

Dietary Patterns, Insulin Resistance, and Incidence of Type 2 Diabetes in the Whitehall II Study

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OBJECTIVE — The aim of this study was to identify a dietary pattern associated with insulin resistance and investigate whether this pattern was prospectively associated with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Analysis was based on 7,339 participants of the Whitehall II study. Dietary intake was measured using a 127-item food frequency questionnaire. We used the reduced rank regression method to determine dietary patterns using the homeostasis model assessment of insulin resistance as the intermediate or response variable. The association between the dietary pattern identified and incidence of type 2 diabetes was investigated using Cox proportional hazard regression models.

RESULTS — We identified a dietary pattern characterized by high consumption of low-calorie/diet soft drinks, onions, sugar-sweetened beverages, burgers and sausages, crisps and other snacks, and white bread and low consumption of medium-/high-fiber breakfast cereals, jam, French dressing/vinaigrette, and wholemeal bread. Higher dietary pattern scores were associated with increased risk of type 2 diabetes (hazard ratio for top quartile 2.95 [95% CI 2.19–3.97]; adjusted for age, sex, and energy misreporting). This relationship was attenuated after adjustment for ethnicity, employment grade, health behaviors (smoking, alcohol use, and physical activity) but remained significant after further adjustment for blood pressure and BMI (1.51 [1.10–2.09]).

CONCLUSIONS — A dietary pattern associated with insulin resistance predicts type 2 diabetes risk after adjustment for a range of confounders. This study adds to the evidence that dietary patterns are an important risk factor for type 2 diabetes.

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The worldwide prevalence of type 2 diabetes is alarmingly high (1). Diabetes is an important cause of morbidity and a major risk factor for cardiovascular disease (2). Dietary intake is a potentially modifiable risk factor (2), and although there is convincing evidence for the role of excess calorie intake in the development of type 2 diabetes, the evidence surrounding other diet-related risk factors is far less complete or convincing (3). Further research is required to identify optimal eating patterns for the prevention of type 2 diabetes and provide the evidence base for dietary targets.

In much of the work surrounding diet and chronic disease, a single nutrient approach has been adopted. Increasingly, dietary patterns are thought to be important determinants of chronic disease (4). A dietary patterns approach recognizes that foods are consumed in many complex combinations and that nutrients may have interactive and synergistic effects (4).

Approaches to studying dietary patterns fall into two categories, using either dietary scores determined by a priori dietary guidelines or multivariate statistical techniques (4). To date, multivariate sta-

tistical approaches have tended to use factor and cluster analysis techniques (4). However, a new approach to dietary pattern analysis has emerged that combines multivariate approaches with existing knowledge of diet-disease relationships (5). In reduced rank regression (RRR) analysis, variations in food intake are used to predict intermediate outcomes such as nutrient intakes, biomarkers of intakes, or biomarkers of the disease process and subsequently relationships between the identified dietary patterns and disease are investigated. This approach has been used to study obesity (6), diabetes (5,7,8), cardiovascular disease (9,10), and all-cause mortality (11). Previous studies of type 2 diabetes and dietary patterns using RRR relied on self-report of diabetes status without an oral glucose tolerance test (OGTT) to identify incident disease (5,7,8).

The aim of this study was to identify a dietary pattern using RRR that is associated with insulin resistance, a phenotype closely associated with development of type 2 diabetes, and, subsequently, to investigate the prospective association between the dietary pattern and disease.

RESEARCH DESIGN AND METHODS

Men and women aged 35–55 years from 20 civil service departments in London were invited by letter in 1985–1988 to participate in the Whitehall II study (phase 1, $n = 10308$). Medical examinations and self-report questionnaires were repeated at 5-year intervals. The cohort was sent a further questionnaire between each clinic visit. Full details of the study are reported elsewhere (12). Ethical approval was obtained from the University College London Medical School Committee on the Ethics of Human Research. Consent was obtained at phase 1 and renewed at each contact. Analysis is based on data from 7,339 participants aged 39–63 years who completed a food frequency questionnaire (FFQ) in 1991–1993 (phase 3), fasted (duration >5 h), and had no history of diabetes. Individuals with self-reported or OGTT-diagnosed diabetes at phase 3 were excluded from

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the analysis. The participation rate (response to questionnaire and/or screening) was 85.0% ($n = 8,637$; 143 deaths) at phase 3 and 71.5% ($n = 6,914$; 499 further deaths) at phase 7 (2003–2004). Of those eligible for analysis of dietary patterns at phase 3, follow-up was available for 94.1% ($n = 6,904$). The sample analyzed with no missing covariates consisted of 92.8% of those eligible ($n = 6,699$).

Outcome ascertainment

Incident cases of diabetes were identified by self-report (doctor's diagnosis or diabetic medication) and a 2-h 75-g OGTT at phases 5 and 7 according to the 1999 World Health Organization classification (13). Incident diabetes was dated at the day of clinic visit for those first identified through an OGTT. For those identified by self-report, the midpoint between the first instance of self-reported diabetes and the previous phase was used. Person-time of exposure was censored at the midpoint between the last known visit and the first missing visit for those lost to follow-up. Participants with an intermediate missing phase were assumed to have continuous follow-up time. For those who had not developed diabetes up to phase 7, follow-up (mean duration 11.6 years) was censored on 30 September 2004 (phase 7 closing date). Of 264 cases of diabetes first diagnosed at phase 7, 172 (65%) were detected through screening (OGTT or fasting glucose) only. New diabetes was self-reported by 92 participants, and of these 21 had confirmation by fasting glucose. Of the 71 remaining self-reported cases, 40 reported diabetic medication at phases 7 or 8 (2006), and 31 (11.7% of total) were unsupported by other evidence.

Blood collection

Blood samples were collected after an overnight fast or in the afternoon, after no more than a light fat-free breakfast eaten before 8 A.M., and stored at -80°C until assay (14). Glucose was determined in plasma by an electrochemical glucose oxidase method. Serum insulin was measured by radioimmunoassay using a polyclonal guinea pig antiserum (14). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting glucose (millimoles per liter) \times fasting insulin (milliunits per liter)/22.5 (15).

Dietary intake

Dietary intake was assessed using a 127-item FFQ. Participants were asked to report the frequency of consumption of standard portion sizes of each food during the previous year. Response options ranged from "never or less than once/month" to "six or more times/day." Responses were converted to food intake in grams per day for analysis. The questionnaire was previously validated in this cohort among 457 male and 403 female subjects using 7-day food diaries (16). Spearman correlation coefficients for energy-adjusted nutrient intakes ranged from 0.35 (β -carotene) to 0.78 (alcohol) for men and 0.33 (vitamin E) and 0.83 (alcohol) for women. FFQ data from phase 3 was used for this analysis.

Total energy intake was evaluated by examining the ratio of energy intake to estimated energy expenditure. The ratio, energy intake to energy expenditure, will be 1 if there is no energy misreporting and <1 if there is underreporting. Energy expenditure was based on estimated basal metabolic rate (17), and a physical activity level of 1.55 (sedentary) was assumed for this cohort of office workers. Energy cost of reported leisure-time physical activity was added using MET values for energy expenditure per kilogram body weight (3 MET/h for moderate activity and 5 MET/h for vigorous activity) (18).

Covariates

Employment grade within the civil service (six levels) was used as the measure of adult socioeconomic position (14). Smoking habits (never, ex-smoker, or current smoker) and leisure-time physical activity (hours of moderate/vigorous activity per week) were self-reported. Alcohol intake (grams per day) was calculated from the FFQ. Weight and height were measured with participants dressed in a cloth gown and underclothes. Blood pressure was measured twice with the Hawksley random-zero sphygmomanometer after a 5-min rest, and the mean value was taken.

Statistical analysis

Dietary patterns were determined using RRR techniques as described by Hoffmann et al. (5) and applied in recent studies (5–11). RRR determines factors from food intake data that maximize the explained variation in an intermediate marker that is hypothesized to be related to the health outcome. The relationship with the health outcome is then investi-

gated. In RRR, the food intake variables are known as predictors and the intermediate markers are known as responses. In previous analyses, response variables have included nutrient intakes (5,6,11), biomarkers of dietary intake (10), and biomarkers of disease risk (7,9).

The HOMA-IR index was chosen as the response variable, as it is influenced by diet and is closely related to the underlying pathophysiology of diabetes (19). HOMA-IR has been shown to be a good measure of insulin resistance when compared with "gold standard" techniques (15). HOMA-IR was log-transformed before analysis. The number of dietary patterns extracted using RRR analysis is determined by the number of response variables; hence, one dietary pattern was extracted. RRR generates dietary pattern scores that are similar to those derived from factor analysis. Each participant receives a score that represents the sum of the food intake variables weighted by the loadings generated from the RRR analysis and reflects how closely their dietary intake matches the dietary pattern. All foods contributed to calculation of the dietary pattern score, whereas foods with absolute factor loadings >0.20 were used to describe the dietary pattern (5,8,11). Factor loadings reflect the correlation of each food group with the dietary pattern (8).

The food and beverage items on the FFQ were aggregated into 71 groups on the basis of nutrient content, cooking and preparation methods, and consistency with other studies of dietary patterns and type 2 diabetes (7,8). Single food items hypothesized to represent specific eating behaviors were retained, consistent with the existing literature (20). As alcohol may have distinct effects on diabetes risk, we excluded alcohol items from the dietary pattern analysis and investigated alcohol as a separate covariate.

To investigate the robustness of the dietary patterns, we randomly split the cohort and repeated the RRR analysis in one-half of the cohort. This was repeated five times. The mean Spearman correlation coefficient between the factor loadings of these dietary patterns and the original dietary pattern factor loadings was 0.93. We additionally performed the dietary pattern analysis using food intakes adjusted for energy intake, sex, and employment grade using the residual method (21). The resulting dietary patterns were similar (data not shown), and unadjusted patterns were used in the analysis. RRR analysis was also repeated

Table 1—Food groups in the dietary pattern with factor loadings >0.20 and the mean intakes across quartiles of the dietary pattern score

Food	Factor loadings	Mean intake (g/day)				P_{trend}
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Direct associations						
Low calorie/diet soft drinks	0.27	12.5 ± 0.8	18.3 ± 1.0	23.5 ± 1.2	73.6 ± 3.6	<0.0001
Onions, leeks, and garlic	0.25	20.3 ± 0.4	20.8 ± 0.4	23.7 ± 0.4	33.9 ± 0.9	<0.0001
Sugar-sweetened beverages	0.23	37.3 ± 1.6	49.7 ± 1.8	65.5 ± 2.2	112.8 ± 4.1	<0.0001
Burgers and sausages	0.22	4.5 ± 0.1	5.8 ± 0.1	6.9 ± 0.1	9.1 ± 0.2	<0.0001
Crisps or other packet snacks	0.22	4.0 ± 0.1	5.1 ± 0.2	6.7 ± 0.2	10.9 ± 0.4	<0.0001
White bread and rolls	0.20	13.3 ± 0.6	20.3 ± 0.7	29.6 ± 0.9	42.3 ± 1.1	<0.0001
Inverse associations						
Medium- and high-fiber breakfast cereals	-0.24	60.6 ± 1.3	38.1 ± 0.8	30.8 ± 0.7	25.5 ± 0.7	<0.0001
Jam, marmalade, and honey	-0.22	17.7 ± 0.5	10.3 ± 0.3	8.3 ± 0.3	5.9 ± 0.2	<0.0001
French dressing and vinaigrette	-0.21	2.8 ± 0.1	1.6 ± 0.1	1.1 ± 0.0	0.9 ± 0.0	<0.0001
Wholemeal bread and rolls	-0.21	72.8 ± 1.5	48.0 ± 1.3	37.0 ± 1.2	26.6 ± 1.0	<0.0001

Data are means ± SE. $n = 7,339$.

excluding participants with a fasting plasma glucose >6.1 mmol/l ($n = 117$) because of concerns that HOMA-IR may not be an accurate measure of insulin resistance in this subgroup. The resulting dietary patterns were unaffected (data not shown). Dietary pattern analysis was performed using SAS (version 9.1; SAS Institute, Cary, NC).

Cox proportional hazard regression analysis was performed using Stata (version 9.2; Stata Corporation, Austin, TX). Participants were grouped according to quartile cut points of the dietary pattern score, which was used as an ordered categorical variable. Initial models were adjusted for age and sex. Further adjustments were made for energy misreporting (energy intake-to-energy expenditure ratio), ethnicity, employment grade, health behaviors (smoking, alcohol use, and physical activity), blood pressure, and BMI. Men and women were combined for analysis, as models tested in-

cluding an interaction term indicated that there was no sex interaction. Sensitivity analysis was performed to check that the diet-diabetes association was the same when ethnic minority participants, mainly of South Asian and Afro-Caribbean origin ($n = 588$), were excluded.

RESULTS— We derived a dietary pattern score using RRR analysis that was positively correlated with HOMA-IR ($r = 0.24$, $P < 0.0001$). The dietary pattern was characterized by high consumption of low-calorie/diet soft drinks, onions, sugar-sweetened beverages, burgers and sausages, crisps and other snacks, and white bread (Table 1). It was also characterized by low consumption of medium-/high-fiber breakfast cereals, jam, French dressing/vinaigrette, and wholemeal bread. The dietary pattern explained 5.7% of variation in HOMA-IR. The 10 food items listed in Table 1 together ex-

plained 66.5% of the variation in the dietary pattern score. Mean intakes of these food groups varied across the quartiles of dietary pattern score and linear trends were significant ($P < 0.0001$). The list of foods used in the analysis and their factor loadings is provided in Table 1 of the online appendix.

There were significant associations between the dietary pattern and sex, ethnicity, and employment grade with participants with higher dietary pattern scores more likely to be female, non-Caucasian, and in lower employment grades (Table 2). Participants with a higher dietary pattern score were also more likely to be smokers, participate less in vigorous physical activity, have higher BMIs, and be hypertensive.

After 77,440 person-years of follow-up, 427 incident cases of diabetes were identified (Table 3). A higher dietary pattern score was associated with increased risk of type 2 diabetes (model 1, adjusted

Table 2—Baseline subject characteristics according to quartiles of the dietary pattern score

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value*
Age (years)	49.5 ± 0.1	49.6 ± 0.1	49.4 ± 0.1	49.5 ± 0.1	49.5 ± 0.1	0.8
Sex (% male)	69.6	70.9	70.8	69.7	66.9	0.03
Ethnicity (% Caucasian)	90.4	97.5	96.4	91.2	76.3	<0.0001
Employment grade (% low employment grade)	16.1	8.5	11.7	16.5	27.9	<0.0001
Smoking (% smokers)	13.5	8.8	12.2	15.0	18.3	<0.0001
Alcohol intake (g/day)	12.1 ± 0.2	11.6 ± 0.3	12.2 ± 0.3	12.5 ± 0.4	12.2 ± 0.4	0.3
Physical activity (times/week of vigorous activity)	1.1 ± 0.0	1.22 ± 0.05	1.09 ± 0.04	1.12 ± 0.04	1.05 ± 0.04	0.04
BMI (kg/m ²)	25.3 ± 0.0	24.0 ± 0.1	24.8 ± 0.1	25.6 ± 0.1	26.6 ± 0.1	<0.0001
Hypertension (%)†	16.7	12.7	15.9	18.2	20.2	<0.0001

Data are means ± SE unless otherwise specified. $n = 7,339$. * χ^2 test for proportion or one-way ANOVA across quartiles as appropriate. †Defined as systolic blood pressure >140 mmHg or as diastolic blood pressure >90 mmHg.

Table 3—HRs and 95% CI of type 2 diabetes across quartiles of dietary pattern score

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
No. of cases/participants	62/1,723	91/1,694	122/1,700	152/1,582	
Model 1: age and sex	1	1.50 (1.08–2.07)	2.08 (1.53–2.82)	3.00 (2.23–4.03)	< 0.0001
Model 2: + energy misreporting	1	1.44 (1.04–2.00)	1.98 (1.46–2.70)	2.95 (2.19–3.97)	< 0.0001
Model 3: + ethnicity	1	1.43 (1.03–1.98)	1.91 (1.40–2.60)	2.50 (1.84–3.40)	< 0.0001
Model 4: + employment grade	1	1.39 (1.01–1.93)	1.81 (1.32–2.47)	2.31 (1.69–3.15)	< 0.0001
Model 5: + smoking, alcohol, physical activity	1	1.38 (1.00–1.91)	1.79 (1.31–2.45)	2.27 (1.67–3.11)	< 0.0001
Model 6: + blood pressure	1	1.34 (0.97–1.86)	1.72 (1.26–2.35)	2.12 (1.54–2.90)	< 0.0001
Model 7: + BMI (without blood pressure)	1	1.27 (0.91–1.76)	1.50 (1.09–2.05)	1.55 (1.13–2.15)	< 0.0001
Model 8: + blood pressure and BMI	1	1.24 (0.90–1.73)	1.48 (1.08–2.02)	1.51 (1.10–2.09)	< 0.0001

$n = 6,699$. HR, hazard ratio.

for age and sex, $P_{\text{trend}} < 0.0001$). This relationship was attenuated after adjustment for energy misreporting, ethnicity, employment grade, and health behaviors (smoking, alcohol use, and physical activity) (model 5) but remained significant even after further adjustment for blood pressure and BMI (model 8, hazard ratio for top quartile 1.51 [95% CI 1.10–2.09]). When ethnic minority participants were excluded, associations between the score and type 2 diabetes remained (1.54 [1.08–2.18]; fully adjusted model including BMI and hypertension, results not shown). When the 10 individual foods contributing most to the dietary pattern were investigated individually none of the foods showed significant associations with risk of type 2 diabetes (data not shown).

CONCLUSIONS— We identified a dietary pattern, characterized by high consumption of low-calorie/diet soft drinks, onions, sugar-sweetened beverages, burgers and sausages, crisps and other snacks, and white bread and low consumption of wholemeal bread, French dressing/vinaigrette, jam, and medium-/high-fiber breakfast cereals, that was positively correlated with insulin resistance and significantly associated with the risk of type 2 diabetes. Previous studies of type 2 diabetes using RRR analysis have used a variety of intermediate markers including nutrient intakes (5), inflammation markers (7), and biomedical risk factors including A1C, HDL cholesterol, and C-reactive protein (8). Despite these differing intermediate markers, there are some similarities between the dietary patterns, with sugar-sweetened beverages, processed meat, and wholegrains/refined grains being identified as important predictors in each case and associated with risk of type 2 diabetes. Although some-

what difficult to compare, our results are also consistent with those from other dietary pattern research using factor and cluster analysis methods. Dietary patterns that have been shown to be protective against insulin resistance, metabolic syndrome, and type 2 diabetes were high in wholegrains (22) and low in soft drinks (23), white bread and refined grains (23,24), crisps and other snacks (22), and processed meat (20,22,24). However, not all dietary patterns identified using these methods were found to be associated with type 2 diabetes or abnormal glucose tolerance (24).

Soft drinks have previously been associated with increased risk of type 2 diabetes (25). We also observed that diet soft drinks loaded highly on a dietary pattern associated with increased risk of diabetes, as did another recent study of dietary patterns and risk of metabolic syndrome (26). This is probably due to reverse causality with those who are overweight or obese switching to diet soft drinks. Duffey and Popkin (27) found that diet beverage consumers were more likely to be overweight, and in the current study, diet soft drink consumption was directly correlated with BMI (data not shown).

It is important to note that some foods in the dietary pattern may be indicators of other foods with which they are consumed. For example, jam and salad dressings are not consumed alone and may not be causally related to the outcome. Jam consumption was correlated with wholemeal/wholegrain bread but not with white bread, and salad dressing was correlated with salad vegetables (data not shown). Correlations between onions and other foods consumed did not appear to explain the presence of onions in the dietary pattern that was directly associated with type 2 diabetes and when investi-

gated separately, onion intake was not associated with risk of type 2 diabetes. We know of no other evidence suggesting a link between onion intake and type 2 diabetes, and these vegetables would usually be considered healthy components of the diet (28). Other studies using RRR have identified unexpected associations with legumes and some vegetables (7–9), and therefore careful interpretation of dietary patterns is warranted. However, we were able to confirm the robustness of the dietary pattern identified after we performed sensitivity analysis in randomly split halves of the cohort and adjusted for energy intake, sex, and employment grade.

RRR is a new approach that uses previous knowledge of diet-disease relationships to inform the analysis process and focuses on the pathways through which diet may influence disease. Previous approaches to dietary pattern analysis such as cluster and factor analysis described the variations in food intake in the population, resulting in behavioral description of food intakes. These methods provide useful insight into the eating patterns actually evident within the population and identify at-risk groups. However, these may not represent optimal eating patterns, and associations with disease are not always detected. It should be acknowledged that not all studies will be able to use RRR, as it requires intermediate markers of exposure or disease (8). Some studies have used nutrient intake as the intermediate or response variable, although a priori evidence may be lacking for strong relationships between nutrients and disease in some cases, one of the reasons for applying food-based dietary pattern approaches.

The dietary pattern in this study explained 5.7% of the variation in HOMA-IR. This result is comparable to that for

other RRR studies that have used biomedical risk factors as the response variable (7,9). Studies using nutrient intakes have tended to explain higher variation in those responses (5,6,11). This finding is unsurprising, as HOMA-IR is a more remote response variable than nutrient intakes. Of note, BMI is a major determinant of HOMA-IR, explaining ~14% of the variation, and, therefore, in comparison, diet is an important contributory factor to insulin resistance.

A weakness of the RRR approach is the cross-sectional nature of underlying dietary pattern analysis. In our analysis, to reduce the impact of possible changes in dietary behavior due to existing disease, those with type 2 diabetes at baseline were excluded from the analysis. In addition, the dietary patterns were derived using HOMA-IR scores, and investigation of their association with diabetes was performed within the same cohort. Future work will test the predictive ability of this dietary pattern in other populations. It should also be noted that in the special case of only one response variable, RRR is identical to multiple linear regression (8,29).

Strengths of this study include the large sample size, the prospective nature of the study, and the rigorous methods of outcome ascertainment. In the current study, type 2 diabetes was diagnosed using a 2-h OGTT in addition to self-report. Other studies investigating dietary patterns and type 2 diabetes, including those using RRR methods, have relied exclusively on self-report (5,7,8,20). A limitation of this study is that whereas the FFQ is known to be a valid measure of nutrient intakes, there are currently no data available on the validity of the food intake data. Sociodemographic factors (age, sex, ethnicity, and employment grade), health behaviors (smoking, physical activity, and alcohol use), and other risk factors (blood pressure and BMI) were shown to attenuate the relationship between the dietary pattern and type 2 diabetes, although the relationship remained significant. Of the confounding factors included in the final model, physical activity is the most prone to measurement error, leading to the possibility of residual confounding. Adjustment for BMI and blood pressure (models 6, 7, and 8) attenuated the relationship between the dietary pattern and risk of diabetes; however, diet is likely to act through these factors and adjustment may lead to an underestimate of the diet-related risk (30).

In this analysis, we identified a dietary pattern that was positively correlated with insulin resistance and significantly associated with the risk of type 2 diabetes. The dietary pattern was characterized by high consumption of low-calorie/diet soft drinks, onions, sugar-sweetened beverages, burgers and sausages, crisps and other snacks, and white bread and low consumption of wholemeal bread, French dressing/vinaigrette, jam, and medium-/high-fiber breakfast cereals. This research adds to the existing evidence that dietary patterns are an important risk factor for type 2 diabetes; however, further work is required to determine alternative pathways through which diet may influence risk of diabetes.

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