Impaired Fasting Plasma Glucose and Type 2 Diabetes Are Related to the Risk of Out-of-Hospital Sudden Cardiac Death and All-Cause Mortality

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OBJECTIVE—The aim of the study was to determine whether impaired fasting plasma glucose (FPG) and type 2 diabetes may be risk factors for sudden cardiac death (SCD).

RESEARCH DESIGN AND METHODS—This prospective study was based on 2,641 middle-aged men 42–60 years of age at baseline. Impaired FPG level (≥5.6 mmol/L) among nondiabetic subjects (501 men) was defined according to the established guidelines, and the group with type 2 diabetes included subjects (159 men) who were treated with oral hypoglycemic agents, insulin therapy, and/or diet.

RESULTS—During the 19-year follow-up, a total of 190 SCDs occurred. The relative risk (RR) for SCD was 1.51-fold (95% CI 1.07–2.14, $P = 0.020$) for nondiabetic men with impaired FPG and 2.86-fold (1.87–4.38, $P < 0.001$) for men with type 2 diabetes as compared with men with normal FPG levels, after adjustment for age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, prevalent coronary heart disease (CHD), and family history of CHD. The respective RRs for out-of-hospital SCDs (157 deaths) were 1.79-fold (1.24–2.58, $P = 0.001$) for nondiabetic men with impaired FPG and 2.26-fold (1.34–3.77, $P < 0.001$) for men with type 2 diabetes. Impaired FPG and type 2 diabetes were associated with the risk of all-cause death. As a continuous variable, a 1 mmol/L increment in FPG was related to an increase of 10% in the risk of SCD (1.10 [1.04–1.20], $P = 0.001$).

CONCLUSIONS—Impaired FPG and type 2 diabetes represent risk factors for SCD.

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Sudden cardiac arrest accounts for one-half of all coronary heart disease (CHD)–related deaths, but there is limited information on the relationship between impaired fasting plasma glucose (FPG) levels and the risk of sudden cardiac death (SCD) in the general population (1–4). Since a large majority of SCDs occur among the general segments of the population and most of these SCD cases occur outside the hospital with few or no early warning signs (1), the problem would require screening methods applicable to the general population. Therefore, there continues to be a great deal of interest in identifying clinically useful markers of SCD. One of the major challenges would be to prevent clinical conditions that may lead to SCD (5,6). Glucose intolerance and type 2 diabetes have been associated with an increased risk of atherosclerotic CHD (3,7). Some case-control studies have shown that type 2 diabetes was associated with the risk of SCD (3,8,9). Furthermore, some prospective studies have proposed that type 2 diabetes may be related to a higher risk of SCD (10,11); although some other studies have suggested that type 2 diabetes was not associated with SCD (12,13). This prospective population-based study was designed to determine if impaired FPG without diagnosed type 2 diabetes is a comparable risk factor for SCD as diabetes is itself. We also studied the predictive accuracy of FPG among nondiabetic subjects and type 2 diabetic subjects with respect to the risk of SCD in the general male population.

RESEARCH DESIGN AND METHODS

Study population

This study was designed to investigate risk predictors for atherosclerotic cardiovascular outcomes in a population-based sample of men from Eastern Finland. The focus of the current prospective study was based on risk markers for SCD. The subjects were a randomly selected sample of 3,433 men 42–60 years of age who resided in the town of Kuopio or its surrounding rural communities (14). Of those who were invited, 2,682 (83%) participated in the study, and those with complete data on FPG and diagnosed type 2 diabetes (2,641 men) were included in the analyses. Baseline examinations were conducted between March 1984 and December 1989. The study was approved by the Research Ethics Committee of the University of Eastern Finland. Each participant gave written informed consent.

Assessment of FPG and type 2 diabetes

FPG was measured using the glucose dehydrogenase method (Merck, Darmstadt, Germany) after proteins had been precipitated with trichloroacetic acid. Fasting serum insulin was measured with a radioimmunoassay (Novo Biolabs; Novo Nordisk, Bagsvaerd, Denmark). An impaired FPG level among nondiabetic subjects was defined according to the recommendations based on the American Diabetes Association (≥5.6 mmol/L = 100 mg/dL) (15). Subjects meeting the following criteria were defined as patients

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with type 2 diabetes: either having regular treatment with an oral hypoglycemic agent, insulin therapy, or having treatment only with diet while also having an FBG level of at least 7.0 mmol/L (16). Dietary treatment indicates that appropriate nutritional advice on diet has been provided for those who were treated only by diet. Insulin resistance was calculated by homeostatic model assessment of insulin resistance (HOMA1-IR), which is defined as follows: HOMA1-IR = fasting plasma insulin (μU/mL) × FPG (mmol/L)/22.5 (17).

Assessment of risk factors

The lifelong exposure to smoking (cigarette pack-years) was estimated as the product of the number of years smoking and the number of tobacco products smoked daily at the time of examination (18). Resting blood pressure was measured between 8:00 and 10:00 A.M. with a random-zero sphygmomanometer (18). The cholesterol contents of serum lipoprotein fractions and triglycerides were measured enzymatically (Boehringer Mannheim, Mannheim, Germany). Serum HDL cholesterol and its subfractions were separated from fresh serum samples using ultracentrifugation and precipitation. Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-Reactive Protein Assay; DPC, Los Angeles, CA). The use of medications and baseline diseases 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 (18). BMI was computed as the ratio of weight in kilograms to the square of height in meters. Electrocardiogram and heart rate were recorded at rest and during the exercise testing. The standardized testing protocol included an increase in the workload of 20 W/min with the direct analyses of respiratory gases (Medical Graphics, St. Paul, MN). Cardiorespiratory fitness was defined as the highest value or the plateau of oxygen uptake (19,20).

Classification of outcomes

All deaths that occurred by the end of 2008 were checked against the hospital documents, health center wards, and death certificates. Deaths were coded using the ICD-9 or ICD-10 codes. The sources of information included interviews, hospital documents, death certificates, autopsy reports, and medico-legal reports (19,20). There were no losses to follow-up. A death was determined an SCD when it occurred either within 1 h after the onset of an abrupt change in symptoms or within 24 h after the onset of symptoms when clinical findings did not reveal a noncardiac cause of sudden death. SCDs that occurred in out-of-hospital conditions had been accurately documented through hospital documents. The deaths due to aortic aneurysm rupture, cardiac rupture or tamponade and pulmonary embolism, cancer, or other noncardiac comorbidities were not included as SCDs. The diagnostic classification of events was based on symptoms, electrocardiographic findings, cardiac enzyme elevations, autopsy findings (80%), and history of CHD together with the clinical and electrocardiographic findings of the paramedic staff. Thus, we had available all hospital documents, including medical records, laboratory and electrocardiographic findings from the hospital and paramedic staff, and the use of medications and a defibrillator. Nonfatal CHD events were also defined. Coronary events that did not lead to death during the following 24 h were considered a nonfatal CHD event (20). The documents related to the death were cross-checked in detail by two physicians. An independent events committee blinded to clinical data performed the classification of deaths.

Statistical analysis

The differences in baseline characteristics were examined using ANOVA and the χ^2 test. Descriptive data are presented as means and percentages. Risk factors for main outcomes were analyzed using the multivariable Cox model. Subjects with normal (<5.6 mmol/L, reference group) and impaired (≥5.6 mmol/L) FPG levels with type 2 diabetes were entered into the forced Cox proportional hazards models. Cox multivariable models were adjusted for age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, alcohol consumption, prevalent CHD, and a family history of CHD (model 1). Multivariable model 1 was additionally adjusted for three different sets of covariates: C-reactive protein, cardiorespiratory fitness, and ischemic ST changes during exercise electrocardiogram (model 2); serum fibrinogen level, heart rate, and duration of the corrected QT interval on resting electrocardiogram (model 3); and the presence of myocardial infarction, the use of medication for hypertension or dyslipidemia, and the use of β-blockers (model 4). Covariates were selected on the basis of their previously established role as a well-defined predictive factor on the basis of overall evidence and available data.

Relative risks (RRs), adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. The fit of the Cox proportional hazards models was examined by plotting the hazard functions in different categories of risk factors over time. The proportional hazards assumption was verified for all variables by inspection of the plots of the Schoenfeld residual for covariates. The linearity assumption was satisfied for all continuous variables and it was assessed with Martingale residuals for each continuous variable against survival time. The cumulative survival from SCD, according to impaired FPG and type 2 diabetes, was calculated using the Kaplan-Meier method. The attributable risk was calculated as an excess RR for SCD that is related to men with impaired FPG or type 2 diabetes, with the risk among those with normal FPG as the referent. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 18.0 for Windows.

The C-index was calculated to assess the model discrimination (the ability of the model to correctly identify subjects with respect to SCD) (21). The Harrell C-index was the primary measure of discrimination. On the basis of the C-index, the incremental values of FPG and type 2 diabetes were evaluated with previously documented cardiovascular risk factors. We calculated the integrated discrimination improvement (IDI) and relative IDI for the model with and without FPG (21–23).

RESULTS

Baseline characteristics

The mean FPG was 5.4 mmol/L (SD 3.6 mmol/L; range 3.4–28.9 mmol/L). The proportion of those with type 2 diabetes was 6.4% (n = 159), of which only six diabetic men were treated with insulin therapy. The number of nondiabetic men with impaired FPG was 501 (20.1%). The mean values of baseline characteristics are shown in Table 1.

Numbers of outcome events during the follow-up

The average follow-up time to death or the end of follow-up was 18.8 years (median 20.7 years; interquartile range

Table 1—*Baseline characteristics*

Characteristics	Mean (SD or *n*)
Age (years)	52.9 (5.1)
BMI (kg/m^2)	26.9 (3.5)
Waist-to-hip ratio	0.95 (0.06)
Smokers (%)	31.9 (795)
Cigarette smoking (pack-years)*	8.4 (16.5)
Alcohol consumption (g/week)	74.2 (121.4)
Serum total cholesterol (mmol/L)	5.91 (1.07)
Serum LDL cholesterol (mmol/L)	4.04 (1.01)
Serum HDL cholesterol (mmol/L)	1.29 (0.30)
Serum triglycerides (mmol/L)	1.28 (0.82)
Systolic blood pressure (mmHg)	134.0 (16.8)
Diastolic blood pressure (mmHg)	88.9 (10.5)
FPG (mmol/L)	5.37 (3.58)
Serum insulin (mU/L)	11.6 (7.0)
High-sensitivity C-reactive protein (mmol/L)	2.28 (3.35)
Cardiorespiratory fitness (mL/kg/min)‡	30.2 (8.0)
Previously diagnosed diseases and family histories	% (*n*)
Type 2 diabetes	5.5 (145)
CHD	23.8 (628)
History of myocardial infarction	7.4 (915)
Family history of CHD	49.3 (1,302)
History of hypertension	30.1 (795)
Family history of hypertension	47.4 (1,252)
Heart failure¶	6.6 (174)
Cardiomyopathy¶	2.1 (56)
Cerebrovascular disease	2.4 (64)
Claudication	3.8 (101)
Arrhythmias§	15.8 (417)
Pulmonary disease‖	12.5 (330)
Cancer	1.6 (39)
Regular use of medications [% (*n*)]	
Antihypertensive medication	21.1 (557)
Medication for dyslipidemia	8.6 (21)
β-Blocker	17.3 (426)
Acetyl salicylic acid	6.9 (170)

*Pack-years denotes the lifelong exposure to smoking, which was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination. ‡Cardiorespiratory fitness was defined as the highest value for or the plateau of oxygen uptake during exercise testing. ¶The diagnosis is based on clinical findings and symptoms and/or echocardiography. §Arrhythmias included extrasystolia, regular or paroxysmal atrial fibrillation, and supraventricular tachycardia. ‖Pulmonary diseases included bronchial asthma, chronic obstructive pulmonary disease, and pulmonary tuberculosis.

18.1–22.6 years). A total of 190 SCDs occurred during the follow-up. Of which, a total of 157 SCDs (82.6%) occurred in out-of-hospital conditions, and 136 (71.9%) out of all documented SCDs were due to documented ventricular tachycardia, ventricular fibrillation, or death, with autopsy revealing no other reason. The number of nonfatal CHD events was 587. Among men with normal FPG levels (<5.6 mmol/L), 146 SCDs were observed (2.8 cases per 1,000 person-years). The numbers of SCDs were 50 (5.6 cases per 1,000 person-years) for nondiabetic men with impaired FPG (≥5.6 mmol/L) and 29 (11.6 cases per 1,000 person-years) for men with type 2 diabetes.

FPG and type 2 diabetes as risk factors for SCD

The RR of SCD was 1.10-fold per 1 mmol/L continuous change in FPG level after adjustment for other risk factors (Table 2). Risk predictors for SCD are shown in Table 2. The respective RR for SCD was 1.32 (95% CI 1.04–1.82, $P < 0.001$) per 1 mmol/L increment in the subgroup of 2,482 men without type 2 diabetes at baseline.

The RR of SCD was 1.51-fold for nondiabetic men with impaired FPG and 2.86-fold for men with type 2 diabetes as compared with men with normal plasma FPG, after adjustment for age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, alcohol consumption, prevalent CHD, and family history of CHD (model 1) (Table 3). When the multivariable model was further adjusted for C-reactive protein, cardiorespiratory fitness, and ischemic ST changes during exercise electrocardiogram (model 2), the respective RR was 1.45 (95% CI 1.05–2.05, $P = 0.030$) for nondiabetic men with impaired FPG and 2.33 (1.50–3.62, $P < 0.001$) for diabetic men as compared with the risk of SCD in study participants with normal FPG levels.

The observed RRs did not substantially change, although serum fibrinogen level, heart rate, and duration of the corrected QT interval on resting electrocardiogram were taken into account (model 3). The association of impaired FPG and type 2 diabetes with the risk of SCD remained significant if a previous history of myocardial infarction and the first myocardial infarction during the interim period of the follow-up, the use of medication for hypertension or dyslipidemia, and the use of β-blockers were included into the multivariable model (model 4). Kaplan-Meier curves for nondiabetic men with impaired FPG and type 2 diabetes are presented in Fig. 1.

The RR of out-of-hospital SCD was 1.79-fold for nondiabetic men with IFG and 2.26-fold for men with type 2 diabetes (Table 3). The respective RR of all-cause death was also increased among nondiabetic subjects with impaired FPG and type 2 diabetes (Table 3). Additionally, the adjusted RR of nonfatal CHD events was higher in men with impaired FPG (RR 1.63 [95% CI 1.16–2.31], $P = 0.005$) and type 2 diabetes (2.49 [1.90–3.27], $P < 0.001$), as compared with men with normal FPG levels.

The inclusion of FPG in the model with other risk factors (model 1) increased the C-index from 0.757 to 0.761, indicating a modest nonsignificant incremental value. The C-index for the total model was 0.762 after the inclusion of type 2 diabetes instead of FPG. Thus, the C-index with FPG or type 2 diabetes did not markedly differ between the two models that included previously established risk factors. The IDI was 0.006 ($P = 0.023$), showing the significant level of discrimination improvement when FPG

Table 2—*Risk factors for SCD among middle-aged men*

	RR*	95% CI	*P* value
FPG (per 1 mmol/L)	1.10	1.04–1.20	0.001
Cigarette smoking (per 10 pack-years)†	1.24	1.16–1.32	<0.001
Prevalent CHD (yes vs. no)‡	2.71	2.10–3.63	<0.001
Systolic blood pressure (per 10 mmHg)	1.13	1.05–1.22	0.001
BMI (per 5 kg/m^2)	1.38	1.15–1.67	0.001
Age (per 1 year)	1.06	1.03–1.10	0.001
Serum LDL cholesterol (per 1 mmol/L)	1.21	1.06–1.39	0.004
Family history of CHD (yes vs. no)	1.34	1.01–1.79	0.047
Alcohol consumption (per 100 g/week)	1.06	0.98–1.15	0.167

*RRs (95% CIs) are based on Cox multivariable model adjusted for all variables shown in the table. †Pack-years denotes the lifelong exposure to smoking that was estimated as the product of years smoked and the number of tobacco products smoked daily at the time of examination. ‡Prevalent CHD includes previous history of myocardial infarction and/or the diagnosis of CHD.

was added in the model. The relative IDI value for the model was 0.083. A total of 14.7% of the SCD cases in this cohort during the follow-up were attributable to impaired FPG (≥5.6 mmol/L) or type 2 diabetes.

FPG, insulin resistance, and type 2 diabetes as risk factors for SCD

The association between impaired FPG, type 2 diabetes, and SCD remained significant even though insulin resistance was taken into account. The RR of SCD was 1.50-fold (95% CI 1.05–2.25, *P* = 0.035) for nondiabetic men with impaired FPG and 1.91-fold (1.09–3.33, *P* = 0.022) for men with type 2 diabetes, as compared with men with normal FPG levels, after adjustment for HOMA1-IR as well as age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, alcohol consumption, prevalent CHD, and family history of CHD. In this multivariable model, HOMA1-IR was not statistically significantly related to the risk of SCD.

CONCLUSIONS—This study demonstrates that impaired FPG and type 2 diabetes are related to the risk of out-of-hospital SCD and all-cause death in the general population. The main finding of this study is that impaired FPG among nondiabetic subjects and type 2 diabetic subjects represents risk factors for SCD. We observed that each 1 mmol/L increment in FPG was related to a 10% elevated risk of SCD.

Sudden cardiac arrest in adults is mainly due to underlying CHD, and the most common electrophysiological mechanism of SCD is ventricular arrhythmias. Previous findings suggest that myocardial as well as electrical abnormalities are likely to influence the risk of SCD (24). Although the exact underlying mechanism is not well known, increased sympathetic activity caused by impaired FPG may decrease the heart rate variability. Cardiac autonomic dysfunction is a complication of the asymptomatic prediabetes state and type 2 diabetes (25,26), and impaired FPG can be considered as a prestage of type 2 diabetes, which suggests the early presence of autonomic nervous dysfunction (25). Increased insulin resistance with elevated glucose levels is associated with a higher resting heart rate and lower heart rate variability, representing the decline of cardiovascular autonomic function (27). Other mechanisms by which impaired FPG and type 2 diabetes may affect SCD risk include intraventricular conduction abnormalities due to autonomic imbalance and disturbed myocardial function (25–28). Other potential factors contributing to the increased risk of SCD observed in subjects with impaired FPG or type 2 diabetes are silent myocardial ischemia, plaque rupture, abnormal cardiac repolarization, and diabetic cardiomyopathy (24). Some studies have found that the hyperglycemic and prothrombotic state could be a factor related to a higher risk of SCD (3,4,29). The association between impaired FPG and SCD may be partly due to a clinically asymptomatic microvascular process as well as macrovascular disease with coronary atherosclerosis (4).

Although the incidence of sudden cardiac arrest is quite low in the general population, the absolute numbers of SCD are high. The definitions of FPG in clinical practice may provide a useful risk marker for SCD in the general population. However, due to the observational nature of this study, it does not allow any estimation of the impact of FPG-lowering therapies on the incidence of SCD. The results suggest that the level of impaired FPG itself may be an important risk factor for out-of-hospital SCD; although the importance of very strict FPG control in the prevention of ventricular arrhythmias would require confirmation from clinical trials. The focus of this study was to show the association of impaired FPG with SCD risk. We explored SCD by incorporating serum measures of hemostatic factors, serum lipids, blood pressure, and inflammatory measures in the multivariable model. The strength of our study includes the availability of autopsy data in 80% of the SCD cases during the long-term follow-up. In our study, the incidence of SCD was somewhat higher than in some of the other lower-risk populations (11,30). The current study has been performed in an area known for its high prevalence of coronary artery disease (as an underlying cause for SCD) in previous

Table 3—*RRs of SCD and all-cause death according to the FPG and type 2 diabetes*

	SCD* (190 deaths)		Out-of-hospital SCD* (157 deaths)		All-cause death (734 deaths)	
	RR† (95% CI)	*P* value	RR† (95% CI)	*P* value	RR† (95% CI)	*P* value
Impaired FPG (≥5.6 mmol/L) (*n* = 501)	1.51 (1.07–2.14)	0.020	1.79 (1.24–2.58)	0.001	1.31 (1.11–2.87)	0.001
Type 2 diabetes (*n* = 159)	2.86 (1.87–4.38)	<0.001	2.26 (1.34–3.77)	0.001	2.30 (1.85–2.86)	<0.001

*A death was determined as SCD when it occurred either within 1 h after the onset of an abrupt change in symptoms or within 24 h after the onset of symptoms when autopsy data did not reveal a noncardiac cause of sudden death. SCDs that occurred in out-of-hospital conditions were also defined. †RRs (95% CIs) are adjusted for age, BMI, systolic blood pressure, serum LDL cholesterol, smoking, alcohol consumption, prevalent CHD, and family history of CHD.

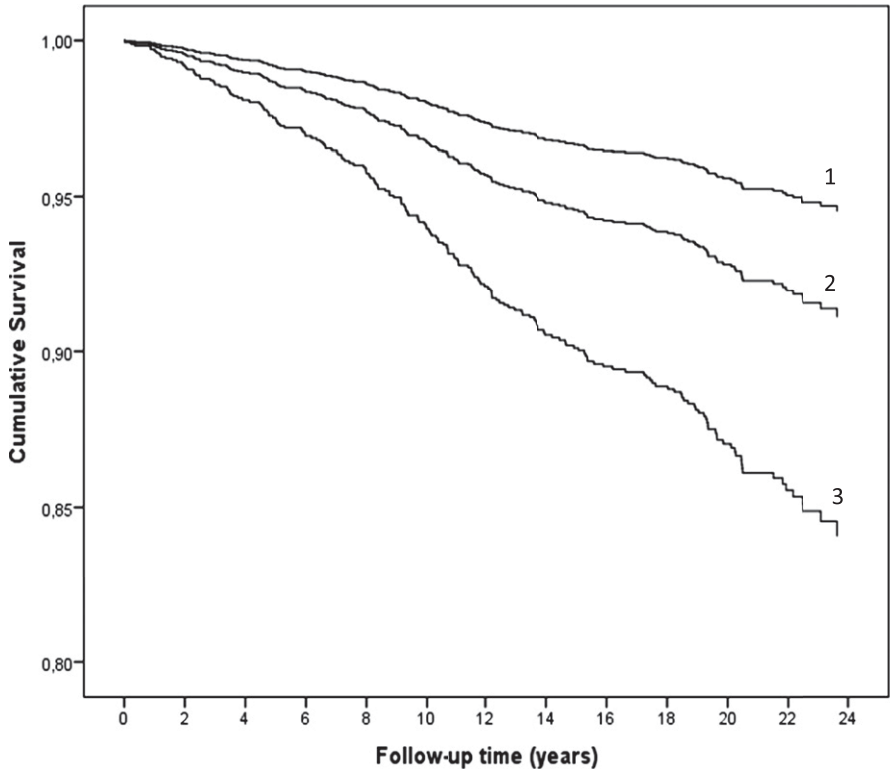

Figure 1—*The proportions of SCD according to FPG levels and type 2 diabetes. The groups were as follows:* 1*) men with normal FPG;* 2*) nondiabetic men with impaired FPG (≥5.6 mmol/L); and* 3*) men with type 2 diabetes.*

decades (31). FPG yielded a modest improvement in SCD prediction when other risk factors were taken into account. There was an improvement in the level of discrimination while using FPG in addition to other risk factors. A discrimination analysis showed a significant level of discrimination between men with and without a known FPG. Our study shows that impaired FPG, which is an easily available everyday clinical method, can be used as a predictive marker for the risk of SCD.

A limitation of this study was that the formal competing risk analyses were not performed. The observed associations between FPG and type 2 diabetes, with the risk of main outcomes including nonfatal CHD events, were statistically significant. The main findings would not have markedly changed even if the formal competing risk analysis was taken into account. Consistently, it has been previously shown that impaired fasting glucose is related to an increased risk of major cardiovascular events (32). The follow-up studies may have been biased by the participants receiving advice on how to change their lifestyle, when appropriate, as well as the reporting of the study findings to their physicians. The single assessment of FPG at baseline may lead to an underestimation, rather than an overestimation, of the prognostic significance of FPG. In clinical practice, however, the assessment of FPG should be repeated to check the effect of dietary and physical activity habits or other therapies. Our representative sample of men makes it possible to generalize the observed results to male populations, but it is important to confirm the results on impaired FPG and the risk of SCD in female populations.

Our results suggest that not only men with type 2 diabetes but also nondiabetic men with impaired FPG have an increased risk of out-of-hospital SCD. Impaired FPG levels can provide valuable information as prevention appears to be a viable approach for substantially decreasing the devastating effects of sudden cardiac arrest in the general population.

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J.A.L. analyzed and researched data and wrote the manuscript. T.H.M. and S.K. researched data and wrote the manuscript. K.R. analyzed data and edited the manuscript. J.K. contributed to discussion and reviewed and edited the manuscript. J.L. is the guarantor of this work and, as such, 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.

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