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Prevention of metabolic diseases: fruits (incl. fruit sugars) vs. vegetables

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Abstract

Purpose of review—To discuss recent evidence from observational and intervention studies on the relationship between fruit and vegetable consumption and metabolic disease.

Recent findings—Observational studies have consistently demonstrated a modest inverse association between the intake of fruit and leafy green vegetables, but not total vegetables, and biomarkers of metabolic disease as well as incident type 2 diabetes mellitus. This is in contrast to limited evidence from recently published randomized controlled dietary intervention trials, which – in sum - suggest little to no impact of increased fruit and vegetable consumption on biomarkers of metabolic disease.

Summary—Evidence from observational studies that fruit and leafy green vegetable intake is associated with lower type 2 diabetes risk and better metabolic health could not be confirmed by dietary intervention trials. It is unclear whether this discrepancy is due to limitations inherent in observational studies (e.g., subjective dietary assessment methods, residual confounding), or due to limitations in the few available intervention studies (e.g., short duration of follow-up, interventions combining whole fruit and fruit juice, or lack of compliance). Future studies that attempt to address these limitations are needed to provide more conclusive insight into the impact of fruit and vegetable consumption on metabolic health.

Keywords

Fruit; vegetables; metabolic disease; type 2 diabetes; insulin

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by an inability of the body to maintain plasma glucose homeostasis. Worldwide, an estimated 382 million people had diabetes, mostly T2DM, in 2013, a number that is expected to increase further (1). There

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Conflicts of interest
None.

is consensus that lifestyle factors, including diet, play a major role in the development of T2DM and related metabolic disease.

Fruit and vegetables (F&V) are considered beneficial to human health, due to their high nutrient and low energy density, and high content of fiber and a wide variety of phytochemicals. Fruit, however, are also a rich source of sugar and specifically fructose, a high intake of which has recently been linked to metabolic disease (2). Because much of the research on fructose has been conducted using sugar- or fructose-sweetened beverages, it has remained largely unclear whether consumption of sugar or fructose in the form of solid foods such as fruit may also trigger adverse metabolic consequences.

According to a recent meta-analysis of nine observational studies (3), T2DM risk is significantly reduced in individuals who consume the highest compared to the lowest amount of fruit. Leafy green vegetable, but not total vegetable, consumption is also inversely associated with incident T2DM (3). Total F&V intake, when analyzed together, is not significantly associated with T2DM (3). Among intervention studies, we are not aware of any long-term randomized controlled trials that specifically tested the impact of F&V intake on incident T2DM. While changes in F&V consumption have been part of numerous intervention trials, such trials with a hard disease endpoint have always also included changes in other dietary or lifestyle factors. Interestingly, randomized controlled intervention studies that tested the effect of total F&V intake on biomarkers of metabolic disease were also not available until recently, as previously published studies tested very specific exposures, such as garlic or specific fruit extracts on metabolic disease biomarkers.

In the last few years, however, several randomized controlled trials have been published that investigated the impact of F&V consumption on biomarkers of metabolic disease. The objective of this article is to discuss these intervention studies, along with more recent observational evidence.

Each author independently conducted a PubMed literature search using clinical subject headings (type 2 diabetes, insulin, glucose, hyperinsulinemia, metabolic syndrome, HOMA, HbA1c, OGTT, MTT, clamp, glycemia, blood sugar) in combination with terms such as fruit, vegetables, leafy green, fruit sugar, berries, and tubers. The search was restricted to studies in humans focusing on whole fruits or vegetables, excluding those studies of single fruits, extracts, supplements, or juice only. All observational studies and randomized controlled intervention trials published between July 2015 and January 2017 were considered for inclusion in this review, unless they had been included in the meta-analysis by Wang and colleagues (3). We also briefly review two particularly relevant studies published in 2013 (4) and 2014 (5).

Fruit and vegetable intake, incident type 2 diabetes, and biomarkers for metabolic disease – observational studies

Using a combined dataset from US and European cohorts on health and ageing, Mamluk and colleagues (6) investigated associations between F&V intake and incident T2DM (see Table 1 for study details). F&V intake was analyzed in several categories, including total fruit, total vegetables, and leafy green vegetables. After a follow-up of 10 to 13 years, the authors found no overall associations between F&V intake and incident T2DM. However, when the US cohort was analyzed separately, fruit intake of 2.5 portions per day was associated with a 5% reduced risk of T2DM compared to fruit intake <1.5 portions per day. In none of the European cohorts was a trend for reduced T2DM incidence apparent in individuals consuming greater amounts of fruit. And even in the US cohort, the association was resoundingly null when fruit intake data were analyzed as a continuous rather than a categorical variable. Thus, taken together, the results from this very large observational study suggest that fruit intake is either not associated with T2DM risk, or that the association is weak, with a small effect size. Total vegetable intake was not associated with incident T2DM in either cohort in the fully adjusted model. Leafy green vegetable intake was strongly inversely associated with incident T2DM in the US cohort, but positively in the European cohort. The source of the substantial heterogeneity between the US and European cohorts remained largely unclear. The authors speculate that between-study differences in dietary assessment methods may partly explain this heterogeneity.

Cooper and colleagues (7) created a composite biomarker score for F&V intake based on baseline plasma vitamin C, beta carotene, and lutein concentrations. In 318 incident T2DM cases and 926 controls identified 10 years after baseline within the EPIC-Norfolk cohort, the composite biomarker score was strongly and inversely associated with incident T2DM (test for trend across quartiles of biomarker score, $p<0.001$), which amounted to a 65% lower T2DM risk in the highest vs. lowest quartile in the fully adjusted model. These data suggest that studies based on subjective dietary assessment methods such as FFQ may underestimate the association between F&V intake and T2DM risk. However, the relative contribution of fruits vs. vegetables to the observed associations could not be determined from this study.

Two recent cross-sectional studies examined the association between F&V intake and the presence of metabolic syndrome (MetS) in two separate cohorts of Korean adults. Park and colleagues (8) reported that moderate and high intake of fruit was inversely associated with MetS prevalence in women only. These associations were not present in men, nor were there significant associations between vegetable intake and MetS prevalence in either men or women (8). Song et al. (9) recruited a separate cohort of 668 Korean adults, and - in contrast to the study by Park et al. - found an inverse association between fruit intake and MetS in men but not in women. Again, there were no significant differences in vegetable intake among those with MetS compared to those without. Taken together, these two studies provide modest evidence that fruit but not vegetable consumption may be inversely associated with the MetS.

In a study of 770 Korean children, Hur and colleagues (10) assessed associations between sugar intake from different foods (fruit, milk, and sugar-sweetened beverages) and metabolic health. While higher intake of fruit sugar was associated with a lower BMI z-score and lower body fat percentage in the fully adjusted model, fruit sugar intake was not associated with a metS composite score. However, sugar intake from sugar-sweetened beverages was positively associated with the metS composite score.

In a cross-sectional analysis in 2,025 children in the UK, Donin and colleagues found no associations between the intake of fruit or vegetables and HOMA-IR or HbA_{1c} (11). In contrast to most other studies in this field, these authors specified that only whole/solid F&V were considered in their analyses, not F&V juices. However, this study suffered from the fact that habitual dietary intake data were based on single-day 24-hr recall.

In a cross-sectional study in 175 Latino adolescents that included deep metabolic phenotyping, Cook et al. (5) found that those who consumed the highest amount of non-starchy vegetables had a 44% lower hepatic fat content compared to those with the lowest intake (5.6±8.7% vs. 10.0±8.5%; p=0.01) (5). Nutrient-rich vegetable (leafy greens and green/orange vegetables) consumers had 31% greater insulin sensitivity and 17% less visceral adipose tissue compared to non-consumers (5). However, total vegetable intake was not associated with fasting glucose, fasting insulin, HOMA-IR, or insulin sensitivity and pancreatic beta-cell function as measured by clamp.

Another cross-sectional analysis of 40 normal weight, healthy female university students found that those who consumed large amounts of fruit had significantly lower fasting insulin and HOMA-IR compared to those who consumed lower amounts of fruit (12). Participants were divided into either ‘high’ or ‘low’ groups based on whether their consumption of fruit (mainly citrus fruits and apples) was above or below the median intake (293 g/d), as assessed by FFQ. The analysis was not adjusted for any covariates, however.

Taken together, these observational studies largely confirm the results of the meta-analysis by Wang and colleagues in that most show a modest inverse association between fruit and leafy green vegetable intake, incident T2DM, and biomarkers for metabolic disease. Total vegetable intake is consistently not associated with incident T2DM or biomarkers for metabolic disease. Intriguingly, the study by Cooper and colleagues that used a biomarker of F&V intake suggests that studies relying on subjective dietary assessment methods such as FFQ may underestimate the effect size of any association. One reason for this may be that the random error from over- vs. underreporting of food intake in participants completing FFQs would be expected to bias any associations towards the null. One way this bias could be minimized is by nutrient density adjustment, i.e. normalizing the exposure variable to total energy intake (i.e., g F&V per 1,000 kcal), rather than expressing it in absolute amounts (i.e., g F&V/d) (13), which is notably different from including energy intake in the regression model. Few of the published studies have taken advantage of this possibility. Another gap in the literature in this area is that few studies disclose whether juices were included in the F&V category (Table 1). Given that one older study suggests a positive association between fruit juice and incident T2DM (14), it would seem critical to analyze juice separately in observational studies. And lastly, it is notable that confounding by other dietary or lifestyle factors was not always taken into account, neither in the observational studies summarized in Table 1 nor in those summarized in the meta-analysis by Wang et al. (3). As individuals with high F&V consumption likely have other healthy dietary or lifestyle habits, it seems possible that at least some of the observed associations may have been due to unmeasured or residual confounding.

Fruit and vegetable intake and biomarkers of metabolic health – intervention studies

Considering that observational studies have relatively consistently shown inverse associations between the intake of fruit and leafy green vegetables, incident T2DM, and biomarkers of metabolic disease, it is timely that several randomized controlled trials on the impact of F&V on intermediate risk factors for T2DM have recently been published (see Table 2 for study details).

In a well-controlled dietary intervention trial, overweight to obese men and women were randomized to one of three 12-week dietary intervention diets providing about two, four, or seven servings of F&V per day (4). Repeated 4-day diet records suggested good compliance, and body weight and fat mass were stable throughout the study, with no difference between the intervention groups. Neither systemic nor hepatic insulin resistance, as measured by euglycemic-hyperinsulinemic clamp, were differentially affected by the three diet groups to a statistically significant degree. It should be noted that participants could consume fruit juice as part of their required daily F&V intake, which previous research suggests may have affected the results (14).

Agebratt et al. (15) randomized 30 healthy, young, and largely normal weight Swedish university students to add either ~500 kcal/d of fruit or nuts to their habitual diet. The primary objective of the study was to investigate whether the substantial increase in sugar consumption in the fruit group would increase hepatic fat content and other markers of cardiovascular risk. Fructose intake indeed increased roughly three fold in the fruit group, and was reduced by ~50% in the nut group. During the 2-month intervention, energy intake was similar in both intervention groups, and participants in both groups gained approximately 0.7 kg in weight, with no difference between the groups. There was no significant difference in the change in liver fat content between groups, as the liver fat content in both intervention groups remained virtually unchanged. Fasting insulin increased slightly in both groups, again with no difference between groups (15).

Jarvi and colleagues (16) randomized 62 overweight or obese Swedish adults to either a control diet or an intervention diet that consisted of at least 500 g/d of F&V for 16 weeks. Those randomized to the intervention group increased their F&V intake approximately 2-fold. There were no statistically significant differences between groups in the changes in body weight, fasting insulin, fasting glucose, or HbA1c during the intervention period (16).

Sahariah et al. (17) carried out an intervention in low-income Indian women who were planning to become pregnant. Participants were randomized to receive a fried dough snack each day filled with green vegetables, dried fruit, and full-fat milk powder (treatment group) or a low-nutrient-density vegetable such as potato or onion (control). Of the 1,008 women who returned for an oral glucose tolerance test at 28-32 weeks gestation, significantly fewer women in the treatment group were diagnosed with gestational diabetes (GDM) compared to the control group ($p=0.007$), according to WHO 1999 diagnostic criteria for GDM. However, the differences were not significant when data were evaluated based on the revised WHO 2013 criteria, which recommended a different 120-min glucose cut-off value for the diagnosis of GDM (17). Important limitations of this study include that both interventions included vegetables, and that the treatment snack had almost twice as much energy and more than 2.5 times as much protein as the control snack. Also, it is possible that the treatment snack did not prevent GDM, but that the control snack increased risk for GDM.

Taken together, the randomized controlled intervention trials conducted thus far do not support a clinically meaningful effect of F&V on metabolic health. Possible limitations in these studies may be the inclusion of fruit juice in the F&V intervention diet in one study, the assessment of metabolic health by measurements in fasting blood only in other studies, relatively study duration, or insufficient focus on the specific F&V categories associated with T2DM in observational studies, i.e. fruit and leafy green vegetables.

Conclusions and future research opportunities

In sum, neither observational nor intervention studies suggest an increased risk of metabolic disease in individuals consuming large amounts of sugar and fructose in the form of fruit. In fact, observational studies show an inverse association between fruit intake and T2DM risk. No association is usually seen for vegetables as a whole, except for leafy green vegetables, which are commonly also inversely associated with T2DM risk. In view of these data from observational studies, it is surprising that - as a whole - the few available intervention studies do not support an effect of increased F&V intake on metabolic disease risk biomarkers. Definitive evidence will require longer-term well-controlled studies in which F&V are administered in their whole form, with a focus on those F&V that are associated with metabolic health in observational studies (i.e., fruit and leafy green vegetables), in which body weight and other dietary variables are well standardized, and in which biomarkers of metabolic health are assessed using state of the art methods including glucose tolerance tests and/or clamps.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

*of special interest

**of outstanding interest

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Key Points

- In observational studies, the intake of fruit and leafy green vegetables, but not total vegetables, is inversely associated with biomarkers for metabolic disease and incident type 2 diabetes mellitus
- However, limited evidence from randomized controlled intervention trials suggests that increased fruit and vegetable consumption has little impact on metabolic health.
- It is unclear whether the discrepancy between observational and intervention studies is due to limitations inherent in observational studies (e.g., subjective dietary assessment methods, residual confounding), or due to limitations in the few available intervention studies (e.g., short duration of follow-up, combined administration of fruit juice and whole fruit in interventions, lack of compliance).
- There is no evidence to suggest that the high content of sugar and fructose in fruit increases risk for metabolic disease even at high intake levels.

Table 1

Observational studies: Relationship between fruit and vegetable intakes and metabolic disease*

Reference	Type	Subjects	Dietary assessment method	Endpoints and covariates	Outcome
Cook et al. (2014) (5)	Cross-sectional	8–18 year old overweight, non-diabetic US Latino boys and girls (n=175)	Multiple 24-hour recalls (at least 2) at baseline Juice included in vegetable category: no	Endpoints: Fasting glucose, fasting insulin, HOMA-IR, insulin sensitivity, acute insulin response to glucose, disposition index (all based on IVGTT); hepatic fat content, subcutaneous and visceral fat volume (all based on abdominal MRI scan) No hierarchy of endpoints defined. Covariates in fully adjusted model: Age, sex, energy intake, and total body fat, fiber intake	Total vegetable intake was not associated with fasting glucose, fasting insulin, HOMA-IR, insulin sensitivity, the disposition index, or the subcutaneous or visceral adipose tissue volume. Total vegetable intake was inversely associated with liver fat content. Consumers of nutrient-rich vegetables had lower visceral adipose tissue volume and higher insulin sensitivity than non-consumers.
Mamluk et al. (2017) (6)	Prospective cohort	50+ year old non-diabetic US men and women (n=401,909)	124-item FFQs at baseline Juice included in F&V category: not stated	Primary endpoint: Incident T2DM Covariates included in fully adjusted model: Age, sex, BMI, physical activity, energy intake, alcohol consumption, education, and smoking	No association between fruit intake and incident T2DM when fruit intake was analyzed as a continuous variable. However, test for trend across four categories of fruit consumption indicated a significant inverse association. No association between total vegetable intake and incident T2DM. However, leafy green vegetable intake was inversely associated with incident T2DM.
Mamluk et al. (2017) (6)	Prospective cohort	50+ year old non-diabetic European men and women (n= 20,629)	200-item FFQs, or 7-day food records, or 14-day food records at baseline Juice included in F&V category: not stated	Primary endpoint: Incident T2DM Covariates included in fully adjusted model: Age, sex, BMI, physical activity, energy intake, alcohol consumption, education, and smoking	No association between fruit and total vegetable intake and incident T2DM. Positive association between leafy green vegetable intake and incident T2DM.
Cooper et al. (2015) (7)	Nested case-control	40–79 year old UK men and women (n=1,244 total; n=318 T2DM cases, n=926 controls)	Biomarker composite score for fruit and vegetable intake, based on plasma vitamin C, beta-carotene, and lutein concentrations, measured at baseline. One 7-day prospective food diary at baseline. Juice included in F&V category: not stated	Primary endpoint: Incident T2DM during a mean follow-up of 10.2 years Covariates in fully adjusted model: Age, sex, education level, occupational social class, smoking status, physical activity level, family history of diabetes, total energy intake, and vitamin supplement use, HDL cholesterol and LDL cholesterol, body mass index, waist circumference	Higher biomarker composite score for fruit and vegetable intake was inversely associated with incident T2DM. One standard deviation increase in the biomarker composite score for fruit and vegetable intake, equivalent to ~71 g of fruit and vegetables per day, was associated with a 40% reduction in T2DM risk.
Park et al. (2015) (8)	Cross-sectional	20+ year old Korean men and women (n=27,656)	Single 63-item FFQ and a single 24-h recall at baseline Juice included in F&V category: not stated	Primary endpoint: Presence of metabolic syndrome Secondary endpoint: individual components of the metabolic syndrome, i.e., waist circumference, fasting serum HDL-cholesterol, fasting serum triglycerides, blood pressure, fasting serum glucose, fasting serum LDL-cholesterol Covariates in fully adjusted model: Age, BMI, residence area, education level, smoking status, drinking status, exercise, walking, serum	In women, fruit intake was inversely associated with the risk of suffering from the metabolic syndrome and the risk of having fasting plasma glucose concentrations >100 mg/dL. There was no association between vegetable intake and metabolic syndrome or fasting glucose in women. In men, neither fruit nor vegetable intake were associated with the risk of suffering from the metabolic syndrome, or the risk of having fasting plasma glucose >100 mg/dL.

Reference	Type	Subjects	Dietary assessment method	Endpoints and covariates	Outcome
				aspartate aminotransferase and alanine aminotransferase levels, menopausal status	
Song et al. (2015) (9)	Cross-sectional	30+ year old Korean men and women (n=668)	Three 24-h recalls at baseline Juice included in F&V category: no	Primary endpoint: Presence of metabolic syndrome Covariates in fully adjusted model: Age, BMI, smoking status, alcohol use, regular physical activity, and total energy intake	Men with the metabolic syndrome consumed less fruit than those without the metabolic syndrome. Women with the metabolic syndrome did not differ from women without the metabolic syndrome in their fruit consumption. No difference in vegetable consumption between individuals with vs. without the metabolic syndrome.
Hur et al. (2015) (10)	Prospective cohort	9–10 year old non-diabetic Korean boys and girls (n=437)	Single 3-day food record at baseline Juice included in fruit category: no	Endpoints: BMI z-score, body fat percentage, composite metabolic syndrome index No hierarchy of endpoints defined. Covariates in fully adjusted model: Age, sex, total energy intake, and household income	Fruit sugar consumption was inversely associated with the BMI z-score and body fat percentage, but not with the metabolic syndrome composite score. Beverage sugar consumption was positively associated with the metabolic syndrome composite score.
Donin et al. (2016) (11)	Cross-sectional	9–10 year old multi-ethnic English boys and girls (n=2,025)	Plasma vitamin C concentrations as a biomarker of F&V intake Single 24-hour dietary recall Juice included in F&V category: no	Endpoints: Fasting glucose, fasting insulin, HOMA-IR, HbA1c No hierarchy of endpoints defined. Covariates in fully adjusted model: Age, sex, total energy intake, ethnicity, school	Dietary F&V intakes were not associated with fasting glucose, fasting insulin, HOMA-IR, or HbA1c. Plasma vitamin C levels were inversely associated with fasting glucose, fasting insulin, and HOMA-IR, but positively with HbA1c.
Carraro et al. (2016) (12)	Cross-sectional	18–28 year old normal weight, non-diabetic Spanish women (n=40)	Single 136-item FFQ at baseline Juice included in fruit category: not stated	Endpoints: fasting glucose, fasting insulin, and HOMA-IR No hierarchy of endpoints defined. Covariates: none.	Participants were divided by their median fruit intake into high vs. low fruit intake categories. Fasting insulin and HOMA-IR were significantly lower among individuals with high vs. low fruit intake. No significant difference for fasting glucose.

*Abbreviations: BMI: body mass index, FFQ: food frequency questionnaire, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, HOMA-IR: homeostasis model assessment index of insulin resistance, IVGTT: intravenous glucose tolerance test, LDL: low-density lipoprotein, MRI: magnetic resonance imaging, T2DM: type 2 diabetes mellitus

Table 2

Randomized controlled trials published 2013–2016 on the impact of fruit and vegetable intake and biomarkers for metabolic disease*

Reference	Study design	Subjects	Intervention	Endpoints	Outcome
Wallace et al. (2013) (4)	Randomized, 3 arms, parallel design, isocaloric	Overweight or obese non-diabetic Irish adults at high risk of cardiovascular disease (n=89)	Dietary advice with provision of F&V: 1–2 vs. 4 vs. 7 servings of F&V per day. Duration of intervention phase: 12 weeks Intervention diets included fruit juice	Primary: insulin resistance (clamp) Secondary: fasting glucose, fasting insulin, HOMA-IR	No significant intervention effect on insulin resistance, fasting glucose, fasting insulin, HOMA-IR
Agebratt et al. (2016) (15)	Randomized, 2 arms, parallel design	Normal weight non-diabetic Swedish university students (n=30)	Supplementation of 7 kcal per kg bodyweight per d of either fruits or nuts Duration of intervention phase: 8 weeks Fruit intervention diet did not include juice	Body weight, hepatic fat content, basal metabolic rate, fasting glucose, fasting insulin, HbA1c Hierarchy of endpoints not defined.	No significant intervention effect on body weight, hepatic fat content basal metabolic rate, fasting glucose, fasting insulin, or HbA1c.
Jarvi et al. (2016) (16)	Randomized, 2 arms, parallel design	Overweight or obese non-diabetic Swedish adults (n=62)	General dietary advice plus provision of 500 g of F&V intake per day (intervention) vs. general dietary advice only (control) Duration of intervention phase: 16 weeks Intervention diets did not include juice	Body weight, fasting glucose, fasting insulin, HbA1c Hierarchy of endpoints not defined.	No significant intervention effect on body weight, fasting glucose, fasting insulin, or HbA1c.
Sahariah et al. (2016) (17)	Randomized, 2 arms, parallel design	Women aged <40 years, intending to become pregnant, and living in slums in Mumbai, India (n=1,008)	Provision of a snack to be consumed >3 times per week: fried dough filled with green leafy vegetables, fruit, and milk (treatment) vs. a low-micronutrient vegetable (control) Duration of intervention phase: ~40–45 weeks Fruit intervention diet did not include juice	Primary: GDM prevalence, as assessed by oral glucose tolerance test, at 28–32 weeks gestation Secondary: fasting glucose, 120-min glucose during oral glucose tolerance test, fasting insulin	Based on WHO 1999 criteria for diagnosis of GDM: significantly lower prevalence of GDM in intervention vs. treatment group Based on WHO 2013 criteria for diagnosis of GDM: no statistically significant difference No significant intervention effect on fasting glucose, 120-min glucose, or fasting insulin

*Abbreviations: DEXA: dual-energy x-ray absorptiometry, F&V: fruit and vegetables, GDM: gestational diabetes mellitus, HbA1c: glycated hemoglobin, HOMA-IR: homeostasis model assessment index of insulin resistance, WHO: world health organization