

# Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index<sup>1-3</sup>

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## ABSTRACT

**Background:** Studies have suggested that replacing saturated fatty acids (SFAs) with carbohydrates is modestly associated with a higher risk of ischemic heart disease, whereas replacing SFAs with polyunsaturated fatty acids is associated with a lower risk of ischemic heart disease. The effect of carbohydrates, however, may depend on the type consumed.

**Objectives:** By using substitution models, we aimed to investigate the risk of myocardial infarction (MI) associated with a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Carbohydrates with different glycemic index (GI) values were also investigated.

**Design:** Our prospective cohort study included 53,644 women and men free of MI at baseline.

**Results:** During a median of 12 y of follow-up, 1943 incident MI cases occurred. There was a nonsignificant inverse association between substitution of carbohydrates with low-GI values for SFAs and risk of MI [hazard ratio (HR) for MI per 5% increment of energy intake from carbohydrates: 0.88; 95% CI: 0.72, 1.07]. In contrast, there was a statistically significant positive association between substitution of carbohydrates with high-GI values for SFAs and risk of MI (HR: 1.33; 95% CI: 1.08, 1.64). There was no association for carbohydrates with medium-GI values (HR: 0.98; 95% CI: 0.80, 1.21). No effect modification by sex was observed.

**Conclusion:** This study suggests that replacing SFAs with carbohydrates with low-GI values is associated with a lower risk of MI, whereas replacing SFAs with carbohydrates with high-GI values is associated with a higher risk of MI. *Am J Clin Nutr* 2010;91:1764-8.

## INTRODUCTION

Epidemiologic prospective cohort studies have suggested that replacing saturated fatty acids (SFAs) with carbohydrates is modestly associated with a higher risk of ischemic heart disease (IHD), whereas replacing SFAs with polyunsaturated fatty acids is associated with a lower risk of IHD (1). The effect of carbohydrates, however, may depend on the type consumed.

Epidemiologic prospective cohort studies have shown a positive association between dietary glycemic index (GI) and risk of IHD (2). The dietary GI is an indicator of the average quality of the carbohydrates consumed in terms of glycemic response. The GI, which was conceived to provide a classification of carbohydrate-containing foods on the basis of their ability to raise blood glucose, was introduced by Jenkins et al (3) in 1981. Blood glucose

concentration is tightly regulated by homeostatic regulatory systems, but the rapid absorption of carbohydrates after consumption of a high-GI meal challenges these homeostatic mechanisms (4). A high-GI meal results in a high blood glucose concentration and a high insulin-to-glucagon ratio, followed by hypoglycemia, counterregulatory hormone secretion, and elevated plasma free fatty acid concentration (4). These events may affect the risk of IHD through promoting dyslipidemia, inflammation, and endothelial dysfunction (4).

The aim of this study was to investigate the risk of myocardial infarction (MI) with a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Carbohydrates with different GI values were investigated. Furthermore, potential effect modification by sex was investigated because of differences in the underlying biology such as hormonal differences.

## SUBJECTS AND METHODS

### Study population

Between December 1993 and May 1997, 160,725 women and men were invited by mail to participate in the Danish prospective cohort study Diet, Cancer, and Health. The criteria for invitation were as follows: age between 50 and 64 y, born in Denmark, and no previous cancer diagnosis registered in the Danish Cancer Registry. All persons fulfilling these criteria and living in the greater Copenhagen or Aarhus areas were invited. With the in-

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<sup>2</sup> This work is part of the project Hepatic and Adipose Tissue and Functions in the Metabolic Syndrome (HEPADIP; www.hepadip.org), which is supported by the European Commission as an Integrated Project under the 6th Framework Programme (contract LSHM-CT-2005-018734), and part of the research program of the Danish Obesity Research Centre (DanORC; www.danorc.dk), which is supported by the Danish Council for Strategic Research (contract 2101-06-0005).

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Received December 17, 2009. Accepted for publication March 16, 2010. First published online April 7, 2010; doi: 10.3945/ajcn.2009.29099.

vation, a validated 192-item semiquantitative food-frequency questionnaire (FFQ) was enclosed (5, 6). At the study center, participants filled in a lifestyle questionnaire, and a physical examination was conducted. The self-administered questionnaires were scanned and interviewer-checked by laboratory technicians. In total, 57,053 persons were recruited (35%). A detailed description of the study design and measurement procedures has been given by Tjønneland et al (7).

### Diet and behavior variables

The 192-item semiquantitative FFQ was designed for the present study (5) and validated against two 7-d weighed diet records (6). The participants were asked to report their average intake of different food and beverage items over the past year within 12 possible categories, which ranged from “never” to “8 times or more per day.” Calculation of daily nutrient intake averages was done by the software program FoodCalc (<http://www.ibt.ku.dk/jesper/foodcalc>), which is based on Danish food composition tables (8). Derived exposure measures were glycemic carbohydrates (total carbohydrates minus fiber, ie, available carbohydrates) expressed as percentage of total energy intake (% energy; not including energy intake from alcohol). A GI database was compiled by using published GI values. For each person, the average dietary GI was calculated by summing the products of the quantity of a given food item consumed (g/d), by the glycemic carbohydrate content of that food (ie, by the proportion of glycemic carbohydrates), and by its GI value, which was divided by the total glycemic carbohydrate intake (g/d) (9). GI was expressed as a percentage of the blood glucose response with the use of white bread as the reference food.

Information on education, smoking status, and leisure-time physical activity was obtained from the lifestyle questionnaire. Length of education was reported in predefined categories (<8, 8–10, and >10 y). Smoking status was reported as “never,” “former,” or “current”; duration of smoking in years; and the number of cigarettes, cigars, cheroots (a type of cigar), and tobacco pipes smoked per day. Current tobacco consumption was calculated in grams per day by using conversion factors of 1.0 for cigarettes, 4.5 for cigars, and 3.0 for cheroots and tobacco pipes. Leisure-time physical activity over the past year was reported as the number of hours per week engaged in walking, biking, gardening, housework, do-it-yourself work, and sports during summer and winter. Leisure-time physical activity was calculated as hours per week spent on biking and sports.

### Anthropometric and clinical variables

Height and weight were measured at the physical examination. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ( $\text{kg}/\text{m}^2$ ) and categorized as BMI of <25, 25–29, and  $\geq 30$ . Information on a history of hypertension and diabetes mellitus was obtained from the lifestyle questionnaire. History of hypertension was defined as reported hypertension and/or use of antihypertensive medication.

### Identification of cases

The outcome measure was incident nonfatal and fatal MI. Information on the outcome measure was obtained by linkage with central Danish registries via the unique identification

number assigned to all Danish citizens (10). We identified all participants registered with a first-time discharge diagnosis of MI or cardiac arrest (*International Classification of Diseases, 8th revision*, codes 410–410.99 and 427.27, and *International Classification of Diseases, 10th revision*, codes I21.0–I21.9 and I46.0–I46.9) in the Danish National Patient Registry (11) from the date of enrollment into the Diet, Cancer, and Health study until 31 December 2003. Medical records were retrieved and reviewed, and patients were classified according to symptoms, coronary biomarkers, electrocardiogram, and/or autopsy findings in accordance with the criteria of MI as recommended by the American Heart Association and other major health organizations for use in epidemiologic studies (12). Only patients that fulfilled the criteria of MI were included as cases. The positive predictive values of MI and cardiac arrest caused by MI in the Danish National Patient Registry were 81.9% (95% CI: 79.5, 84.2) and 50.0% (95% CI: 34.2, 65.8), respectively (13). By stratifying on the type of department of discharge, the positive predictive values were 92.4% (95% CI: 90.4, 94.0) for patients diagnosed with a MI in a ward and 26.0% (95% CI: 19.6, 33.3) for patients diagnosed with a MI in an emergency room or in an outpatient clinic (13). From 1 January 2004 and onward, we used register information and restricted the case definition to patients with MI discharged from wards and patients with a diagnosis of cardiac arrest and verified MI. Furthermore, participants registered with MI or cardiac arrest as cause of death in the Causes of Death Register (14) were included as cases.

### Exclusion criteria

Persons with a cancer diagnosis that was not at the time of invitation registered in the Danish Cancer Registry (due to processing delay) were later excluded. Furthermore, persons with incomplete questionnaires were excluded. Finally, persons registered with a diagnosis of MI or cardiac arrest and persons registered with a diagnosis of diabetes mellitus or self-reported diabetes mellitus before enrollment were also excluded. The rationale for exclusion of persons with diabetes mellitus was potential effect modification and potential changes in dietary habits as a result of diagnosis and treatment.

### Statistical analyses

Analyses were carried out among all participants and separately for women and men. Hazard ratios (HRs) with 95% CIs for the incidence of MI were calculated by using the Cox proportional hazards regression with age as the time metric to ensure that the estimation procedure was based on comparisons of participants at the same age. The observation time for each participant was the period from the date of enrollment in the Diet, Cancer, and Health study (between December 1993 and May 1997) to the date of a registered diagnosis of MI or cardiac arrest caused by MI, death from another cause, emigration, or 27 April 2008 (the Cause of Death Register until 31 December 2006), whichever came first.

Two models were used for investigation of the risk of MI with a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Model 1 included intake of carbohydrates, proteins, monounsaturated fatty acids, and polyunsaturated fatty acids expressed as percentages of total energy intake, total energy intake (kcal/d) (as continuous



variables), an indicator variable for alcohol consumption (0 and >0 g/d), and alcohol consumption (g/d). Adjustment of alcohol consumption was expanded beyond simple linear or categorical approaches to include flexible curves via restricted cubic splines that make use of within-category risk variation (15). Model 2 included variables in model 1 and BMI (<25, 25–29, and ≥30), education (<8, 8–10, and >10 y), smoking status (“never,” “former,” and “currently smoking” 1–14, 15–24, or ≥25 g tobacco/d), leisure-time physical activity (<3.5 and ≥3.5 h/wk), and history of hypertension (“yes,” “no,” and “do not know”). In analyses among all participants, sex was entered into the model through the strata statement. The estimated HRs for carbohydrates may be interpreted as the estimated differences in risk for a 5% higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs, ie, substitution of 5% of energy intake from carbohydrates for 5% of energy intake from SFAs. In further analyses, the type of carbohydrate was taken into account by investigating carbohydrates with different GI values. We calculated tertiles of dietary GI based on the distribution of dietary GI among cases. The estimated HRs may be interpreted as the estimated difference in risk for a 5% higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs among persons who consume carbohydrates with low-GI values (ie, substitution of 5% of energy intake from carbohydrates with low-GI values for 5% of energy intake from SFAs) (first tertile), medium-GI values (ie, substitution of 5% of energy intake from carbohydrates with medium-GI values for 5% of energy intake from SFAs) (second tertile), or high-GI values (ie, substitution of 5% of energy intake from carbohydrates with high-GI values for 5% of energy intake from SFAs) (third tertile).

Effect modification was tested on the multiplicative scale by a likelihood-ratio test of nested models with and without cross-product terms. We tested the continuous variables for non-linearity in restricted cubic spline regression models and used

a log-rank test based on Schoenfeld residuals to assess the proportional-hazards assumption. No violations were detected. Data analyses were performed by using Stata statistical software, release 10.1 (Stata Corporation, College Station, TX).

## RESULTS

Among the 57,053 women and men recruited, 569 persons with a cancer diagnosis that was not at the time of invitation registered in the Danish Cancer Registry (due to processing delay) were later excluded. Three persons were excluded because they wanted to be omitted from further studies based on data from the Diet, Cancer, and Health study. Among the remaining 56,481 participants, persons with incomplete questionnaires ( $n = 646$ ) were excluded. Furthermore, persons with a diagnosis of MI ( $n = 899$ ) or diabetes mellitus ( $n = 1292$ ) before enrollment were also excluded. The final population consisted of 53,644 persons (53% women). Baseline characteristics are shown in **Table 1**. Among women and men, the median age was 56 y (80% central range: 51–63), the median intake of carbohydrates was 45% energy (80% central range: 38–52), and the median dietary GI was 87 (80% central range: 80–94) (Table 1).

During a median of follow-up of 12 y, 1943 incident cases of MI (537 among women and 1406 among men) were identified. HRs and 95% CIs for MI for a 5% higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs are shown in **Table 2**. HRs and 95% CIs for MI for a 5% higher energy intake from carbohydrates with low-, medium-, or high-GI values and a concomitant lower energy intake from SFAs are shown in **Table 3**. Among women and men, substitution of carbohydrates for SFAs was not associated with risk of MI (HR: 1.04; 95% CI: 0.92, 1.17) (Table 2). The  $P$  value for effect modification by sex was 0.21. However, there was a non-significant inverse association between substitution of carbohydrates with low-GI values for SFAs and risk of MI (HR in the

**TABLE 1**  
Baseline characteristics of the study population<sup>1</sup>

Characteristic	All participants	Women	Men
<b>Physiologic and anthropometric</b>			
Age (y)	56 (51, 63) <sup>2</sup>	56 (51, 63)	56 (51, 63)
Postmenopausal (%)	—	59	—
BMI (kg/m <sup>2</sup> )	25 (21, 31)	25 (21, 31)	26 (22, 31)
<b>Behavioral</b>			
More than 10 y of education (%)	21	19	24
Current smoker (%)	36	33	39
Leisure-time physically active (%)	40	41	38
Alcohol consumption (g/d)	13 (2, 47)	9 (1, 35)	19 (4, 63)
<b>Diet</b>			
Energy (kcal)	2024 (1391, 2865)	1827 (1285, 2541)	2254 (1622, 3096)
Glycemic carbohydrates (% energy)	45 (38, 52)	46 (39, 54)	43 (37, 51)
Dietary glycemic index	87 (84, 94)	85 (78, 92)	89 (82, 95)
Proteins (% energy)	18 (15, 22)	18 (15, 22)	18 (15, 22)
Total fat (% energy)	37 (30, 43)	36 (29, 42)	38 (31, 44)
Saturated fatty acids (% energy)	14 (11, 18)	14 (10, 17)	15 (11, 18)
Monounsaturated fatty acids (% energy)	12 (10, 15)	12 (9, 14)	13 (10, 16)
Polyunsaturated fatty acids (% energy)	6 (4, 8)	6 (4, 8)	6 (4, 8)
<b>Clinical</b>			
History of hypertension (%)	15	17	14

<sup>1</sup>  $n = 53,644$  for all participants,  $n = 28,495$  for women, and  $n = 25,149$  for men.

<sup>2</sup> Median; 80% central range in parentheses (all such values).

**TABLE 2**

Hazard ratios for myocardial infarction per 5% increment of energy intake from carbohydrates and a concomitant lower energy intake from saturated fatty acids<sup>1</sup>

	All participants	Women	Men
Model 1 <sup>2</sup>	1.04 (0.93, 1.17)	1.09 (0.88, 1.36)	1.03 (0.90, 1.18)
Model 2 <sup>3</sup>	1.04 (0.92, 1.17)	1.02 (0.82, 1.28)	1.05 (0.92, 1.21)

<sup>1</sup> All values are hazard ratios; 95% CIs in parentheses.  $n = 53,644$  for all participants,  $n = 28,495$  for women, and  $n = 25,149$  for men.

<sup>2</sup> Model 1 included intake of glycemic carbohydrates, proteins, monounsaturated fatty acids, and polyunsaturated fatty acids expressed as percentages of total energy intake, total energy intake (kcal/d), an indicator variable for alcohol consumption (0 and  $>0$  g/d), and alcohol consumption (g/d). Hazard ratios with 95% CIs for the incidence of myocardial infarction were calculated by using Cox proportional hazards regression with age as the time metric. In analyses among all participants, sex was entered into the model.

<sup>3</sup> Model 2 included variables in model 1 and BMI (in  $\text{kg}/\text{m}^2$ ;  $<25$ , 25–29, and  $\geq 30$ ), education ( $<8$ , 8–10, and  $>10$  y), smoking status (never, former, and currently smoking 1–14, 15–24, or  $\geq 25$  g tobacco/d), physical activity ( $<3.5$  and  $\geq 3.5$  h/wk), and history of hypertension (yes, no, and do not know).

first tertile of dietary GI: 0.88; 95% CI: 0.72, 1.07) and a statistically significant positive association between substitution of carbohydrates with high-GI values for SFAs and risk of MI in the third tertile of dietary GI: 1.33; 95% CI: 1.08, 1.64) (Table 3). There was no association for carbohydrates with medium-GI values (HR in the second tertile of dietary GI: 0.98; 95% CI: 0.80, 1.21) (Table 3). As assessed from the 95% CIs, the measures of associations for extreme tertiles of GI were statistically significantly different. The  $P$  value for effect modification by tertiles of dietary GI was 0.06 in women, 0.29 in men, and 0.16 in all participants. The  $P$  value for effect modification by sex was 0.86.

## DISCUSSION

The findings from this study suggest that the effect of substitution of carbohydrates for SFAs varies depending on the type of carbohydrates. There was a nonsignificant inverse association

between substitution of carbohydrates with low-GI values for SFAs and risk of MI but a significant positive association between substitution of carbohydrates with high-GI values for SFAs and risk of MI. In this study, dietary GI was used as an indicator of the average quality of carbohydrates consumed, but other classifications of carbohydrates may also be relevant, such as the extent of processing, which also reflects the intake of dietary fiber (16, 17).

Selection bias is unlikely to have affected the results. However, if censoring due to death from other causes is associated with intake of carbohydrates and risk of MI, then the true associations between intake of carbohydrates and risk of MI may have been underestimated. Random measurement error cannot be excluded from having affected the results. A potential source of random measurement error arises from dietary self-reporting methods. Generally, random measurement error leads to underestimation of the true risk and to loss of statistical power. However, dietary intake was determined by using a FFQ, which may reflect the habitual eating pattern. Information bias is unlikely to have affected the results because cases were identified by record linkage with central Danish registries and diagnoses were established independently of the FFQs of the participants. We included carbohydrates, proteins, monounsaturated fatty acids, and polyunsaturated fatty acids expressed as percentages of the total energy intake and the total energy intake in the models because of potential confounding and extraneous variation. This also allowed us to estimate the difference in the risk for a higher energy intake from carbohydrates and a concomitant lower energy intake from SFAs. Relevant control for established risk factors for IHD did not change the measures of associations, and thus residual confounding seems unlikely. However, confounding from other IHD risk factors not taken into account remains a possible explanation for the observed associations.

Only 2 epidemiologic studies have investigated the substitution of carbohydrates for SFAs (1, 18). In the prospective cohort study by Hu et al (18), substitution of carbohydrates for SFAs was nonsignificantly associated with a lower risk of IHD, whereas in the prospective cohort study by Jakobsen et al (1), in which data from 11 American and European cohort studies were pooled, substitution of carbohydrates for SFAs was modestly

**TABLE 3**

Hazard ratios (HRs) for myocardial infarction per 5% increment of energy intake from carbohydrates with low-glycemic index (low-GI), medium-GI, or high-GI values and a concomitant lower energy intake from saturated fatty acids<sup>1</sup>

Tertiles of dietary GI <sup>2</sup>	All participants		Women		Men	
	Median dietary GI (80% central range)	HR (95% CI)	Median dietary GI (80% central range)	HR (95% CI)	Median dietary GI (80% central range)	HR (95% CI)
Carbohydrates with low-GI values (first tertile)	82 (77, 85)	0.88 (0.72, 1.07)	80 (75, 82)	1.17 (0.80, 1.71)	84 (79, 86)	0.83 (0.65, 1.04)
Carbohydrates with medium-GI values (second tertile)	88 (86, 90)	0.98 (0.80, 1.21)	85 (84, 87)	0.80 (0.54, 1.18)	89 (87, 91)	1.08 (0.84, 1.38)
Carbohydrates with high-GI values (third tertile)	93 (91, 98)	1.33 (1.08, 1.64)	91 (88, 96)	1.10 (0.75, 1.63)	94 (92, 98)	1.34 (1.04, 1.71)

<sup>1</sup> All models included intake of glycemic carbohydrates, proteins, monounsaturated fatty acids, and polyunsaturated fatty acids expressed as percentages of total energy intake, total energy intake (kcal/d), an indicator variable for alcohol consumption (0 and  $>0$  g/d), alcohol consumption (g/d), BMI (in  $\text{kg}/\text{m}^2$ ;  $<25$ , 25–29, and  $\geq 30$ ), education ( $<8$ , 8–10, and  $>10$  y), smoking status (never, former, and currently smoking 1–14, 15–24, or  $\geq 25$  g tobacco/d), physical activity ( $<3.5$  and  $\geq 3.5$  h/wk), and history of hypertension (yes, no, and do not know). HRs with 95% CIs for the incidence of myocardial infarction were calculated by using Cox proportional hazards regression with age as the time metric. In analyses among all participants, sex was entered into the model.

<sup>2</sup> Tertiles of dietary GI were based on the distribution of dietary GI among cases.  $n = 22,144$ , 17,000, and 14,400 for all participants in the first, second, and third tertiles of dietary GI, respectively;  $n = 9594$ , 10,202, and 8699 for women in the first, second, and third tertiles of dietary GI, respectively; and  $n = 8941$ , 8127, and 8081 for men in the first, second, and third tertiles of dietary GI, respectively.

associated with a higher risk of IHD. The inconsistent findings may be due to differences in the quality of carbohydrates, which was not taken into account in these previous studies. Findings in this study suggested that replacing SFAs with carbohydrates with low-GI values is associated with a lower risk of MI, whereas replacing SFAs with carbohydrates with high-GI values is associated with a higher risk of MI. A high-GI meal results in a high blood glucose concentration and a high insulin-to-glucagon ratio, followed by hypoglycemia, counterregulatory hormone secretion, and elevated plasma free fatty acid concentration (4). These events may affect the risk of IHD through promoting dyslipidemia, inflammation, and endothelial dysfunction (4). In the Nurses' Health Study, a nonsignificant positive association between dietary GI and risk of IHD was found (19). Furthermore, in a prospective cohort study in men (20) and in a case-control study in women and men (21), nonsignificant positive associations between dietary GI and MI were found.

The associations between substitution of carbohydrates for SFAs and risk of MI may be modified by sex due to differences in the underlying biology, such as hormonal differences. This study, however, suggests that, to prevent MI, the type of carbohydrates should be considered among middle-aged women and men.

The classification of carbohydrate-containing foods on the basis of their ability to raise blood glucose has been shown to have clinical relevance (2, 4), but the public health application is not straightforward. However, recommendations of food choices such as less-refined foods, nonstarchy vegetables, fruit, and legumes may promote dietary patterns with a low dietary GI. Indeed, these recommendations would also tend to promote dietary patterns high in fiber and micronutrients, dietary factors also considered to play a role in the prevention of IHD (22).

In conclusion, this study suggests that replacing SFAs with carbohydrates with low-GI values is associated with a lower risk of MI, whereas replacing SFAs with carbohydrates with high-GI values is associated with a higher risk of MI.

The authors' responsibilities were as follows—MUJ and KO: study design; KO and AT: collection of data; CD: analysis of data; MUJ, CD, AMJ, JS, AT, EBS, and KO: interpretation of data and critical revision of the manuscript for important intellectual content; and MUJ: writing of the manuscript. None of the authors had a conflict of interest.

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