Inverse association between fasting plasma glucose and risk of ventricular arrhythmias

Francesco Zaccardi [1]
David R Webb [1]
Sudhir Kurl [2]
Kamlesh Khunti [1]
Melanie J Davies [1]
Jari A Laukkanen [2]

[1] Diabetes Research Centre, University of Leicester, Leicester, UK

[2] Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

Corresponding Author
Dr Francesco Zaccardi
Diabetes Research Centre, Leicester General Hospital, Leicester, UK
Phone: +44 0116 258 4389 – Fax: +44 0116 258 4499
Email: frazac@fastwebnet.it

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ABSTRACT

Aims: In nondiabetic subjects, low values of fasting plasma glucose have been associated with an increased risk of cardiovascular events. The identification of the potential mechanisms behind this association could help elucidate the relationship between glycaemia and cardiovascular disease. We aimed to determine the association between fasting plasma glucose and ventricular arrhythmias.

Methods: Fasting plasma glucose and other cardiometabolic risk factors were measured in a population-based cohort of 2482 men without a known history of type 2 diabetes mellitus at baseline. Associations between fasting plasma glucose levels and incident cases of ventricular arrhythmias (ventricular tachycardia or fibrillation events ascertained using the national hospital discharge register) were estimated using Cox regression analyses adjusted for potential confounders.

Results: During a median follow-up of 23.3 (interquartile range: 18.5-25.3) years, 74 (2.9%) incident events were recorded. In a multivariable analysis adjusted for age, systolic blood pressure, smoking status, low- and high-density lipoprotein cholesterol, and C-reactive protein, the hazard ratio for ventricular arrhythmia per 1 mmol/l higher baseline fasting plasma glucose was 0.58 (95% Confidence Interval (CI): 0.34, 0.98); the estimate did not materially change after further adjustment for body mass index, alcohol consumption, triacylglycerols, and history of ischaemic heart disease (0.50, 95% CI: 0.28, 0.89).

Conclusions: In this nondiabetic male population, fasting plasma glucose was inversely associated with incident risk of ventricular arrhythmias. Whilst our results could help clarify the relationship between low glucose levels and cardiovascular risk, further studies are required to confirm these findings in other populations.

Keywords: Cardiac Arrhythmias, Blood Glucose, Observational Study, Cox Models, Cardiovascular Diseases.

Abbreviations:

FPG	Fasting Plasma Glucose
HR	Hazard Ratio
KIHD	Kuopio Ischaemic Heart Disease
SD	Standard Deviation

INTRODUCTION

Large prospective observational studies demonstrate a "J-shaped" relationship between fasting plasma glucose (FPG) and major cardiovascular events in nondiabetic subjects [1-5]. Whilst increased risk associated with higher values of FPG is commonly considered related to more severe atherosclerosis, the link between lower FPG values and the risk of cardiovascular events is not fully understood. It has been proposed that a lower FPG could be a marker of conditions associated with an increased risk [1, 6]; however, this hypothesis has not been confirmed.

Cardiac rhythm disturbances, and ventricular arrhythmias in particular, are considered to be the final event in a chain of complications leading to cardiac death from atherothrombotic occlusion of coronary arteries [7]. However, arrhythmic abnormalities can be also caused by hypoglycaemia [8-10], potentially explaining the lack of efficacy in reducing fatal events in a randomized clinical trial of intensively-treated type 2 diabetic subjects [11].

To help clarify epidemiological and clinical trial observations, we evaluated the association between fasting plasma glucose and risk of incident ventricular tachycardia or fibrillation in a general male population (i.e., not selected on the basis of pre-existing disease) who participated in the Kuopio Ischaemic Heart Disease (KIHD) prospective study [12].

METHODS

This study follows the STROBE guidelines for reporting observational studies in epidemiology [13].

Setting and Participants

The KIHD study was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland: details of the study have been reported previously [12]. The subjects were a randomly selected sample of 3433 men 42 to 60 years of age resident in the town of Kuopio or its surrounding rural communities, and baseline examinations were conducted between 1984 and 1989. Of those invited, 2682 (78.1%) participated in the study. After the exclusion of 162 subjects with prevalent diabetes (either having regular treatment with an oral hypoglycaemic agent, insulin therapy, or having treatment only with diet while also having a FPG level of at least 7.0 mmol/l) and 38 with missing information on FPG, 2482 participants were included in the analyses.

Blood samples and measurements were taken between 8 and 10 am. In addition to fasting, participants were instructed to abstain from drinking alcohol for at least 3 days prior and from smoking for at least 12 hours. A glucose dehydrogenase method (Merck, Darmstadt, Germany) was used to assess the blood glucose after precipitation of proteins by trichloroacetic acid. The cholesterol contents of lipoprotein fractions and serum triacylglycerols were measured enzymatically (Boehringer Mannheim, Mannheim Germany) on the day after the high-density lipoprotein was separated from fresh samples by ultracentrifugation and precipitation. Serum creatinine concentrations were measured by using colorimetric Jaffe method with Konelab 20XT automatic analyser (Thermo Fisher Scientific Inc., Espoo, Finland). Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA).

The resting systolic blood pressure was measured with a random-zero sphygmomanometer (Hawksley, Lancing England) by two trained nurses using the following protocol: after supine rest of 5 minutes, 3 measurements in supine, 1 in standing and 2 in sitting position with 5-minute intervals. The systolic blood pressure was taken as the mean of all 6 measurements [14]. Baseline diseases, smoking habits and years of education were assessed by self-administered questionnaires. The diagnosis of chronic diseases was checked during a medical examination by the internist. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory [14]. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters.

Outcomes and Follow-up

All incident ventricular tachycardia or fibrillation cases that occurred from study baseline (March 1984 to December 1989) through 2012 were included. Annually updated data on new incident outcome events were obtained by computer linkage to the national hospital discharge register, and ICD-9 (427.41) or ICD-10 (I47.2, I49.0) codes were used to define ventricular arrhythmias. The definition of non-sustained, sustained ventricular tachycardia and/or ventricular fibrillation was based on electrocardiography. The documents were cross-checked in detail by two physicians, and an independent events committee blinded to clinical data performed the classification of outcomes [15]. There were no losses to follow-up.

Statistical analysis

For all the analyses, natural logarithm transformed values of non-normal distributed variables (C-reactive protein, triacylglycerols, and alcohol consumption) were used. Descriptive data are presented as means and standard deviation (SD) for continuous variables and numbers and percentages for categorical ones; their differences were estimated with ANOVA and $\chi 2$ test, respectively. Correlation coefficients were calculated to assess the correlation between FPG levels

and other continuous variables, whereas mean differences between groups were calculated for categorical factors.

Analyses of the associations between FPG and outcomes involved Cox-regression modelling. The proportional hazards assumption was verified for all variables by inspection of the plots of the Schoenfeld residual for covariates. Hazard ratios (HRs) were estimated within quartiles of FPG relative to the bottom quartile against the mean FPG level in each quartile; 95% confidence intervals (CIs) were estimated from variances attributed to the groups to reflect the amount of information within each group (including the reference category [16]). To assess the independence of association between FPG and incident cases of ventricular arrhythmias, we calculated HRs by quartiles and per 1 mmol/l higher baseline FPG with progressive adjustment for potential confounders selected on the basis of their previously established role as predictive cardiovascular risk factors.

Two-sided analyses were performed using Stata version 13 (Stata Corp, College Station, TX, USA), and confidence intervals are presented at the 95% level.

RESULTS

At baseline, 32% were smokers, mean (SD) age was 53 (5) years and mean FPG 4.6 (0.5) mmol/l. Baseline characteristics of the study participants by quartile of fasting plasma glucose are reported in Table 1. With the exception of systolic blood pressure and triacylglycerols, levels of other cardiometabolic risk factors were not significantly different in subjects who had an arrhythmic event throughout the follow-up as compared to subjects who had not (Supplementary Table S1). During a median follow-up time of 23.3 (interquartile range: 18.5-25.3) years, there were 152 (6.1%) cases of diabetes (risk factors are shown in Supplementary Table S2); 318 (12.8%) fatal coronary heart disease events; and 74 (2.9%) cases of ventricular arrhythmias, with a crude incidence rate of 1.43 (95% CI: 1.14, 1.80) per 1000 person-years.

The relationship between 1 mmol/l higher baseline FPG and incident ventricular tachycardia or fibrillation events, adjusted for potential confounders, is reported in Table 2 (HRs by quartiles of FPG are given in Supplementary Table S3). In the analysis adjusted for age, SBP, current smoking, LDL and HDL cholesterol, and C-Reactive protein, 1 mmol/l higher baseline FPG was associated with a HR of 0.58 (95% CI: 0.34, 0.98) of ventricular arrhythmic events; further progressive adjustment for body mass index, alcohol consumption, triacylglycerols, and history of ischaemic heart disease at baseline did not materially change the estimate (Table 2; Figure 1). Similarly, additional inclusion of glomerular filtration rate, use of β-blockers, serum sodium, and serum potassium resulted in comparable associations (Table 2; Supplementary Table S3).

DISCUSSION

Our results suggest that, in a general male population, lower fasting plasma glucose levels are associated with a higher risk of ventricular tachycardia/fibrillation independently from other cardiovascular risk factors.

Although nondiabetic hyperglycaemic states have been associated with major vascular events, the precise relationship between FPG and cardiovascular outcomes remains unclear. Indeed, a graded continuous [17, 18], threshold [19], or "J-shaped" relationship [1-5] has been reported. The reasons behind these divergences are unclear, being possibly related to different study characteristics and methods, or due to inherent diversity in subjects involved. In studies showing a "J-shaped" association, the nadir has been variably reported between 3.3 and 5.6 mmol/l; moreover, it has been suggested that low glucose values could be a marker of conditions associated with an increased risk of vascular events, such as liver or kidney dysfunction [20]; however, this hypothesis has not yet been clearly confirmed.

On the other hand, experimental studies have shown that low plasma glucose levels can cause ventricular electrophysiological abnormalities (i.e., QT interval prolongation) associated with an increased risk of ventricular arrhythmias in both diabetic and nondiabetic individuals [8-10]. Hypoglycaemia can increase the risk of ventricular arrhythmias through direct (effect of low glucose on ion channels [21]) and indirect (hypokalaemia, catecholamine release) mechanisms. However, no study has prospectively demonstrated a link between FPG and risk of ventricular arrhythmic events in a nondiabetic population.

These results have important ramifications. First, although large epidemiological studies tend to combine outcomes, the heterogeneity of mechanisms eventually resulting in what collectively (and simplistically) is classified as a single outcome is increasingly recognized, for both cardiovascular [22, 23] and other diseases [24, 25]. Our result could suggest that, across the range of FPG, increased risk at upper and lower extremities could be attributable to different pathophysiological pathways leading to the same-defined outcome. We propose better definition of the multiple mechanisms driving cardiovascular disease outcomes is essential.

Second, our findings could help interpret recent trials in subjects with type 2 diabetes mellitus. While early studies have demonstrated a reduction of major vascular events associated with glucose control, more recent ones with "near-to-normal" glucose targets have conversely evidenced a nonsignificant reduction or even an increased vascular risk in intensively-treated participants [11]. Though controversial, hypoglycaemia has been considered one of the potential explanations [26], and an increased specific risk of arrhythmic death has been associated with severe hypoglycaemia in a post-hoc trial analysis [27]. Indeed, the increasingly recognized risk associated with hypoglycaemic events has driven the adoption by the European Medicines Agency of a higher blood glucose level cut-off (3.9 mmol/l) to define hypoglycaemia [28], in line with the American Diabetes Association and Endocrine Society consensus report [29]. From this perspective, our results would support hypoglycaemia as a plausible mechanism that could contribute to increased cardiovascular mortality during intensive glycaemic therapy.

In a previous analysis exploring the association between FPG and sudden cardiac death (SCD) in nondiabetic subjects from the general population, a positive relationship has been evidenced [30]. Notably, of 190 SCDs events occurred during the follow-up, 157 SCDs were out-of-hospital events: therefore, for the large majority of events (82.6%) it was not possible to assess the presence of ventricular arrhythmias. While SCD is generally considered to be the consequence of ventricular fibrillation/tachycardia, it is also well-know that other causes can lead to SCD as well, and only about 50% of SCD events are attributable to ventricular fibrillation/tachycardia [31]. This could explain the divergence in the relationship between FPG/SCD and FPG/ventricular arrhythmias, and further underlines as the identification of multiple mechanisms behind cardiovascular outcomes is critical.

We should acknowledge some limitations of this study. First, a generalisation of our findings is limited by the study population, consisting of middle-age Finnish men only; these results need to be confirmed in other ethnic groups. Second, no information on the nature of ventricular arrhythmic events was recorded. Third, the association evidenced does not necessarily indicate a cause-effect relationship between FPG and arrhythmic disorders. Although experimental studies would support this, low FPG could be a confounder of a condition increasing the risk of ventricular

arrhythmias. Fourth, the independence of association between FPG and ventricular arrhythmias has been assessed by adjusting for several well-known and potential confounders, including drugs for hypertension and dyslipidaemia; however, baseline data on other specific medications (i.e., diuretics) were not available. On the other hand, strengths of this study include the rigorous measurement of baseline risk factors and the assessment of ventricular arrhythmias, the large and homogeneous community-based sample, and the long-term follow-up.

In conclusion, in this nondiabetic male population FPG was inversely associated with incident risk of ventricular arrhythmias. Further studies are warranted to confirm these results in other populations to help clarify the complex association between glucose and cardiovascular disease.

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Some of the data were presented as an abstract at the Diabetes UK meeting (London, 11-13 March 2015).

Contribution

FZ: conception of the idea, analysis of data, drafting of the manuscript.
DW, KK, MD: interpretation of data, critical revision of the manuscript for important intellectual content, drafting of the manuscript.
SK: acquisition and interpretation of data, drafting of the manuscript.
JL: conception of the idea, interpretation of data, critical revision of the manuscript for important intellectual content, drafting of the manuscript.

FZ had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version to be published.

The manuscript represents valid work and neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere. Data are available on request to the corresponding author.

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Duality of interest

Kamlesh Khunti has acted as a consultant and speaker for Novartis, Novo Nordisk, Sanofi-Aventis, Lilly and Merck Sharp & Dohme. He has received grants in support of investigator and investigator initiated trials from Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, Pfizer, Boehringer Ingelheim and Merck Sharp & Dohme. KK has received funds for research, honoraria for speaking at meetings and has served on advisory boards for Lilly, Sanofi-Aventis, Merck Sharp & Dohme and Novo Nordisk.
Melanie Davies has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. She has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly.

Francesco Zaccardi, David Webb, Sudhir Kurl and Jari Laukkanen report no conflict of interest.

Ethics

The study was approved by the Research Ethics Committee of the University of Eastern Finland. Each participant gave written informed consent.

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FIGURE TITLES AND LEGENDS

Figure 1: Cumulative Hazards of Ventricular Arrhythmias comparing quartiles of baseline fasting plasma glucose

Legend: Hazard ratio higher (dotted line) vs lower (solid line) quartile of fasting plasma glucose: 0.39 (95% CI: 0.19, 0.78), adjusted for age, systolic blood pressure, LDL- and HDL-cholesterol, smoking status, C-reactive protein, body mass index, alcohol consumption, triacylglycerols, and prevalent ischaemic heart disease.
Range fasting plasma glucose quartiles: lower, 3.2-4.3 mmol/l; higher, 5.0-6.2 mmol/l.

Table 1: Baseline characteristics of the study participants (N=2482) by quartile of fasting plasma glucose

	Fasting plasma glucose quartiles, mmol/l [min-max]				
Characteristics	**1st [3.2-4.3]**	**2nd [4.4-4.5]**	**3rd [4.6-4.9]**	**4th [5.0-6.2]**	**p for trend**
Sample size, % (n)	32.4 (804)	19.0 (473)	28.4 (704)	20.2 (501)	-
Age, years	52.7 (5.2)	53.0 (5.1)	53.2 (5.0)	53.0 (5.1)	0.137
Body mass index, kg/m^2	25.6 (3.1)	26.7 (3.1)	27.0 (3.3)	27.9 (3.8)	<0.001
Systolic blood pressure, mmHg	131 (16)	134 (17)	134 (17)	137 (17)	<0.001
LDL cholesterol, mmol/l	3.99 (0.99)	4.05 (1.04)	4.10 (1.02)	4.04 (1.00)	0.135
HDL cholesterol, mmol/l	1.32 (0.32)	1.29 (0.28)	1.30 (0.30)	1.28 (0.30)	0.055
Triacylglycerols[a], mmol/l	1.02 (0.76-1.40)	1.11 (0.79-1.54)	1.17 (0.79-1.54)	1.18 (0.83-1.76)	<0.001
Fasting plasma glucose, mmol/l	4.1 (0.2)	4.4 (0.1)	4.7 (0.1)	5.3 (0.3)	<0.001
Sodium, mmol/l	140.9 (1.4)	140.8 (1.5)	140.8 (1.5)	140.6 (1.7)	0.001
Potassium, mmol/l	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	3.9 (0.3)	0.777
Glomerular filtration rate[b], ml/min/1.73m^2	78 (13)	79 (14)	79 (13)	81 (18)	<0.001
High sensitivity C-reactive protein[a], mg/l	1.17 (0.63-2.24)	1.23 (0.70-2.33)	1.25 (0.73-2.27)	1.55 (0.81-2.83)	<0.001
Alcohol consumption[a], g/week	27 (6-76)	37 (5-88)	25 (5-90)	43 (7-121)	0.008
Previously Diagnosed Diseases					
Current smoking	33.9 (273)	33.8 (160)	29.5 (208)	32.1 (161)	0.192
Ischaemic heart disease	24.0 (193)	20.9 (99)	25.4 (179)	25.7 (129)	0.283
Hypertension	25.1 (202)	28.2 (133)	30.3 (212)	28.8 (165)	0.001
Heart failure[c]	4.6 (37)	6.7 (32)	7.6 (53)	8.2 (41)	0.006
Cerebrovascular disease	2.1 (17)	2.5 (12)	0.8 (6)	2.9 (15)	0.915
Claudication	3.4 (27)	2.9 (14)	4.8 (34)	4.2 (21)	0.191
Pulmonary disease[d]	13.3 (95)	14.2 (60)	14.6 (94)	12.4 (56)	0.905
Cancer	1.9 (15)	1.9 (9)	1.9 (14)	1.6 (8)	0.822
Regular Use of Medications					
Antidyslipidaemic	0.8 (7)	0.2 (1)	0.4 (3)	0.9 (5)	0.967
Antihypertensive	18.8 (151)	18.4 (87)	22.1 (156)	24.7 (124)	0.005
β-blockers	14.8 (119)	14.4 (68)	18.6 (131)	19.9 (100)	0.004
Acetylsalicylic acid	7.6 (61)	4.9 (23)	7.5 (53)	8.4 (42)	0.453
Incident events					
Fatal coronary heart disease	11.6 (93)	12.0 (57)	11.4 (80)	17.6 (88)	0.012
Type 2 diabetes mellitus	2.5 (20)	4.2 (20)	6.7 (47)	12.9 (65)	<0.001

Unless otherwise stated, data are reported as mean (standard deviation) for continuous variables and as % (number) for categorical ones.
LDL: Low-density lipoprotein; HDL: High density lipoprotein

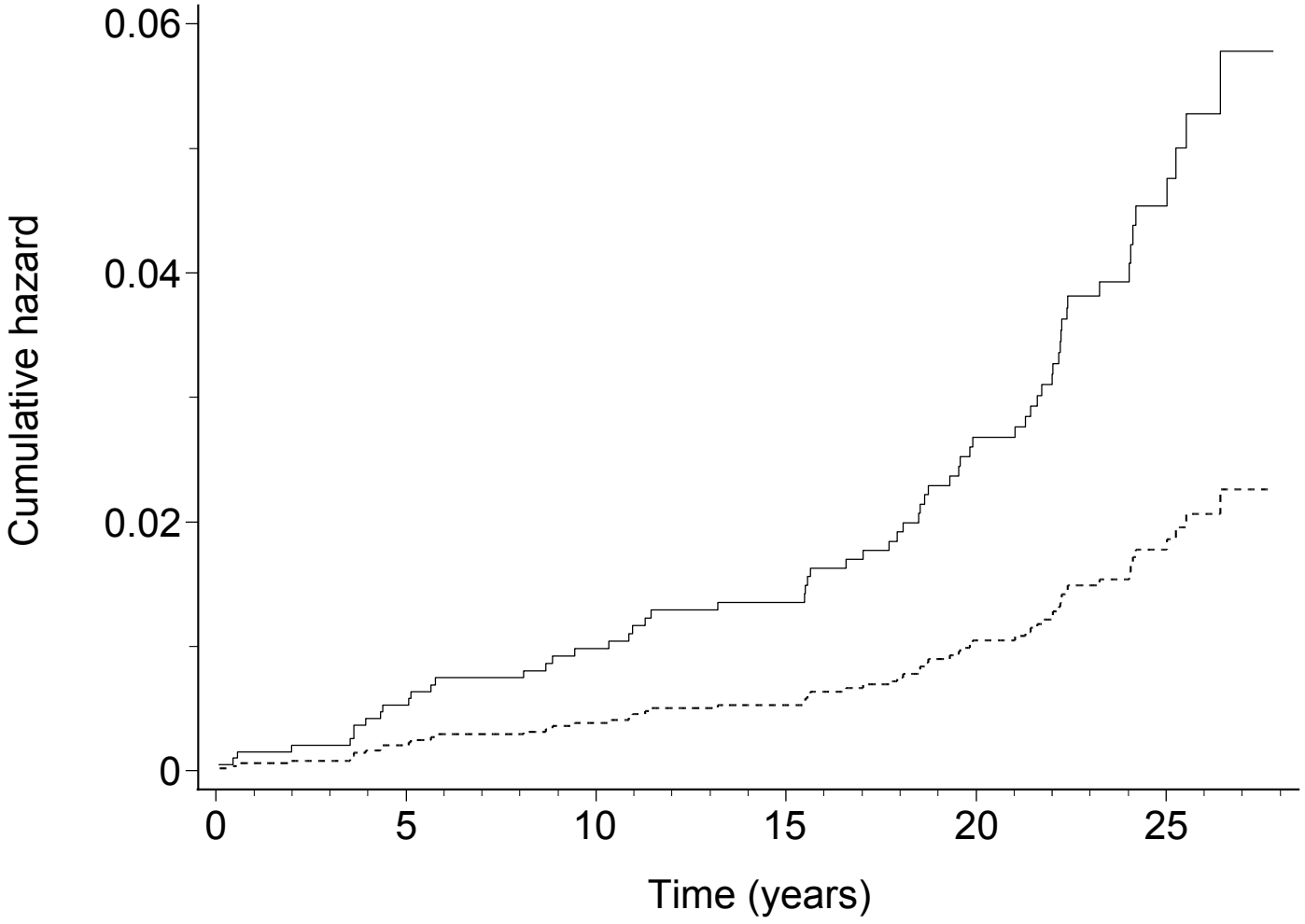
[a] Data reported as median and interquartile range
[b] Estimated with the MDRD formula: $175 \times (\text{Creatinine}/88.4)^{-1.154} \times \text{Age}^{-0.203}$
[b] Diagnosis based on clinical findings and symptoms and/or echocardiography
[c] Including bronchial asthma, chronic obstructive pulmonary disease and pulmonary tuberculosis

Table 2: Hazard ratio (HR) of ventricular tachycardia/fibrillation per 1 mmol/l higher baseline fasting plasma glucose

Level of Adjustment	HR (95% CI)	p-Value
Age, SBP, smoking, LDL, HDL, C-Reactive protein	0.58 (0.34, 0.98)	0.042
Above + body mass index, alcohol consumption, triacylglycerols	0.50 (0.28, 0.89)	0.019
Above + history of ischaemic heart disease	0.50 (0.28, 0.89)	0.020
Above + eGFR, β-blockers use	0.51 (0.28, 0.92)	0.025

CI: confidence interval; SBP: Systolic blood pressure; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate

Figure 1



Supplementary Table S1: Baseline characteristic of study subjects (N=2482) according to incident ventricular arrhythmias during follow-up

Variable	Ventricular Tachycardia/Fibrillation		p-Value
	Yes (N=74)	No (N=2408)	
Age (years)	54.0 ± 4.2	52.9 ± 5.2	0.078
Body mass index (kg/m^2)	27.4 ± 3.4	26.7 ± 3.4	0.067
Systolic blood pressure (mmHg)	139 ± 20	133 ± 17	0.001
LDL-Cholesterol (mmol/l)	4.08 ± 1.18	4.05 ± 1.01	0.764
HDL-Cholesterol (mmol/l)	1.27 ± 0.31	1.30 ± 0.30	0.452
Triacylglycerols (mmol/l) [a]	1.24 (0.87–1.79)	1.10 (0.80–1.53)	0.034
Fasting plasma glucose (mmol/l)	4.5 ± 0.4	4.6 ± 0.5	0.089
Serum sodium (mmol/l)	140 ± 1	140 ± 2	0.506
Serum potassium (mmol/l)	3.9 ± 0.3	3.9 ± 0.3	0.783
Glomerular filtration rate [b] (ml/min/1.73m^2)	77 ± 15	79 ± 15	0.192
C-Reactive protein (mg/l) [a]	1.31 (0.82–2.34)	1.26 (0.69–2.39)	0.566
Alcohol consumption (g/week) [a]	37 (9-93)	31 (6-89)	0.372
Current smoking (Yes)	30% (22)	32% (780)	0.629
History of ischaemic heart disease (Yes)	32% (24)	24% (576)	0.092

Unless otherwise stated, values are reported as mean ± standard deviation or % (n)

LDL: Low-density lipoprotein; HDL: High-density lipoprotein

[a] Median and interquartile range

[b] Estimated with the MDRD formula: $175 \times (\text{Creatinine}/88.4)^{-1.154} \times \text{Age}^{-0.203}$

Supplementary Table S2: Risk factors of incident type 2 diabetes mellitus (N=152)

Risk Factor	Hazard Ratio (95%CI)	p-Value
Age (years)	1.04 (0.99, 1.08)	0.051
Body mass index (Kg/m^2)	1.14 (1.08, 1.20)	<0.001
Fasting plasma glucose (mmol/l)	3.85 (2.69, 5.51)	<0.001
Systolic blood pressure (mmHg)	0.99 (0.98, 1.00)	0.148
LDL cholesterol (mmol/l)	0.98 (0.82, 1.17)	0.820
HDL cholesterol (mmol/l)	0.82 (0.39, 1.70)	0.605
Log_e triacylglycerols (mmol/l)	1.80 (1.22, 2.64)	0.003
Serum sodium (mmol/l)	1.05 (0.94, 1.18)	0.338
Serum potassium (mmol/l)	0.61 (0.34, 1.10)	0.103
Glomerular filtration rate [a] ($ml/min/1.73m^2$)	1.01 (0.99, 1.02)	0.091
Log_e C-reactive protein (mg/l)	1.02 (0.82, 1.27)	0.847
Log_e alcohol consumption (g/week)	0.97 (0.86, 1.09)	0.623
Current smoking (Yes)	1.93 (1.30, 2.87)	0.001
History of ischaemic heart disease (Yes)	1.64 (1.12, 2.40)	0.011

The Cox regression analysis is simultaneously adjusted for all risk factors shown; Hazard ratios are estimated per unit change of the risk factor

[a] Estimated with the MDRD formula: $175 \times (Creatinine/88.4)^{-1.154} \times Age^{-0.203}$
CI: confidence interval; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Log_e: Natural logarithm

Supplementary Table S3: Hazard ratios for ventricular fibrillation/tachycardia according to quartiles of baseline fasting plasma glucose in progressive multivariable-adjusted models

	Fasting plasma glucose (mmol/l)			
Quartiles	**Quartile 1st**	**Quartile 2nd**	**Quartile 3rd**	**Quartile 4th**
Mean [Min-Max]	**4.1 [3.2-4.3]**	**4.4 [4.4-4.5]**	**4.7 [4.6-4.9]**	**5.3 [5.0-6.2]**
Progressive adjustment				
Age	1.00 (0.69, 1.44)	0.77 (0.44, 1.33)	0.89 (0.60, 1.34)	0.56 (0.29, 1.07)
Systolic blood pressure	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.56, 1.25)	0.49 (0.25, 0.93)
LDL cholesterol	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.56, 1.25)	0.48 (0.25, 0.93)
Smoking	1.00 (0.69, 1.46)	0.72 (0.42, 1.24)	0.84 (0.57, 1.26)	0.49 (0.25, 0.94)
HDL cholesterol	1.00 (0.69, 1.46)	0.72 (0.42, 1.23)	0.84 (0.56, 1.26)	0.49 (0.25, 0.94)
Log_e C-reactive protein	1.00 (0.69, 1.46)	0.71 (0.41, 1.22)	0.84 (0.56, 1.25)	0.48 (0.25, 0.92)
Body mass index	1.00 (0.68, 1.47)	0.69 (0.40, 1.18)	0.80 (0.53, 1.18)	0.44 (0.23, 0.85)
Log_e alcohol consumption	1.00 (0.66, 1.51)	0.57 (0.31, 1.06)	0.76 (0.49, 1.16)	0.40 (0.20, 0.81)
Log_e triacylglycerols	1.00 (0.66, 1.51)	0.57 (0.31, 1.06)	0.75 (0.49, 1.14)	0.38 (0.19, 0.78)
Ischaemic heart disease	1.00 (0.66, 1.51)	0.58 (0.31, 1.08)	0.75 (0.49, 1.14)	0.39 (0.19, 0.78)
Glomerular filtration rate	1.00 (0.65, 1.54)	0.59 (0.32, 1.01)	0.79 (0.52, 1.22)	0.40 (0.19, 0.82)
β-blockers use	1.00 (0.65, 1.53)	0.62 (0.33, 1.16)	0.79 (0.52, 1.22)	0.41 (0.20, 0.83)
Serum sodium	1.00 (0.65, 1.53)	0.63 (0.34, 1.17)	0.76 (0.49, 1.17)	0.42 (0.20, 0.85)
Serum potassium	1.00 (0.65, 1.53)	0.64 (0.34, 1.19)	0.76 (0.48, 1.18)	0.42 (0.21, 0.85)

The table indicates the number of variables included in the models (i.e., the first model is only age-adjusted, the second is adjusted for age and systolic blood pressure, the final is adjusted for all variables). Number of participants by quartile is reported in Table 1.

Log_e: natural logarithm