Lipids**

Fruit, vegetables, and legumes have been shown to decrease LDL cholesterol concentrations in humans. In the Dietary Approaches to Stop Hypertension (DASH) trial, a diet high in fruit and vegetables was associated with a reduction in LDL cholesterol compared to a control diet. However the association did not reach standard levels of statistical significance (126). In the Indian Diet Heart Study, fruit and vegetable consumption decreased LDL cholesterol concentrations by approximately 7% (127). In a randomized trial among persons who had suffered acute myocardial infarction, a reduction in LDL cholesterol was shown to occur after 12 weeks of fruit and vegetable intake (128). More recently, in the US National Heart, Lung, and Blood Institute Family Heart study, the consumption of fruits and vegetables was inversely related to LDL cholesterol concentrations in men and women (129). Beans, peas, and other legumes have also been shown to lower cholesterol levels. In a meta-analysis of 29 clinical trials (130) soybean protein has been shown to reduce total and LDL cholesterol concentrations in serum. Legume intake other than soybean has also been associated with a reduction in serum

cholesterol in clinical studies (131-136). A meta-analysis of 11 clinical trials examining the effects of legumes other than soybeans demonstrated a 7.2% reduction in total cholesterol, 6.2% reduction in LDL cholesterol, and a 16.6% reduction in triglycerides with no effect on HDL cholesterol (137). Legumes are a significant source of soluble fibre which may be partially responsible for their cholesterol-lowering effects. One half cup of cooked beans contains on average 6 g total fibre and 2 g soluble fibre, which is the same amount of soluble fibre and more total fibre than that contained in one third of a cup of dry oat bran (138). Other constituents of legumes including oligosaccharides, isoflavones, phospholipids, saponins, and known and unknown phytochemicals may also be part of the cholesterol-lowering effects of these foods (137).

### 4.3 Hypertension

Dietary modification has long been known to aid in the control of hypertension, and fruit and vegetable intake in particular has been shown to reduce blood pressure in a variety of settings, including randomized controlled trials (139-141). Several decades ago, it was noted that people on vegetarian diets had consistently lower blood pressure than those with omnivorous diets (142). In trials of vegetarian diets, replacing animal products with vegetable products reduced blood pressure in normotensive and hypertensive adults (139, 141). However, fewer investigations have specifically examined whole fruit and vegetable intake and hypertension. A recent report of 1710 men, aged 41–57 years and followed for 40 years, demonstrated that intake of fruit and vegetables was inversely associated with an age-related rise in blood pressure over the course of the study (143).

The recent randomized controlled DASH trial showed that a diet supplemented with fruit and vegetables lowered blood pressure in a multiethnic population. In the study, 459 adults with systolic blood pressure < 160 mmHg and diastolic blood pressure 80–95 mmHg were randomly assigned to receive the control diet, a diet rich in fruit and vegetables, or a combination diet rich in fruit, vegetables, and low-fat dairy products with reduced saturated and total fat, for eight weeks (140). Sodium intake and body weight were maintained at constant levels. The fruit and vegetable diet reduced systolic blood pressure by 2.8 mmHg ( $p < 0.001$ ) and diastolic blood pressure by 1.1 mmHg ( $p = 0.07$ ) compared to the control

diet. The combination diet resulted in even greater reductions in systolic and diastolic blood pressures.

Singh and colleagues conducted a randomized controlled trial examining the effects of supplementing guava fruit in the diet of 72 participants (144). They found a significant decrease in mean systolic and diastolic pressures (7.5/8.5 mmHg net decrease, respectively) among participants on the guava-supplemented diet. Several studies have combined increases in fruit and vegetables with other dietary interventions, weight loss, and increases in physical activity, thus obscuring the specific effects of fruit and vegetable intake on blood pressure (145).

## **5. Fruit and vegetable intake and risk of CVD – review of prospective studies**

### **5.1 Search strategy and inclusion criteria for literature review**

This review focuses on prospective evidence including those cohort studies reviewed previously. Data from prospective cohort studies have the advantage of temporality in long periods of follow-up, and suffer less from information bias than that of case-control studies. This review set out to include all individual level, prospective studies where the primary outcome was documented CVDs (specifically, ischaemic heart disease or stroke) and exposure was a fruit or vegetable intake as a whole food or food group rather than a biomarker or nutrient. Studies of total mortality or mortality due to CVD other than stroke or ischaemic heart disease were not included. Studies of adults of both sexes were included. Children were excluded as documented CVD from atherosclerotic mechanisms is rare in this population except in those with genetic defects of metabolism.

In order to identify prospective studies of fruit and vegetable intake and CVD, a MEDLINE search was conducted using the MeSH terms “vegetables” and “fruit” to identify studies that mapped to either of these subject headings with exploded focus, and combined these with the term “cardiovascular diseases” also with exploded focus to include all subheadings. The searches were limited to human studies published in English. This strategy yielded 296 references which were then evaluated for inclusion.

Studies were included if they were prospective and reported a measure of association (standardized mortality ratio, RR, odds ratio (OR), or hazard ratio) between whole food intake (rather than biomarker or nutrient intake) and CVD. When studies meeting these criteria were identified, their bibliographies were also searched, and other articles which appeared appropriate for this review were obtained. Table 1 summarizes the available prospective studies which examine the relationship between fruit and vegetable consumption as whole foods and risk of ischaemic heart disease. Table 2 summarizes the available prospective studies of fruit and vegetable consumption in relation to stroke.

## 5.2 Previous reviews

On the whole, ecologic and case-control studies focusing on fruit and vegetable consumption in relation to CVD risk in non-vegetarian populations have consistently shown inverse associations (146-155). The evidence regarding fruit and vegetable intake and CVD has been reviewed previously by Ness and Powles in 1997 (155), and that regarding fruit and vegetable intake and stroke was reviewed by the same authors in 1999 (156). Subsequently, several large prospective cohort studies have also identified an inverse association between intake of fruit and vegetables and CVD. In 1997, Ness and Powles (155) identified only five prospective studies (19, 157-161) that examined fruit and vegetable intake as whole foods rather than nutrients (e.g. fibre from fruit or vegetable sources, vitamin C) or phytochemicals (e.g. carotenoids, flavonoids) in relation to CVD. Of those, three showed significant inverse associations (19, 157-159), while the other two (160, 161) showed no significant association. Small sample sizes and low event rates may partially explain these inconsistent findings.

## 5.3 Prospective evidence

Since the review by Ness and Powles (155), nine prospective cohort studies have been conducted relating intake of fruit and vegetables to ischaemic heart disease. Of those, four found significant inverse associations (162-165), while five found inverse associations which tended toward, but did not reach, statistical significance after appropriate adjustment

(18, 93, 166-168). Eight prospective cohort studies evaluating intake of fruit and vegetables and risk of stroke have been conducted since the review by Ness and Powles (156), and of these, five found significant inverse relationships between fruit and vegetable consumption and risk of stroke (162, 169-172), and three had inverse findings that tended toward significance (18, 173, 174).

In a study of 4336 male and 6435 female participants in the United Kingdom recruited through health food shops, vegetarian societies and magazines, Key and colleagues found that the daily consumption of fresh fruit was associated with significantly reduced mortality from ischaemic heart disease (RR, 0.76; 95% CI, 0.60–0.97), stroke (RR, 0.68; 95% CI, 0.47–0.98), and for causes combined (RR, 0.79; 95% CI, 0.70–0.90), after adjustment for smoking (175). Participants in this study were followed for an average of 17 years and 43% were vegetarian.

Results from the Nurses Health Study and Health Professionals Follow-up Study showed a 31% lower risk (RR, 0.69; 95% CI, 0.52–0.92) of ischaemic stroke for persons in the highest quintile of fruit and vegetable intake (median 9.2 servings per day among men, 10.2 servings per day among women) compared to those in the lowest quintile of intake (median 2.6 servings per day among men, 2.9 servings per day among women) after adjustment for age, smoking, alcohol, family history of myocardial infarction, BMI, supplement use, physical activity, hypertension, hypercholesterolemia, total energy intake, and among women, postmenopausal hormone use (169). A significant inverse relationship was also found for coronary heart disease, with a 20% lower risk (RR, 0.80; 95% CI, 0.69–0.93) for coronary heart disease seen among persons in the highest quintile of fruit and vegetable intake as compared with those in the lowest (165). This was a well-designed study with a very large sample size and repeated measures of validated, semi-quantitative dietary assessment. In addition, participants generally consumed a large number of servings of fruit and vegetables per day and there was a wide range in their dietary habits.

In a study of 730 men born in 1913 and followed in later life for 16 years, frequent fruit, but not vegetable, consumption (6–7 times per week) was associated with significantly lower risk of total mortality (RR, 0.87; 95% CI, 0.76–0.96) than infrequent fruit consumption (0–1 time per week) after adjustment for smoking, hypertension, and serum cholesterol concentrations (176). CVD mortality was lower in the group with more



frequent consumption of fruit and vegetables in univariate analyses; however the relationship was not statistically significant after multivariate adjustment. It should be noted that food habits were assessed with a FFQ at baseline and were not updated during the study. Also, the very small sample size may have limited the power of the study.

A study of 9608 male and female participants in the NFEHS followed for an average of 19 years found an independent inverse association between frequency of fruit and vegetable intake and risk of CVDs (162). Fruit and vegetable intake at least three times per day compared with less than once per day was associated with a 27% lower risk of stroke (RR, 0.73; 95% CI, 0.57–0.95; *p*-value for trend = 0.01), a 42% lower stroke mortality (RR, 0.58; 95% CI, 0.33–1.02; *p*-value for trend = 0.05), a 24% lower ischaemic heart disease mortality (RR, 0.76; 95% CI, 0.56–1.03; *p*-value for trend = 0.07), a 27% lower CVD mortality (RR, 0.73; 95% CI, 0.58–0.92; *p*-value for trend = 0.008), and a 15% lower all-cause mortality (RR, 0.85; 95% CI, 0.72–1.00; *p*-value for trend = 0.02), after adjustment for established CVD risk factors including age, sex, ethnicity, education, smoking status, regular alcohol intake, physical activity, diabetes, hypertension, and serum cholesterol levels. However this study used a single 24-h recall which is less likely to be representative of usual fruit and vegetable intake, and lacked portion size information.

In the Women's Health Study of 39 876 female health professionals, in women in the highest quintile of fruit and vegetable intake (median servings/day 10.2) the RR of CVD was 0.68 (95% CI, 0.51–0.92; *p*-value for trend = 0.01), and of myocardial infarction was 0.47 (95% CI, 0.28–0.79; *p*-value for trend = 0.004), after adjustment for age, smoking, and randomized treatment status (167). There was a significant linear trend across quintiles indicating a dose–response relationship for increasing fruit and vegetable intake. However, further adjustment for known CVD risk factors including diabetes, hypertension, and serum cholesterol among others, attenuated the statistical significance of the RR estimates.

Among a cohort of 15 220 men enrolled in the Physicians Health Study, a randomized controlled trial of aspirin and beta-carotene in the prevention of CVD, participants who consumed at least 2.5 servings per day of vegetables (mainly green leafy) had a 23% lower risk of coronary heart disease (RR, 0.77; 95% CI, 0.60–0.98) than those consuming less than one serving per day, after adjustment for age, randomized treatment,

BMI, tobacco use, alcohol intake, physical activity, diabetes, hypertension, hypercholesterolaemia, and use of multivitamins (164). Design limitations of the study prevented the examination of fruit intake and CVD in this cohort.

An examination of the seasonal consumption of salad vegetables and fresh fruit in relation to the development of CVD in 1489 men and 1900 women aged 35–75 years followed for six years in the United Kingdom found a protective role for frequent salad vegetable consumption at any season among women (OR winter 0.76, 95% CI 0.65–0.89; OR summer 0.76, 95% CI 0.65–0.89) and frequent fruit consumption in women (OR winter 0.84, 95% CI 0.74–0.94; OR summer 0.85, 95% CI 0.74–0.97) (163). Among men, frequent winter salad vegetable consumption was more closely protective than summer (OR winter 0.85, 95% CI 0.72–1.00; OR summer 0.95, 95% CI 0.82–1.10). There was no protective association for fruit consumption in men. This may be due to the smaller amounts of fruit consumed by men than women.

Rissanen and colleagues evaluated the relationship between fruit and vegetable intake and CVDs among 2641 men in Finland aged 42–60 years who were followed for an average of 13 years (168). After adjustment for major CVD risk factors, the RR of all-cause mortality and CVD-related mortality for participants in the highest quintile of fruit, berry and vegetable intake was 0.66 (95% CI, 0.50–0.88) and 0.59 (95% CI, 0.33–1.06) respectively, compared with men in the lowest quintile.

Using data from the ARIC study of 15 792 men and women in the USA followed for 11 years, Steffen and colleagues found a strong inverse association between fruit and vegetable intake and all-cause mortality (18). RRs (95% CI) of mortality for quintiles of fruit and vegetable intake were 1.08 (0.88–1.33), 0.94 (0.75–1.17), 0.87 (0.68–1.10), and 0.78 (0.61–1.01), respectively;  $p$  for trend = 0.02. An inverse association between fruit and vegetable intake and CVD was observed among African Americans but not among whites ( $p$ -value = 0.01). In this study, the risk of ischaemic stroke was not significantly related to fruit and vegetable consumption. On average, intake of fruit and vegetables was higher among nurses, male health professionals and men in the Framingham studies (19), all of which showed inverse associations with ischaemic stroke, than among participants in the ARIC study. In addition, potato was included as a vegetable in the ARIC study.

#### **5.4 Potential impact of increased fruit and vegetable intake on CVD risk**

Taken as a whole, these data support the hypothesis that fruit and vegetables may play an important role in dietary strategies for the prevention of ischaemic heart disease and stroke. Recent estimates of the potential contribution of increased fruit and vegetable intake to health gain in various countries have ranged from 8000 CVD deaths prevented annually in the population of the Netherlands (177) to 26 000 deaths before the age of 65 years annually in the European Union as a whole (in 2001) (178). Across studies, the risk of ischaemic heart disease is about 15% lower at the 90<sup>th</sup> than the 10<sup>th</sup> percentile of fruit and vegetable consumption (179). Figure 1 shows a summary measure of the recent studies of fruit and vegetable intake and risk of ischaemic heart disease. Figure 2 shows a summary measure of studies examining the association between fruit and vegetable intake and risk of stroke.

## **6. Fruit and vegetable intake and risk of diabetes mellitus – review of epidemiological studies**

### **6.1 Search strategy and inclusion criteria**

The same search criteria described for identification of studies relating fruit and vegetable intake and CVDs were adapted for use in identifying studies relating to diabetes. No emphasis was placed on identifying prospective studies regarding diabetes; the aim was to include all individual level studies (cross-sectional, case-control, prospective cohort studies) where the primary outcome was diabetes mellitus, glycosylated haemoglobin or blood glucose, and exposure was fruit or vegetable intake as a whole food or food group rather than biomarker or nutrient. In order to identify studies of fruit and vegetable intake and diabetes mellitus, a MEDLINE search was conducted using the MeSH terms “vegetables” and “fruit” to identify studies that mapped to either of these subject headings with exploded focus, and combined these with the term “diabetes mellitus” also with exploded focus to include all subheadings. The searches were limited to human studies published in English. This strategy yielded 62 references which were then evaluated for inclusion.

Studies were included if they reported a measure of association (standardized mortality ratio, RR, OR, beta coefficient) between whole food intake, rather than biomarker or nutrient intake, and diabetes mellitus, glycosylated haemoglobin, or blood glucose. Studies of children were excluded. When studies meeting these criteria were identified, their bibliographies were also searched, and other articles which appeared appropriate were obtained for this review.

## 6.2 Epidemiological evidence

A small but growing body of evidence links a diet rich in fruit and vegetables with a lower risk of developing type 2 diabetes mellitus. This link was first noted among vegetarians. Snowdon and colleagues examined diet in relation to diabetes among a population of 25 698 adult Seventh-day Adventists. In this population, vegetarians were half as likely as omnivores to develop diabetes over the course of 21 years' follow-up (180). Fruit and vegetable intake was subsequently associated with lower risks of diabetes in non-vegetarian populations as well. Table 3 lists the studies of this association identified and discussed in this literature review.

Several cross-sectional studies have suggested that a higher intake of fruit and vegetables protects against development of diabetes. A population-based study in the United Kingdom examined the association between fruit and vegetable intake and abnormal glucose tolerance in 1122 middle-aged men and women without known diabetes (181). All participants underwent a glucose tolerance test and had their food consumption assessed using a FFQ. Non-obese participants who reported frequent intake of salad and raw vegetables throughout the year had significantly lower prevalence of type 2 diabetes and abnormal glucose tolerance test results than those who reported infrequent consumption (OR, 0.18; 95% CI, 0.04–0.81) after adjustment for age, sex, and family history. Associations with fruit consumption were not significant in this study. However in another cross-sectional study of 5996 middle-aged participants not known to have diabetes, Sargeant et al. observed a direct association between fruit and vegetable consumption and concentrations of glycosylated haemoglobin (17). Participants who reported frequent consumption of fruit and green leafy vegetables had significantly lower mean percent glycosylated haemoglobin concentrations (5.34%; standard error (se), 0.01) than their counterparts who reported seldom or never consuming these foods (5.41%; se, 0.03;  $p = 0.046$ ) after adjustment for age, sex, BMI, waist–hip ratio, energy intake, family history, tobacco use, alcohol intake, education, physical activity, supplement use, and vegetarian diet. The relationship remained significant after further adjustment for dietary intake and plasma concentration of vitamin C, saturated fat intake, and fibre intake. Similar results were found among patients with type 1 diabetes.

Fewer prospective studies have directly related intake of fruit and vegetables to risk of type 2 diabetes. In a cohort of 338 European men followed for 30 years, higher consumption of vegetables and legumes was inversely associated with impaired glucose tolerance, as substantiated by 2-h blood glucose concentration (100). However the results were obtained using multivariate linear regression to predict 2-h post-load glucose rather than a RR of diabetes. Hence these results are less readily comparable to other studies.

Results from the Nurses Health Study showed an inverse relationship between intake of vegetables and development of diabetes, but no association with fruit (71). Non-obese women ( $BMI \leq 29$ ) in the highest quintile of vegetable intake ( $\geq 2.9$  servings per day) had a 24% lower risk (RR, 0.76; 95% CI, 0.50–1.16) of developing type 2 diabetes when compared with those consuming  $< 1.2$  servings per day. This study has the largest sample size of the available studies and used a validated FFQ with repeated measurements.

A significant inverse relation between intake of fruit and vegetables and diabetes risk was observed in women enrolled in NHEFS in the USA (182). Among the 5791 women participants, those consuming five or more servings of fruit and vegetables per day had a significantly lower risk (RR, 0.61; 95% CI, 0.42–0.88) of developing diabetes than those consuming none. However, associations of fruit and vegetable intake with diabetes incidence were not significant among men in this study (RR, 1.14; 95% CI, 0.67–1.93). A single dietary recall was used as the measure of dietary assessment in this study; the limitations of single 24-h dietary recalls are well-known and include significant misclassification of usual intakes. In addition, total energy intake was not included in the adjustment scheme and is likely to have affected results.

The results from these prospective investigations regarding fruit and vegetable intake and risk of diabetes are not entirely consistent. For instance, evidence from the Iowa Women's Health Study did not show an association between fruit and vegetable consumption and the incidence of diabetes over six years of follow-up (50). However, in this study, only a single dietary assessment was obtained. Questionnaires and death certificates were used to identify end-points rather than oral glucose tolerance tests or blood glucose concentrations used in other studies. In addition, BMI and waist-hip ratio were both included in the above models which may lead to over-adjustment for obesity. In a randomized trial of three strategies for diabetes prevention in China involving 577

participants with impaired glucose tolerance, those assigned to a diet with emphasis on higher intake of fruit and vegetables experienced a 24% lower incidence of type 2 diabetes than the control group during six years of study follow-up (8).

In summary, results of the available studies support a role for fruit and vegetables in the prevention of type 2 diabetes independently of other dietary and lifestyle factors. Large randomized controlled trials which specifically evaluate the efficacy of fruit and vegetables independent of other factors in the prevention of type 2 diabetes may not be feasible at present. Therefore, additional larger and high-quality prospective cohort studies are needed to evaluate the effectiveness of intake of general and specific types of fruit and vegetables in the prevention of type 2 diabetes.

## **7. Conclusions**

### **7.1 Summary of evidence**

Since the reviews by Ness and Powles (155, 156) which identified five prospective studies in which intake was measured in terms of whole fruit and vegetables, nine prospective cohort studies relating intake to ischaemic heart disease and eight prospective cohort studies evaluating intake and risk of stroke have been conducted. Five prospective cohort studies of the relationship between fruit and vegetable intake and the development of diabetes type 2 were identified. These studies are on the whole strongly suggestive of a causal role for fruit and vegetable intake in the primary prevention of CVDs and diabetes.

Random-effect models were used to combine measures of association from 14 prospective studies producing a summary RR of 0.85 for ischaemic heart disease, with a 95% CI of 0.80–0.90, ( $p < 0.001$ ) for persons in the highest quantile of fruit and vegetable intake compared with those in the lowest. For stroke, data from 11 studies demonstrated a summary RR of 0.80, and 95% CI of 0.67–0.94, ( $p = 0.005$ ) for persons in the highest quantile of fruit and vegetable intake compared with those in the lowest.

Few prospective data were available relating fruit and vegetable intake to risk of diabetes mellitus. On the whole, studies were difficult to compare due to their methodological differences and the above summary RR measures should be interpreted

with caution. Due to these important differences, Ness and Powles declined to create a summary measure in their review. The issues involved in preparing such a summary measure for fruit and vegetable intake have also been reviewed by Ness, Eggers, and Powles (183).

## **7.2 Review of causality**

Nutritional recommendations are often made in the absence of randomized controlled trials, because little such evidence exists. The general criteria used to support causality include consistency, strength of association, dose–response, biological plausibility, and temporality (184). The inverse relationship between the consumption of fruit and vegetables and CVDs (ischaemic heart disease and stroke) is supported by evidence from ecologic, cross-sectional, case–control, and prospective studies (155). The inverse relationship between fruit and vegetable intake and diabetes is supported by cross-sectional, case–control, and prospective studies. To date, the majority of these studies also reported significant dose–response relationships between intake of fruit and vegetables and risk of both diabetes and CVDs.

Often biological plausibility cannot be demanded of a hypothesis because the current state of knowledge is inadequate to explain observations. However in terms of the findings presented here, experimental and physiological evidence supports the roles of nutrients abundant in fruit and vegetables such as fibre, potassium, flavonoids, carotenoids, folic acid and vegetable proteins, and their low glycaemic index, in reducing risk of ischaemic heart disease, stroke and diabetes. Since dietary data were collected at baseline and persons with CVD or diabetes at baseline were excluded in all of the cohort studies reported for these outcomes, respectively, exposure preceded the clinical outcome of interest and the criterion of a temporal relationship is fulfilled. Taken together, the totality of the evidence strongly supports the notion that fruit and vegetable intake reduces risk of ischaemic heart disease, stroke and diabetes, independently of other health habits.

## **7.3 Studies in developing countries**



Ecologic studies of fruit and vegetable intake and CVDs have been conducted across countries including those that are developing and in epidemiologic transition (155). However, individual level dietary data and outcome measures are needed to examine prospectively the associations between fruit and vegetable intake and CVDs. Because of the difficulties inherent in accurately measuring dietary intake, and the large sample sizes and long follow-up often needed to provide adequate power in studies of nutritional exposures and chronic disease, the cost of conducting cohort studies to examine fruit and vegetable intake in relation to diabetes and CVD is high. The study populations included in the review of prospective evidence regarding fruit and vegetable intake were in Europe (Denmark, Finland, Netherlands, United Kingdom), Japan, and USA. The literature search described above did not identify prospective studies of fruit and vegetable intake and CVD or diabetes incidence from developing countries. As a first step, evidence from food balance sheets may be helpful to estimate the impact of inadequate fruit and vegetable intake on health in developing countries.

#### **7.4 Future research needs**

CVD takes a long time to develop. This fact together with the difficulty of managing long-term dietary interventions or controlled feeding trials, and the large sample size required to obtain an appropriate level of statistical power, means that randomized controlled trials of fruit and vegetable-enriched diets to prevent CVDs are not feasible at this time. It is therefore particularly important that additional larger and high-quality prospective cohort studies are conducted to evaluate the effectiveness of intake of general and specific types of fruit and vegetables for the prevention of CVDs and diabetes. Low power due to small event rates can significantly affect studies of fruit and vegetable intake and CVD because of the inherent difficulty in measuring diet. Effect sizes in nutritional epidemiology are often small but important. Large studies that are well-conducted and have high power to detect such associations are needed.

Studies to evaluate which particular fruit and vegetables are most effective in the prevention of diabetes and CVDs would be helpful. For example, differences in the nutrient content of different groups of fruits and vegetables (e.g. cruciferous versus leafy

vegetables) may have an impact on their protective effects. The associations of glycaemic index and glycaemic load should be investigated in relation to ischaemic heart disease and stroke, particularly regarding the roles of starchy vegetables such as potato and yam. The physiological aspects of foods change with heat and pressure, such that their preparation is particularly important in relation to their effects in the body. Hence regional differences in food preparation can have important ramifications on the risk for CVDs and diabetes and deserve evaluation. Moreover, types of fruit and vegetables differ in different regions of the world. Thus studies in developing countries may help to evaluate the importance of specific fruits and vegetables which are not yet widely consumed.

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Table 1. Prospective studies reporting measures of association between intake of whole fruits and vegetables and ischaemic heart disease

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
160	Japanese	265 118 >40 M&F	Census-based cohort 1965	NS	Not described	Age, smoking, alcohol, meat	16	Record linkage	Deaths – nos. not given	RR 0.92 (0.87–0.98); age-adjusted RR 1.07 in persons who did not smoke, drink, or eat meat	Green and yellow vegetables (“daily vs. not”)
161	Seventh Day Adventists, CA, USA	26 473 >25 M&F	Adventists in CA in 1976	IHD, diabetes, Hispanic, non-white	65 item FFQ	Age, sex, smoking, exercise, BMI, BP, vegetarian, bread	6 for 97%	Questionnaire, hospital notes	134 MI definite; 260 definite IHD deaths	Fruit index RR 1.18 (0.82–1.70) > 2/d vs < 1/d	Low-risk cohort
166	Vegetarians in UK	10 802 16–79 M&F	Recruits from vegetarian society, media, their friends, 1980-1984	Existing disease	FFQ	Age, sex, smoking, social class	13.3	Record linkage	64 IHD deaths	RR fruit 0.89 (0.44–1.80) RR carrots 0.76 (0.37–1.57) RR vegetables 1.34 (0.47–3.84)	Fresh or dried fruit, ≥ 10/wk vs. < 5/wk; carrots, ≥ 5/wk vs. < 1/wk; green vegetables, ≥ 5/wk vs. < 1/wk

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case Identification	No. of events	Association	Notes
159	Several regions of Finland	5133 30-69 M&F	Finnish regions, 1966-1972	IHD	Diet history	Age, sex, smoking, IHD risk factors, obesity, total energy intake	14	Record linkage	244 IHD deaths	RR T3/1 men for vegetables 0.66 ( $p = 0.02$ ); T3/1 men for fruit 0.77 ( $p = 0.28$ ); women similar but NS	Focus on anti-oxidant vitamins
158 (same cohort as 159)	Several regions of Finland	5133 30-69 M&F	Finnish regions, 1966-1972	IHD	Diet history	Age, sex, smoking, IHD risk factors, obesity, total energy intake	26	Record linkage	473 IHD deaths	Protective association Q4/1, RR 0.50-0.89 for apples, berries (only in women), other fruit, onions and vegetables	Focus on flavonoids
185	Residents of Zutphen, Netherlands	805 65-84 M	Survivors of 1960 cohort and new recruits in 1985	NS	Cross-check diet history method (1h interview)	Age, BMI, exercise, IHD risk factors, nutrients, total energy intake	5, 100%	5 yr re-exam, municipality registers	38 cases of MI, 13 fatal, 43 total IHD deaths	RR IHD death, apples (g/d) tertiles, T3/1, 0.51 (NS)	Main focus on flavonoids, protective association

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case Identification	No. of events	Association (95% CI)	Notes
162	NHANES I, USA	9608 25-74 M&F	National health survey conducted 1971-1975	CVD	FFQ	Age, race, sex, SBP, TC, BMI, DM, physical activity, education, smoking, alcohol, total energy intake	19	Follow-up questionnaire, death certificate	1786 IHD events, 639 IHD deaths	RR 0.76 (0.56–1.03) for IHD death, RR 0.73 (0.58–0.92) for CVD death	≥ 3 times/d vs. < 1 time/d, portion size not part of the FFQ
93	Post menopausal women in IA, USA	34 486 55-69 F	Random sample with valid driver's license. Mailed 1986	Pre-meno-pause, low reported energy intake, IHD, FFQ in-complete	127 item FFQ	Age, energy, BMI, elevated blood pressure, DM, HRT, fat, fibre, alcohol, smoking, physical activity, marital status, education, TC, vitamin E	10	Death register, biennial questionnaire, national death index	438 IHD deaths	RR Q5/1 apples 0.82 (0.60–1.12)	Focus on flavonoid intake, apple intake (times /wk)
175	Vegetarians and health-conscious people, UK	10 771 > 16 M&F	Customers of health food shops and others with interest in health foods 1973–1979	NS	FFQ	Age, sex, smoking	16.8 for 95.3%	Record linkage	350 IHD deaths	SMR fresh fruit 0.74 (0.60–97) SMR raw salad 0.76 (0.59–0.92)	Daily vs. < daily, crude FFQ, 70-80% ate fresh fruit daily

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
164	Female health professionals, USA	39 876 >45 F	Female health professionals recruited to an RCT, 1993	History of CVD or cancer	131 item FFQ	Age, randomized treatment status, smoking, other CVD risk factors	195 647 person yr = 5 yr	Death certificate and medical record	126 MI	RR Q5/1 0.63 (0.38–1.17)	Intake Q5/1, 10.2 vs. 2.6 servings per day
176	Men born in 1913, Gothenburg, Sweden	792 80 M	Survivors of cohort born in 1913, screened in 1967 aged 54	NS	FFQ	Smoking, cholesterol, BP	16 and 26, 92% follow-up	7-yearly re-examination, death certificate, medical records	Total no. not given	Age 74, RR 0.87 (0.76–0.96) Age 84, RR 0.92 (0.84–1.00)	RR multivariate survival analysis all cause mortality

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
165	Nurses and Health Professionals Follow-up studies, USA	84 251 34–59 F 42 148 40–75 M	Female nurses (recruited 1976) and male health professionals (recruited 1986)	In-complete FFQ, cancer, CVD, or DM	Repeated FFQ	Age, smoking, alcohol, family history of CVD, BMI, multivitamin use, aspirin use, physical activity, BP, TC, total energy intake, HRT	F 14 M 8	Medical records, death certificates, national death index	F, 1127 incident IHD M, 1063 incident IHD	RR 0.80 (0.69–0.93) for Q5/1	Total fruit and vegetable intake
163	British	3389 35–75 M&F	Respondents to the British Health and Lifestyle Survey, representative sample of UK, 1984–1985	CVD at baseline	31 item FFQ	Age, smoking, socioeconomic group	7	Record linkage	F, 187 CVD M, 205 CVD	M: RR 0.85–0.95 for frequent salad vegetable consumption; RR for fruit NS, F: RR 0.76 for frequent salad consumption, RR 0.84–0.85 for fresh fruit consumption	FFQ without portion size, analysis divided by season, outcome is CVD

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
168	Finnish	1950 42–60 M	Men from Finland who took part in the Kuopio Ischaemic Heart Disease Risk Factor Study, 1984–1989	CVD at baseline	4-day food records	Age, smoking, alcohol, BMI, blood pressure, DM, serum lipids	13	Record linkage	245 CVD deaths	RR 0.59 (0.33–1.06) for Q5/1 of fruit, berry, and vegetable intake	Q5 (> 408 g/d) vs. Q1 (< 133 g/d)
22	Adults (ARIC cohort) in USA	15792 45–64 M&F	Probability sample of communities in MD, MN, MS and NC, USA	IHD at baseline	Repeated 66 item FFQ	Age, sex, race, energy intake, education, BMI, WHR, SBP, smoking, physical activity, alcohol	11	Medical records, death certificates, telephone contact	535 IHD	RR 0.82 (0.57–1.17) Q5/1 of fruit and vegetable intake	Q5 (7.5 servings /d) vs. Q1 (1.5 servings /d)

ARIC: Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease including both ischaemic heart disease and stroke; DM, diabetes mellitus; F, female; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; IHD, ischaemic heart disease; M, male; MI, myocardial infarction; NHANES: US National Health and Nutrition Examination Study; NS, not stated; Q, quantile; RCT, randomized controlled trial; RR, relative risk; SBP, systolic blood pressure; SMR, standardized mortality ratio; T, tertile; TC, total cholesterol; WHR, waist-to-hip ratio.

Table 2. Prospective studies reporting measures of association between intake of whole fruits and vegetables and stroke

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
160	Japanese	265 118 > 40 M&F	Census-based cohort 1965	NS	Not described	Age, smoking, alcohol, meat	16	Record linkage	Deaths—nos. not given	RR 1.20 (0.99–1.06)	Green and yellow veg (“daily vs. not”)
157	Nurses, USA	87 245 34–59 F	US Nurses recruited 1980	CVD, cancer	FFQ	Age, smoking	8	Biannual questionnaire	345 CVA cases	RR Q5/1 of veg adjusted 0.74 ( $p = 0.03$ )	Null for fruit, RR carrots 0.32, RR spinach 0.57, 5+/wk vs. < 1 month
19	Residents of Framingham USA	832 45–65 M	Framingham men examined 1966–1974	CVD	24-h recall	IHD risk factors, BMI, exercise, left ventricular hypertrophy, fat, alcohol	20	Biennial exam	73 CVA, 24 TIA, 14 CVA deaths	RR for 3 servings/day: 0.78 (0.62–0.98). Same assoc. for fruit, veg and death	Potatoes included as fruit and veg; poor exposure measure.
175	Vegetarians and health conscious people, UK	10771 >16 M&F	Customers of health food shops and others with interest in health foods 1973-1979	NS	FFQ	Age, sex, smoking	16.8 for 95.3%	Record linkage	350 IHD deaths	SMR fresh fruit 0.68 (0.43–98) SMR raw salad 1.21 (0.87–1.68)	Daily vs. < daily; crude FFQ; 70–80% ate fresh fruit daily



Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
173	Residents of Zutphen, Netherlands	552 50–69 M	Residents in the Zutphen area examined in 1970	CVA	Repeated dietary cross-check	Age, IHD risk factors, energy intake, fish, alcohol	15	Repeated examinations	42 CVA	RR T3/1 solid fruit: 0.53 (0.21–1.31); citrus fruit: 0.93 (0.39–2.22); vegetables: 0.82 (0.35–1.94)	Intake (g/d) T3/1 solid fruit < 41 vs. ≥ 99.8; citrus fruit < 28 vs. ≥ 91.7; vegetables < 153.2 vs. ≥ 215.8; main focus was flavonoids
169	Nurses & health professionals in USA; follow-up studies pooled	75 596 34–59 F 98 683 40–75 M	Female nurses (recruited 1976) and male health professionals (recruited 1986)	Those with incomplete FFQ, cancer, CVD, or DM	Repeated FFQ	Age, smoking, alcohol, family history of CVD, BMI, multivitamin use, aspirin use, physical activity, BP, TC, total energy, HRT	F: 14 M: 8	Medical records, death certificates, national death index	F: 336 CVA; M: 317 CVA	RR 0.94 (0.90–0.99) F: 0.93 (0.87–1.00) M: 0.96 (0.89–1.03)	RR per 1 serving per day

Ref no.	Population	No. of subjects, age (yr), sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
171	Several regions of Finland	9208 >15 M&F	Residents of Finnish regions, 1966–1972	CVA or other CVD	Diet history	Age, TC, BMI, elevated BP, DM, area, occupation, beta-carotene, vit C, fibre, saturate, mono-/poly-unsaturated, fats, energy, quecertin	28	Record linkage	824 CVA	RR Q4/1 apples in men 0.65 (0.45–0.94); RR Q4/1 apples in women 0.95 (0.60–1.51)	Main focus was quecertin
162	NHANESI (USA)	9608 25–74 M&F	National health survey conducted 1971–1975	CVD	FFQ	Age, race, sex, SBP, TC, BMI, DM, physical activity, education, smoking, alcohol, total energy intake	19	Follow-up questionnaire, death certificate	888 CVA; 218 CVA death	RR 0.73 (0.57–0.95) for CVA; RR 0.58 (0.33–1.02) for CVA death	≥ 3 times/d vs. < 1 time/d; portion size not part of the FFQ
170	Male smokers in Finland	26 497 50–69 M	Male smokers of at least 5 cigs/d in south-west Finland	Cancer, stroke, other serious illness, vitamin E, A, or beta carotene > specified dose, anti-coagulation	Self-admin modified diet history method	Age, supplementation group, BP, lipids, BMI, smoking, DM, CHD, alcohol, education	6.1	Record linkage	736 CVA	Q4/1 vegetables RR 0.71 (0.57–0.87); Q4/1 fruit RR 0.96 (0.78–1.18); Q4/1 berries RR 0.81 (0.66–1.00)	Also analysed by type of stroke, haemorrhagic (SAH, ICH) vs. ischaemic

Ref no.	Population	No. of subjects age (yr) sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow- up (yr)	Case identification	No. of events	Association (95% CI)	Notes
18	Adults in USA (ARIC cohort)	15 792 45–64 M&F	Probability sample of communities in states of MD, MN, MS, and NC, USA	CVD at baseline	Repeated 66 item FFQ	Age, sex, race, energy intake, education, BMI, WHR, SBP, smoking, physical activity, alcohol	11	Medical records, death certificates, telephone contact	270 CVA	RR, 0.94 (0.54– 1.63) Q5/1 of fruit and veg intake	Q5 (7.5 servings/d) vs. Q1 (1.5 servings/d)
174	Danish	54 506 50–64 M&F	Danish men and women, 1993–1997	Cancer, CVD including CVA, incomple e FFQ	192 item FFQ	Age, sex, total energy, smoking, BP, TC, DM, BMI, alcohol, red meat, poly- unsaturated fats, physical activity, education	168 388 person- yr; median 3.09	Record linkage	266 CVA	RR Q5/1 0.72 (0.47–1.12)	Q5 median intake 673 g/d vs. Q1 median 147 g/d

Ref no.	Population	No. of subjects age (yr) sex	Recruitment period	Exclusion	Exposure measure	Potential confounders considered	Follow-up (yr)	Case identification	No. of events	Association (95% CI)	Notes
172	Japanese	40 349 34–103 M&F	Japanese persons living in Hiroshima or Nagasaki and not exposed to radiation 1950–1979	CVA	22 item FFQ	Age, radiation, city, BMI, smoking, alcohol, education, hypertension, MI, DM, consumption of animal products	18	Record linkage	1926 CVA deaths	M: green yellow vegetables: RR 0.77 (0.62–0.95); fruits: RR 0.65 (0.53–0.80); F: green yellow vegetables: RR 0.81 (0.68–0.96) fruits: RR 0.75 (0.64–0.88)	RR for consumption daily vs. 0-1 time/wk, no portion size

ARIC: Atherosclerosis Risk in Communities Study; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CVA, cerebrovascular accident; CVD, cardiovascular disease including both ischaemic heart disease and stroke; DM, diabetes mellitus; F, female; FFQ, food frequency questionnaire; HRT, hormone replacement therapy; ICH, ?  
IHD, ischaemic heart disease; M, male; MI, myocardial infarction; NHANES: US National Health and Nutrition Examination Study;  
NS, not stated; Q, quantile; RR, relative risk; SAH, sub-arachnoid haemorrhage; SBP, systolic blood pressure; SMR, standardized mortality ratio; T, tertile; TC, total cholesterol; TIA, transient ischaemic attack; WHR, waist-to-hip ratio.

Table 3. Studies reporting measures of association between intake of fruits and vegetables and diabetes mellitus

<i>Ref no.</i>	<b>Population</b>	<b>No. of subjects, age (yr), sex</b>	<b>Recruitment period</b>	<b>Exclusion</b>	<b>Exposure measure</b>	<b>Potential confounders considered</b>	<b>Study design (follow-up)</b>	<b>Case identification</b>	<b>No. of events</b>	<b>Association (95% CI)</b>	<b>Notes</b>
181	Residents, Isle of Ely, UK	1122 40–64 M&F	Residents of Isle of Ely, UK, date not given	DM, physically unable to come to study centre	35 item FFQ	Age, sex, family history of DM, BMI	Cross-sectional	OGTT	51 DM, 188 IGT	OR for DM 0.27 (0.06–1.22) vegetable consumption all year; OR for DM 0.57 (0.26–1.25) fruit consumption all year	Frequency measure
17	Norfolk region of UK, EPIC study	5996 45–74 M&F	Residents of the Norfolk, UK, 1993–1998	In-complete information, DM	FFQ	Sex, age, BMI, total energy intake, family history of DM, smoking, alcohol, education, supplement use, vegetarian, physical activity, nutrients	Cross-sectional	Blood % HbA <sub>1c</sub>	NS	Inverse association of % HbA <sub>1c</sub> with frequent fruit and green leafy vegetable consumption	Frequency of consumption ≥ 5 times/wk vs. never or seldom

<i>Ref no.</i>	<b>Population</b>	<b>No. of subjects age (yr), sex</b>	<b>Recruitment period</b>	<b>Exclusion</b>	<b>Exposure measure</b>	<b>Potential confounders considered</b>	<b>Study design (follow-up)</b>	<b>Case identification</b>	<b>No. of events</b>	<b>Association (95% CI)</b>	<b>Notes</b>
186	Rural Japanese	Cases: 284 Controls: 568 M&F	Residents of rural area of Hokkaido, Japan,	NS	FFQ	Age, sex	Case-control	Blood % HbA <sub>1c</sub> , medical record	NS	OR for elevated HbA <sub>1c</sub> 0.49 (0.29–0.85); OR for DM, 1.21 (0.79–1.84)	OR for high intake frequency of carrot and pumpkin
180	Seventh Day Adventists, California	25 698 30-89, M+F	Adventists in CA, USA, recruited 1960	In-complete FFQ	FFQ	Age, weight, physical activity, meat, eggs, milk, desserts, candy, soft drinks	Prospective cohort (21 yr)	Record linkage, death certificates	NS	SMR 0.45 (0.38–0.54)	Instrument not well described
71	US Nurses	84 360 34–59, F	Nurses in USA recruited 1980	DM, BMI > 29	FFQ	BMI, weight change, alcohol	Prospective cohort (6 yr)	Follow-up questionnaire	702 DM	RR Q5/1 0.76 (0.50–1.16) vegetable intake;	Q5/1, ≥ 2.9 servings of vegetables vs. < 1.2
100	Finnish and Dutch	338 70–89, M	Dutch (Zutphen) and Finnish men from the Seven Countries Cohort, recruited 1958–1964	DM	Cross-check diet history	Age, cohort, BMI, past BMI, past energy intake	Prospective cohort (30 yr)	OGTT	71 incident IGT, 26 incident DM	Inverse association of 2-h post-load glucose and intake of vegetables and legumes	Multivariate regression predicting 2-h post-load glucose

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50	Post-menopausal women, IA, USA	35 988 55–69, F	Random sample with valid driver's license. Mailed 1986	DM, cancer, IHD	127 item FFQ	Age, total energy, BMI, WHR, education, smoking, alcohol, physical activity	Prospective cohort (6 yr)	Death register, biennial questionnaire, national death index	1141 DM	RR Q5/1 fruit and vegetables 1.05 (0.84–1.31)  RR vegetables 1.07 (0.86–1.32)  RR fruit 1.14 (0.93–1.39)	Q5 > 51 servings/wk fruit and vegetables vs. < 23 servings/wk
182	NHANES I, USA	9665 25–74, M+F	National health survey conducted 1971-1975	DM, incomplete information, pregnant, non-white or African American	24-h recall	Age, sex, smoking, SBP, lipids, anti-hypertensive medication, physical activity, alcohol, BMI	Prospective cohort (19 yr)	Follow-up questionnaire, hospital records, death certificates	1018 DM	RR 0.73 (0.54–0.98)	5 or more servings/d vs. 0 serving/d; strong sex interaction

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; HbA<sub>1c</sub>: glycosylated haemoglobin; IGT, ?; IHD, ischaemic heart disease; M, male; NHANES: US National Health and Nutrition Examination Study; NS, not stated; OGTT, ?; OR, odds ratio; Q, quantile; RR, relative risk; SBP, systolic blood pressure; SMR, standardized mortality ratio; T, tertile; WHR, waist-to-hip ratio.

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BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; EPIC, European Prospective Investigation into Cancer and Nutrition; F, female; FFQ, food frequency questionnaire; HbA<sub>1c</sub>, glycosylated haemoglobin; IGT, ?; IHD, ischaemic heart disease; M, male; NHANES: US National Health and Nutrition Examination Study; NS, not stated; OGTT, ?; OR, odds ratio; Q, quantile; RR, relative risk; SBP, systolic blood pressure; SMR, standardized mortality ratio; T, tertile; WHR, waist-to-hip ratio.