Association between changes in carbohydrate intake and long term weight changes: prospective cohort study

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ABSTRACT

OBJECTIVE
To comprehensively examine the associations between changes in carbohydrate intake and weight change at four year intervals.

DESIGN
Prospective cohort study.

SETTING
Nurses' Health Study (1986-2010), Nurses' Health Study II (1991-2015), and Health Professionals Follow-Up Study (1986-2014).

PARTICIPANTS
136 432 men and women aged 65 years or younger and free of diabetes, cancer, cardiovascular disease, respiratory disease, neurodegenerative disorders, gastric conditions, chronic kidney disease, and systemic lupus erythematosus before baseline.

MAIN OUTCOME MEASURE
Weight change within a four year period.

RESULTS
The final analyses included 46 722 women in the Nurses' Health Study, 67 186 women in the Nurses' Health Study II, and 22 524 men in the Health Professionals Follow-up Study. On average, participants gained 1.5 kg (5th to 95th centile −6.8 to 10.0) every four years, amounting to 8.8 kg on average over 24 years. Among men and women, increases in glycemic index and glycemic load were positively associated with weight gain. For example, a 100 g/day increase in starch or added sugar was associated with 1.5 kg and 0.9 kg greater weight gain over four years, respectively, whereas a 10 g/day increase in fiber was associated with 0.8 kg less weight gain. Increased carbohydrate intake from whole grains (0.4 kg less weight gain per 100 g/day increase), fruit (1.6 kg less weight gain per 100 g/day increase), and non-starchy vegetables (3.0 kg less weight gain per 100 g/day increase) was inversely associated with weight gain, whereas increased intake from refined grains (0.8 kg more weight gain per 100 g/day increase) and starchy vegetables (peas, corn, and potatoes) (2.6 kg more weight gain per 100 g/day increase) was positively associated with weight gain. In substitution analyses, replacing refined grains, starchy vegetables, and sugar sweetened beverages with equal servings of whole grains, fruit, and non-starchy vegetables was associated with less weight gain. The magnitude of these associations was stronger among participants with overweight or obesity compared with those with normal weight (P<0.001 for interaction). Most of these associations were also stronger among women.

CONCLUSIONS
The findings of this study highlight the potential importance of carbohydrate quality and source for long term weight management, especially for people with excessive body weight. Limiting added sugar, sugar sweetened beverages, refined grains, and starchy vegetables in favor of whole grains, fruit, and non-starchy vegetables may support efforts to control weight.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The role of carbohydrates in weight gain and obesity is controversial

Few studies have evaluated the association between changes in carbohydrate intake over time and long term changes in body weight

WHAT THIS STUDY ADDS

Increases in consumption of starch, added sugar, and carbohydrate from refined grains and starchy vegetables over four year periods were associated with concurrent greater weight gain

Increases in fiber and carbohydrate from whole grains, fruit, and non-starchy vegetables were associated with less weight gain

These associations were larger among participants with overweight or obesity

Introduction

Obesity continues to increase globally[1] despite numerous public health strategies targeting weight loss and prevention. The role of carbohydrate in weight gain and obesity remains controversial, and diets of varying macronutrient compositions, such as low fat, low carbohydrate, and high protein, are widely promoted.[2-7] Randomized trials of one year or more suggest a small advantage of lower carbohydrate diets for weight loss compared with low fat diets, but many of these trials included low intensity treatment and the diets were heterogeneous and differed in caloric restriction strategy, limiting inferences about efficacy of total carbohydrate reduction in itself.[8-11] Furthermore, weight loss trials have not directly dealt with potential causes of the small gradual weight gain accrued over midlife that typically lead to obesity.[12]

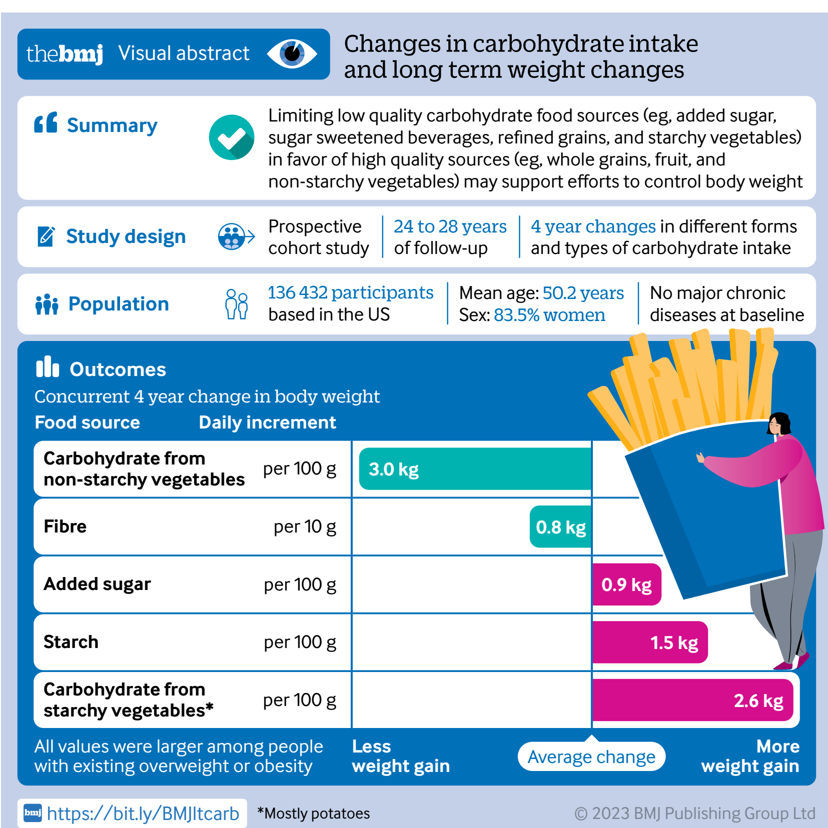
In contrast with carbohydrate quantity, more consistent evidence supports a role for the quality and source of carbohydrates with weight control.[13-15] For example, higher intakes of whole grains and dietary fiber have been related to favorable changes in body weight, whereas refined grains have been positively associated with weight gain.[16] Also, two metrics of carbohydrate quality, the glycemic index and glycemic load, have been investigated in many studies, with small benefits observed for weight management.[13 17] The Dietary Guidelines for Americans recommend that at least half the intake of grains should be from whole grains; all types of vegetables, including starchy vegetables, should be increased; and added sugar should be limited to less than 10% of daily energy intake.[18]

Until now most prospective observational studies of carbohydrate intake and body weight were limited by the use of single baseline diet assessments in relation to subsequent long term weight gain. Because recent or current diet is likely most relevant for body weight, repeated assessments of diet and examination of dietary changes concurrent with body weight change may better characterize weight gain prevention strategies. Thus, we prospectively investigated alterations in carbohydrate quantity and quality with weight change among women and men from three distinct cohorts with 24 to 28 years of follow-up. We investigated carbohydrate quality using the dietary glycemic index (response of blood glucose to a fixed amount of carbohydrate)[19] and dietary glycemic load (the arithmetic product of glycemic index and carbohydrate amount),[20] as well as different forms of carbohydrate and major food sources. We hypothesized that associations between alterations in carbohydrate intake depend on quality and source, and that weight changes would be stronger in people with overweight or obesity, a group predisposed to weight gain in the modern food environment.[21 22]

Methods

Study design and population

The Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study prospective cohorts enrolled 121 700 women (age 30-55 years) in 1976, 116 429 women (25-42 years) in 1989, and 51 529 men (40-75 years) in 1986, respectively.[23 24] Participants in all the cohorts completed self-administered questionnaires on personal characteristics, medical history, lifestyle, and other health related characteristics at baseline, and this information is updated every 2-4 years.



For the current analysis, baseline was the years in which the detailed dietary assessment was first administered: 1986 for the Nurses' Health Study, 1991 for the Nurses' Health Study II, and 1986 for the Health Professionals Follow-up Study. Participants were excluded if they were older than 65 years (because subsequent weight loss may represent unintentional decreases in lean mass rather than body fat loss) and if they reported a history of several conditions before baseline: diabetes, cancer, cardiovascular disease, respiratory disease, neurodegenerative disorders, gastric conditions, chronic kidney disease, and systemic lupus erythematosus. We also excluded those with missing data on diet or body weight and those who reported implausible energy intakes (<600 or >3500 kcal/day for women; <800 or >4200 kcal/day for men). Over follow-up, participants were censored on reaching age 65 or six years before diagnoses of any of the baseline disease exclusions. Participants in the Nurses' Health Study II who reported a pregnancy two years before or during the four year interval were excluded from the analysis for that interval. For pregnant participants, therefore, we only considered body weight at least one year post partum. The final analyses included 46 722 women in the Nurses' Health Study, 67 186 women in the Nurses' Health Study II, and 22 524 men in the Health Professionals Follow-up Study. The return of completed questionnaires was considered informed consent.

Dietary assessment

Diet was assessed using validated and reproducible semiquantitative food frequency questionnaires (>130 items) about usual frequency of intake of a specified portion size of each food during the preceding year.[25 26] Total carbohydrate intake (g/day) was derived from the responses to the food frequency questionnaires by multiplying the amount and frequency of carbohydrate in a questionnaire item and summing across all foods that contained carbohydrate. Similarly, we derived participants' typical intakes of fiber, starch, added sugar, natural sugar (present in foods such as fruit, fruit juices, and dairy products), and major foods, including whole grains, refined grains, fruit, non-starchy vegetables, and starchy vegetables. Consistent with our previous work[15] and the United States Department of Agriculture definition, we grouped peas, corn, fried potatoes (French fries and potato chips (crips)), and other potatoes (baked, boiled, or mashed, sweet, and yams) into starchy vegetables. We derived total glucose equivalents (glucose and glucose in sucrose, maltose, lactose, and starch) and total fructose equivalents (fructose and fructose in sucrose). Galactose equivalent was not derived as its only source is lactose (disaccharide of glucose and galactose). As a

Table 1 | Baseline characteristics and average changes in dietary intake over four years among 136 432 women and men in three prospective cohorts*

	Nurses' Health Study (n=46 722)		Nurses' Health Study II (n=67 186)		Health Professionals Follow-up Study (n=22 524)	
Characteristics	Mean (SD) at baseline	Four year change (5th-95th centile)	Mean (SD) at baseline	Four year change (5th-95th centile)	Mean (SD) at baseline	Four year change (5th-95th centile)
Age (years)	55.3 (6.6)	–	45.3 (8.0)	–	54.2 (7.2)	–
Weight (kg)	69.1 (13.6)	1.2 (−6.8 to 9.1)	69.9 (15.8)	1.8 (−6.8 to 11.3)	82.7 (12.1)	0.8 (−5.4 to 6.8)
Body mass index	25.7 (4.8)	0.4 (−2.4 to 3.3)	25.7 (5.5)	0.7 (−2.5 to 4.1)	25.8 (3.3)	0.2 (−1.6 to 2.2)
Physical activity (Met-hours/week)	18.1 (22.8)	0.7 (−27.6 to 30.2)	21.0 (25.8)	1.6 (−30.8 to 36.6)	30.3 (30.0)	4.6 (−39.5 to 53.2)
Alcohol (g/day)	5.9 (10.0)	−0.2 (−8.6 to 8.0)	4.9 (8.6)	0.7 (−5.8 to 9.1)	11.7 (15.0)	0.3 (−13.8 to 15.3)
Total daily sleep (hours/day)	7.0 (1.0)	–	7.0 (1.0)	–	7.1 (0.9)	–
Carbohydrate quantity:						
Total carbohydrate (g/day)	221.8 (74.7)	3.9 (−104.0 to 112.3)	223.6 (79.4)	−2.0 (−120.8 to 115.6)	244.6 (85.3)	2.3 (−115.5 to 119.0)
Carbohydrate quality:						
Glycemic index	52.5 (3.7)	0.1 (−6.0 to 6.2)	52.5 (4.1)	−0.5 (−7.1 to 5.9)	53.1 (3.5)	−0.2 (−5.8 to 5.3)
Glycemic load	116.3 (41.8)	2.9 (−58.4 to 65.0)	118.1 (44.9)	−2.1 (−70.0 to 64.5)	130.1 (47.9)	1.0 (−66.0 to 67.4)
Form of carbohydrate (g/day):						
Fiber	19.8 (7.8)	0.7 (−10.0 to 11.8)	20.1 (8.6)	0.9 (−10.8 to 13.0)	21.9 (9.1)	0.9 (−10.8 to 12.9)
Starch	73.8 (29.2)	3.4 (−41.4 to 48.9)	81.9 (33.3)	−0.5 (−54.1 to 52.8)	83.4 (35.6)	5.5 (−48.5 to 59.2)
Added sugar	45.1 (28.9)	1.3 (−40.0 to 43.4)	49.1 (34.6)	−1.8 (−49.3 to 43.5)	50.8 (33.9)	−0.1 (−44.6 to 43.4)
Natural sugar	59.6 (27.1)	0.4 (−37.0 to 37.8)	53.4 (26.1)	−0.4 (−36.9 to 35.6)	60.0 (29.3)	0.7 (−37.3 to 38.3)
Total glucose equivalents	125.8 (43.9)	4.6 (−60.0 to 69.6)	133.5 (48.7)	−1.7 (−76.3 to 72.4)	138.5 (51.6)	5.84 (−67.5 to 79.0)
Total fructose equivalents	43.7 (20.2)	0.3 (−28.9 to 29.6)	42.1 (21.9)	−0.8 (−32.1 to 29.5)	47.7 (23.1)	0.1 (−31.0 to 30.2)
Sources of carbohydrate (g/day):						
Whole grains	15.0 (14.2)	3.3 (−18.2 to 26.6)	20.4 (16.2)	2.5 (−21.9 to 28.0)	20.0 (17.3)	2.8 (−21.2 to 28.3)
Refined grains	50.5 (24.1)	0.0 (−38.1 to 39.2)	53.2 (27.2)	−2.8 (−45.1 to 39.5)	55.8 (27.7)	−0.8 (−43.4 to 42.5)
Fruit	22.6 (20.1)	0.7 (−28.3 to 30.4)	19.9 (19.1)	2.1 (−25.4 to 31.4)	22.7 (23.5)	2.0 (−28.3 to 33.6)
Non-starchy vegetables	12.8 (6.5)	0.3 (−9.1 to 10.1)	12.3 (7.0)	0.4 (−9.5 to 10.7)	12.5 (6.7)	0.6 (−8.9 to 10.6)
Starchy vegetables	19.6 (11.1)	−0.3 (−17.2 to 16.5)	18.6 (11.1)	−0.6 (−18.0 to 16.7)	21.5 (12.4)	−0.4 (−19.3 to 18.3)
Major foods containing carbohydrate (serving/day):						
Whole grains	1.4 (1.1)	0.1 (−1.8 to 2.0)	1.3 (1.1)	−0.1 (−1.9 to 1.6)	1.6 (1.4)	0.1 (−2.0 to 2.1)
Refined grains	1.6 (1.2)	0.0 (−2.0 to 1.9)	1.5 (1.1)	−0.1 (−1.9 to 1.7)	1.6 (1.2)	0.0 (−2.0 to 2.0)
Fruit	1.6 (1.1)	0.0 (−1.6 to 1.6)	1.3 (1.0)	0.1 (−1.4 to 1.7)	1.6 (1.2)	0.1 (−1.4 to 1.6)
Non-starchy vegetables	3.3 (1.9)	0.0 (−2.5 to 2.6)	3.2 (2.0)	0.1 (−2.5 to 2.9)	3.1 (1.8)	0.1 (−2.3 to 2.6)
Starchy vegetables	0.8 (0.5)	0.0 (−0.7 to 0.7)	0.7 (0.5)	0.0 (−0.8 to 0.7)	0.9 (0.5)	0.0 (−0.8 to 0.7)
Sugar sweetened beverages	0.2 (0.5)	0.0 (−0.7 to 0.7)	0.4 (0.7)	0.0 (−0.9 to 0.8)	0.4 (0.6)	0.0 (−0.8 to 0.7)
Other dietary nutrient intakes:						
Total energy (kcal/day)	1762 (505)	−6 (−728 to 713)	1783 (536)	2 (−790 to 794)	2005 (597)	−6 (−826 to 814)
Total protein (g/day)	80.3 (24.7)	−1.1 (−37.5 to 35.4)	81.6 (26.4)	−1.3 (−41.6 to 38.8)	88.9 (28.4)	−1.5 (−42.6 to 39.2)
Total fat (g/day)	61.5 (22.8)	−1.6 (−34.4 to 31.1)	62.7 (23.7)	1.2 (−34.6 to 37.8)	69.8 (27.4)	−0.7 (−38.2 to 37.0)
Polyunsaturated to saturated fat ratio	0.6 (0.2)	0.0 (−0.3 to 0.4)	0.6 (0.2)	0.0 (−0.3 to 0.4)	0.6 (0.2)	0.0 (−0.3 to 0.4)
Trans fatty acids (g/day)	2.6 (1.4)	−0.2 (−2.2 to 1.8)	2.3 (1.4)	−0.4 (−2.2 to 1.2)	2.8 (1.6)	−0.1 (−2.4 to 2.2)

MET=metabolic equivalent of task.
*Data are based on 24 years of follow-up (1986-2010) in the Nurses' Health Study, 24 years of follow-up (1991-2015) in the Nurses' Health Study II, and 28 years of follow-up (1986-2014) in the Health Professionals Follow-up Study. Supplementary table 1 lists the major foods contributing to each carbohydrate related variable.

result, total fructose equivalent and glucose equivalent do not add up to non-fiber carbohydrates. We estimated participants' average glycemic index by summing the products of carbohydrate content of each food per serving multiplied by the average daily servings, multiplied by glycemic index, and divided by total carbohydrate intake.[20] Glycemic load was calculated as for the glycemic index but without dividing by total carbohydrate intake.[20] In previous validation studies in these cohorts, the Pearson correlation coefficients comparing responses in the food frequency questionnaires with seven day dietary records was 0.69 for total carbohydrate, 0.66 for fiber, and 0.74 for sugar.[26] Supplementary table 1 summarizes the top food contributors for different carbohydrate variables.

Body weight change

The outcome of weight change was derived from body weight self-reported at baseline and biennially. Previous validation studies indicated the Spearman correlation coefficient was 0.96 compared with body weight measured in-person by staff.[27]

Covariates

The cohort questionnaires updated information on physical activity, smoking status, sleep duration, hours of sitting and watching television, and other important covariates every 2-4 years.

Statistical analysis

We calculated the alteration in carbohydrate intakes (carbohydrates as the nutrient, and foods containing carbohydrate) and change in body weight as the difference between baseline and follow-up for each four year interval, spanning a total follow-up period of 24 years in the Nurses' Health Study (1986-2010) and Nurses' Health Study II (1991-2015), and 28 years in the Health Professionals Follow-up Study (1986-

Table 2 | Pooled results for association between changes in glycemic index (per 10 units increment), glycemic load (per 100 units increment), and carbohydrates (per 100 g increment) and weight changes (kg) in all participants*

Variables	Minimally adjusted model† (95% CI)	P value	Multivariable adjusted model‡ (95% CI)	P value
Carbohydrate quantity:				
Total carbohydrate	0.3 (0.2 to 0.3)	<0.001	0.2 (0.2 to 0.2)	<0.001
Carbohydrate quality:				
Glycemic index	1.2 (1.1 to 1.2)	<0.001	1.2 (1.2 to 1.3)	<0.001
Glycemic load	0.6 (0.5 to 0.6)	<0.001	0.7 (0.6 to 0.7)	<0.001
Form of carbohydrate:				
Fiber (per 10 g increment)	−0.9 (−1.0 to −0.9)	<0.001	−0.8 (−0.8 to −0.8)	<0.001
Starch	1.8 (1.7 to 1.8)	<0.001	1.5 (1.4 to 1.5)	<0.001
Added sugar	1.4 (1.3 to 1.4)	<0.001	0.9 (0.8 to 1.0)	<0.001
Natural sugar	−0.3 (−0.4 to −0.2)	<0.001	−0.1 (−0.2 to 0.0)	0.005
Total glucose equivalents	1.8 (1.7 to 1.8)	<0.001	1.5 (1.4 to 1.5)	<0.001
Total fructose equivalents	0.0 (−0.1 to 0.1)	0.81	−0.2 (−0.4 to −0.1)	<0.001
Source of carbohydrate:				
Whole grains	−0.9 (−1.0 to −0.8)	<0.001	−0.4 (−0.5 to −0.3)	<0.001
Refined grains	1.1 (1.0 to 1.2)	<0.001	0.8 (0.7 to 0.9)	<0.001
Fruit	−1.8 (−1.9 to −1.7)	<0.001	−1.6 (−1.7 to −1.5)	<0.001
Non-starchy vegetables	−4.3 (−4.6 to −4.0)	<0.001	−3.0 (−3.3 to −2.7)	<0.001
Starchy vegetables	3.5 (3.3 to 3.6)	<0.001	2.6 (2.4 to 2.8)	<0.001

CI=confidence interval.

*Data are based on 24 years of follow-up (1986-2010) in the Nurses' Health Study, 24 years of follow-up (1991-2015) in the Nurses' Health Study II, and 28 years of follow-up (1986-2014) in the Health Professionals Follow-up Study.

†Includes age (continuous) and questionnaire cycle (every four years); for different carbohydrates, these variables were mutually adjusted.

‡Includes body mass index (continuous) at beginning of each four year period, sleep duration (≤6, 7, 8, >8 hours/day), and changes in physical activity (continuous), alcohol use (continuous), time spent watching television (baseline only in Nurses' Health Study and Nurses' Health Study II (0-1, 2-5, 6-20, 21-40, >40 hours/week); and also change over four years in Health Professionals Follow-up Study (continuous)), smoker status (stayed never, stayed former, stayed current, former to current, never to current, current to former), total fat (continuous), total protein (continuous), polyunsaturated to saturated fat ratio (continuous), and trans fatty acids (continuous). For glycemic index and glycemic load, additional adjustment was done for changes in cereal fiber (continuous).

2014). Multivariable generalized linear regression models with an unstructured correlation matrix and robust variance accounting for within person repeated measures were used, with change in body weight as the dependent variable. Both intake and outcome were analyzed as continuous variables, and outliers were truncated at the 0.5th and 99.5th centiles. We adopted a unified change unit of 100 g increment/day for ease of comparisons among different carbohydrates (10 g increment for fiber) but noting that the range of intakes varied considerably for different carbohydrates (see supplementary table 2). We also evaluated carbohydrate intake categorically by fifths of changes in intake.

In multivariable models we adjusted for age, questionnaire cycle, and body mass index (BMI) at the beginning of each four year period, sleep duration, and changes over four years in physical activity, time spent watching television, smoking, alcohol intake, protein intake, total fat intake, polyunsaturated to saturated fat ratio, and trans fatty acid intake in each four year interval. In the primary analysis we did not adjust for change in total energy intake because it may mediate an effect of carbohydrate on weight change. Also, adjusting for change in total energy intake might lead to multicollinearity in some analyses owing to a high correlation (see supplementary table 3). Missing covariate data were handled with a missing indicator for categorical variables (6.1% (n=8322) missing for sleep duration, 4.3% (n=5866) for time spent watching television, and 0.3% (n=409) for smoking) and last value carried forward for continuous variables (5.6% (n=7640) missing for physical activity). Results using 10 times multiple imputation to impute missing data or excluding participants with missing data remained similar (data not shown for simplicity). We additionally adjusted for change in cereal fiber intake in the glycemic index and glycemic load analyses and mutually adjusted for different forms or sources of carbohydrates. For example, we mutually adjusted for fiber, starch, added sugar, and natural sugar. We did the same for five types of sugar, total glucose equivalent, total fructose equivalent, and carbohydrates from five sources.

Secondarily, we conducted analyses for changes in BMI in the same four year period. We also performed substitution models between increases and decreases in major foods containing carbohydrate, as well as carbohydrates as nutrients, with concurrent change in weight. To estimate effects of substitutions, we included continuous changes in intake for the two foods or two carbohydrates simultaneously in the same multivariable model, which also contained total energy intake and other covariates. We then calculated the difference between the β coefficients; variances and covariance were used to estimate the 95% confidence intervals.[28]

In sensitivity analyses, we additionally adjusted for baseline carbohydrate intake or total energy intake at the beginning of each four year period, or changes in total energy intake or neighborhood socioeconomic status over the four year period.[29] Effect modification was also examined according to BMI category (<25, 25-30, and ≥30), age (<50 years, ≥50 years), sex (female or male), physical activity (below or above median), smoking status (ever or never smoker), alcohol intake (never, 0-15, and ≥15 g/day), and self-reported race (white, black, and Asian) at each four year baseline. Wald P values for interactions were calculated by adding a multiplicative interaction term

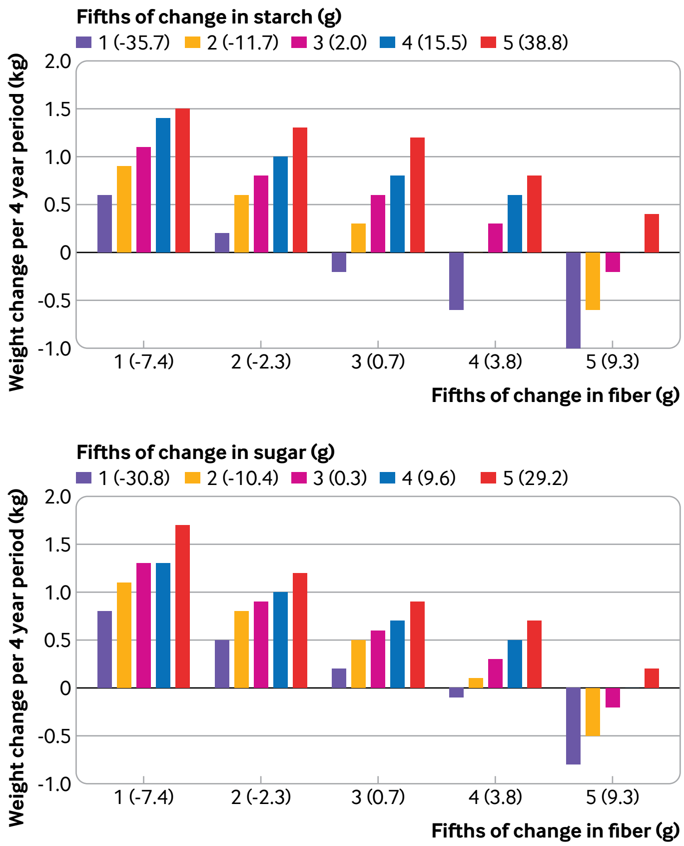


Fig 1 | Associations between cross stratified fifths of changes in fiber and starch or added sugar and weight change. Data were pooled from three cohorts. Positive values indicate weight gain, and negative values indicate weight loss. Weight change values were calculated based on a reference participant from the Nurses' Health Study: woman aged 55 years who had never smoked, had a body mass index of 25, watched television for 0-1 hour daily, slept for 7-8 hours daily, and had no changes in physical activity, alcohol intake, or other dietary intake during the 2006-10 questionnaire cycle. Numbers in parentheses are the median values of the groups

between an ordinal subgroup variable and the change in carbohydrate intake. All analyses were carried out with SAS version 9.4 in each cohort and then pooled through fixed effect meta-analysis. We used a two sided α <0.005 for statistical significance.[30]

Patient and public involvement

No participants were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study or asked to advise on the interpretation or writing up of the manuscript. They did, however, provide feedback about our questionnaires throughout follow-up, and this has been incorporated when feasible. The participants are also updated on findings and developments of the cohorts through annual newsletters and the official websites (https://www.nurseshealthstudy.org and https://www.hsph.harvard.edu/hpfs).

Results

Descriptive characteristics

Table 1 shows the baseline characteristics of the 136 432 women and men in the three cohorts. For the cohorts combined, the average weight gain over a four year period was 1.5 kg (5th to 95th centile −6.8 to 10.0), a gain of 8.8 kg on average over 24 years. The cohort specific average weight gain over four years was 1.2 kg (−6.8 to 9.1) in the Nurses' Health Study, 1.8 kg (−6.8 to 11.3) in the Nurses' Health Study II, and 0.8 kg (−5.4 to 6.8) in the Health Professionals Follow-up Study. Given these findings, the inverse associations of the changes in carbohydrate intake with weight change (ie, negative values) were interpreted as less weight gain instead of weight loss, although for some participants this would have been weight loss.

Changes in total carbohydrates, glycemic index, and glycemic load

Table 2 shows the results for age adjusted and multivariable adjusted continuous models of carbohydrate increase with weight change. Overall, increases in total carbohydrate intake and in dietary glycemic index and glycemic load were associated with greater weight gain. For example, a 100 g/day increase in total carbohydrates was associated with concurrent greater weight gain of 0.2 kg (95% confidence interval 0.2 to 0.2) over a four year period. Similarly, each 10 unit increase in glycemic index and 100 unit increase in glycemic load was associated with 1.2 kg (1.2 to 1.3) and 0.7 kg (0.6 to 0.7) greater weight gain, respectively. Findings were similar, in direction and magnitude, across the three cohorts (see supplementary figure 1). Analyses by fifths support generally linear associations between changes in total carbohydrate, glycemic index, and glycemic load and weight change (see supplementary figure 2).

Changes in carbohydrate forms and food sources

Dietary increases in starch, added sugar, and total glucose equivalents were associated with greater weight gain, whereas increases in fiber, natural sugars, and total fructose equivalents were associated with less weight gain (table 2). For example, after multivariable adjustment, each 100 g/day increase in starch, added sugar, or total glucose equivalents was associated with 1.5 kg (1.4 to 1.5), 0.9 kg (0.8 to 1.0), and 1.5 kg (1.4 to 1.5) greater weight gain over four years, respectively. In contrast, each 10 g/day increase in fiber and 100 g/day increases in natural sugars and total fructose equivalents were related to concurrent −0.8 kg (−0.8 to −0.8), −0.1 kg (−0.2 to 0.0), and −0.2 kg (−0.4 to −0.1) less weight gain over four years. Increases in fiber intake specifically from cereals, fruit, and vegetables were related to less weight gain (see supplementary table 4), with the largest magnitude for increased fiber from fruit. Increases in various sugar forms were also variably related to weight change, indicating greater weight gain over four years in association with glucose and sucrose. However, increases in fructose and lactose were associated with less weight gain.

Increases in intake of equal amounts of carbohydrates from various foods were differentially related to concurrent weight gain (table 2). After multivariable adjustment, each 100 g/day increase

Decreased consumption (one serving per day)

Increased consumption (one serving per day)

	Whole grains	Refined grains	Fruit	Non-starchy vegetables	Starchy vegetables	Peas	Corn	Fried potatoes	Other potatoes	Fruit juices	Sugar sweetened beverages
Whole grains	0	-0.2 (-0.2 to -0.2)	0.3 (0.3 to 0.3)	0.1 (0.0 to 0.1)	-0.7 (-0.7 to -0.6)	-0.1 (-0.2 to 0.0)	-0.7 (-0.8 to -0.6)	-1.8 (-1.9 to -1.7)	-0.2 (-0.3 to -0.2)	-0.3 (-0.3 to -0.3)	-0.5 (-0.5 to -0.5)
Refined grains		0	0.5 (0.5 to 0.5)	0.3 (0.3 to 0.3)	-0.5 (-0.5 to -0.4)	0.1 (0.0 to 0.2)	-0.5 (-0.6 to -0.4)	-1.6 (-1.7 to -1.6)	0.0 (-0.1 to 0.1)	-0.1 (-0.1 to -0.1)	-0.3 (-0.4 to -0.3)
Fruit			0	-0.2 (-0.3 to -0.2)	-1.0 (-1.0 to -0.9)	-0.6 (-0.7 to -0.5)	-1.2 (-1.3 to -1.1)	-1.9 (-2.0 to -1.8)	-0.5 (-0.6 to -0.4)	-0.6 (-0.7 to -0.6)	-0.8 (-0.8 to -0.7)
Non-starchy vegetables				0	-0.9 (-0.9 to -0.9)	-0.6 (-0.8 to -0.5)	-1.3 (-1.4 to -1.2)	-1.8 (-1.8 to -1.7)	-0.4 (-0.4 to -0.3)	-0.4 (-0.4 to -0.4)	-0.6 (-0.6 to -0.5)
Starchy vegetables					0	1.6 (1.4 to 1.7)	0.8 (0.7 to 1.0)	-1.5 (-1.7 to -1.4)	1.7 (1.6 to 1.9)	0.4 (0.4 to 0.4)	0.2 (0.1 to 0.2)
Peas						0	-0.8 (-1.0 to -0.6)	-1.7 (-1.8 to -1.5)	-0.1 (-0.2 to 0.0)	-0.2 (-0.3 to -0.1)	-0.4 (-0.5 to -0.2)
Corn							0	-1.2 (-1.3 to -1.0)	0.5 (0.4 to 0.7)	0.4 (0.3 to 0.5)	0.2 (0.1 to 0.3)
Fried potatoes								0	1.7 (1.6 to 1.8)	1.5 (1.5 to 1.6)	1.3 (1.2 to 1.4)
Other potatoes									0	-0.1 (-0.2 to 0.0)	-0.3 (-0.3 to -0.2)
Fruit juices										0	-0.2 (-0.3 to -0.2)
Sugar sweetened beverages											0

Fig 2 | Associations of substituting major foods containing carbohydrate with weight change (kg). Data are from a multivariable adjusted model including age (continuous), questionnaire cycle (four year intervals), body mass index (continuous) at beginning of each four year period, sleep duration (≤6, 7, 8, >8 hours/day), and changes in physical activity (continuous), alcohol use (continuous), time spent watching television (baseline only in Nurses' Health Study and Nurses' Health Study II (0-1, 2-5, 6-20, 21-40, >40 hours/week); and also four year change in Health Professionals Follow-up Study (continuous)), smoker status (stayed never, stayed former, stayed current, former to current, never to current, current to former), total energy intake, and intake of foods not containing carbohydrate (continuous). Red indicates positive associations and blue indicates inverse associations. Numbers in parentheses are 95% confidence intervals. See supplementary table 14 for gram weights for a standard serving of different foods

was associated with greater weight gain over four years of 0.8 kg (0.7 to 0.9) for refined grains and 2.6 kg (2.4 to 2.8) for starchy vegetables; however, increases in carbohydrates from whole grains (−0.4 kg (−0.5 to −0.3)), fruit (−1.6 kg (−1.7 to −1.5)), and non-starchy vegetables (−3.0 kg (−3.3 to −2.7)) were associated with less weight gain.

In analyses by fifths of intake, changes in weight with decreases in intake of carbohydrate variables were generally the inverse of changes in weight with increases in intake (see supplementary figure 2). In cross stratification analyses, changes in intake of fiber and starch or added sugar were independently associated with weight change (fig 1); although participants overall gained weight, those who reduced intake of starch or added sugar and increased fiber intake could lose weight. In substitution analyses, replacing carbohydrates from refined grains or from starchy vegetables with equal energy from carbohydrates from whole grains, fruit, or non-starchy vegetables was associated with less weight gain (see supplementary figure 3). Replacing total fat with carbohydrates from these three food sources was also associated with less weight gain.

Changes in major foods containing carbohydrate

Increased intakes of whole grains, fruit, and non-starchy vegetables were associated with less weight gain, whereas increased intakes of refined grains, total starchy vegetables, and sugar sweetened beverages were associated with more weight gain (see supplementary table 5). In substitution analyses, generally, increasing one serving per day of whole grains, fruit, or non-starchy vegetables—while simultaneously decreasing an equal serving of starchy vegetables, fried potatoes, or sugar sweetened beverages—was associated with less weight gain (fig 2).

Additional analyses

Results remained similar when we further adjusted the multivariable models for baseline carbohydrate intake or total energy intake during each four year period, or for changes in socioeconomic status (see

Table 3 | Association between changes in glycemic index (per 10 units increment), glycemic load (per 100 units increment), and carbohydrates (per 100 g increment) and weight changes (kg) according to body mass index at beginning of each four year period*

Variables	Normal weight: BMI <25 (95% CI)	Overweight: BMI 25-29 (95% CI)	Obese: BMI ≥30 (95% CI)	P for interaction
No of participants	82 858	37 050	16 524	
Carbohydrate quantity:				
Total carbohydrate	0.1 (0.1 to 0.1)	0.4 (0.4 to 0.5)	0.8 (0.7 to 0.9)	<0.001
Carbohydrate quality:				
Glycemic index	0.6 (0.5 to 0.6)	1.7 (1.6 to 1.7)	2.8 (2.6 to 2.9)	<0.001
Glycemic load	0.3 (0.2 to 0.3)	1.1 (1.0 to 1.3)	2.1 (1.9 to 2.3)	<0.001
Form of carbohydrate:				
Fiber (per 10 g increment)	−0.4 (−0.5 to −0.4)	−1.0 (−1.0 to −0.9)	−1.9 (−2.0 to −1.8)	<0.001
Starch	0.8 (0.7 to 0.8)	2.1 (2.0 to 2.2)	4.0 (3.8 to 4.3)	<0.001
Added sugar	0.4 (0.3 to 0.4)	1.2 (1.1 to 1.3)	1.9 (1.7 to 2.1)	<0.001
Natural sugar	−0.1 (−0.2 to 0.0)	−0.3 (−0.5 to −0.1)	0.0 (−0.3 to 0.4)	<0.001
Total glucose equivalents	0.3 (0.3 to 0.4)	1.2 (1.0 to 1.3)	2.1 (1.8 to 2.3)	<0.001
Total fructose equivalents	−0.3 (−0.5 to −0.2)	−0.8 (−1.0 to −0.5)	−1.0 (−1.4 to −0.6)	<0.001
Source of carbohydrate:				
Whole grains	−0.4 (−0.5 to −0.2)	−0.3 (−0.5 to −0.1)	−0.8 (−1.2 to −0.3)	<0.001
Refined grains	0.5 (0.5 to 0.6)	1.5 (1.3 to 1.6)	2.7 (2.5 to 3.0)	<0.001
Fruit	−0.8 (−0.9 to −0.7)	−1.9 (−2.1 to −1.7)	−3.4 (−3.7 to −3.0)	<0.001
Non-starchy vegetables	−1.8 (−2.1 to −1.5)	−3.6 (−4.1 to −3.0)	−5.8 (−6.8 to −4.8)	<0.001
Starchy vegetables	1.3 (1.1 to 1.5)	3.7 (3.4 to 4.0)	5.8 (5.3 to 6.4)	<0.001

CI=confidence interval.
*Data were pooled from three cohorts and stratified analyses conducted. Data are from a multivariable adjusted model including age (continuous), questionnaire cycle (every four years), mutual adjustment as appropriate, body mass index (continuous) at beginning of each four year period, sleep duration (≤6, 7, 8, >8 hours/day), and changes in physical activity (continuous), alcohol use (continuous), time spent watching television (baseline only in Nurses' Health Study and Nurses' Health Study II (0-1, 2-5, 6-20, 21-40, >40 hours/week); and also change over four years in Health Professionals Follow-up Study (continuous)), smoker status (stayed never, stayed former, stayed current, former to current, never to current, current to former), total fat (continuous), total protein (continuous), polyunsaturated to saturated fat ratio (continuous), and trans fatty acids (continuous). For glycemic index and glycemic load, additional adjustment was done for changes in cereal fiber (continuous).

supplementary table 6). When we further adjusted for change in total energy intake during the same four year period, the positive associations for starch, added sugar, and carbohydrates from refined grains and starchy vegetables were all attenuated but still statistically significant, suggesting that changes in energy intake mediate some, but not necessarily all, of the underlying associations. Analysis for changes in BMI showed similar results to that for weight changes (see supplementary table 7). In analysis stratified by BMI at the beginning of each four year period, the positive associations of glycemic index, glycemic load, and carbohydrates with weight change were substantially stronger among participants with overweight or obesity at baseline compared with participants with normal weight; similarly, inverse associations were stronger among those with overweight and obesity (all P for interaction <0.001) (table 3). Most of the observed associations were also stronger among women compared with men (see supplementary table 8). Specifically, the small positive association for change in total carbohydrate intake was only observed in women. The magnitudes of weight change were generally larger among participants younger than 50 years and those with lower physical activity or lower alcohol intake (see supplementary tables 9-11). Findings for all carbohydrate variables were generally similar in analyses stratified by smoking status and race or ethnicity (see supplementary tables 12 and 13).

Discussion

In this large prospective study of US men and women, moderate increases in usual dietary glycemic index and glycemic load, starch, added sugar, refined grains, and starchy vegetables were associated with more concurrent weight gain throughout midlife. In contrast, increasing intake of fiber, natural sugars, whole grains, fruit, and non-starchy vegetables were associated with less weight gain. These associations were particularly strong among participants with overweight and obesity at baseline. In substitution models, replacing refined grains, potatoes and other starchy vegetables, and sugar sweetened beverages with equal servings of whole grains, fruit, or non-starchy vegetables was associated with less weight gain. Also, we found that increases in starch intake were more strongly associated with weight gain than increases in added sugar. Increases in total glucose equivalents were associated with greater weight gain, and increases in total fructose equivalents were associated with less weight gain.

Comparison with other studies

Evidence on the association of overall carbohydrate intake, glycemic index, and glycemic load with weight change has been mixed and controversial.[17 31 32] In a meta-analysis of weight loss trials with isocaloric and non-isocaloric restriction strategies but equal intensity of intervention and lasting more than one year,[8] slightly greater weight loss was seen with diets that were lower in carbohydrate and higher in fat compared with the opposite. The relevance of these weight loss interventions to gradual, long term weight gain is, however, unclear, and evidence from randomized trials is limited. The directionally opposite associations that we observed with different forms of carbohydrate suggest that total carbohydrate in itself may not be the critical factor in weight change. In one randomized trial a modest reduction in glycemic index improved maintenance of weight loss.[33] However, dietary glycemic index and glycemic load were not clearly related to BMI in studies that were cross sectional or had single dietary assessments.[17] Potential mechanisms for adverse effects of carbohydrate overall, glycemic index, and glycemic load on body weight include heightened responses to insulin and other hormonal changes that favor fat deposition.[4 6 34 35]

Observations across cultures and over time have suggested that the refining of grains and increases in sugar consumption may contribute importantly to weight gain.[36] Consistent with our findings, previous cohort analyses support an inverse associations between fiber intake and weight change,[16 37-39] and added sugar intake has been positively associated with weight gain.[40] Fiber may reduce food intake by promoting satiation or satiety, increasing fat oxidation, decreasing fat storage, or altering the microbiome.[41 42] Added sugar and the consumption of sugar sweetened beverages may blunt satiety and promote energy intake.[43] Notably, starch (mainly from refined grains and starchy vegetables) was slightly more strongly associated with weight increases than was the same amount of added sugar. We observed attenuated associations for changes in added sugar and starch after adjusting for concurrent changes in total energy intake, suggesting a partial mediating role of energy intake. Nevertheless, associations remained statistically significant after adjustment for energy, suggesting that other resultant changes (for example, changes in energy expenditure) may also lead to weight gain. Low calorie and no calorie sweetened beverages have been proposed as an alternative replacement strategy for sugar sweetened beverages in adults with overweight or obesity, to reduce extra energy intake.[44] The latest guidelines from the World Health Organization recommend avoiding non-sugar sweeteners (low calorie and no calorie sweeteners) to control weight but also highlight the need for further research.[45]

Consistent with our previous reports,[14 15] we also observed that women and men who increased their intakes of whole grains, fruit, and non-starchy vegetables concurrently gained less weight over time, and those who increased their intakes of refined grains and starchy vegetables (including French fries and potato chips) had more weight gain. The findings for whole grain intake have been observed in other longitudinal cohorts,[46] whereas evidence for fruit being favorably related to weight gain has been mixed.[15 47 48] Our findings for starchy vegetables raise concerns about the current recommendation of the Dietary Guidelines for Americans to increase consumption of all types of vegetables, specifically including starchy vegetables.[18]

In our subgroup analyses, the direction of associations between carbohydrate variables and weight change was generally consistent across categories of sex, BMI, age, physical activity level, smoker status, alcohol intake, and race or ethnicity, although some heterogeneity was statistically significant. Importantly, compared to participants with normal weight, participants with overweight or obesity had substantially larger average weight change values associated with carbohydrate intake, specifically much more weight gain for increased consumption of added sugar and starchy vegetables and much less weight gain for fiber, fruit, and non-starchy vegetables. This effect modification by BMI has been observed for other aspects of diet and physical activity.[49 50] The susceptibility to weight change for participants with overweight or obesity could be possibly related to underlying insulin resistance, dysfunctional adipose tissue lipolysis, and reduced brown adipose tissue activity.[51] This susceptibility may be related to both genetic and environmental factors. Future analyses could be performed to explore whether these associations were also modified by insulin resistance or impaired insulin secretion. We also observed stronger associations among women compared with men, suggesting that women may exhibit greater susceptibility to weight change after carbohydrate consumption. The biological reasons behind this finding are, however, unclear.

Strengths and limitations of this study

Strengths of our study include the large sample sizes across the three cohorts and the long duration of follow-up, spanning the important period of weight gain in midlife. With the repeated dietary assessments and validated questionnaires, we could specifically evaluate within person changes in diet and weight that more closely emulated changes observed in the context of dietary interventions. In contrast, single measures of baseline diet are limited from evaluating change in itself and may miss gradual changes in diet and weight, including those that occurred before baseline and had reached a new steady state. In addition to changes in carbohydrate quantity, we also comprehensively investigated changes in several aspects of carbohydrate quality represented by both nutrients and foods.

Limitations of our analysis include reliance on self-reported estimates of both the carbohydrate intakes and the weight outcomes. Errors in dietary measurement could bias results if those with high BMI differentially under-reported or over-reported their intake. However, controlling for baseline BMI did not statistically significantly affect the results. Although these self-reported data have been repeatedly validated in subsets of the cohorts,[25 26] data on the validity of the change measures are lacking. Also, changes in carbohydrate variables may be associated with changes in other dietary factors. We adjusted for simultaneous changes in dietary protein and fat intake to deal with these sources of confounding, as well as changes in physical activity and other lifestyle behaviors during the same periods. Furthermore, because changes in weight are assessed within the same four year interval as the change in diet, reverse causation is possible. Generalizability to other populations is an additional limitation. However, analysis of women stratified by race or ethnicity indicated generally similar associations across these groups. In addition, we do not have data on free sugars as defined by WHO.[52]

Conclusion and public health implications

The findings of this study suggest that an increase in dietary glycemic index, glycemic load, and amounts of starch, added sugars, refined grains, and starchy vegetables are associated with greater weight gain in mid-life. In contrast, an increase in amounts of fiber, whole grains, fruit, and non-starchy vegetables was associated with less weight gain. These findings support the potential importance of carbohydrate quality and source for long term weight control.

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Ethical approval: The study was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Data sharing: No additional data available.

The lead author (YW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: The results will be disseminated to all study participants through an annual newsletter accessible by the general public (https://nurseshealthstudy.org/participants/newsletters), and through lay and social media.

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Supplementary information: Additional tables 1-14 and figures 1-3