Glycemic index, glycemic load, and the risk of acute myocardial infarction in Finnish men: The Kuopio Ischaemic Heart Disease Risk Factor Study

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KEYWORDS
Acute myocardial infarction; Carbohydrates; Cohort; Glycemic index; Glycemic load; Overweight

Abstract Background and aim: The role of dietary glycemic index (GI) and glycemic load (GL) in coronary heart disease (CHD) is unclear. Our aim was to study the association between the dietary GI and GL and the risk of acute myocardial infarction (AMI).

Methods and results: The study population consisted of 1981 Finnish men from the prospective population-based Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study, aged 42–60 years and free of CHD at baseline. During an average follow-up time of 16.1 years, 376 new AMI events occurred. In multivariable-adjusted Cox proportional hazards models, the relative risk (RR) for AMI in the highest quartile of GI was 1.25 (95% CI: 0.92–1.69; P for trend = 0.08) and for GL 1.11 (95% CI: 0.79–1.57; P for trend = 0.21) when compared with the lowest quartile.

For overweight (BMI ≥ 27.5 kg/m²) men, the multivariable-adjusted RR for AMI in the highest compared to the lowest tertile of GI and GL were 1.58 (95% CI: 1.03–2.43; P for trend = 0.04, P for interaction = 0.01) and 2.05 (95% CI: 1.30–3.23; P for trend = 0.002, P for interaction = 0.002), respectively. For physically less active men; energy expenditure for leisure-time physical activity <50 kcal/d, the RR for AMI was 1.72 (95% CI: 1.07–2.76; P for trend = 0.04, P for interaction 0.80) with higher GL.

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Conclusions: Our results suggest that both high dietary GI and GL are associated with increased risk of AMI among overweight and GL possibly among less physically active men.
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Introduction

The dietary glycemic index (GI) was originally developed to qualitative classification for a carbohydrate containing foods in the diet of diabetic patients [1]. GI is a measure of the blood glucose response to a standard amount of carbohydrate from a food, compared with a reference (glucose or white bread). Later developed glycemic load (GL) takes also into account the amount of carbohydrate in a food [2].

Epidemiological studies have suggested that high dietary GI and GL could be detrimental in regard to CVD risk, especially among overweight persons [3–7]. The first findings were reported from the Nurses Health Study where high GI was found to be associated with the risk of coronary heart disease (CHD) [4] and later with hemorrhagic stroke [6], and these associations were the most evident in overweight women in both studies. Later, similar findings for CVD risk have been reported in several [3,5,7], although not all, studies [8–10].

Carbohydrates with higher GI and GL may have adverse effects on several markers of CVD risk, such as serum LDL [11,12] and HDL cholesterol [13], triglycerides [14] and C-reactive protein [14]. In obese [15] and possibly physically inactive [16], because of underlying insulin resistance and other related metabolic disturbances, these deleterious physiological changes may be exacerbated.

The primary aim of our study was to assess the association between GI and GL and the risk of acute myocardial infarction (AMI) in Finnish men, and whether body mass index (BMI) and leisure-time physical activity (LTPA) modify the association. Secondly, we also evaluated the impact of total carbohydrate intake on the risk.

Methods

Study participants

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is an ongoing population-based study designed to investigate risk factors for CVD, atherosclerosis and related outcomes in middle-aged men from Eastern Finland [17]. The study was approved by the Research Ethics Committee of the University of Kuopio. All study participants gave their written informed consent. A total of 2682 participants (82.9% of those eligible), aged 42, 48, 54, or 60 years, were enrolled in the study between March 1984 and December 1989. Men who had a history of CHD were excluded from the present analyses, which left 1981 men with complete dietary data available.

Collection and classification of AMI

Data on AMI were obtained from the National Hospital Discharge Data Register by record linkage. The diagnostic classification of coronary events was based on symptoms, electrocardiographic findings, and cardiac enzyme elevations. Each suspected coronary event was coded according to the Ninth (code numbers 410–414) or Tenth (code numbers I20–I25) International Classification of Diseases (ICD) and was classified into (1) a definite AMI, (2) a probable AMI, (3) a typical acute chest pain episode of more than 20 min indicating CHD, (4) an ischaemic cardiac arrest with successful resuscitation, or (5) no acute coronary event by a physician using the original patient records. All AMI cases that occurred from the study entry until 31 December 2005 were included. If a participant had multiple events, the first was considered as the end point.

Assessment of nutrient intake

The consumption of foods at the study baseline was assessed with an instructed 4-day food recording by household measures. The instructions were given and the completed food records were checked by a nutritionist. The intakes of nutrients were estimated using the NUTRICA® version 2.5 software (Social Insurance Institution, Helsinki, Finland) [18]. The databank of the software is mainly based on Finnish values of nutrient composition of foods. To calculate dietary GI and GL, we used primarily recently published GI and GL values of individual foods [19]. For the most commonly used food items; such as rye bread, we used values estimated for Finnish foods [20]. The average daily GL value of the diet was calculated by summing the GL values of carbohydrate containing foods for each day and calculating the 4-day average. The average daily GI was calculated from the GL values by dividing the average GL value of the diet by the average daily intake of carbohydrates. The intakes of nutrients used in the Cox models were energy adjusted by the residual method [21]. Energy adjustment is based on the notion that a larger, more physically active person requires a higher caloric intake, which is associated with a higher absolute intake of all nutrients. Therefore energy adjustment takes into account differences in the energy requirements among individuals. The residuals were standardized by the mean nutrient intake of a subject consuming 10 MJ/d, the approximate average total energy intake in this study population.

Measurements

Blood samples were taken between 8am and 10am. Participants were instructed to abstain from ingesting alcohol for three days and from smoking and eating for 12 h. After the participant had rested in supine position for 30 min, blood was drawn with the Terumo Venoject (Leuven, Belgium) vacuum tubes without tourniquet. The serum LDL cholesterol, HDL cholesterol, and triglycerides were determined as previously described [22].
Blood glucose was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany) after proteins had been precipitated with trichloroacetic acid. Diabetes was assessed by previous diagnosis of diabetes or fasting blood glucose concentration $\geq 6.7$ mmol/L. Body weight was measured using a balance scale and BMI was computed as the ratio of weight to the square of height (kg/m$^2$). Resting blood pressure was measured with a random-zero mercury sphygmomanometer (Hawksley, United Kingdom) as previously described [23]. The number of cigarettes, cigars, and pipefuls of tobacco currently smoked daily, duration of regular smoking in years, alcohol consumption, history of myocardial infarction, angina pectoris, and medication were recorded with a self-administered questionnaire [23], which was checked by an interviewer. Leisure-time physical activity was assessed using the KIHd 12 Month LTPA Questionnaire, which covers the type, frequency, duration and intensity of the activity [24].

### Statistical analysis

The distributions were expressed as means $\pm$ standard deviations (SD). The means were compared using analysis of variance (ANOVA) and categorical variables using chi-square tests. Participants were classified into quartiles according to their energy adjusted GI or GL or intake of carbohydrates, and the relationships with the risk of an event was analyzed using Cox proportional hazards models. Statistical models were adjusted for age, examination years, smoking (numbers of cigarettes/day $\times$ years of smoking), BMI, systolic blood pressure, hypertension medication, serum HDL and LDL cholesterol, triglycerides, LTPA, education, family history of CVD, diabetes, alcohol intake, and dietary intakes of energy and energy adjusted folate, fiber, vitamin C, polyunsaturated (PUFA) and saturated fat (SAFA). In addition, to test whether BMI and LTPA modify the relation between total carbohydrates, GI and GL and risk of an event, we performed stratified analyses by BMI ($<27.5$ or $\geq 27.5$ kg/m$^2$) and by LTPA ($<50$ kcal/d or $\geq 50$ kcal/d). Relative risks (RR), adjusted for other risk factors, were estimated as antilogarithms of coefficients for independent variables. The confidence intervals (CI) were estimated based on the assumption of asymptotic normality of estimates. Interactions between GI and GL and BMI and LTPA were assessed by stratified analyses and by use of a cross-product (multiplicative) term, with GI and GL in tertiles and BMI and LTPA as binary variables. All statistical tests were two-tailed. $P$-values $<0.05$ were considered as statistically significant. Data were analyzed using SPSS for Windows version 14 statistical software (SPSS Inc., Chicago, IL).

### Results

The mean age $\pm$ SD of the study population at baseline was $52.5 \pm 5.3$ years and the mean $\pm$ SD GI and GL were $56 \pm 7$ and $141 \pm 31$, respectively. When compared with men with lower GL, men with higher GL were more likely to be older, have lower BMI, and higher level of LTPA, lower concentration of HDL cholesterol, and less likely to be smokers (Table 1). Men with higher GL also had lower intakes of alcohol, total fat, SAFA, PUFA, monounsaturated fat (MUFA) and protein and higher intakes of carbohydrates, sugar, fiber, folate and vitamin C. In quartiles of GI, compared with men with lower GI, men with higher GI were less likely to be smokers and have a higher number of years of education, and had lower intakes of total fat, protein, folate, fiber, sugar, vitamin C and higher intakes of carbohydrates (data not shown).

During the average follow-up time of 16.1 years, we documented 376 new cases of AMI. For the whole study population, no significant associations were found between dietary GI and the risk of AMI (Table 2). The multivariable-adjusted RR in the highest vs. the lowest GI quartile was $1.25$ (95% CI: 0.92–1.69; $P$ for trend across quartiles $= 0.08$) for AMI. Similarly, we did not find significant associations between GL and risk of AMI (Table 2). The multivariable-adjusted RR in the highest vs. the lowest GL quartile was $1.11$ (95% CI: 0.79–1.57; $P$ for trend $= 0.21$).

In the stratified analyses, we found a significantly increased risk of AMI with higher GI in men with the BMI $\geq 27.5$ (35% of the study population) (RR in the highest vs. the lowest tertile: 1.58; 95% CI: 1.03–2.43; $P$ for trend across tertiles $= 0.04$), whereas no statistically significant association was found in men with the BMI $< 27.5$ (Table 3). As for GI, we found a significantly increased risk of AMI with higher GL in men with the BMI $\geq 27.5$ (RR in the highest vs. the lowest tertile: 2.05; 95% CI: 1.30–3.23; $P$ for trend $= 0.02$), whereas no association was found in men with the BMI $< 27.5$ (Table 3). However, the interaction was not statistically significant ($P$ for interaction $= 0.80$). No effect modification by LTPA for GI was observed (Table 3).

We also assessed the relation of the intakes of total carbohydrates with the risk of AMI, but no significant association was found. The multivariable-adjusted RR for AMI in the highest vs. the lowest quartile of total carbohydrate intake was $0.86$ (95% CI: 0.56–1.33; $P$ for trend $= 0.77$). In further analyses, no effect modification by BMI or LTPA was found for total carbohydrates (BMI: $P$ for interaction $= 0.62$; LTPA: $P$ for interaction $= 0.46$).

### Discussion

In this population of middle-aged or older Finnish men, both high dietary GI and GL were found to be associated with significantly increased risk of AMI among overweight (BMI $\geq 27.5$ kg/m$^2$) men after multivariable adjustments, while no association was found among men with lower BMI ($<27.5$ kg/m$^2$). Similarly, increased risk of AMI was found for men with higher dietary GL and lower LTPA ($<50$ kcal/d). The associations were stronger for GL than GI, which was expected as GI describes both quality and quantity of carbohydrates while GI represents only quality. No associations were found for dietary carbohydrates, not even in stratified analyses with BMI or LTPA.
Strength of the study was the longitudinal population-based study setting with high participation rate. In addition, due to the complete follow-up system of CVD cases in the Finnish population, there were no losses to follow-up. A minor drawback of the study was that it included only men, and thus our results cannot necessarily be generalized to women, although the current evidence does not suggest that the relation between GI and GL and CVD would be different for men and women. Additional drawback was that the GI and GL values used in the study were mainly based on the values estimated for foods available and thus may not be accurate for Finnish foods. This was done because of the lack of comprehensive national GI and GL databases at the time of the study. In addition, in our analyses we used baseline data for nutrients and other lifestyle factors, and during the relatively long follow-up period some changes in these values may have occurred. However, the correlation between baseline and 11-year follow-up values of GI and GL were relatively strong, being 0.26 and 0.42, respectively. Altogether these limitations may have resulted in a classification bias and thus attenuated the associations in our study.

Our findings are in line with those studies that suggest that high dietary GI or GL is associated with increased risk of CHD, especially in overweight persons [3–5,7]. Originally, in the Nurses Health Study, higher GL was associated with increased risk of CHD and the association was the most evident in overweight women [4]. In an Italian case-control study, high GI was associated with risk of AMI (EPIC) study [3]. In the Estrogen Replacement and Atherosclerosis (ERA) trial, high GI was associated with accelerated progression of atherosclerosis in postmenopausal US women, of whom about 75% were overweight [5]. In contrast, no association was found with CHD in men in the Dutch Zutphen Elderly Study cohort [10]. Similarly, in Swedish men, dietary GI or GL were not related either with the risk of the first [9] or recurrent CVD event [8]. In a recent meta-analysis gathering data from three prospective studies, high dietary GI was associated with an increased risk of CHD [25]. In some studies, total carbohydrate intake has also been associated with accelerated progression of atherosclerosis [5], increased risk of stroke [6] and a slight increase in the risk of CVD [4], while no such association was found in this study.

Even though the mechanism of action was not evaluated, it is possible that obesity related metabolic disorders,
such as dyslipidemia, insulin resistance, and hyperglycemia, which are important risk factors for CHD, are aggravated by the high GI and GL diet. Carbohydrates with higher GI and GL produce augmented postprandial blood glucose and insulin responses particularly among obese [15] and physically less active [16], which may then lead to decreased blood HDL cholesterol [13], and increased blood triglyceride [14] and LDL cholesterol [11,12] concentrations, which may thus increase the risk of CHD. High dietary GI and GL have been also found to be associated with increased plasma concentrations of C-reactive protein [26], which is also associated with the risk of CHD [27].

### Table 2

Relative risk of acute myocardial infarction according to the quartiles of energy-adjusted glycemic index and glycemic load.\textsuperscript{d}

<table>
<thead>
<tr>
<th>Glycemic Index</th>
<th>Quartiles</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (lowest)</td>
<td>2</td>
</tr>
<tr>
<td>Number of events</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>Model 1\textsuperscript{a}</td>
<td>1</td>
<td>1.00 (0.75—1.35)</td>
</tr>
<tr>
<td>Model 2\textsuperscript{b}</td>
<td>1</td>
<td>1.07 (0.80—1.45)</td>
</tr>
<tr>
<td>Model 3\textsuperscript{c}</td>
<td>1</td>
<td>1.11 (0.82—1.50)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glycemic load</th>
<th>Number of events</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101</td>
<td>77</td>
</tr>
<tr>
<td>Model 1\textsuperscript{a}</td>
<td>1</td>
<td>0.72 (0.54—0.97)</td>
</tr>
<tr>
<td>Model 2\textsuperscript{b}</td>
<td>1</td>
<td>0.73 (0.54—0.99)</td>
</tr>
<tr>
<td>Model 3\textsuperscript{c}</td>
<td>1</td>
<td>0.76 (0.56—1.03)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Model 1 adjusted for age, examination years, and smoking.

\textsuperscript{b} Model 2 adjusted for Model 1 plus body mass index, systolic blood pressure, hypertension medication, serum HDL and LDL cholesterol, triglycerides, leisure-time physical activity, education, family history of cardiovascular disease, and diabetes.

\textsuperscript{c} Model 3 adjusted for Model 2 plus alcohol, energy intake and energy adjusted intake of folate, fiber, vitamin C, polyunsaturated and saturated fat.

\textsuperscript{d} All values: relative risk (95% confidence interval).

### Table 3

Relative risk of acute myocardial infarction according to the tertiles of energy-adjusted glycemic index and glycemic load, stratified by BMI\textsuperscript{a} and leisure-time physical activity (LTPA).\textsuperscript{b,c}

<table>
<thead>
<tr>
<th>Tertiles</th>
<th>1 (lowest)</th>
<th>2</th>
<th>3 (highest)</th>
<th>P for trend</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 27.5 kg/m²</td>
<td>1</td>
<td>1.05 (0.76—1.44)</td>
<td>0.93 (0.66—1.32)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>79 (18.8%)</td>
<td>81 (18.3%)</td>
<td>66 (15.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 27.5 kg/m²</td>
<td>1</td>
<td>1.52 (1.00—2.32)</td>
<td>1.58 (1.03—2.43)</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>41 (17.1%)</td>
<td>52 (23.9%)</td>
<td>57 (24.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTPA &lt; 50 kcal/d</td>
<td>1</td>
<td>1.15 (0.75—1.75)</td>
<td>1.22 (0.80—1.87)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>44 (19.1%)</td>
<td>49 (21.5%)</td>
<td>52 (21.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTPA ≥ 50 kcal/d</td>
<td>1</td>
<td>1.24 (0.90—1.71)</td>
<td>1.08 (0.77—1.51)</td>
<td>0.64</td>
<td>0.66</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>76 (17.7%)</td>
<td>84 (19.4%)</td>
<td>71 (17.0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Glycemic load |          |            |             |             |                   |
| BMI < 27.5 kg/m² | 1        | 0.90 (0.64—1.29) | 0.90 (0.60—1.34) | 0.60 |
| Number of events (%) | 80 (20.2%) | 74 (17.1%) | 72 (15.6%) |
| BMI ≥ 27.5 kg/m² | 1        | 1.09 (0.71—1.68) | 2.05 (1.30—3.23) | 0.002 | 0.002 |
| Number of events (%) | 49 (18.6%) | 45 (19.7%) | 56 (28.3%) |
| LTPA < 50 kcal/d | 1        | 0.98 (0.63—1.52) | 1.72 (1.07—2.76) | 0.04 |
| Number of events (%) | 57 (22.0%) | 39 (18.1%) | 49 (21.8%) |
| LTPA ≥ 50 kcal/d | 1        | 0.99 (0.70—1.40) | 1.07 (0.73—1.58) | 0.71 | 0.80 |
| Number of events (%) | 72 (18.0%) | 80 (18.0%) | 79 (18.2%) |

\textsuperscript{a} Adjusted for age, examination years, smoking, systolic blood pressure, hypertension medication, serum HDL and LDL cholesterol, triglycerides, LTPA, education, family history of cardiovascular disease, diabetes, alcohol, energy intake and energy adjusted intake of folate, fiber, vitamin C, polyunsaturated and saturated fat.

\textsuperscript{b} Adjusted for age, examination years, smoking, systolic blood pressure, hypertension medication, serum HDL and LDL cholesterol, triglycerides, body mass index, education, family history of cardiovascular disease, diabetes, alcohol, energy intake and energy adjusted intake of folate, fiber, vitamin C, polyunsaturated and saturated fat.

\textsuperscript{c} All values: relative risk (95% confidence interval).
Theoretically, it is possible that the high dietary GI or GL among overweight or physically less active men could merely be an overall marker of an unhealthy lifestyle rather than a causative factor. However, in the whole study population (Table 1), as well as among the overweight men (data not shown), those with higher GL were more likely to have a healthier lifestyle, which argues against such confounding.

In conclusion, in this population of middle-aged Finnish men, both high dietary GI and GL may be associated with increased risk of AMI among overweight men and GL possibly among physically less active men.

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