**Glycemic index, glycemic load and risk of coronary heart disease: a pan-European case-cohort study**

Sabina Sieri1, Claudia Agnoli1, Sara Grioni1, Elisabete Weiderpass2, Amalia Mattiello3, Ivonne Sluijs4, Maria Jose Sanchez5,6, Marianne Uhre Jakobsen7, Michael Sweeting8,9,Yvonne T van der Schouw4, Lena Maria Nilsson10, Patrik Wennberg11, Verena A Katzke12, Tilman Kühn12, Kim Overvad13, Tammy YN Tong14, Moreno-Iribas Conchi15, José Ramón Quirós16, Juan Manuel García-Torrecillas17,Olatz Mokoroa18, Jesús-Humberto Gómez19, Anne Tjønneland20,21,Emiliy Sonestedt22,Antonia Trichopoulou23, Anna Karakatsani23,24, Elissavet Valanou23, Jolanda MA Boer25, WM Monique Verschuren 25,Marie-Christine Boutron-Ruault26,27, Guy Fagherazzi26,27 , Anne-Laure Madika26, 27, *28*, Manuela M Bergmann29, Matthias B. Schulze30,31,32, Pietro Ferrari2, Heinz Freisling2, Hannah Lennon2, Carlotta Sacerdote33, Giovanna Masala34, Rosario Tumino35, Elio Riboli36, Nicholas J Wareham37, Nita G Forouhi37,Adam Butterworth8, John Danesh8**‡** and Vittorio Krogh1**‡**.

**‡**These authors are joint Principal Investigators on this work

1Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (SS,CA,SG,VK)

2International Agency for Research on Cancer, World Health Organization, Lyon, France (EW,PF,HF,HL)

3Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy (AM)

4Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands (IS,YTV)

5Andalusian School of Public Health, Granada, Spain (MJS)

6CIBER Epidemiología y Salud Pública, Madrid, Spain (MJS)

7National Food Institute, Division for Diet, Disease Prevention and Toxicology, Technical University of Denmark, Kongens Lyngby, Denmark (MUJ)

8MRC/BHF Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK (MS, AB,JD)

9Department of Health Sciences, University of Leicester, UK (MS)

10Department of Public Health and Clinical Medicine, Sustainable Health, Umeå University, Umeå, Sweden (LMN)

11Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Umeå, Sweden (PW)

12Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany (VAK, TK)

13Department of Public Health, Aarhus University, Aarhus , Denmark (KO)

14Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (TYNT)

15Public Health Institute of Navarra, IdiSNA, Pamplona, Spain (MIC)

16Public Health Directorate, Asturias, Spain (JRQ)

17Hospital Universitario Torre Cárdenas, Almería, Spain (JMG)

18Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain (OM)

19Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain (JHG)

20Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark (AT)

21Department of Public Health, University of Copenhagen, Copenhagen, Denmark (AT)

22Nutritional Epidemiology, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden (ES)

23Hellenic Health Foundation, Athens, Greece (AT, AK, EV)

24Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, “ATTIKON” University Hospital, Haidari, Greece (AK)

25National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands (JMAB, WMMV)

26CESP, Fac. de médecine, Univ. Paris-Sud, Fac. de médecine UVSQ, INSERM, Université Paris-Saclay, 94805, Villejuif, France (MCB,GF,ALM)

27Gustave Roussy, F-94805, Villejuif, France (MCB,GF,ALM)

28Université Lille, CHU Lille, EA2694, Lille, France (ALM)

29 Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany (MMB)

30Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany (MBS)

31DZHK (German Center for Cardiovascular Research), partner site Berlin, Berlin, Germany (MBS)

32University of Potsdam, Institute of Nutritional Sciences, Nuthetal, Germany (MBS)

33Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy (CS)

34Cancer Risk Factors and Lifestyle Epidemiology Unit. Institute for cancer research, prevention and clinical network (ISPRO) Florence, Italy (GM)

35Cancer Registry and Histopathology Department, ‘Civic-M.P.Arezzo’ Hospital, ASP Ragusa, Ragusa Italy (RT)

36Department of Epidemiology and Public Health, Imperial College London, London, UK (ER)

37MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Cambridge, UK (NJW,NGF)

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Address for correspondence

Claudia Agnoli, MSc

Epidemiology and Prevention Unit

Fondazione IRCCS Istituto Nazionale dei Tumori

Via Venezian 1,

I-20133 Milan, Italy

Tel: +39 02 23903509; Fax: +39 02 23903516

e-mail: [claudia.agnoli@istitutotumori.mi.it](mailto:claudia.agnoli@istitutotumori.mi.it)

**Funding**

EPIC-CVD was supported by the European Union Framework 7 (HEALTH-F2-2012-279233), the European Research Council (268834), the UK Medical Research Council (G0800270 and MR/L003120/1), the British Heart Foundation (SP/09/002 and RG/08/014 and RG13/13/30194), and the UK National Institute of Health Research. The establishment of the study subcohort was supported by the EU Sixth Framework Programme (FP6) (grant LSHM\_CT\_2006\_037197 to the InterAct project) and the Medical Research Council Epidemiology Unit (grants MC\_UU\_12015/1 and MC\_UU\_12015/5). NJW and NGF acknowledge support from NIHR Biomedical Research Centre Cambridge: Nutrition, Diet, and Lifestyle Research Theme (IS-BRC-1215-20014). EPIC-Asturias was supported by the Regional Government of Asturias. EPIC-Greece was supported by the Hellenic Health Foundation. EPIC-Heidelberg was supported by German Cancer Aid, the German Cancer Research Centre, and the German Federal Ministry of Education and Research. EPIC-Oxford was supported by the UK Medical Research Council (MR/M012190/1) and Cancer Research UK (570/A16491). EPIC-Ragusa was supported by the Sicilian Regional Government, the Iblean Charitable Association for Epidemiological Research (AIRE), Ragusa, and the Italian Association of Blood Donors (AVIS) Ragusa. EPIC-Turin was supported by the Compagnia di San Paolo and the Human Genetics Foundation (HuGeF) Turin. EPIC-NL was supported by the Dutch Ministry of Public Health, Welfare and Sports (VWS), the Netherlands Organisation for Health Research and Development (ZonMW); and the World Cancer Research Fund (WCRF). EPIC-Umeå was supported by the Swedish Cancer Society, the Swedish Scientific Council and the Regional Government of Västerbotten.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data described in the manuscript will be made available upon request pending application (see website <http://epic.iarc.fr/access/index.php>.)

**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 coronary heart disease (CHD) risk. 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 was a case-cohort study nested within the European Prospective Investigation into Cancer and Nutrition, on 7435 cases and a sub-cohort of 17,162 participants. HRs with 95% confidence intervals (CI) for a CHD event, in relation to intake of GI, GL and carbohydrates, were estimated using covariate-adjusted Prentice-weighted Cox models.

**Results:** After 10.9 years (median), 4970 men and 2465 women had a CHD event. High GL was associated with increased coronary risk: HR 1.23 95% CI 1.03,1.46;p-trend 0.02, highest quintile of intake vs. lowest; HR 1.18 95% CI 1.03,1.34 per 50 g/day GL increase. The GL-CHD association remained after excluding participants with diabetes; and did not differ between men (HR 1.18 95% CI 1.02,1.36 per 50 g/day) and women (HR 1.22 95% CI 0.88,1.68 per 50 g/day) or between BMI≥25 (HR 1.22 95% CI 1.05,1.42) and BMI <25 (HR 1.08 95% CI 0.84,1.38)(tests for interaction not significant). GI was not associated with coronary risk (HR 1.03 95% CI 0.98,1.09 per 5 unit/day increase). High available carbohydrate was associated with increased coronary risk: HR 1.22; 95% CI 1.01,1.48, p-trend 0.032, highest vs. lowest quintile; HR 1.12 (95% CI 1.02,1.23) per 50 g/day increase.

Bonferroni correction for multiple tests reduced the p-value significance threshold to 0.01, so that GL and carbohydrate were no longer significantly associated with CHD risk.

**Conclusions:** This large pan-European study does not provide strong support for the hypotheses that high dietary GL and carbohydrate increase 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 saturated 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 (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 case-cohort study. We compared 7,435 incident CHD cases with a representative sample (sub-cohort) of 17,162 participants from the European Prospective Investigation into Cancer and Nutrition cardiovascular disease (EPIC-CVD), providing adequate power for sex-specific and combined analyses.

**METHODS**

**Study Population**

EPIC design and methods are described elsewhere (14). Briefly, EPIC recruited 366,521 women and 153,457 men, mostly 35-70 years, between 1991 and 1999 from 23 centers in ten European countries: Denmark, France, Greece, Germany, Italy, The Netherlands, Norway, Spain, Sweden, and the UK. Ethical committees of the International Agency for Research on Cancer and local centers approved the EPIC protocol. All participants gave written informed consent.

For this study we selected a representative sub-cohort of 18,157 EPIC participants by random sampling from all centers (with stratification by center) (15). After exclusion of 609 with a history of myocardial infarction or stroke, 17,548 remained. We next identified 7,435 persons in the entire cohort who had a first incident CHD event during the study period. As expected some cases (386) formed part of the sub-cohort while other CHD events occurred in EPIC participants not in the sub-cohort (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 registers, hospital admissions records, and self-report(16). 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 (17). Published values of GIs (glucose as reference) (18-20), were assigned to carbohydrate-containing foods as described elsewhere(21).

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 weight/height2.Blood pressure was measured using standard procedures. Physical activity was categorized according to the Cambridge Physical Activity Index (22).

Blood pressure was measured using standard procedures, but was only available for 62% of participants (23). We therefore used a composite blood pressure variable available for 98% of participants: if one or more of self-reported hypertension, self-reported use of anti-hypertensive medication, systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg were present, the participant was considered as having ‘high blood pressure’. Participants who reported having, or receiving treatment for diabetes were considered to have this condition.

A non-fasting blood sample was obtained from most participants at recruitment. On stored plasma samples the following were determined: high-sensitivity C-reactive protein, total cholesterol, HDL cholesterol and triglycerides (Stichting Huisartsen Laboratorium, Etten-Leur, the Netherlands), erythrocyte hemoglobin A1c (G8 HPLC analyzer, Tosoh Bioscience, Japan), and glucose (Cobas enzymatic assay, Roche Diagnostics, Mannheim, Germany). Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol, since LDL cholesterol was not directly assayed. These data were not available for Norwegian participants.

**Statistical methods**

Participant characteristics are presented as means and standard deviations (continuous variables), or percentages (categorical variables), by quintiles of energy-adjusted GI and GL. Primary outcome variables were hazard ratios (HR) for CHD in relation to variation in GI and GL. Secondary outcome variables were HRs for CHD in relation to available carbohydrate, starch, and sugar. HRs with 95% confidence intervals (CI) were estimated by Prentice-weighted Cox proportional hazard models, using center, age and sex-stratified baseline hazards, with calculation of standard errors by the robust method to take account of the case-cohort design(24). The Bonferroni method was used to account for multiple testing: the conventional significance level of 0.05 was divided by the number of variables investigated (n=5) so that p values were considered significant at <0.01.

Age (years) was the time variable: participant entry was age at recruitment; exit was age at first CHD event, death for other causes, loss to follow-up, or end of CHD follow-up (whichever came first). Dietary intakes of interest were adjusted for energy intake using the regression-residual method (25) and categorized (quintiles) based on the sub-cohort. Models were run on men and women together, with stratification by sex only in subgroup analyses. The study variables were also modeled as continuous variables, in which case HRs indicate risks associated with 50 g/day or 5 units/day (GI) intake increments. Available carbohydrate was defined as starch and sugars: indigestible carbohydrate was excluded.

Three models are presented: model 1 stratified by center, age, and sex; model 2 additionally adjusted for smoking status (current: 1-15 cig/day, 16-25 cig/day, >25 cig/day; former: quit ≤10 years, 11-20 years, >20 years previously; never), physical activity (inactive, moderately inactive, moderately active, active), BMI (<25, 25-29.9, ≥30 kg/m2), alcohol consumption (<12, 12-24, >24 g/day), education (no schooling, primary, secondary, vocational/university) and blood pressure (high, normal); model 3 additionally adjusted for intakes of energy, saturated fat, monounsaturated fat, protein, and fiber, or cereal fiber (all continuous) for analyses investigating GI and GL. Model 3 was further run with the adjustment for energy, polyunsaturated and monounsaturated fat (not saturated fat), protein, and fiber, or cereal fiber and with the adjustment for energy, polyunsaturated, saturated monounsaturated fat, (not protein), and 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 fixed effects meta-analyses. Pooled HRs were then plotted and between-country heterogeneity was quantified by the I2 statistic (26). The proportional hazards assumption for all variables in relation to CHD risk was tested using the Grambsch and Therneau method (27). 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 incident 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, and after excluding those with diabetes. In the analyses on women, models were further adjusted for menopause (yes/no) and hormone use (yes/no). 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 a median follow-up of 10.9 years, 7435 incident CHD cases (4970 men, 2465 women) were identified in the entire EPICcohort. Table 1 shows baseline characteristics of the sub-cohort by quintiles of energy-adjusted dietary GL. Mean GL varied substantially across quintiles (97.2-167.9);while mean GI ranged from 53.4 (lowest quintile) to 58.8 (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 sub-cohort characteristics by quintiles of energy-adjusted dietary GI. Mean GI ranged from 50.8 (lowest quintile) to 61.4 (highest quintile); GL ranged from 114.3 (lowest quintile) to 149.4 (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 and sugar intake increased with increasing GL but decreased with increasing GI. sugar

Table 3 shows baseline means of selected biomarkers by quintiles of energy-adjusted GL and GI. Those in the highest GL 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 appeared associated with increased CHD risk, with p trend 0.02. For 50 g/day GL increments the HR was 1.18 (95% CI 1.03,1.34). In this model − with monounsaturated fat, saturated fat and protein held constant –the GL variable represents the effect of substituting GL for polyunsaturated fat and low-GI carbohydrate on CHD risk. When model 3 was adjusted for polyunsaturated and monounsaturated fat (not saturated fat), the HR for 50 g/day GL increments was 1.13 (95% CI 1.00,1.27); and when adjusted for polyunsaturated, monounsaturated and saturated fat (not protein), the HR for 50 g/day GL increments was 1.11 (95% CI 0.99,1.25) (Data not in Tables).

For available carbohydrate in model 3, those in the highest quintile of consumption had greater CHD risk than those in the lowest (HR 1.22; 95% CI 1.01,1.48, p trend 0.032); the risk for 50 g/day GL increments was HR 1.12; 95% CI 1.02,1.23. When model 3 was further adjusted for polyunsaturated fat, monounsaturated fat, and protein (not saturated fat), the HR for 50 g/day increments was 1.10 (95% CI 1.01,1.20); when adjusted for polyunsaturated, monounsaturated, and saturated fat (not protein), the HR for 50 g/day increments was 1.08 (95% CI 0.99,1.17) (Data not in Tables).HRs for 50 g/day increments of starch and sugar were 1.11 (95% CI 1.00,1.22) and 1.10; 95% CI 1.00,1.21 respectively. After Bonferroni correction for multiple testing, associations of GL and available carbohydrate with CHD risk were never significant since all p values were >0.01. GI was never associated with CHD risk either before or after Bonferroni correction.

Estimates of country-specific HRs (data pooled from centers) with corresponding I2 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 persons with diabetes, cases diagnosed in the first two years, and also by sex and BMI. The association between GL and CHD was similar in participants without diabetes (HR for 50 g/day increments: 1.24; 95% CI 1.08,1.42) to that in the entire cohort. Associations between GL and CHD attenuated after excluding those with a CHD event during the first two years of follow-up (HR for 50 g/day increments: 1.16; 95% CI 1.01,1.32).

Model 3 HR estimates for each sex were in the same direction as for the sexes combined. The interaction of dietary GL with sex was not significant.

Finally, high GL was associated with higher risk of CHD among participants with BMI ≥25 mg/kg2 (HR for 50 g/day increments 1.22; 95% CI 1.05,1.42); nevertheless, there was no significant interaction of GL with BMI.

**DISCUSSION**

In this prospective case-cohort study with 7,435 incident CHD cases from ten European countries, high dietary GL and high dietary available carbohydrate appeared associated with increased CHD risk; however, the risk increases were never significant after Bonferroni correction for multiple testing. HR estimates for starch and sugar intakes were lower than, but in the same direction as, those for available carbohydrate. By contrast HR estimates for dietary GI did not suggest that this variable was associated with CHD risk.

Three 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 (28,29) − 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 null or inconsistent findings for GI across observational studies for CHD endpoints (mortality and incidence), and a moderate positive association for GL (13).

CHD risk in relation to available carbohydrate consumption has also been examined in prospective studies, again with inconsistent results: a positive association was found in both sexes that consumed carbohydrate mainly from white rice and refined wheat products(30); while other studies found no associations in women (31,32) or men(33). The PURE study found that high carbohydrate intake was associated with increased risk of total mortality but not with the risk of CVD (34).

It is important to note that an apparent association between dietary GL and CHD risk in our study only became evident after adjustment for dietary variables (model 3). And that this association was never significant after applying the Bonferroni correction for multiple statistical tests.

Like most previous studies (31;35-38), we found that high dietary GL was associated with high cereal fiber intake and low saturated fat and protein intake. So it is reasonable that associations of dietary GL with CHD only became apparent after additional adjustment for these variables, even though such adjustments can be considered over-adjustments since the fiber, fat and protein content of foods influence their GI/GL. Furthermore, substitution of GL or available carbohydrate for polyunsaturated or saturated fat did not change the strength of the GL-CHD association, whereas the association weakened when protein intake was omitted. A randomized controlled trial that investigated CHD in relation to replacing dietary fat with carbohydrates (39) found no risk change. We found that replacing dietary saturated and polyunsaturated fat − but not protein − with high GL foods or carbohydrate was associated with increased CHD risk.

We found no association between dietary GI and CHD in both sexes together or either sex separately, whereas previous studies reported positive associations (31,35,40). However, foods that contribute to GI differ markedly across European populations; also the range of GI intake was rather narrow in our study: both are likely to have masked any association of GI with CHD risk.

The mediators of the association of high available 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 (41). If such behavior is habitual, it may lead to insulin resistance and obesity (42,43), with increased triglycerides and LDL cholesterol, and lowered HDL cholesterol, 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 (44). In people with high BMI, greater insulin demand in response to a high GL diet may further exacerbate insulin resistance and lipid imbalance (45).

This scenario is supported by a meta-analysis of randomized intervention trials (46) which found that lowering dietary GI reduced CVD risk factors, with lowered triglycerides and LDL cholesterol and raised HDL cholesterol. However such responses are not always observed (47;48).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 increased. These cross-sectional (and non significant) 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(49).

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 (50). 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 (51).

**CONCLUSIONS**

This large pan-European study has revealed only weak associations of dietary GL and available carbohydrate with CHD risk and does not provide strong support for the hypotheses that high dietary GL and carbohydrate increase CHD risk.

**Acknowledgements**

We thank all EPIC participants. We also thank EPIC staff, including those at the EPIC-CVD and EPIC-InterAct Coordinating Centres, for sample preparation and data handling, particularly Sarah Spackman (EPIC-CVD Data Manager)and Nicola Kerrison (EPIC-InterAct Data Manager, MRC Epidemiology Unit).We are also pleased to acknowledge Statistics Netherlands for providing causes of death information on Dutch EPIC participants. Thanks are also due to Don Ward for help with the English.

**Authors’ contributions to the manuscript:**

SS, VK, AC, SG, AB 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, JMAB, WMMV, MCB, MMB, MBS, PF, RT, GM, AM, ER, AB, JD; SG, TK, PW, OM, JMG, AK, EV, GF, ALM, HF, HL take responsibility for the databases and follow-up data. PC, CA, SG, AM, GF, GM, were responsible for data collection and storage in the EPIC-Italy centers. All authors contributed to data interpretation, and critical revision of the article, and approved the final manuscript.

**Disclosures**

Adam Butterworth has received grants unrelated to the present study from AstraZeneca, Biogen, Merck, Novartis, and Sanofi. All other authors affirm that they have no relationships with industry relevant to present study

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**References**

1. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG et al. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. Circulation 2017;136:e1-e23.PM:28620111

2. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491-9.PM:9366580

3. Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, Sampson L, Rexrode KM, Rimm EB, Willett WC et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. J Am Coll Cardiol 2015;66:1538-48.PM:26429077

4. Parks EJ, Hellerstein MK. Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms. Am J Clin Nutr 2000;71:412-33.PM:10648253

5. Siri PW, Krauss RM. Influence of dietary carbohydrate and fat on LDL and HDL particle distributions. Curr Atheroscler Rep 2005;7:455-9.PM:16256003

6. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414-23.PM:11988062

7. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, Goff DV. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362-6.PM:6259925

8. Dong JY, Zhang YH, Wang P, Qin LQ. Meta-analysis of dietary glycemic load and glycemic index in relation to risk of coronary heart disease. Am J Cardiol 2012;109:1608-13.PM:22440121

9. Fan J, Song Y, Wang Y, Hui R, Zhang W. Dietary glycemic index, glycemic load, and risk of coronary heart disease, stroke, and stroke mortality: a systematic review with meta-analysis. PLoS One 2012;7:e52182.PM:23284926

10. Mirrahimi A, de Souza RJ, Chiavaroli L, Sievenpiper JL, Beyene J, Hanley AJ, Augustin LS, Kendall CW, Jenkins DJ. Associations of glycemic index and load with coronary heart disease events: a systematic review and meta-analysis of prospective cohorts. J Am Heart Assoc 2012;1:e000752.PM:23316283

11. Mirrahimi A, Chiavaroli L, Srichaikul K, Augustin LS, Sievenpiper JL, Kendall CW, Jenkins DJ. The role of glycemic index and glycemic load in cardiovascular disease and its risk factors: a review of the recent literature. Curr Atheroscler Rep 2014;16:381.PM:24271882

12. Livesey G, Livesey H. Coronary Heart Disease and Dietary Carbohydrate, Glycemic Index, and Glycemic Load: Dose-Response Meta-analyses of Prospective Cohort Studies. Mayo Clin Proc Innov Qual Outcomes 2019;3:52-69.PM:30899909

13. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te ML. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet 2019;393:434-45.PM:30638909

14. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26 Suppl 1:S6-14.PM:9126529

15. Langenberg C, Sharp S, Forouhi NG, Franks PW, Schulze MB, Kerrison N, Ekelund U, Barroso I, Panico S, Tormo MJ et al. Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. Diabetologia 2011;54:2272-82.PM:21717116

16. Danesh J, Saracci R, Berglund G, Feskens E, Overvad K, Panico S, Thompson S, Fournier A, Clavel-Chapelon F, Canonico M et al. EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries. Eur J Epidemiol 2007;22:129-41.PM:17295097

17. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, Salvini S, Parpinel M, Moller A, Ireland J et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. Eur J Clin Nutr 2007.PM:17375121

18. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5-56.PM:12081815

19. Henry CJ, Lightowler HJ, Strik CM, Renton H, Hails S. Glycaemic index and glycaemic load values of commercially available products in the UK. Br J Nutr 2005;94:922-30.PM:16351769

20. Human Nutrition Unit SoMaMB, University of Sydney. The Official Website of the Glycemic Index and GI Database. Sydney, 2006. 2006.   
Ref Type: Generic

21. Cust AE, Slimani N, Kaaks R, van BM, Biessy C, Ferrari P, Laville M, Tjonneland A, Olsen A, Overvad K et al. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. Am J Epidemiol 2007;166:912-23.PM:17670911

22. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr., Schmitz KH, Emplaincourt PO et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498-S504.PM:10993420

23. Schulze MB, Kroke A, Saracci R, Boeing H. The effect of differences in measurement procedure on the comparability of blood pressure estimates in multi-centre studies. Blood Press Monit 2002;7:95-104.PM:12048426

24. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika 1986;73:1-11.

25. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17-27.PM:0003521261

26. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007;335:914-6.PM:17974687

27. Grambsch PTT. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515-26.

28. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjonneland A, Schmidt EB, Overvad K. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. Am J Clin Nutr 2010;91:1764-8.PM:20375186

29. Hardy DS, Hoelscher DM, Aragaki C, Stevens J, Steffen LM, Pankow JS, Boerwinkle E. Association of glycemic index and glycemic load with risk of incident coronary heart disease among Whites and African Americans with and without type 2 diabetes: the Atherosclerosis Risk in Communities study. Ann Epidemiol 2010;20:610-6.PM:20609341

30. Yu D, Shu XO, Li H, Xiang YB, Yang G, Gao YT, Zheng W, Zhang X. Dietary carbohydrates, refined grains, glycemic load, and risk of coronary heart disease in Chinese adults. Am J Epidemiol 2013;178:1542-9.PM:24008907

31. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, Hennekens CH, Manson JE. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455-61.PM:10837285

32. Halton TL, Willett WC, Liu S, Manson JE, Albert CM, Rexrode K, Hu FB. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 2006;355:1991-2002.PM:17093250

33. Simila ME, Kontto JP, Mannisto S, Valsta LM, Virtamo J. Glycaemic index, carbohydrate substitution for fat and risk of CHD in men. Br J Nutr 2013;110:1704-11.PM:23534456

34. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, Iqbal R, Kumar R, Wentzel-Viljoen E, Rosengren A et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. The Lancet 2017;390:2050-62.<http://www.sciencedirect.com/science/article/pii/S0140673617322523>

35. Beulens JW, de Bruijne LM, Stolk RP, Peeters PH, Bots ML, Grobbee DE, van der Schouw YT. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. J Am Coll Cardiol 2007;50:14-21.PM:17601539

36. Levitan EB, Mittleman MA, Hakansson N, Wolk A. Dietary glycemic index, dietary glycemic load, and cardiovascular disease in middle-aged and older Swedish men. Am J Clin Nutr 2007;85:1521-6.PM:17556687

37. Levitan EB, Mittleman MA, Wolk A. Dietary glycemic index, dietary glycemic load, and incidence of heart failure events: a prospective study of middle-aged and elderly women. J Am Coll Nutr 2010;29:65-71.PM:20595647

38. Mursu J, Virtanen JK, Rissanen TH, Tuomainen TP, Nykanen I, Laukkanen JA, Kortelainen R, Voutilainen S. Glycemic index, glycemic load, and the risk of acute myocardial infarction in Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Nutr Metab Cardiovasc Dis 2011;21:144-9.PM:19836217

39. Prentice RL, Aragaki AK, Van HL, Thomson CA, Beresford SA, Robinson J, Snetselaar L, Anderson GL, Manson JE, Allison MA et al. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr 2017;106:35-43.PM:28515068

40. Grau K, Tetens I, Bjornsbo KS, Heitman BL. Overall glycaemic index and glycaemic load of habitual diet and risk of heart disease. Public Health Nutr 2011;14:109-18.PM:20576198

41. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. Crit Rev Food Sci Nutr 2003;43:357-77.PM:12940416

42. Pi-Sunyer FX. Glycemic index and disease. Am J Clin Nutr 2002;76:290S-8S.PM:12081854

43. Saris WH. Sugars, energy metabolism, and body weight control. Am J Clin Nutr 2003;78:850S-7S.PM:14522749

44. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.PM:20863953

45. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr 2002;76:274S-80S.PM:12081851

46. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS, Jr., Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006;166:285-93.PM:16476868

47. Clar C, Al-Khudairy L, Loveman E, Kelly SA, Hartley L, Flowers N, Germano R, Frost G, Rees K. Low glycaemic index diets for the prevention of cardiovascular disease. Cochrane Database Syst Rev 2017;7:CD004467.PM:28759107

48. Goff LM, Cowland DE, Hooper L, Frost GS. Low glycaemic index diets and blood lipids: a systematic review and meta-analysis of randomised controlled trials. Nutr Metab Cardiovasc Dis 2013;23:1-10.PM:22841185

49. Jenkins DJ, Kendall CW, Keown-Eyssen G, Josse RG, Silverberg J, Booth GL, Vidgen E, Josse AR, Nguyen TH, Corrigan S et al. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. JAMA 2008;300:2742-53.PM:19088352

50. Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. Am J Clin Nutr 2001;73:560-6.PM:11237932

51. Wolever TM, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in glycemic index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. Am J Clin Nutr 2006;83:1306-12.PM:16762941

**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: HRs are adjusted for age, sex, study center, smoking, education, physical activity, BMI, and blood pressure, intakes of energy, protein, alcohol, fiber, saturated and monounsaturated fat (Model 3). Analyses were stratified by country and combined with random-effects meta-analysis.

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| --- | --- | --- | --- | --- | --- |
| **Table 1.** Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic load (GL) in the EPIC-CVD sub-cohort1 | | | | | |
|  | **Quintiles of energy-adjusted**2 **dietary GL** | | | | |
|  | I | II | III | IV | V |
| **N persons** | 3586 | 3550 | 3584 | 3466 | 3362 |
| **Dietary GL** | 97.2 (15.1) | 119.4 (3.8) | 131.2 (3.2) | 143.3 (4.1) | 167.9 (18.3) |
| **Dietary GI** | 53.4 (3.8) | 55.0 (3.3) | 56.1 (3.2) | 57.0 (3.1) | 58.8 (3.3) |
| **Protein** (g/day) | 104.0 (32.0) | 87.7 (26.5) | 83.7 (25.9) | 83.1 (25.9) | 89.3 (28.1) |
| **Saturated Fat** (g/day) | 37.0 (14.7) | 31.4 (12.6) | 29.5 (12.2) | 29.0 (12.1) | 30.1 (12.4) |
| **Monounsaturated Fat** (g/day) | 43.6 (17.2) | 33.3 (13.0) | 29.6 (12.0) | 28.1 (11.7) | 29.6 (12.4) |
| **Polyunsaturated Fat** (g/day) | 15.8 (7.5) | 13.4 (6.0) | 12.5 (5.6) | 12.2 (5.6) | 12.9 (5.8) |
| **Carbohydrate** (g/day) | 200.7 (63.4) | 202.9 (61.1) | 214.5 (59.8) | 238.3 (62.9) | 301.2 (80.2) |
| **Starch** (g/day) | 105.7 (42.1) | 107.1 (40.4) | 115.3 (40.5) | 129.7 (42.8) | 170.5 (63.2) |
| **Sugars** (g/day) | 89.3 (36.4) | 91.4 (35.7) | 95.8 (35.5) | 105.7 (40.2) | 128.1 (53.9) |
| **Fiber** (g/day) | 22.0 (7.4) | 21.1 (7.1) | 21.6 (7.0) | 22.9 (7.3) | 26.5 (8.4) |
| **Energy** (kcal/day) | 2340 (666) | 2022 (588) | 1964 (577) | 2021 (592) | 2320 (652) |
| **Alcohol (g/day)** | 26.1 (27.7) | 13.9 (16.8) | 10.1 (13.5) | 8.15 (11.8) | 6.89 (10.8) |
| **Age** | 51.6 (8.9) | 52.5 (9.1) | 53.3 (9.4) | 52.7 (9.7) | 52.2 (9.8) |
| **Systolic blood pressure** (mmHg) | 132.5 (20.1) | 132.6 (20.0) | 132.7 (19.8) | 132.6 (20.1) | 131.7 (19.2) |
| **Diastolic blood pressure** (mmHg) | 82.3 (11.1) | 81.7 (11.1) | 81.3 (10.6) | 81.4 (11.0) | 81.2 (10.7) |
| **Body mass index** (kg/m2) | 27.0 (4.40) | 26.4 (4.34) | 26.3 (4.32) | 26.0 (4.18) | 25.6 (4.16) |
| **Sex** |  |  |  |  |  |
| Male (%) | 49.6 | 35.1 | 31.0 | 32.9 | 43.0 |
| **Physical activity** |  |  |  |  |  |
| Inactive (%) | 24.9 | 25.7 | 24.5 | 23.7 | 24.5 |
| Moderately inactive (%) | 33.0 | 35.6 | 34.1 | 34.0 | 31.5 |
| Moderately active (%) | 23.9 | 22.3 | 22.8 | 22.0 | 22.8 |
| Active (%) | 18.2 | 16.3 | 18.7 | 20.2 | 21.2 |
| **Education** |  |  |  |  |  |
| No schooling (%) | 10.6 | 9.9 | 9.4 | 8.4 | 6.2 |
| Primary (%) | 32.3 | 33.7 | 33.3 | 33.1 | 38.3 |
| Secondary (%) | 15.0 | 13.8 | 14.4 | 15.0 | 17.1 |
| Vocational/University (%) | 42.1 | 42.5 | 43.0 | 43.5 | 38.3 |
| **Current smoker** (%) | 27.5 | 24.4 | 20.9 | 19.0 | 19.9 |
| **Never smoker** (%) | 37.4 | 45.2 | 49.5 | 52.8 | 50.0 |
| **History of high blood pressure (%)** | 35.6 | 37.9 | 38.7 | 37.5 | 36.0 |
| **History of diabetes (%)** | 4.2 | 4.2 | 3.3 | 2.9 | 2.6 |
| **Menopausal (%**3**)** | 19.7 | 30.1 | 35.6 | 33.7 | 27.4 |
| **Sometime hormone user (%‡)** | 21.7 | 22.7 | 24.5 | 27.0 | 23.1 |

1Table entries are means with standard deviations, except where indicated; 2Energy adjustment by residual method; 3percentage of women only

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 2.** Baseline nutrient intakes and cardiovascular risk factors by quintiles of energy-adjusted dietary glycemic index (GI) in the EPIC-CVD sub-cohort 1 | | | | | |
|  | **Quintiles of energy-adjusted**2 **dietary GI** | | | | |
|  | I | II | III | IV | V |
| **Npersons** | 3756 | 3564 | 3494 | 3398 | 3336 |
| **Dietary GI** | 50.8 (2.32) | 54.3 (0.60) | 56.2(0.51) | 58.1 (0.62) | 61.4 (1.84) |
| **Dietary GL** | 114.3 (22.6) | 125.3 (20.6) | 131.1 (22.0) | 138.9 (22.1) | 149.4 (27.3) |
| **Protein** (g/day) | 91.3 (30.0) | 90.3 (28.5) | 89.8(28.0) | 88.1 (27.4) | 88.3 (29.9) |
| **Saturated Fat** (g/day) | 31.8 (14.0) | 32.6 (13.0) | 32.0 (13.1) | 31.2 (12.6) | 29.3 (12.7) |
| **Monounsaturated Fat** (g/day) | 34.1 (16.4) | 33.6 (15.0) | 33.1 (14.1) | 32.1 (13.4) | 31.5 (13.3) |
| **Polyunsaturated Fat** (g/day) | 13.3 (6.5) | 13.6 (6.2) | 13.5 (6.1) | 13.4 (6.3) | 13.0 (6.3) |
| **Carbohydrate** (g/day) | 218.4 (75.8) | 229.2 (71.6) | 231.6 (73.2) | 236.0 (74.2) | 239.4 (80.2) |
| **Starch** (g/day) | 98.8 (42.4) | 117.2 (43.0) | 125.6 (45.5) | 134.8 (50.8) | 152.8 (61.6) |
| **Sugar** (g/day) | 114.9 (46.9) | 107.3 (41.4) | 101.9 (42.2) | 97.8 (39.6) | 84.9 (38.3) |
| **Fiber** (g/day) | 23.3 (8.1) | 23.2 (7.6) | 22.8 (7.5) | 22.5 (7.4) | 21.9 (7.7) |
| **Energy** (kcal/day) | 2111 (661) | 2149 (629) | 2147 (628) | 2133 (618) | 2123 (645) |
| **Alcohol** (g/day) | 14.1 (20.6) | 13.2 (18.0) | 13.3 (18.6) | 12.3 (17.1) | 12.8 (18.8) |
| **Age** (years) | 52.0 (9.2) | 52.8 (9.3) | 52.8 (9.5) | 52.7 (9.6) | 52.3 (9.3) |
| **Systolic blood pressure** (mmHg) | 131.0 (19.8) | 132.6 (19.8) | 133.0 (19.8) | 132.4 (19.8) | 133.0 (19.8) |
| **Diastolic blood pressure** (mmHg) | 81.3 (11.1) | 81.6(10.7) | 81.8 (10.8) | 81.1 (10.9) | 81.9 (10.8) |
| **Body mass index** (kg/m2) | 26.5 (4.45) | 26.2 (4.30) | 26.2 (4.26) | 26.1 (4.17) | 26.3 (4.32) |
| **Sex** |  |  |  |  |  |
| Male (%) | 31.3 | 35.2 | 39.4 | 41.2 | 45.3 |
| **Physical activity** |  |  |  |  |  |
| Inactive (%) | 23.3 | 22.5 | 24,3 | 24.5 | 29.1 |
| Moderately inactive (%) | 34.1 | 34.8 | 32.8 | 34.1 | 32.4 |
| Moderately active (%) | 22.9 | 22.4 | 23.9 | 22.4 | 22.1 |
| Active (%) | 19.7 | 20.2 | 19.1 | 18.9 | 16.3 |
| **Education** |  |  |  |  |  |
| No schooling (%) | 9.1 | 7.0 | 8.8 | 8.8 | 11.3 |
| Primary (%) | 30.3 | 31.6 | 32.1 | 35.3 | 41.9 |
| Secondary (%) | 15.1 | 14.1 | 14.8 | 15.5 | 15.5 |
| Vocational/University (%) | 45.4 | 47.3 | 44.3 | 40.4 | 31.3 |
| **Current smoker** (%) | 21.1 | 20.2 | 21.0 | 22.8 | 27.4 |
| **Never smoker** (%) | 49.5 | 48.2 | 46.9 | 46.1 | 43.3 |
| **History of high blood pressure** (%) | 35.3 | 39.0 | 38.3 | 37.5 | 35.8 |
| **History of diabetes** (%) | 3.9 | 3.0 | 3.6 | 3.0 | 3.8 |
| **Menopausal** (%3) | 30.9 | 31.8 | 29.0 | 29.5 | 25.0 |
| **Sometime hormone user** (%‡) | 24.8 | 26.1 | 24.8 | 23.2 | 19.8 |

1Table entries are means with standard deviations, except where indicated; 2Energy adjustment by residual method; 3Percentage of women

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 3.** Mean1 values of selected markers of lipid and glucose metabolism (with 95% confidence intervals) 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 (4.36-4.46) | 4.43 (4.39-4.47) | 4.48 (4.44-4.52) | 4.50 (4.46-4.54) | 4.52 (4.47-4.58) | 0.0400 |
| HDL-cholesterol (mmol/l) | 1.55 (1.53-1.56) | 1.50 (1.48-1.51) | 1.47 (1.46- 1.49) | 1.45 (1.44- 1.47) | 1.43 (1.41-1.45) | <0.0001 |
| Triglycerides (mmol/l) | 1.31 (1.27-1.35) | 1.33 (1.29-1.36) | 1.37 (1.34-1.40) | 1.38 (1.35-1.42) | 1.41 (1.37-1.45) | 0.0298 |
| C-reactive protein (mg/l) | 2.12 (1.93-2.31) | 2.26 (2.11-2.41) | 2.34 (2.20-2.49) | 2.34 (2.19-2.49) | 2.41 (2.21-2.60) | 0.4542 |
| Glucose (mmol/l) | 5.10 (5.03-5.17) | 5.03 (4.97-5.08) | 4.98 (4.93-5.03) | 5.05 (4.99-5.11) | 5.00 (4.92-5.07) | 0.0665 |
| Hemoglobin A1c (%) | 5.55 (5.53-5.58) | 5.54 (5.52-5.56) | 5.52 (5.50-5.54) | 5.54 (5.52-5.56) | 5.51 (5.48-5.53) | 0.1783 |
| **Dietary GI** |  |  |  |  |  |  |
| Non-HDL cholesterol (mmol/l) | 4.43 (4.39-4.47) | 4.43 (4.39-4.46) | 4.50 (4.46-4.53) | 4.47 (4.43- 4.51) | 4.52 (4.48-4.56) | 0.0053 |
| HDL cholesterol (mmol/l) | 1.49 (1.48-1.51) | 1.49 (1.48-1.50) | 1.47 (1.46- 1.48) | 1.47 (1.46- 1.49) | 1.47 (1.46-1.49) | 0.0313 |
| Triglycerides (mmol/l) | 1.35 (1.32-1.38) | 1.31 (1.28-1.34) | 1.36 (1.33-1.39) | 1.36 (1.33-1.39) | 1.41 (1.38-1.44) | 0.0004 |
| C-reactive protein (mg/l) | 2.12 (1.97-2.26) | 2.19 (2.05-2.33) | 2.29 (2.15-2.44) | 2.31 (2.16-2.45) | 2.56 (2.40-2.71) | 0.0021 |
| Glucose (mmol/l) | 5.08 (5.03-5.13) | 5.00 (4.94-5.05) | 5.01 (4.96-5.06) | 5.04 (4.98-5.09) | 5.04 (4.98-5.10) | 0.2328 |
| Hemoglobin A1c (%) | 5.55 (5.53-5.57) | 5.52 (5.50-5.54) | 5.53 (5.51-5.55) | 5.54 (5.52-5.56) | 5.53 (5.515.55) | 0.3444 |

1Means 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. 2Analysis of covariance

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 4.** Hazard ratios (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-CVD study | | | | | | | | | | | | | | |
|  | **Quintiles of energy-adjusted dietary variables** | | | | | | | | | **P trend6** | | | **Continuous7** |
|  | **I** | **II** | | **III** | **IV** | | **V** | | |  | | |  |
| **Dietary GL** |  |  | |  |  | |  | | |  | |  | |
| Range | ≤112.1 | | 112.2-125.5 | 125.6-136.4 | 136.4-150.4 | | | >150.4 | | |  | |  | |
| N cases | 1376 | | 1408 | 1397 | 1530 | | | 1724 | | |  | |  | |
| Model 11 | 1 | | 1.02 (0.91-1.13) | 0.94 (0.84-1.05) | 1.00 (0.90-1.12) | | | 0.97 (0.87-1.08) | | | 0.524 | | 0.98 (0.91-1.05) | |
| Model 22 | 1 | | 1.04 (0.93-1.17) | 1.01 (0.90-1.14) | 1.08 (0.95-1.22) | | | 1.04 (0.92-1.18) | | | 0.420 | | 1.02 (0.94-1.10) | |
| Model 33,4 | 1 | | 1.08 (0.96-1.22) | 1.08 (0.95-1.24) | 1.19 (1.03-1.37) | | | 1.23 (1.03-1.46) | | | 0.020 | | 1.18 (1.03-1.34) | |
| **Dietary GI** |  | |  |  |  | | | |  | |  | |  | |
| Range | ≤53.0 | | 53.1-55.1 | 55.2-56.9 | 57.0-59.1 | >59.1 | | | | |  | |  | |
| N cases | 1149 | | 1337 | 1521 | 1640 | 1788 | | | | |  | |  | |
| Model 11 | 1 | | 0.92 (0.83-1.02) | 1.04 (0.93-1.15) | 1.04 (0.93-1.15) | 1.17 (1.05-1.31) | | | | | 0.000 | | 1.09 (1.04-1.14) | |
| Model 22 | 1 | | 0.95 (0.85-1.07) | 1.01 (0.90-1.13) | 1.01 (0.90-1.13) | 1.06 (0.94-1.19) | | | | | 0.220 | | 1.03 (0.98-1.09) | |
| Model 33,4 | 1 | | 0.95 (0.84-1.07) | 1.00 (0.89-1.13) | 1.01 (0.90-1.13) | 1.06 (0.94-1.19) | | | | | 0.228 | | 1.03 (0.98-1.09) | |
| **Available carbohydrate** |  | |  |  |  | | | |  | |  | |  | |
| Range | ≤203.1 | | 203.1-224.1 | 224.2-241.6 | 241.7-262.7 | >262.7 | | | | |  | |  | |
| N cases | 1523 | | 1362 | 1438 | 1446 | 1666 | | | | |  | |  | |
| Model 11 | 1 | | 0.93 (0.84-1.03) | 0.94 (0.84-1.04) | 0.89 (0.80-0.99) | 0.90 (0.80-1.00) | | | | | 0.034 | | 0.95 (0.91-1.00) | |
| Model 22 | 1 | | 0.98 (0.87-1.10) | 1.03 (0.91-1.16) | 0.98 (0.87-1.11) | 1.01 (0.89-1.14) | | | | | 0.886 | | 1.00 (0.95-1.05) | |
| Model 33 | 1 | | 1.02 (0.91-1.16) | 1.12 (0.98-1.28) | 1.11 (0.95-1.29) | 1.22 (1.01-1.48) | | | | | 0.032 | | 1.12 (1.02-1.23) | |
| **Starch** |  | |  |  |  | | | |  | |  | |  | |
| Range | ≤99.7 | | 99.7-116.3 | 116.4-131.2 | 131.3-150.8 | >150.8 | | | | |  | |  | |
| N cases | 1546 | | 1473 | 1434 | 1560 | 1422 | | | | |  | |  | |
| Model 11 | 1 | | 0.95 (0.86-1.06) | 0.89 (0.80-0.99) | 1.00 (0.91-1.11) | 0.90 (0.80-1.01) | | | | | 0.201 | | 0.95 (0.90-1.00) | |
| Model 22 | 1 | | 1.00 (0.90-1.12) | 0.90 (0.80-1.01) | 1.05 (0.94-1.18) | 1.00 (0.88-1.13) | | | | | 0.755 | | 1.00 (0.94-1.06) | |
| Model 33,5 | 1 | | 1.03 (0.92-1.16) | 0.96 (0.84-1.09) | 1.16 (1.00-1.33) | 1.17 (0.98-1.40) | | | | | 0.044 | | 1.11 (1.00-1.22) | |
| **Sugar** |  | |  |  |  | | | |  | |  | |  | |
| Range | ≤76.0 | | 76.1-92.7 | 92.8-107.5 | 107.6-127.6 | >127.6 | | | | |  | |  | |
| N cases | 1477 | | 1498 | 1372 | 1431 | 1657 | | | | |  | |  | |
| Model 11 | 1 | | 1.04 (0.94-1.16) | 0.92 (0.83-1.03) | 0.89 (0.79-0.99) | 0.97 (0.87-1.08) | | | | | 0.075 | | 0.98 (0.93-1.03) | |
| Model 22 | 1 | | 1.07 (0.96-1.20) | 1.01 (0.90-1.13) | 0.98 (0.87-1.11) | 1.03 (0.91-1.16) | | | | | 0.813 | | 1.00 (0.95-1.05) | |
| Model 33,5 | 1 | | 1.10 (0.98-1.24) | 1.06 (0.93-1.21) | 1.06 (0.92-1.22) | 1.17 (0.99-1.40) | | | | | 0.170 | | 1.10 (1.00-1.21) | |

1Adjusted by age, sex, and recruitment center. 2 Additionally adjusted for smoking, education, physical activity, BMI, and blood pressure variable.

3Additionally adjusted for intakes of energy, protein, alcohol, fiber, saturated and monounsaturated fat. 4Models 3 for GL and GI were adjusted for cereal fiber instead of fiber. 5Models 3 for sugar and for starch adjusted for starch and sugar, respectively.6Inter-quintile test for trend calculated by orthogonal polynomial contrasts. 7For 50 g/day increase in GL carbohydrate, starch and sugar, or 5 units/day increase in GI.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 5.** Subgroup analyses: hazard ratios (with 95% confidence intervals) for first coronary heart disease event according to quintiles dietary glycemic load (GL) and index (GI) in the EPIC-CVD study | | | | | | | | | | | | |
|  | | **Quintiles of energy-adjusted dietary GL or GI** | | | | | | | **P trend4** | | **Continuous5** | |
|  | | **I** | **II** | | **III** | | **IV** | **V** |  | |  | |
| **Dietary GL** | | | | | | | | | | | | |
| **Excluding people with diabetes** (5811 cases) | | | | | | | | | | | | |
| Model 31,2 | | 1 | 1.09 (0.96-1.24) | | 1.12 (0.97-1.30) | | 1.22(1.04-1.43) | 1.25 (1.03-1.52) | 0.013 | | 1.24 (1.08-1.42) | |
| Excluding cases diagnosed in the first 2 years (6282 cases) | | | | | | | | | | | | |
| Model 31,2 | | 1 | 1.07 (0.94-1.21) | | 1.01 (0.88-1.16) | | 1.15 (0.99-1.33) | 1.19 (0.99-1.42) | 0.052 | | 1.16 (1.01-1.32) | |
| Men only (4970 cases) | | | | | | | | | | | | |
| Model 31 | 1 | | | 0.95 (0.82-1.11) | | 1.04 (0.88-1.23) | 1.07 (0.89-1.29) | 1.01 (0.80-1.27) | | 0.610 | | 1.18 (1.02-1.36) |
| **Women only** (2465 cases) | | | | | | | | | | | | |
| Model 31,3 | 1 | | | 0.94 (0.76-1.17) | | 0.97 (0.76-1.24) | 1.19 (0.91-1.55) | 1.30 (0.93-1.80) | | 0.055 | | 1.22 (0.88-1.68) |
| P heterogeneity |  | | |  | |  |  |  | |  | | 0.627 |
| **By body mass index** | | | | | | | | | | | | |
| <25 kg/m2 (2211 cases) | |  |  | |  | |  |  |  | |  | |
| Model 31,2 | | 1 | 0.87 (0.70-1.08) | | 0.86 (0.68-1.09) | | 1.00 (0.78-1.29) | 1.08 (0.79-1.46) | 0.433 | | 1.08 (0.84-1.38) | |
| ≥25 kg/m2 (4846 cases) | |  |  | |  | |  |  |  | |  | |
| Model 31,2 | | 1 | 1.19 (1.02-1.38) | | 1.21 (1.03-1.42) | | 1.26 (1.06-1.50) | 1.35 (1.09-1.68) | 0.008 | | 1.22 (1.05-1.42) | |
| P heterogeneity | |  |  | |  | |  |  |  | | 0.363 | |
| **Dietary GI** | | | | | | | | | | | | |
| **Excluding persons with diabetes** (5811 cases) | | | | | | | | | | | | |
| Model 31,2 | | 1 | 0.96 (0.85-1.09) | | 1.05 (0.93-1.20) | | 1.01 (0.89-1.52) | 1.11 (0.97-1.27) | 0.083 | | 1.05 (0.99-1.11) | |
| **Excluding cases diagnosed in the first 2 years**(6282 cases) | | | | | | | | | | | | |
| Model 31,2 | | 1 | 0.94 (0.83-1.06) | | 0.99 (0.88-1.11) | | 1.01 (0.90-1.14) | 1.03 (0.91-1.17) | 0.343 | | 1.02 (0.97-1.08) | |
| **Men only** (4970 cases) | | | | | | | | | | | | |
| Model 31 | 1 | | | 1.03 (0.90-1.19) | | 1.05 (0.91-1.22) | **1.16(1.00-1.34)** | 1.06 (0.90-1.24) | | 0.211 | | 1.04 (0.97-1.11) |
| **Women only**(2465 cases) | | | | | | | | | | | | |
| Model 31,3 | 1 | | | 0.84 (0.69-1.02) | | 0.96 (0.79-1.16) | 0.96(0.79-1.17) | 0.97 (0.79-1.19) | | 0.725 | | 1.05 (0.96-1.14) |
| P for heterogeneity |  | | |  | |  |  |  | |  | | 0.649 |
| **According to Body mass index** | | | | | | | | | | | | |
| <25 kg/m2 (2211 cases) | |  |  | |  | |  |  |  | |  | |
| Model 31,2 | | 1 | 0.99 (0.81-1.22) | | 1.04 (0.84-1.28) | | 1.00 (0.81-1.23) | 1.10 (0.88-1.38) | 0.424 | | 1.01 (0.921.12) | |
| ≥25 kg/m2 (4846 cases) | |  |  | |  | |  |  |  | |  | |
| Model 31,2 | | 1 | 0.91 (0.79-1.05) | | 0.99 (0.86-1.14) | | 0.98 (0.85-1.14) | 1.07 (0.931.24) | 0.190 | | 1.05 (0.99-1.12) | |
| P heterogeneity | |  |  | |  | |  |  |  | | 0.437 | |

1Adjusted for age, recruitment center, smoking, education, physical activity, body mass index, blood pressure variable, and intakes of energy, protein, alcohol, cereal fiber, saturated and monounsaturated fat. 2Additionally adjusted for sex.3Additionally adjusted for menopausal status and hormone use.4Inter-quintile test for trend calculated by orthogonal polynomial contrasts.5For50 g/day increase in GL or 5 unit/day increase in GI