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Short Title: Dietary glycemic load and coronary heart disease

Abbreviations List

CHD Coronary heart disease; CVD Cardiovascular disease; BMI Body mass index; GL Glycemic load; GI Glycemic index; HR Hazard ratio; CI Confidence interval; CRP C-reactive protein; HDL High density lipoprotein; HbA1c Hemoglobin A1c

ABSTRACT

Background: High carbohydrate intake raises blood triglycerides, glucose, and insulin, reduces high density lipoproteins, and may increase risk of coronary heart disease (CHD).

Epidemiological studies indicate that high dietary glycemic index (GI) and load (GL) are associated with increased CHD risk.

Objectives: To determine whether dietary GI, GL, and available carbohydrates are associated with CHD risk in both sexes.

Methods: This large prospective study - the European Prospective Investigation into Cancer and Nutrition- consisted of 338,325 participants who completed a dietary questionnaire. Hazard ratios (HRs) with 95% confidence intervals (CI) for a CHD event, in relation to intake of GI, GL and carbohydrates were estimated using covariate-adjusted Cox proportional hazard models.

Results: After 12.8 years (median), 6378 participants had a CHD event. High GL was associated with greater CHD risk: HR 1.16 95% CI 1.02,1.31; p-trend 0.035 highest vs. lowest quintile; HR 1.18 95% CI 1.07,1.29 per 50 g/day of GL intake. The association between GL and CHD risk was evident in those subjects with BMI ≥25 kg/m^2 (HR 1.22 95% CI 1.11,1.35 per 50 g/day), but not in those with BMI<25 kg/m^2 (HR 1.09 95% CI 0.98,1.22 per 50 g/day) (p for interaction 0.022).

The GL-CHD association did not differ between men (HR 1.19 95% CI 1.08,1.30 per 50 g/day) and women (HR 1.22 95% CI 1.07,1.40 per 50 g/day) (test for interaction not significant). GI was associated with CHD risk only in the continuous model (HR 1.04 95% CI 1.00,1.08 per 5 units/day). High available carbohydrate was associated with greater CHD risk: HR 1.11 (95% CI 1.03,1.18) per 50 g/day. High sugar intake was associated with greater CHD risk (HR 1.09 95% CI 1.02,1.17 per 50 g/day)

Conclusions:

This large pan-European study provides robust additional support for the hypothesis that a diet that induces a high glucose response is associated with greater CHD risk.

Keywords

Glycemic index, Glycemic load, Coronary heart disease, Case-cohort study, EPIC-CVD study.

INTRODUCTION

Dietary guidelines have long emphasized that reducing consumption of fat, particularly saturated fat, and getting more calories from unsaturated fat or carbohydrate, lowers risk of cardiovascular disease (CVD), including coronary heart disease (CHD) (1). Conversely, evidence from observational studies suggests that replacing saturated fat by sugars or refined starch does not reduce risk but may increase it (1,2); while replacing fat with carbohydrates from whole fruits, vegetables, pulses, and whole grains may decrease risk (3).

High intake of carbohydrates, particularly refined carbohydrates, can raise fasting triglycerides (4), reduce high density lipoproteins (HDL) (5), and increase blood glucose and insulin (6); and may increase CHD risk.

Variation in the ability of carbohydrates to increase blood glucose is captured by the glycemic index (GI) (7), which ranks carbohydrate foods according to their blood-glucose-raising ability. Dietary GI is a measure of the overall ability of consumed carbohydrates to raise blood glucose. Glycemic load (GL), the product of a food's GI and its available carbohydrate, incorporates the effect of the total amount of carbohydrate consumed (7). Dietary GL is the sum of the GLs for all carbohydrate-containing foods consumed, and reflects the quantity as well as the blood-glucose-raising ability of consumed carbohydrates.

Recent reviews and meta-analyses on GI/GL and CHD risk (8-11) found that high GI and GL diets were associated with increased CHD risk in women, especially women with high body mass index (BMI), but in men findings were inconsistent. A 2019 meta-analysis of prospective studies found that high dietary GI and GL were strongly associated with increased CHD risk in both sexes (12). However, a large and comprehensive 2019 review and meta-analyses on carbohydrate quality and several non-communicable disease endpoints including CHD, reported that, across observational studies and clinical trials, GI had no or inconsistent association with CHD, while high GL was moderately associated with increased CHD risk (13).

We estimated associations between risk of first CHD event and dietary GL, GI, and available carbohydrate in a large pan-European cohort of men and women recruited to the European Prospective Investigation into Cancer and Nutrition (EPIC).

METHODS

Study Population

EPIC is a prospective study of ≈520,000 men and women, mostly 35-70 years, recruited between 1991 and 1999 from 23 centers in ten European countries: Denmark, France, Greece, Germany, Italy, The Netherlands, Norway, Spain, Sweden, and the UK. Details of EPIC design and methods are described elsewhere (14). Briefly, volunteers completed dietary and lifestyle questionnaires, had their anthropometric measurements recorded by trained health professionals (self-reported in France, Norway and Oxford); most also provided blood samples. All participants gave written informed consent. Ethical committees of the International Agency for Research on Cancer and local centers approved the EPIC protocol.

After exclusion of 10,455 with a history of myocardial infarction or stroke, 44,318 with a history of diabetes, 6837 with no dietary data, and 7412 in the top or bottom 1% of the ratio of energy intake to energy requirement, 452,752 remained. After also eliminating participants from France and Norway for incomplete follow up and 2254 cases whose date of CHD diagnosis was before the date of EPIC baseline (prevalent cases), a total of 338,325 participants remained, including 6378 CHD incident cases (Supplementary Figure 1).

Measurements

First fatal and non-fatal CHD events were defined by codes 410-414 of the 9th edition, or I20-I25 of the 10th edition, of the International Classification of Diseases. EPIC centers identified events by various methods including primary and secondary care databases, hospital admissions records, and self-report (15). Non-fatal CHD events were validated from medical

records or databases. Fatalities were usually confirmed from mortality databases. End of follow-up varied with center: from end of 2003 to end of 2010.

Diet over the year up to recruitment was assessed by country-specific (in some cases center-specific) questionnaires designed to capture local eating habits. Nutrient values of consumed foods were obtained from the EPIC Nutrient Database (16). Published values of GIs (glucose as reference) (17-19), were assigned to carbohydrate-containing foods as described elsewhere (20).

Average dietary GI for each participant was calculated as the sum of the GIs of each food item consumed, multiplied by the average daily amount consumed and percentage carbohydrate content, all divided by the total daily carbohydrate intake. Dietary GL was calculated similarly except that there was no division by daily carbohydrate intake.

A standardized lifestyle questionnaire at recruitment recorded menopausal status, hormone treatment, medical history, physical activity, alcohol consumption, smoking, education, and other information. Weight (kg) and height (m) were measured at recruitment, except in France, the Oxford center, and Norway where they were measured in a subset and self-reported in the rest. BMI was calculated as kg/m^2. Physical activity was categorized according to the Cambridge Physical Activity Index (21).

Blood pressure was measured using standard procedures, but was only available for 62% of participants (22). We therefore used a composite blood pressure variable available for 92.4% of participants: if one or more of self-reported hypertension, self-reported use of anti-hypertensive medication, systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg were present, the participant was considered hypertensive. Other categories were: normotensive or unknow/missing (7.6%).

Circulating CHD risk factors were available for sub-cohort of 18,157 EPIC participants randomly sampled from all 23 EPIC centers, with stratification by center (23). The following

106 factors were measured: high-sensitivity C-reactive protein, total cholesterol, HDL cholesterol
107 and triglycerides (Stichting Huisartsen Laboratorium, Etten-Leur, the Netherlands), erythrocyte
108 hemoglobin A1c (G8 HPLC analyzer, Tosoh Bioscience, Japan), and glucose (Cobas enzymatic
109 assay, Roche Diagnostics, Mannheim, Germany). Non-HDL cholesterol was calculated as total
110 cholesterol minus HDL cholesterol, since LDL cholesterol was not directly assayed. These data
111 were not available for Norwegian participants.

112 **Statistical methods**

113 Participant characteristics are presented as means and standard deviations (continuous
114 variables), or percentages (categorical variables), by quintiles of energy-adjusted GI and GL.
115 Primary outcome variables were hazard ratios (HRs) for CHD in relation to variation in GI and
116 GL. Secondary outcome variables were HRs for CHD in relation to available carbohydrate,
117 starch, and sugar. HRs with 95% confidence intervals (CI) were estimated by Cox proportional
118 hazard models, using center, age and sex-stratified baseline hazards.

119 Age (years) was the time variable: participant entry was age at recruitment; exit was age at first
120 CHD event, death for other causes, loss to follow-up, or end of CHD follow-up (whichever
121 came first). Dietary intakes of interest were adjusted for energy intake using the regression-
122 residual method (24) and categorized (quintiles) based on the entire cohort. Models were run
123 on men and women together, with stratification by sex only in subgroup analyses. The study
124 variables were also modeled as continuous variables, in which case HRs indicate risks
125 associated with 50 g/day (GL) or 5 units/day (GI) increments of intake. Available carbohydrate
126 was defined as starch and sugars: indigestible carbohydrate was excluded.

127 Three models are presented: model 1 stratified by center, age, and sex; model 2 additionally
128 adjusted for smoking status (current: 1-15 cig/day, 16-25 cig/day, 26+ cig/day; former: quit $\leq$10
129 years, 11-20 years, 20+ years previously; never), physical activity (inactive, moderately
130 inactive, moderately active, active), BMI (<25, 25-29.9, $\geq$30 kg/m^2), alcohol consumption (not

drinker, sex-specific quintiles of intake: cut points in men 4.1, 10.6, 19.6, and 37.5 g/d; cut points in women 1.1, 3.4, 7.7, and 14.7 g/d), education (no schooling, primary, technical/professional, secondary, longer education) and blood pressure (high, normal, unknown/missing); model 3 additionally adjusted (all continuous) for intakes of energy, saturated fat, monounsaturated fat, protein, and fiber (or cereal fiber for the analyses investigating GI and GL). Model 3, analyzing GL and available carbohydrate, was also run adjusting for energy, polyunsaturated and monounsaturated fat (not saturated fat), protein, and fiber (or cereal fiber); another model 3 was run adjusting for energy, polyunsaturated, saturated monounsaturated fat, (not protein), and fiber (or cereal fiber).

To assess the significance of trends we employed orthogonal polynomial contrasts. Country-specific HRs for dietary GI and GL (continuous) were also estimated, and combined with random effects meta-analyses. Pooled HRs were then plotted and between-country heterogeneity was quantified by the I^2 statistic (25). The proportional hazards assumption for all variables in relation to CHD risk was tested using the Grambsch and Therneau method (26). In all cases, the assumption was satisfied.

To assess whether dietary factors might act through circulating CHD risk factors, we performed analysis of covariance to examine associations of GL/GI with biomarkers of CHD risk (CRP, HDL cholesterol, non-HDL cholesterol, triglycerides, HbA1c, glucose), calculating mean levels in each quintile of GL, and adjusting for the covariates used in model 3. We also examined whether associations of CHD with dietary variables were influenced by reverse causality by excluding CHD events diagnosed in first 2 years of follow up.

To examine whether associations of CHD with dietary variables were consistent across sub-groups of other risk factors, we conducted subgroup analyses by sex and BMI. Tests for heterogeneity of trend were performed adding appropriate interaction terms to the models and

testing for significance using a Wald chi-square test. All analyses were conducted using Stata software (version 14.0, Stata Corp, College Station, TX)

RESULTS

After 12.8 years (median), 6378 incident CHD cases (4267men, 2111 women) were identified in the EPIC cohort. Table 1 shows baseline characteristics of the cohort by quintiles of energy-adjusted dietary GL. Mean GL varied substantially across quintiles (96.5-164.8); while mean GI ranged from 53.4 (lowest quintile) to 58.3 (highest quintile). Participants in the highest GL quintile consumed more carbohydrate and starch, and less fat, protein, and alcohol, and had lower BMI, than those in the lowest; they were often more active and less often current smokers. Table 2 shows cohort characteristics by quintiles of energy-adjusted dietary GI. Mean GI ranged from 50.7 (lowest quintile) to 60.8 (highest quintile); GL ranged from 113.7 (lowest quintile) to 146.6 (highest quintile). Those in the highest GI quintile consumed less saturated fat, monounsaturated fat, and protein, and more carbohydrate and starch, than those in lower quintiles; they were also less educated and more often smokers. Fiber intake and sugar intake increased with increasing GL but decreased with increasing GI.

Table 3 shows baseline means of selected biomarkers by quintiles of energy-adjusted GL and GI. Those in the highest GL and GI quintiles had significantly lower HDL cholesterol than those in the lowest quintiles; those in the highest GI quintile had significantly higher triglycerides and CRP than those in the lowest quintile.

Table 4 shows HRs for CHD by quintiles of energy-adjusted GL, GI, available carbohydrate, starch, and sugar. In models 1 (minimally-adjusted) and 2 (adjusted for CHD risk factors) CHD risk was unrelated to GL. After adjusting for nutrient intake (model 3), the 4th and 5th GL quintiles were associated with greater CHD risk, with p trend 0.035. For 50 g/day GL increments the HR was 1.18 (95% CI 1.07,1.29). In this model, in which the only nutrients not included were polyunsaturated and low-GI carbohydrate, the GL variable represents the effect of substituting GL for polyunsaturated fat and low-GI carbohydrate on CHD risk. When the adjustments in model 3 included polyunsaturated and monounsaturated fat (not saturated fat),

the HR for 50 g/day GL increments was 1.19 (95% CI 1.09,1.29). When the adjustments in model 3 included polyunsaturated, monounsaturated and saturated fat (not protein), the HR for 50 g/day GL increments was 1.13 (95% CI 1.04,1.23) (data not in Tables).

GI was associated with greater CHD risk only in the continuous GI model (HR 1.04 95% CI 1.00,1.08 per 5 unit/day increment).

For available carbohydrate in model 3, those in the highest quintile of consumption had greater CHD risk than those in the lowest (HR 1.15; 95% CI 1.00,1.32, p trend 0.065); the risk for 50 g/day GL increments was HR 1.11; 95% CI 1.03,1.18. When model 3 was run adjusting for polyunsaturated fat, monounsaturated fat, and protein (not saturated fat), the HR for 50 g/day increments was 1.14 (95% CI 1.07,1.22); when run adjusting for polyunsaturated, monounsaturated, and saturated fat (not protein), the HR for 50 g/day increments was 1.08 (95% CI 1.02,1.15) (data not in Tables). Sugar intake was associated with greater CHD risk in all quintiles of consumption, and the HR for 50 g/day increments was 1.09 (95% CI 1.02,1.17). Starch was not associated with CHD risk.

Estimates of country-specific HRs (data pooled from centers) with corresponding I^2 for between-country heterogeneity are shown in Figure 1. Associations of dietary variables with CHD risk did not vary greatly across countries.

Table 5 shows sensitivity analyses for GL/GI after excluding cases diagnosed in the first two years, and also by sex and BMI. Associations between GL/GI and CHD attenuated after excluding those with an early CHD event during the first two years of follow-up (HR for 50 g/day intake: 1.15; 95% CI 1.04,1.27 for GL and 1.03; 95% CI 0.99,1.08 for GI).

Model 3 HR estimates for each sex were in the same direction as for the sexes combined. GL was significantly associated with CHD risk in both sexes (HR for 50 g/day intake: 1.19; 95% CI 1.08,1.30 for men and 1.22; 95% CI 1.07,1.40 for women) whereas GI was significantly associated only in women (HR for 50 g/day intake: 1.09; 95% CI 1.02,1.16 for women and 1.02;

95% CI 0.98,1.07 for men). However, the interaction of dietary GL and GI with sex was not significant.

Finally, associations between CHD and GL varied with BMI category. High GL was associated with greater CHD risk among participants with BMI ≥25 mg/kg^2 (HR for 50 g/day increments 1.22; 95% CI 1.11,1.35); whereas no association was found in participants with BMI <2525 mg/kg^2 (HR for 50 g/day increments 1.09; 95% CI 0.96,1.22). The interaction of GL with BMI was significant (p 0.022).

DISCUSSION

In this prospective study with 6,378 incident CHD cases from eight European countries, high dietary GL and GI were associated with greater CHD risk. Dietary GL was also significantly associated with greater CHD risk in overweight and obese persons, but not in those of normal weight. High consumption of carbohydrate and sugar, but not starch, were also associated with greater CHD risk.

Three recent meta-analyses of cohort studies (8-11) found that high dietary GL was significantly associated with increased CHD risk, while high dietary GI was inconsistently associated with risk, and the risk increases were significant only in women (when the sexes were analyzed separately). However, some studies − that found (non-significant) risk increases in men (27,28) − were not included in the meta-analyses because the data were unavailable in suitable form. When we analyzed men and women separately, HR estimates for dietary GL were in the same direction as those for both sexes combined. A 2019 meta-analysis (that only included prospective studies in which the correlation between carbohydrate intake from questionnaires and ascertained food records was >0.55) found a strong relationship between GL and CHD risk that did not vary between men and women (12). Finally, a large and comprehensive review and meta-analysis, again published in 2019, that used the GRADE approach to assess evidence quality, reported a moderate positive association, across observational studies, of GL with CHD endpoints (mortality and incidence) (13).

We found a weak positive association between dietary GI and CHD only in the continuous model. When we analyzed men and women separately, HR estimates for dietary GI were in the same direction as those for both sexes combined, although the association was significant only in women, but test for interaction was not significant.

Three previous meta-analyses showed that a high GI diet was significantly associated with CHD events in women but not men (8,9,11). However, a recent large and comprehensive review and

meta-analysis reported a null or inconsistent finding for GI across observational studies for CHD endpoints (13).

CHD risk in relation to available carbohydrate consumption has also been examined in prospective studies but with inconsistent results: a positive association was found in both sexes that consumed carbohydrate mainly from white rice and refined wheat products (29); while other studies found no associations in women (30,31) or men (32). The PURE study found that high carbohydrate intake was associated with increased risk of total mortality but not with the risk of CVD (33).

Regarding our finding of a greater risk of CHD with high sugar consumption, few studies have investigated this association. The Nurses' Health Study and the Women's Health Initiative Observational Study found that sugar intake was not significantly related to CHD risk (30, 34). Moreover, a recent meta-analysis of prospective studies found that neither total sugar nor sucrose were associated with CVD incidence, either in extreme quantile analyses or in linear and nonlinear dose-response models (35).

Many other studies have evaluated the relationship of sugars in the form of sugar-sweetened beverages (SSBs) to CHD. A meta-analysis of cohort studies reported that intake of SSBs was associated with CHD risk (36). More recently, data from the Nurses' Health Study and the Health Professional Follow-up Study reaffirmed a strong positive association foods rich in refined starches and added sugars and CHD risk (37). These findings are consistent with the results of randomized trials which indicate that high sugar increases blood pressure and also blood triglycerides, total cholesterol and LDL-cholesterol (38).

It is important to note that the association between dietary GL and CHD risk was evident in our study only after adjustment for dietary variables (model 3).

Like most previous studies (30,39-42), we found that high dietary GL was associated with high fiber intake and low saturated fat and protein intake. So, it is reasonable that associations of

dietary GL with CHD risk only became significant after additional adjustment for these variables, even though such adjustments can be considered over-adjustments since fiber, fat and protein in foods influence their GI/GL. Furthermore, the strength of the GL-CHD association did not change when the substitution of GL for polyunsaturated or saturated fat or protein was evaluated. A randomized controlled trial that investigated CHD in relation to replacing dietary fat with carbohydrates (43) found no risk change. We also found that replacing dietary fat (saturated or polyunsaturated fat) or protein with carbohydrate was associated with greater CHD risk.

Our findings are in line with a meta-analysis of 6 observational studies (9) which found that persons with higher BMI, who consumed a high GL diet, were at greater risk of CHD, so body weight may serve as an effect modifier on this association. The Nurses' Health Study was the first to report that, in women with high BMI (>23 kg/m2) the risk of CHD increased as intake of high- GI foods increased (30).

The mediators of the association of high carbohydrate intake with increased CHD risk are not completely understood, but it is likely that insulin resistance is involved. A high carbohydrate meal (particularly of high GI carbohydrate) substantially increases postprandial blood glucose and insulin. The subsequent insulin-induced decline in blood glucose precipitates hunger within a few hours, stimulating further consumption (of typically high GI foods) so that blood glucose remains elevated over a prolonged period (45). If such behavior is habitual, it may lead to insulin resistance and obesity (46,47), with increased triglycerides and LDL cholesterol, and lowered HDL, leading to metabolic syndrome.

Hyperinsulinemia and hyperglycemia may also trigger peripheral vasoconstriction, sodium retention and increased liver production of very low-density lipoprotein, leading to atherosclerosis (48). In people with high BMI, greater insulin demand in response to a high GL diet may further exacerbate insulin resistance and lipid imbalance thereby increasing CHD risk

(49). This scenario is supported by a meta-analysis of randomized intervention trials (50) which found that lowering dietary GI reduced CVD risk factors, lowering triglycerides and LDL cholesterol and raising HDL cholesterol. However, such responses are not always observed (5152). From Table 3 it is evident that as dietary GI increased so did triglyceride and non-HDL cholesterol levels; while as dietary GL increased HDL cholesterol decreased. These cross-sectional associations are nevertheless consistent with the hypothesis that insulin resistance mediates the high carbohydrate-CHD association. A randomized intervention trial on patients with diabetes found higher HDL cholesterol levels in the low GI treatment group (53).

Strengths of our study are: large number of CHD cases, prospective design, and long follow-up, limiting the likelihood of reverse causation and selection bias. Although we had extensive data on potential confounders that were used as covariates in the models, we cannot rule out the presence of residual confounding.

A limitation of our study is that the dietary questionnaires (14) were not designed to specifically estimate dietary GI/GL, although application of GI values to food items is straightforward, and Liu et al., found it was possible to accurately estimate dietary GI and GL from questionnaire responses (54). Another limitation is that diet was only assessed at baseline. Some participants may have changed their diet during follow-up, giving rise to misclassification of exposure which would have weakened diet-disease associations. Finally, most people do not eat single foods, but meals, and a food's GI can vary depending on how it is prepared and combined with other foods: it is not possible to take such interactions into account using a food questionnaire. However strong correlations have been found between observed and calculated GIs for mixed meals (55).

CONCLUSIONS

This large pan-European study has revealed a robust positive association between a diet that induces a high glucose response and increased CHD risk.

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Authors' contributions to the manuscript:

SS, VK, AC, SG, ASB and JD designed the study, had full access to all study data and take responsibility for the integrity of the data and the accuracy of the analyses. SS drafted the manuscript. SS and VK did the statistical analyses. VK, YTV, IS, LMN, VAK, KO, TYNT, JRQ, JHG, AT, ES, AT, EW, JMAB, ATr, WMMV, MJF, MCB, MMB, MBS, PF, RT, GM, AM, ER, ASB, AB, MS, JD, SG, TK, PW, OM, MUJ, JMG, AK, EV, IS, GF, ALM, HF, HL, MIC, CS, NGF take responsibility for the databases and follow-up data. All authors contributed to data interpretation, and critical revision of the article, and approved the final manuscript.

Disclosures

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Figure 1.

Title: Forest plots showing country-specific hazard ratios (HRs) and 95% confidence intervals (CI) for coronary heart disease in relation to dietary glycemic load, dietary glycemic index, and intakes of available carbohydrate, starch and sugar.

Legend: The HRs were obtained from model 3, which was adjusted for age, sex, study center, smoking, education, physical activity, BMI, blood pressure and intakes of energy, protein, alcohol, fiber (available carbohydrate, starch and sugar), or cereal fiber (GI and GL), saturated and monounsaturated fat. The analyses were stratified by country and combined with random-effects meta-analysis. Weights are from random effects analysis.

Table 1. Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic load (GL) in the EPIC cohort[1]

	Quintiles of energy-adjusted dietary GL[2]				
	I	II	III	IV	V
N persons	68,116	68,116	68,116	68,116	68,115
Dietary GL	96.5 (14.3)	118.0 (3.7)	129.5 (3.7)	141.2 (3.8)	164.8 (16.8)
Dietary GI	53.4 (3.6)	54.9 (3.2)	55.8 (3.1)	56.7 (3.1)	58.3 (3.3)
Protein (g/day)	98.9 (30.2)	84.6 (25.6)	80.0 (25.4)	78.8 (25.4)	85.9 (27.4)
Saturated Fat (g/day)	37.1 (14.4)	31.2 (12.1)	29.3 (11.7)	28.4 (11.7)	29.2 (12.2)
Monounsaturated Fat (g/day)	42.1 (17.4)	31.9 (12.6)	28.3 (11.6)	26.5 (11.4)	28.1 (12.2)
Polyunsaturated Fat (g/day)	15.5 (7.7)	13.1(6.0)	12.5 (5.6)	12.3 (5.6)	13.0 (5.8)
Carbohydrate (g/day)	201.7 (63.5)	203.8 (61.1)	215.5 (61.2)	237.1 (62.6)	301.0 (79.5)
Starch (g/day)	104.1 (40.6)	106.3 (39.1)	113.3 (39.2)	126.1 (41.0)	166.2 (60.6)
Sugars (g/day)	90.5 (36.8)	92.4 (35.9)	98.2 (37.4)	107.8 (40.7)	132.1 (54.5)
Fiber (g/day)	21.5 (7.4)	21.0 (6.9)	21.7 (7.1)	23.2 (7.4)	27.5 (8.9)
Energy (kcal/day)	2303 (656)	1997 (579)	1939 (575)	1979 (583)	2287 (649)
Alcohol (g/day)	25.5 (27.1)	14.0 (16.1)	10.2 (12.8)	8.12 (11.2)	7.17 (10.8)
Age	51.1 (9.3)	51.4 (9.9)	50.9 (10.6)	49.9 (11.2)	48.8 (11.4)

Systolic blood pressure (mmHg)	132.2 (20.0)	131.9 (19.8)	131.2 (19.8)	130.4 (19.8)	129.4 (19.0)
Diastolic blood pressure (mmHg)	82.2 (10.8)	81.5 (10.8)	81.0 (10.8)	80.6 (10.8)	80.2 (10.7)
Body mass index (kg/m^2)	26.7 (4.30)	26.2 (4.32)	25.8 (4.26)	25.4 (4.16)	25.1 (4.08)
Sex					
Male (%)	47.8	33.1	29.3	30.2	40.5
Physical activity					
Inactive (%)	23.2	22.4	20.8	19.5	20.5
Moderately inactive (%)	33.5	33.9	33.9	33.4	30.9
Moderately active (%)	23.3	22.9	23.3	23.7	23.1
Active (%)	19.5	19.7	20.5	21.6	23.2
Education					
No schooling (%)	7.2	6.7	5.7	4.4	3.3
Primary (%)	30.6	29.1	27.2	25.4	27.4
Technical/professional (%)	21.9	24.8	25.8	26.0	24.4
Secondary (%)	14.4	14.3	14.7	16.3	17.8
Longer Education (%)	24.8	23.3	24.0	24.8	23.4
Current smoker (%)	34.6	26.1	22.5	20.2	21.3
Never smoker (%)	36.7	46.3	50.1	53.0	52.3

History of high blood pressure (%)	34.8	34.7	33.7	32.0	29.8

[1]Table entries are means with standard deviations, except where indicated; [2]Energy adjustment by residual method.

Table 2. Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic index (GI) in the EPIC cohort [1]

	Quintiles of energy-adjusted[2] dietary GI				
	I	II	III	IV	V
N persons	68,116	68,116	68,116	68,116	68,115
Dietary GI	50.7 (2.14)	54.0 (0.57)	55.8 (0.49)	57.6 (0.59)	60.8 (1.81)
Dietary GL	113.7 (22.7)	124.0 (20.5)	129.9 (20.9)	135.7 (21.5)	146.6 (26.0)
Protein (g/day)	87.5 (29.0)	86.3 (27.5)	85.4 (27.1)	84.6 (26.9)	84.6 (28.4)
Saturated Fat (g/day)	31.9 (13.9)	32.0 (12.9)	31.5 (12.6)	30.8 (12.4)	29.0 (12.2)
Monounsaturated Fat (g/day)	32.9 (16.8)	32.0 (14.7)	31.3 (13.9)	30.7 (13.2)	30.1 (12.9)
Polyunsaturated Fat (g/day)	13.1 (6.6)	13.5 (6.3)	13.5 (6.2)	13.3 (6.1)	13.1 (6.2)
Carbohydrate (g/day)	222.1 (77.4)	230.7 (73.0)	233.0 (72.9)	234.1 (73.8)	239.2 (79.2)
Starch (g/day)	98.0 (40.8)	115.3 (42.5)	123.5 (44.9)	130.8 (48.0)	148.3 (59.2)
Sugar (g/day)	118.4 (49.5)	110.2 (43.0)	104.9 (41.5)	99.2 (41.1)	88.4 (40.1)
Fiber (g/day)	23.2 (8.5)	23.4 (7.9)	23.2 (7.8)	22.8 (7.7)	22.4 (7.8)
Energy (kcal/day)	2093 (658)	2118 (627)	2110 (618)	2095 (613)	2090 (633)
Alcohol (g/day)	13.8 (19.6)	13.2 (17.3)	12.9 (17.3)	12.6 (17.5)	12.4 (18.4)
Age (years)	50.4 (10.1)	50.6 (10.5)	50.5 (10.8)	50.4 (10.9)	50.1.3 (9.3)

Systolic blood pressure (mmHg)	130.0 (19.5)	131.0 (19.5)	131.5 (19.8)	131.5 (20.0)	130.9 (19.8)
Diastolic blood pressure (mmHg)	81.0 (10.6)	81.2 (10.7)	81.2 (10.8)	81.1 (10.9)	81.0 (10.9)
Body mass index (kg/m^2)	26.1 (4.35)	25.8 (4.25)	25.7 (4.20)	25.7 (4.22)	25.9 (4.29)
Sex					
Male (%)	27.3	32.6	36.3	39.3	45.3
Physical activity					
Inactive (%)	20.0	19.4	20.4	21.5	25.0
Moderately inactive (%)	33.9	34.1	33.3	32.9	31.4
Moderately active (%)	23.6	24.0	23.9	23.2	21.5
Active (%)	21.9	21.8	21.2	20.6	18.8
Education					
No schooling (%)	5.3	4.3	4.8	5.3	7.5
Primary (%)	26.6	25.6	26.3	28.7	32.8
Technical/Professional	25.4	25.1	24.8	24.1	23.2
Secondary (%)	14.8	15.1	15.6	15.9	16.2
Longer education (%)	26.2	27.0	25.7	23.2	18.2
Current smoker (%)	23.5	22.1	23.1	25.3	30.6
Never smoker (%)	48.7	50.0	46.2	47.2	43.1

History of high blood pressure (%)	32.0	33.1	33.1	33.6	33.2

[1]Table entries are means with standard deviations, except where indicated; [2]Energy adjustment by residual method.

Table 3. Mean[1] values of selected markers of lipid and glucose metabolism (with 95% confidence intervals) in the EPIC-CVD sub-cohort according to quintiles of energy-adjusted dietary glycemic index (GI) and load (GL).

	Quintiles of energy-adjusted dietary GI or GL					P value [2]
	I	II	III	IV	V	
Dietary GL						
Non-HDL cholesterol (mmol/l)	4.41 (4.35,4.46)	4.39 (4.35,4.43)	4.44 (4.40,4.48)	4.47 (4.43,4.51)	4.47 (4.41,4.53)	0.1155
HDL-cholesterol (mmol/l)	1.54 (1.52,1.56)	1.50 (1.49,1.52)	1.48 (1.47,1.50)	1.47 (1.46,1.48)	1.46 (1.44,1.48)	<0.001
Triglycerides (mmol/l)	1.32 (1.28,1.36)	1.28 (1.25,1.32)	1.34 (1.31,1.37)	1.35 (1.31,1.38)	1.35 (1.31,1.39)	0.0878
C-reactive protein (mg/l)	2.06 (1.86,2.25)	2.16 (2.01,2.31)	2.30 (2.15,2.45)	2.27 (2.11,2.42)	2.37 (2.17,2.58)	0.3424
Glucose (mmol/l)	4.94 (4.88,4.99)	4.92 (4.87,4.96)	4.92 (4.88,4.96)	4.94 (4.89,4.98)	4.96 (4.90,5.03)	0.7453
Hemoglobin A1c (%)	5.46 (5.44,5.49)	5.47 (5.45,5.49)	5.47 (5.46,5.49)	5.49 (5.47,5.50)	5.48 (5.46-5.50)	0.6893
Dietary GI						
Non-HDL cholesterol (mmol/l)	4.39 (4.35,4.43)	4.39 (4.35,4.43)	4.46 (4.42,4.50)	4.44 (4.40,4.48)	4.49 (4.45,4.53)	0.0055
HDL cholesterol (mmol/l)	1.51 (1.49,1.52)	1.50 (1.49,1.52)	1.48 (1.47,1.50)	1.48 (1.47,1.50)	1.49 (1.47,1.50)	0.0423
Triglycerides (mmol/l)	1.32 (1.29,1.35)	1.28 (1.25,1.31)	1.33 (1.30,1.36)	1.32 (1.29,1.36)	1.38 (1.35,1.41)	0.0011
C-reactive protein (mg/l)	2.08 (1.92,2.23)	2.15 (2.00,2.30)	2.22 (2.07,2.36)	2.28 (2.13,2.42)	2.43 (2.28,2.59)	0.0340
Glucose (mmol/l)	4.95 (4.90,4.99)	4.91 (4.87,4.96)	4.93 (4.88,4.97)	4.93 (4.88,4.97)	4.95 (4.90,5.00)	0.6923
Hemoglobin A1c (%)	5.47 (5.45,5.49)	5.47 (5.45,5.49)	5.48 (5.46,5.50)	5.48 (5.46,5.49)	5.48 (5.46,5.49)	0.8679

[1]Means adjusted for age (continuous), sex and EPIC center, smoking, education, physical activity, body mass index, and blood pressure, intakes of energy, protein, alcohol, fiber, saturated and monounsaturated fat. [2]Analysis of covariance

Table 4. Hazard ratios[1] (with 95% confidence intervals) for first coronary heart disease event according to dietary glycemic load (GL) dietary glycemic index (GI), and intakes of available carbohydrate, starch, and sugar in the EPIC study

	Quintiles of energy-adjusted dietary variables					**P trend[7]**	**Continuous[‡8]**
	I	**II**	**III**	**IV**	**V**		
Dietary GL							
Range	≤111.2	111.3-124.1	124.2-134.9	135.0-148.3	>148.3		
N cases	1386	1255	1175	1208	1354		
Model 1[2]	1	1.02 (0.94,1.10)	1.00 (0.92,1.08)	1.01 (0.93,1.10)	1.05 (0.96,1.14)	0.373	1.04 (0.99,1.10)
Model 2[3]	1	1.05 (0.97,1.14)	1.02 (0.94,1.11)	1.04 (0.96,1.14)	1.06 (0.97,1.16)	0.248	1.05 (1.00,1.11)
Model 3[4,5]	1	1.08 (0.99,1.17)	1.07 (0.97,1.17)	1.11 (1.00,1.23)	1.16 (1.02,1.31)	0.035	1.18 (1.07,1.29)
Dietary GI							
Range	≤52.9	53.0,54.9	55.0,56.7	56.8,58.7	>58.7		
N cases	958	1054	1265	1395	1706		
Model 1[2]	1	0.97 (0.89,1.06)	1.05 (0.96,1.14)	1.06 (0.97,1.15)	1.17 (1.08,1.27)	0.001	1.09 (1.05,1.13)
Model 2[3]	1	0.98 (0.90,1.07)	1.04 (0.96,1.14)	1.02 (0.93,1.11)	1.05 (0.96,1.14)	0.172	1.03 (0.99,1.07)
Model 3[4,5]	1	1.00 (0.91,1.09)	1.07 (0.98,1.16)	1.04 (0.95,1.13)	1.08 (0.99,1.18)	0.053	1.04 (1.00,1.08)

Available carbohydrate							
Range	≤202.0	202.0,222.9	223.0,240.4	240.5,261.5	>261.5		
N cases	1542	1250	1206	1145	1235		
Model 1[2]	1	0.97 (0.90,1.05)	0.97 (0.90,1.05)	0.94 (0.87,1.02)	1.00 (0.92,1.08)	0.701	1.00 (0.97,1.03)
Model 2[3]	1	1.02 (0.94,1.10)	1.02 (0.94,1.11)	1.00 (0.92,1.09)	1.06 (0.97,1.15)	0.355	1.03 (0.99,1.06)
Model 3[4]	1	1.04 (0.96,1.14)	1.06 (0.96,1.17)	1.06 (0.95,1.19)	1.15 (1.00,1.32)	0.065	1.11 (1.03,1.18)
Starch							
Range	≤97.4	97.5,113.3	113.4,127.7	127.8,147.0	>147.0		
N cases	1355	1224	1205	1322	1272		
Model 1[2]	1	0.95 (0.88,1.03)	0.90 (0.83,0.97)	0.92 (0.85,1.00)	0.86 (0.79,0.93)	0.001	0.93 (0.90,0.97)
Model 2[3]	1	0.99 (0.91,1.07)	0.95 (0.87,1.03)	0.97 (0.90,1.05)	0.93 (0.85,1.02)	0.116	0.98 (0.94,1.02)
Model 3[4,6]	1	1.02 (0.94,1.11)	0.99 (0.90,1.09)	1.04 (0.93,1.15)	1.02 (0.89,1.16)	0.737	1.06 (0.99,1.14)
Sugar							
Range	≤77.2	77.3,93.5	93.6,108.8	108.9,129.3	>129.3		
N cases	1509	1306	1200	1181	1182		
Model 1[2]	1	1.05 (0.97,1.13)	1.05 (0.97,1.13)	1.07 (0.99,1.16)	1.13 (1.04,1.23)	0.006	1.05 (1.01,1.09)
Model 2[3]	1	1.09 (1.01,1.18)	1.09 (1.01,1.18)	1.12 (1.03,1.21)	1.13 (1.04,1.23)	0.007	1.04 (1.00,1.08)

Model 3[4,6]	1	1.12 (1.03,1.22)	1.14 (1.04,1.24)	1.18 (1.07,1.31)	1.24 (1.09,1.40)	0.001	1.09 (1.02,1.17)

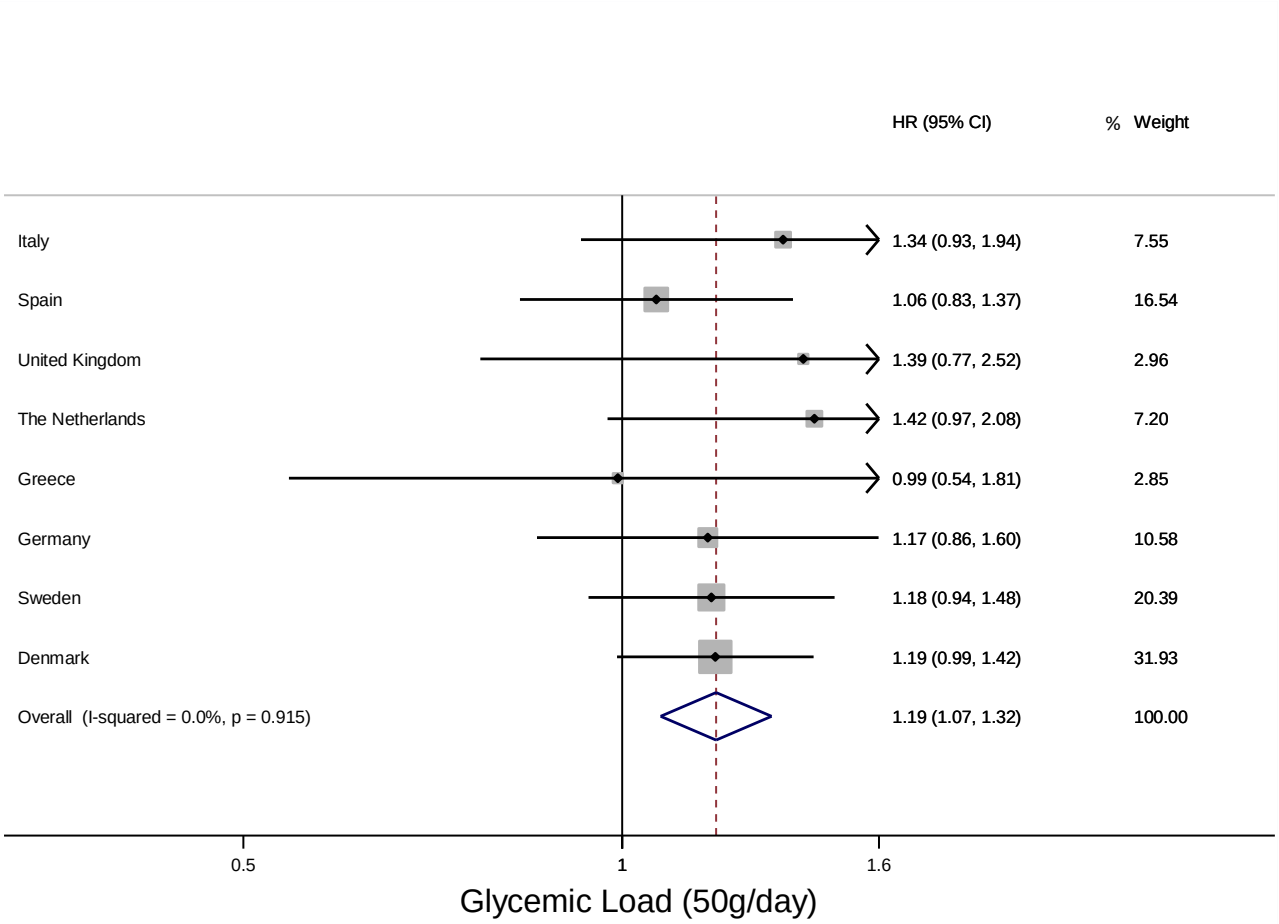
[1] Hazard ratio and 95% confidence interval estimated from Cox proportional hazard models. [2] Stratified by age, sex, and recruitment center. [3] Additionally adjusted for smoking, education, physical activity, BMI, and blood pressure variable. [4]Additionally adjusted for intakes of energy, protein, alcohol, fiber, saturated and monounsaturated fat. [5]Models 3 for GL and GI were adjusted for cereal fiber instead of fiber. [6]Models 3 for sugar and for starch adjusted for starch and sugar, respectively.[7]Inter,quintile test for trend calculated by orthogonal polynomial contrasts. [8]For 50 g/day increments of dietary GL, carbohydrate, starch and sugar, or 5 units/day increments of dietary GI.

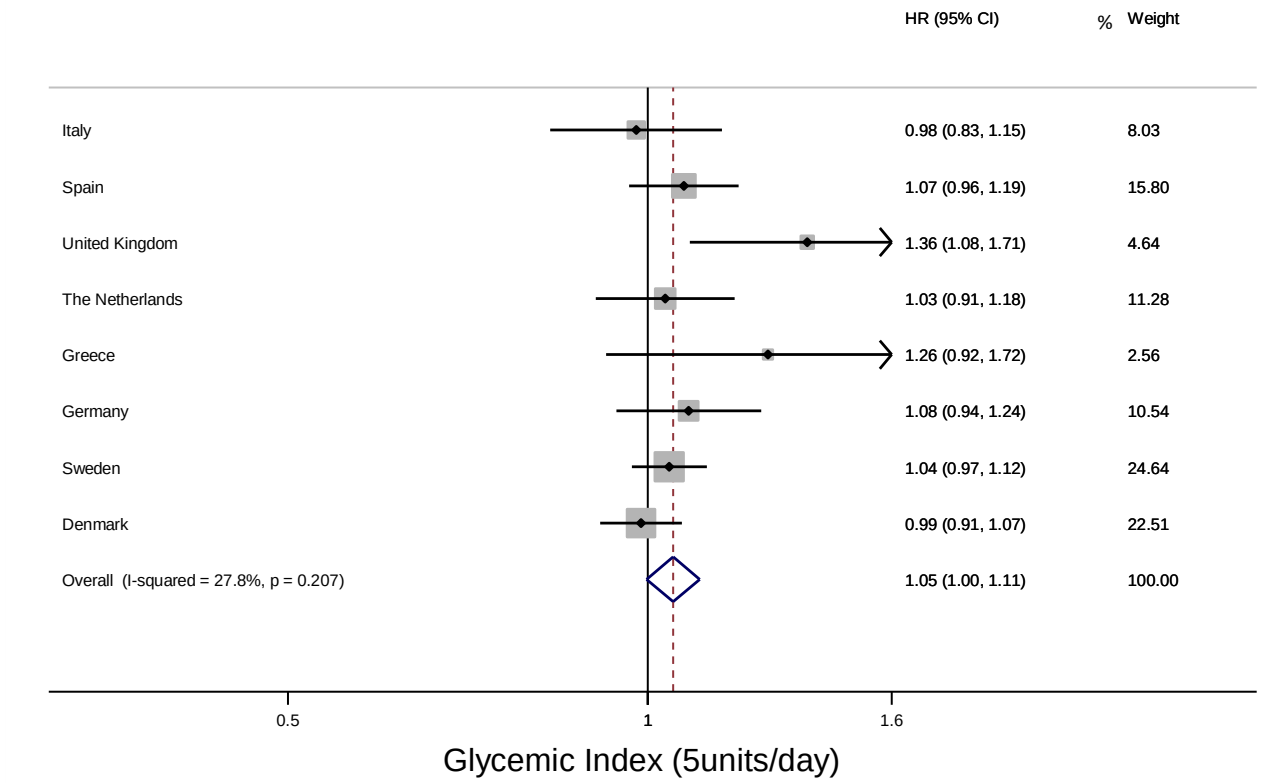
Table 5. Subgroup analyses: hazard ratios[1] (with 95% confidence intervals) for first coronary heart disease event according to quintiles dietary glycemic load (GL) and index (GI) in the EPIC study

	Quintiles of energy-adjusted dietary GL or GI					P trend[4]	Continuous[5]
	I	**II**	**III**	**IV**	**V**		
Dietary GL							
Excluding cases diagnosed in the first 2 years (5648 cases)							
Model 3[2,3]	1	1.05 (0.96,1.15)	1.00 (0.91,1.11)	1.07 (0.95,1.19)	1.10 (0.97,1.26)	0.186	1.15 (1.04,1.27)
Men only (4251 cases)							
Model 3[2]	1	1.07 (0.97,1.18)	1.08 (0.97,1.20)	1.13 (1.01,1.27)	1. 17 (1.02,1.34)	0.027	1.19 (1.08,1.30)
Women only (2103 cases)							
Model 3[2]	1	1.12 (0.96,1.30)	1.11 (0.96,1.30)	1.14 (0.97,1.34)	1.23 (1.02,1.47)	0.062	1.22 (1.07,1.40)
P heterogeneity							0.588
According to Body mass index							
<25 kg/m^2 (2025 cases)							
Model 3[2,3]	1	0.94 (0.81,1.09)	0.90 (0.78,1.05)	0.99 (0.85,1.16)	0.98 (0.83,1.16)	0.984	1.09 (0.96,1.22)
≥25 kg/m^2 (4329 cases)							
Model 3[2,3]	1	1.14 (1.03,1.26)	1.15 (1.03,1.28)	1.16 (1.03,1.31)	1.26 (1.10,1.44)	0.004	1.22 (1.11,1.35)
P heterogeneity							0.022
Dietary GI							
Excluding cases diagnosed in the first 2 years (5648 cases)							
Model 3[2,3]	1	0.98 (0.89,1.07)	1.05 (0.96,1.15)	1.04 (0.95,1.14)	1.05 (0.96,1.16)	0.115	1.03 (0.99,1.08)
Men only (4251 cases)							

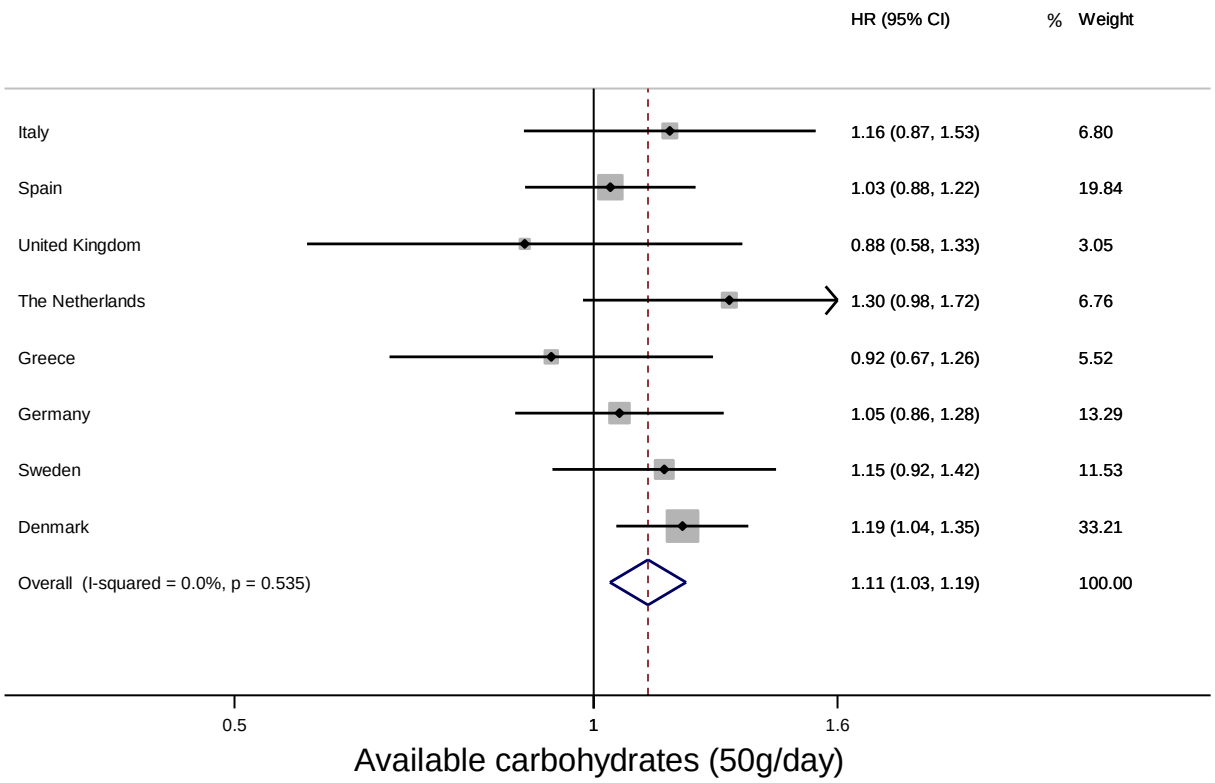
Model 3[2]	1	0.94 (0.84,1.05)	0.98 (0.88,1.09)	0.99 (0.89,1.11)	1.01 (0.91,1.12)	0.396	1.02 (0.98,1.07)
Women only (2103 cases)							
Model 3[2]	1	1.11 (0.97,1.28)	1.24 (1.08,1.42)	1.11 (0.96,1.28)	1.22 (1.06,1.40)	0.014	1.09 (1.02,1.16)
P for heterogeneity							0.090
According to Body mass index							
<25 kg/m^2 (2025 cases)							
Model 3[2,3]	1	1.03 (0.88,1.21)	0.99 (0.85,1.16)	1.00 (0.86,1.16)	1.04 (0.90,1.21)	0.686	1.03 (0.97,1.10)
≥25 kg/m^2 (4329 cases)							
Model 3[2,3]	1	0.98 (0.88,1.09)	1.10 (0.99,1.22)	1.06 (0.96,1.18)	1.10 (0.99,1.22)	0.026	1.05 (1.00,1.10)
P heterogeneity							0.674

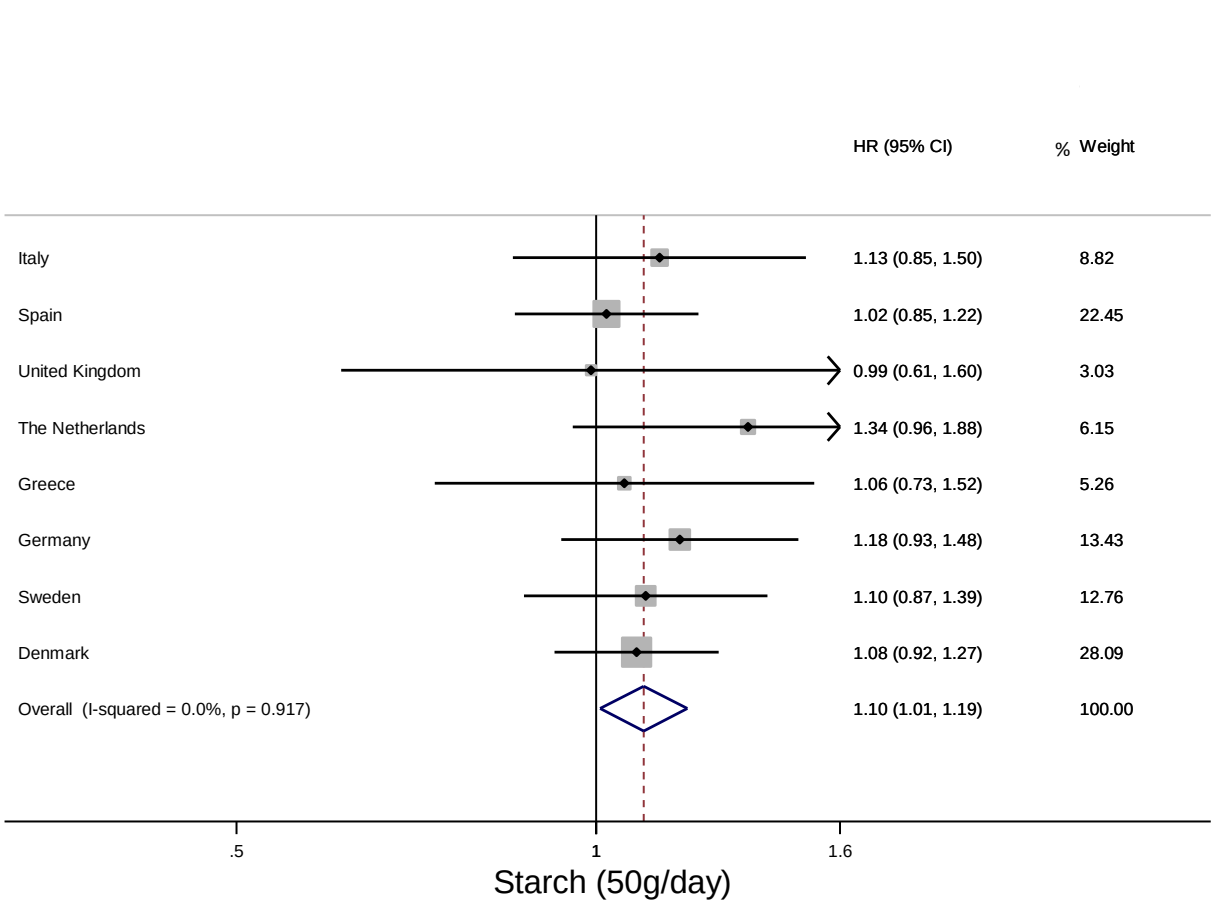
[1] Hazard ratio and 95% confidence interval estimated from Cox proportional hazard models. [2] Stratified by age, recruitment center and adjusted for smoking, education, physical activity, body mass index, blood pressure variable, and intakes of energy, protein, alcohol, cereal fiber, saturated and monounsaturated fat. [3]Additionally stratified by sex. [4] Inter-quintile test for trend calculated by orthogonal polynomial contrasts.[5]For 50 g/day increments of dietary GL or 5 units/day increments of dietary GI.

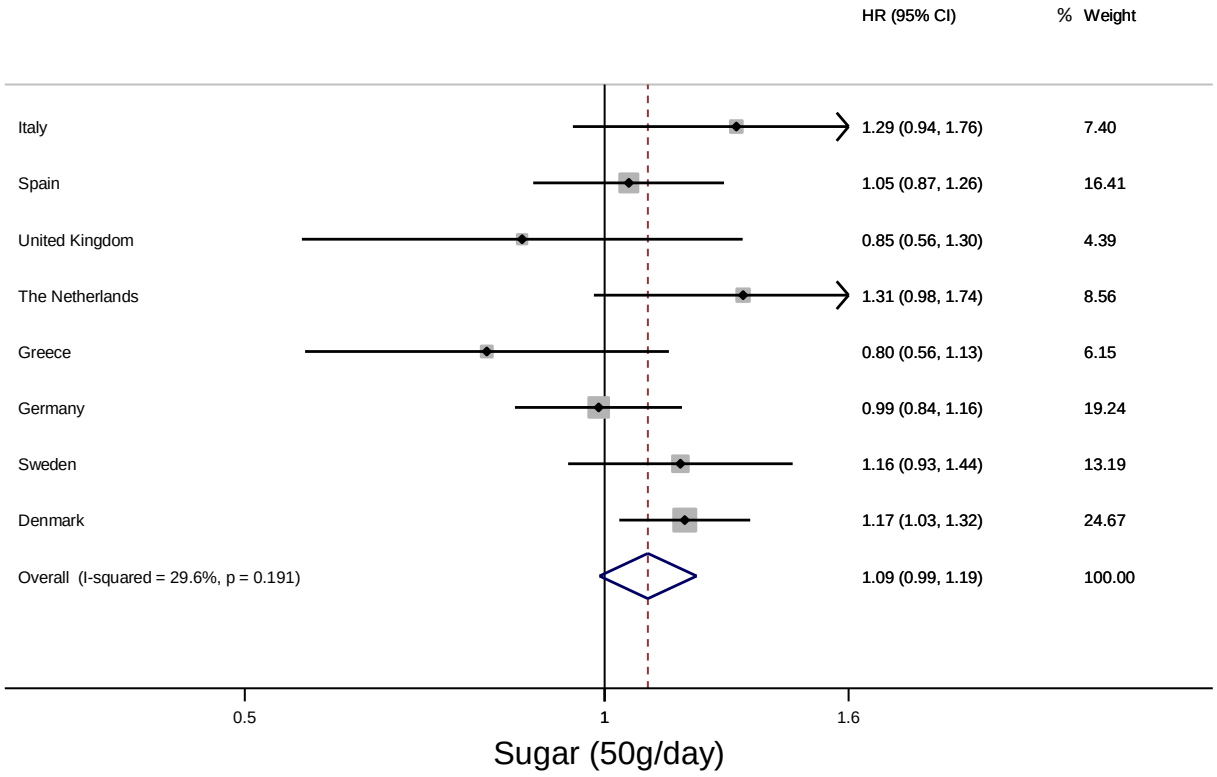

HR (95% CI)
% Weight
Italy
1.34 (0.93, 1.94)
7.55
Spain
1.06 (0.83, 1.37)
16.54
United Kingdom
1.39 (0.77, 2.52)
2.96
The Netherlands
1.42 (0.97, 2.08)
7.20
Greece
0.99 (0.54, 1.81)
2.85
Germany
1.17 (0.86, 1.60)
10.58
Sweden
1.18 (0.94, 1.48)
20.39
Denmark
1.19 (0.99, 1.42)
31.93
Overall (I-squared = 0.0%, p = 0.915)
1.19 (1.07, 1.32)
100.00
0.5
1
1.6
Glycemic Load (50g/day)


HR (95% CI)
% Weight
Italy
0.98 (0.83, 1.15)
8.03
Spain
1.07 (0.96, 1.19)
15.80
United Kingdom
1.36 (1.08, 1.71)
4.64
The Netherlands
1.03 (0.91, 1.18)
11.28
Greece
1.26 (0.92, 1.72)
2.56
Germany
1.08 (0.94, 1.24)
10.54
Sweden
1.04 (0.97, 1.12)
24.64
Denmark
0.99 (0.91, 1.07)
22.51
Overall (I-squared = 27.8%, p = 0.207)
1.05 (1.00, 1.11)
100.00
0.5
1
1.6
Glycemic Index (5units/day)

%


HR (95% CI)
% Weight
Italy
1.16 (0.87, 1.53)
6.80
Spain
1.03 (0.88, 1.22)
19.84
United Kingdom
0.88 (0.58, 1.33)
3.05
The Netherlands
1.30 (0.98, 1.72)
6.76
Greece
0.92 (0.67, 1.26)
5.52
Germany
1.05 (0.86, 1.28)
13.29
Sweden
1.15 (0.92, 1.42)
11.53
Denmark
1.19 (1.04, 1.35)
33.21
Overall (I-squared = 0.0%, p = 0.535)
1.11 (1.03, 1.19)
100.00
0.5
1
1.6
Available carbohydrates (50g/day)


HR (95% CI)
% Weight
Italy
1.13 (0.85, 1.50)
8.82
Spain
1.02 (0.85, 1.22)
22.45
United Kingdom
0.99 (0.61, 1.60)
3.03
The Netherlands
1.34 (0.96, 1.88)
6.15
Greece
1.06 (0.73, 1.52)
5.26
Germany
1.18 (0.93, 1.48)
13.43
Sweden
1.10 (0.87, 1.39)
12.76
Denmark
1.08 (0.92, 1.27)
28.09
Overall (I-squared = 0.0%, p = 0.917)
1.10 (1.01, 1.19)
100.00
.5
1
1.6
Starch (50g/day)


HR (95% CI)
% Weight
Italy
1.29 (0.94, 1.76)
7.40
Spain
1.05 (0.87, 1.26)
16.41
United Kingdom
0.85 (0.56, 1.30)
4.39
The Netherlands
1.31 (0.98, 1.74)
8.56
Greece
0.80 (0.56, 1.13)
6.15
Germany
0.99 (0.84, 1.16)
19.24
Sweden
1.16 (0.93, 1.44)
13.19
Denmark
1.17 (1.03, 1.32)
24.67
Overall (I-squared = 29.6%, p = 0.191)
1.09 (0.99, 1.19)
100.00
0.5
1
1.6
Sugar (50g/day)