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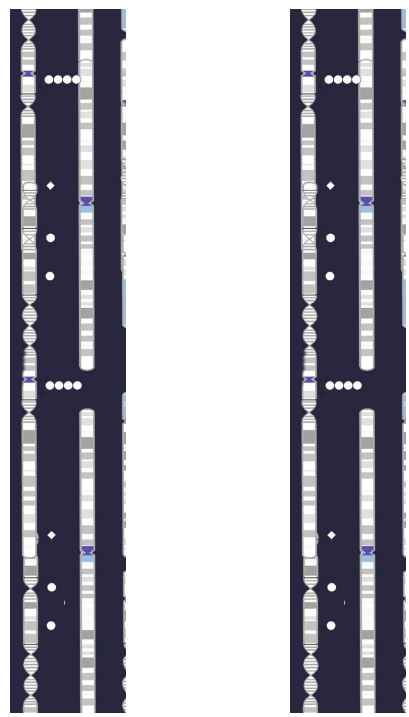

CARDIOMETABOLIC RISK FACTORS FOR VENOUS THROMBOSIS

Glucose levels and diabetes are not associated with the risk of venous thrombosis: results from the MEGA case-control study

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SUMMARY

It is unclear whether hyperglycaemia or diabetes mellitus are risk factors for a first venous thrombosis (VT). Self-reported diabetes status and fasting glucose (FG) measures were collected from the Multiple Environmental and Genetic Assessment (MEGA) study to confirm these associations. FG levels were categorized based on the WHO criteria (<6.1 (reference), 6.1-7.0 (2nd), ≥7.0 (3rd) mmol/L). Logistic regression models were performed to quantify the associations. Neither increased levels of fasting glucose (OR (95% confidence interval [CI]): 0.98 (0.69-1.37) 2nd vs. reference, 0.97 (0.58-1.63) 3rd vs. reference) nor self-reported diabetes (1.12 (0.80-1.58)) were associated with an increased risk of a first VT.

INTRODUCTION

In recent years, several studies indicated that venous thrombosis (VT) and atherosclerotic cardiovascular disease (CVD) might share common risk factors (Ageno*, et al* 2008, Lijfering*, et al* 2011). Diabetes mellitus, a chronic metabolic disease that is associated with CVD (Nathan 2015), is diagnosed by elevated fasting glucose levels and has been increasingly investigated as a possible risk factor for VT (Braekkan*, et al* 2012, Chung*, et al* 2015, Dowling*, et al* 2003, Glynn and Rosner 2005, Heit*, et al* 2009, Holst*, et al* 2010, Hong*, et al* 2005, Lidegaard*, et al* 2002, Lutsey*, et al* 2010, Mahmoodi*, et al* 2009, Movahed*, et al* 2005, Petrauskiene*, et al* 2005, Quist-Paulsen*, et al* 2010, Stein*, et al* 2009, Sveinsdottir*, et al* 2014, Tsai*, et al* 2002). In several case-control studies, glucose levels were measured at the time of the VT diagnosis, which levels may have been affected by the thrombotic event (i.e., acute phase effect), rather than representing levels before the event (Cohn*, et al* 2012, Hermanides*, et al* 2009, Tichelaar*, et al* 2011).

In the current study, we explored whether fasting glucose levels (after VT events were diagnosed for the patients as a surrogate for the glucose levels before the event), are associated with an increased risk of a first VT in the population with non-diabetic and free of recent cancer diagnosis. Furthermore, we studied the association between self-reported diabetes and the risk of a first VT. Analyses were performed in a large, population-based case-control study, the Multiple Environmental and Genetic Assessment (MEGA) of Risk Factors for VT study.

MATERIALS AND METHODS

Study design

The MEGA study is a population-based case-control study with the aim of studying the aetiology of VT. The study design was approved by the Ethics Committee of the Leiden University Medical Center, the Netherlands, and written informed consent was obtained from all participants. From 1999 to 2004, 4,956 consecutive VT patients with an objectively confirmed first event of VT or pulmonary embolism (PE) were included in the study. The control subjects were recruited from two sources, i.e., partners of VT patients without a history of VT (n=3,297); and from the general population, by random-digit dialling (RDD), further matched for age and sex with the VT cases (n=3,000). A detailed description of study design, study population selection and VT risk factor assessment can be found in the Supplementary information.

Laboratory tests

Patients and controls visited one of the anticoagulation clinics for an interview and blood sampling at least three months after discontinuation of anticoagulation, or during

anticoagulant therapy in patients who continued this therapy for more than one year. Glucose levels were measured on stored (-80°C) and previously unthawed fasting serum samples by hexokinase method on a Modular P800 Clinical Chemistry analyser (Roche Diagnostics, Mannheim, Germany).

Fasting glucose concentrations were firstly categorized into three categories by the World Health Organization (WHO) criteria (Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. 2006) of diagnosing diabetes mellitus and intermediate hyperglycemia (≤6.0, ≥6.1 and <7.0, ≥7.0 mmol/L). Additionally, they were categorized into quintiles based on the empirical fasting glucose distribution from the entire MEGA control population [<4.5 (<25th), 4.5-4.8 [25th-50th), 4.8-5.2 [50th-75th), 5.2-6.6 [75th-97.5th), ≥6.6 mmol/L (≥97.5th)].

Statistical analyses

Logistic regression models were used to estimate the odds ratios (OR) with 95% confidence intervals (95% CIs) for the associations of continuous and categorized fasting glucose levels with a first event of VT. In the basic model, age- and sex-adjusted ORs with 95% CIs were estimated. In addition, estrogen use at both index date and blood draw, BMI, statin use at blood draw, and CRP levels were added as confounders in a fully adjusted model. To adjust for lifestyle as a confounder in a model, we performed an additional 1:1 matched analysis by conditional logistic regression, taking only the VT patient partner controls into account. The risk of VT associated with fasting glucose levels was estimated for provoked and unprovoked VT events separately. Unprovoked VT was defined previously (van Hylckama Vlieg*, et al* 2014). Several sensitivity analyses were performed in addition to the main analyses to assess the robustness of the risk estimates (Supplemental information). For diabetes as a risk factor for VT, similarly as the analyses described above, two models with different confounders (basic model and fully adjusted model) were taken into account in both the logistic as well as conditional logistic regression. In addition, analyses were performed both for provoked and unprovoked VT.

All statistical analyses were performed with SPSS for Windows, release 23 (SPSS Inc, Chicago, IL).

TABLE 1. The association of fasting glucose levels categorized by the diabetes mellitus diagnosis according to WHO criteria and the risk of a first event of VT

FG levels (mmol/L)	Patients (n=1888)	Controls (n=2531)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	Matched patients (n=869)	Matched controls (n=869)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
Total population with all patients								
<6.1	1777	2402	Ref	Ref	818	822	Ref	Ref
≥6.1& <7.0	76	92	1.12 [0.82,1.53]	0.98 [0.69,1.37]	32	37	0.88 [0.54, 1.42]	0.68 [0.38, 1.22]
≥7.0	35	37	1.29 [0.80,2.05]	0.97 [0.58,1.63]	19	10	1.85 [0.86, 4.00]	2.19 [0.78, 6.11]
Continuous variable	1888	2531	1.05 [0.98,1.13]	0.97 [0.89, 1.05]	869	869	1.11 [0.97,1.27]	1.08 [0.96, 1.22]
VT patients with provoked VT								
<6.1	1221	2402	Ref	Ref	575	566	Ref	Ref
≥6.1& <7.0	38	92	0.96 [0.65,1.42]	0.85 [0.55,1.32]	14	28	0.53 [0.27, 1.04]	0.44 [0.18, 1.04]
≥7.0	18	37	1.24 [0.70,2.20]	0.95 [0.51,1.80]	12	7	1.58 [0.60, 4.15]	2.42 [0.62, 9.41]
Continuous variable	1277	2531	1.06 [0.98,1.15]	0.99 [0.90, 1.08]	601	601	1.12 [0.96, 1.31]	1.13 [0.98, 1.29]

TABLE 1. Continued.

FG levels (mmol/L)	Patients (n=1888)	Controls (n=2531)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	Matched patients (n=869)	Matched controls (n=869)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
VT patients with unprovoked VT								
<6.1	534	2402	Ref	Ref	238	251	Ref	Ref
≥6.1& <7.0	38	92	1.34 [0.89,2.01]	1.13 [0.74,1.71]	18	9	0.89 [0.35,2.23]	0.71 [0.26, 1.91]
≥7.0	16	37	1.23 [0.66,2.27]	1.01 [0.54,1.92]	7	3	1.18 [0.24,5.80]	1.95 [0.31, 12.24]
Continuous variable	588	2531	1.02 [0.90,1.16]	0.92 [0.81, 1.06]	263	263	1.00 [0.73, 1.37]	0.98 [0.69, 1.38]

* adjusted for sex and age
** adjusted for age, sex, BMI, statin use, estrogen use and CRP
*** adjusted for sex, age and matched by lifestyle
**** adjusted for age, sex, BMI, statin use, estrogen use and CRP, and matched by lifestyle

TABLE 2. The association of self-reported diabetes with the risk of a first event of VT

	No. Patients (No. diabetes)	No. Controls (No. diabetes)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	No. Matched patients (No. diabetes)	No. Matched controls (No. diabetes)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
Total population	3280 (149)	4930 (184)	0.90 [0.72,1.13]	1.12 [0.80,1.58]	1565 (64)	1565 (63)	1.02 [0.71,1.46]	1.26 [0.69,2.29]
Provoked VT patients	2068 (78)	4930 (184)	0.94 [0.72,1.24]	1.14 [0.75,1.72]	1030 (36)	1030 (35)	1.09 [0.66,1.81]	1.47 [0.64,3.37]
Unprovoked VT patients	1152 (67)	4930 (184)	0.84 [0.62,1.13]	1.06 [0.68,1.66]	520 (27)	520 (27)	1.29 [0.68,2.45]	1.08 [0.40,2.90]

* adjusted for sex and age
** adjusted for age, sex, BMI, statin use, estrogen use and CRP
*** adjusted for sex, age and matched by lifestyle
**** adjusted for age, sex, BMI, statin use, estrogen use and CRP, and matched by lifestyle

RESULTS

Supplemental Table 1 summarizes the baseline characteristics of all participants in both of the analyses. No association was found between fasting glucose levels as a continuous variable and the risk of VT (OR: 0.97, 95% CI 0.89-1.05) in the fully adjusted model (Table 1). After categorizing fasting glucose levels by WHO criteria of diabetes mellitus diagnosis and adjusting for all potential confounders, there was still no association observed between increased levels of fasting glucose and the risk of VT, with an OR of 0.97 (95% CI 0.58-1.63) for the highest (≥7 mmol/L) versus the reference category (<6.1 mmol/L). Similar results were observed for separate analyses for provoked and unprovoked VT. The sensitivity analysis by adding self-reported diabetic individuals to the highest glucose level group also yielded no association by any of the different models (Supplemental Table 2).

Subsequently, fasting glucose concentrations were categorized into quintiles. If anything, there was a weakly decreased risk, with an 0.84-fold (95% CI 0.69-1.03), 0.77-fold (95% CI 0.63-0.94), 0.74-fold (95% CI 0.61-0.92) and 0.73-fold (95% CI 0.48-1.14) decreased risk of VT in the 2nd, 3rd, 4th and 5th category of fasting glucose levels compared with the lowest reference category (Supplemental Table 3). The sensitivity analysis by restricting to blood samples with 2- to 4-hour room temperature transportation showed no association in different models (Supplemental Table 4).

Self-reported diabetes was not associated with an increased risk of VT (Table 2), with an OR of 1.12 (95% CI 0.80-1.58) in the fully adjusted model.

DISCUSSION

Previous case-control studies provided evidence that hyperglycaemia was associated with the risk of VT, but in nearly all these studies blood was drawn at the time of the thrombotic event, where stress-induced hyperglycaemia either by the thrombotic event (Hermanides*, et al* 2009, Tichelaar*, et al* 2011) or surgery (Cohn*, et al* 2012) could have occurred, leading to spurious results. In two large cohort studies, no association was found between HbA1c and the incidence of subsequent VT (Bell*, et al* 2013, Lerstad*, et al* 2014), where reverse causation could not have occurred. While a limited number of cases were identified within the follow-ups (n=345 VT cases out of 12,298 participants and n=333 VT cases out of 16,156 participants, respectively), these findings are consistent with our observations in the current analysis.

Type 2 diabetes is considered a prothrombotic condition in some studies, with the hypothesized mechanism of suppressing fibrinolysis through increasing fibrinolytic inhibitor PAI-1 levels (Grant 2007). Our null findings may for this reason come as

surprising. Nevertheless both a recent meta-analysis as well as an individual patients meta-analysis of cohort studies are in line with our findings, in which confounding was meticulously taken into account (Gariani*, et al* 2016, Mahmoodi*, et al* 2017).

There are a couple of strengths in the current study. Firstly, the large sample size allowed for subgroup analysis. Secondly, detailed information was available on many risk factors for VT to adjust for potential confounders. Thirdly, conditional logistic regression in partner controls alone enabled us to fully adjust for further confounding by socio-economic factors and lifestyle.

Several limitations should also be considered. Firstly, HbA1c levels, as a more accurate measure than fasting glucose to reflect hyperglycaemia and diabetes status, were not available in the study. Meanwhile, fasting glucose levels were measured in patients after the first VT to surrogate glucose levels before the event. However, possibly, specifically the VT patients adopted more healthier lifestyles after the disease, which led to decreased levels of fasting glucose compared with the controls and therefore a weakening of the association with VT. Secondly, we cannot rule out misclassification by self-reported diabetes. However, this misclassification was minimalized by including medication use. Moreover, around 4% of current study population reported as diabetes, which is comparable to the Dutch diabetes prevalence of 4% in the period of 2001/2002 (data from Dutch Centraal Bureau voor de Statistiek). Thirdly, the number of diabetic individuals was limited in both the VT patients and controls, which resulted in limited power in some of the subgroup analyses.

In conclusion, current findings confirm that neither elevated fasting glucose levels in the non-diabetic population nor self-reported diabetes are associated with an increased risk of VT.

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AUTHOR CONTRIBUTIONS

R. Li-Gao analysed and drafted the manuscript; R. Li-Gao, V. M. Morelli, W. M. Lijfering, A. van Hylckama Vlieg interpreted the data; F. R. Rosendaal, S.C. Cannegieter and A. van Hylckama Vlieg designed the study. All the authors reviewed the manuscript.

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APPENDIX

Study population

From March 1999 to September 2004, the MEGA case-control study included 4,956 consecutive VT patients aged between 18 and 70 years with an objectively confirmed first event of VT or pulmonary embolism (PE) (Roach*, et al* 2013). The control subjects were recruited from two sources, i.e., partners of VT patients if between 18 and 70 years of age and without a history of VT (n=3,297); and from the general population, by random-digit dialling (RDD), further matched for age and sex with the VT cases (n=3,000). All participants completed a comprehensive questionnaire on risk factors for VT at the index date, which was defined as the date of diagnosis of VT for patients and their partners, or the date of completing the questionnaire for the RDD controls. For logistic reasons, a blood sample was provided only by patients and controls recruited before June 2002.

For the analysis of fasting glucose levels and the association with the risk of VT, participants were selected (1) with valid fasting glucose measurements, (2) without history of malignancy within five years before the index date, (3) without pregnancy at both the index date and the blood draw date (women aged below 55 years with missing information on pregnancy were also removed), to avoid the influence from gestational diabetes on glucose measurements, and (4) without a history of diabetes (Fig S1.(B)). For the association analysis of diabetes and the risk of VT, participants were selected (1) with diabetes status information, (2) without history of malignancy within five years before the index date, and (3) without pregnancy at both the index date and the blood draw date (Fig S1.(A)). Diabetes was defined as either self-reported diabetes or reporting use of glucose-lowering drugs in the baseline questionnaire.

In total, 1,888 VT patients and 2,531 controls were eligible for the analysis on the association between fasting glucose levels and the risk of a first VT (Fig S1), and 3,280 VT patients and 4,930 controls were included in the analysis on diabetes and a first VT (Fig S1). Table SI summarizes the baseline characteristics of all participants in both of the analyses. Patients and controls included in the fasting glucose analysis had a similar median age around 49 years. The median BMI was higher in the patients (26.2 kg/m^2) than the controls (25.0 kg/m^2). Of all VT events 68% was provoked. Matched by partner controls alone, a total of 869 patient-control pairs remained for the conditional logistic regression analysis. The mean fasting glucose levels was comparable between VT cases and controls (mean (standard deviation): 4.9 (1.1) vs. 4.9 (0.7)) and the proportion of self-reported T2D was slightly higher among VT patients (4.5% vs. 3.7%).

VT risk factor assessment

Anthropometric measurements (weight, height), lifestyle information, medication usage (oral contraceptive/hormone replacement therapy use, statin use and glucose-lowering drug use) and self-reported diabetes status were collected from the questionnaire. Body mass index (BMI) was calculated as dividing weight (in kilograms) by height squared (m^2). The measurements of other blood parameters (C-Reactive Protein and other lipid profiles) have been described previously (Blom*, et al* 2005).

The impact of time interval between blood sampling and laboratory storage on fasting glucose measures

Since blood samples were transported at room temperature with varied time intervals from less than one hour to more than seven hours before they were stored in the laboratory, we further verified whether time intervals between blood sampling and laboratory storage would have an influence on glucose measurements. For all the participants, time intervals were derived from the time difference between the time of laboratory storage and the time of blood sampling, recorded in minutes. The continuous time interval measures were further categorised into one hour periods. One-way ANOVA was used, adjusted for age, sex, BMI, and case/control status, to evaluate whether average fasting glucose measurements were the same across different time interval categories. Depending on the location of clinics, it took from less than ten minutes to more than seven hours before stored in the laboratory, resulting in seven categories. Each category included both patients and controls, and no difference was observed between the proportions of patients and controls in each category. For more than 80% of the blood samples, the time interval between blood sampling and laboratory storage was over 2 hours. From the subgroup with a time interval less than one hour to the subgroup with a time interval more than seven hours, there was a step-wise decrease in the average fasting glucose levels, after adjusting for age, sex, BMI, and case/control status. (Fig S2.).

Sensitivity analyses

As all individuals with self-reported diabetes were excluded from this analysis, the number of individuals falling into the highest fasting glucose category was very limited. We performed an additional sensitivity analysis including the individuals with self-reported diabetes, and adjusted the fasting glucose values of those individuals below 7.0 mmol/l (assumed to be due to glucose-lowering medication) to the average measurement of the diabetic group (fasting glucose = 8.0 mmol/l). By adding self-reported diabetic individuals into the analyses, similar point estimations of ORs were obtained (Table SIII).

In order to verify whether non-differential glucose measurement bias (due to the varied time interval between blood sampling and laboratory storage) would influence the association to the risk of VT, an additional sensitivity analysis was conducted including only blood samples with a time interval from two to four hours, as there was only a small difference observed on the group mean fasting glucose levels and these groups composed of the majority of the study population. Again, similar results were obtained for the relation between glucose levels and thrombotic risk, i.e., all risk estimates were close to the null (Table SIV).

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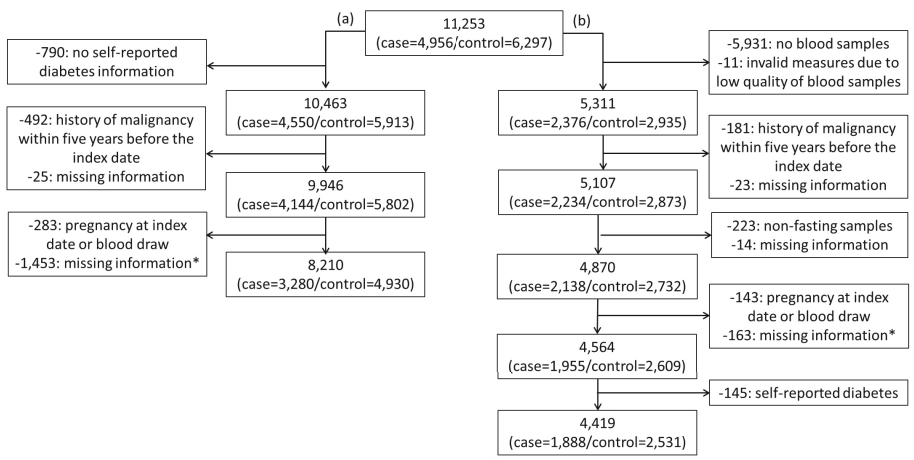

FIG S1. Flowchart of sample selection from the MEGA study. (A). The selection for the analysis of self-reported diabetes to the risk of a first event of VT, with the number of cases and controls in the brackets. (B). The selection for the analysis of hyperglycaemia in non-diabetic population to the risk of VT.
*Missing information applied to women age below 55 years.

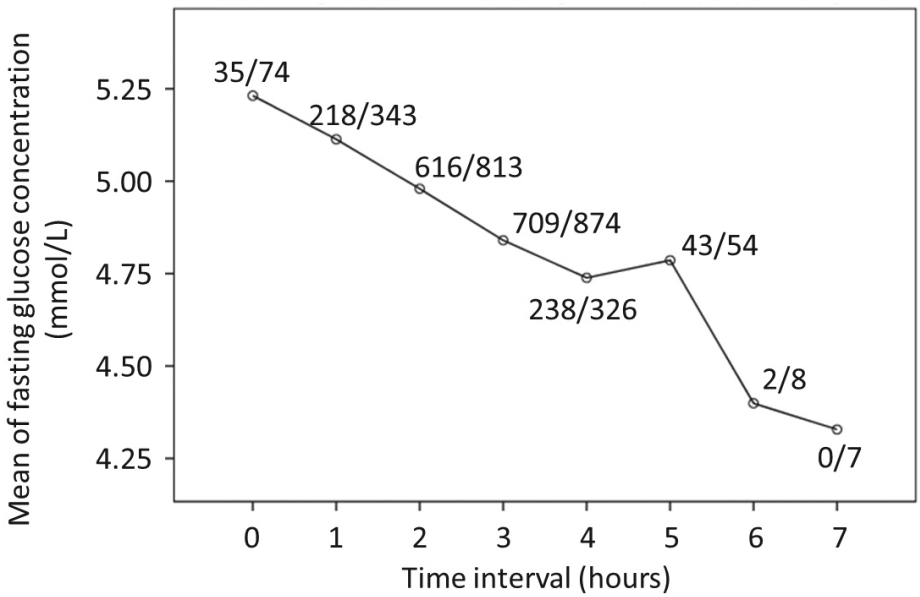

FIG S2. Group average fasting glucose levels across seven time interval categories, tested by one-way ANOVA and controlled by age, sex, BMI and case/control status. The numbers labelled above the dots in the figure corresponded to the numbers of patients/controls falling into a time interval category.

SUPPLEMENTAL TABLE 1. Baseline characteristics

	Population characteristics for fasting glucose analysis				Population characteristics for self-reported diabetes analysis			
Characteristics	**Cases (n=1,888)**	**Controls (n=2,531)**	**Matched cases (n=869)**	**Matched controls (n=869)**	**Cases (n=3,280)**	**Controls (n=4,930)**	**Matched cases (n=1,565)**	**Matched controls (n=1,565)**
Age, years	49 [39, 58]	50 [39, 58]	50 [41, 58]	50 [42, 58]	52 [41, 61]	50 [38, 58]	53 [43, 61]	53 [43, 60]
Women, n (%)	962 (51.0%)	1275 (50.4%)	422 (48.6%)	443 (51.0%)	1405 (42.8%)	2251 (45.7%)	727 (46.5%)	823 (52.6%)
BMI (kg/m²)	26.2 [23.8, 29.1]	25.0 [22.7, 27.6]	26.2 [24.0, 28.7]	25.5 [23.2, 27.8]	26.4 [24.0, 29.2]	25.2 [22.9, 27.8]	26.4 [24.1, 29.2]	25.7 [23.2, 28.2]
Unprovoked VT, n (%)	588 (31.1%)	NA	263 (30.3%)	NA	1152 (35.1%)	NA	520 (33.2%)	NA
Provoked VT, n (%)	1277 (67.6%)[a]	NA	601 (69.2%)[b]	NA	2068 (63.0%)[c]	NA	1030 (65.8%)[d]	NA
- Surgery, trauma, immobility, n (%)	650 (50.9%)	NA	575 (66.2%)	NA	1290 (62.4%)	NA	582 (71.4%)	NA
- Hormone use, n (%)	627 (49.1%)	NA	294 (33.8%)	NA	778 (37.6%)	NA	448 (28.6%)	NA
Statin user, n(%)	110 (5.8%)	121 (4.8%)	55 (6.4%)	46 (5.3%)	135 (4.1%)	162 (3.3%)	78 (5%)	68 (4.3%)
C-reactive protein (mg/L)	2.0 [0.9, 4.4]	1.4 [0.7, 3.0]	1.9 [0.9, 4.2]	1.5 [0.8, 3.2]	2.0 [0.9, 4.5]	1.4 [0.7, 3.0]	1.9 [0.9, 4.4]	1.5 [0.8, 3.2]

Continuous variables denoted as median [IQR].
Categorical variables as number (%).
There were missing values for some participants in some subgroups.
[a.] 23 VT patients with missing provoking factors.
[b.] 5 VT patients with missing provoking factors.
[c.] 60 VT patients with missing provoking factors.
[d.] 15 VT patients with missing provoking factors.

SUPPLEMENTAL TABLE 2. Sensitivity analysis of the association of fasting glucose levels categorized by the diabetes mellitus diagnosis according to WHO criteria and the risk of a first event of VT, by including self-reported diabetic individuals

FG levels (mmol/l)	Patients (n=1955)	Controls (n=2609)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	Matched patients (n=931)	Matched controls (n=931)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
Total population with all patients								
<6.1	1777	2402	Ref	Ref	842	848	Ref	Ref
≥6.1& <7.0	76	92	1.12 [0.82,1.53]	0.98 [0.69,1.37]	36	40	0.90 [0.57, 1.44]	0.70 [0.40, 1.22]
≥7.0	102	115	1.20 [0.91,1.58]	0.91 [0.67,1.24]	53	43	1.23 [0.80, 1.90]	1.09 [0.62, 1.91]
VT patients with provoked VT								
<6.1	1221	2402	Ref	Ref	591	580	Ref	Ref
≥6.1& <7.0	38	92	0.96 [0.65,1.42]	0.85 [0.55,1.32]	15	30	0.53 [0.27, 1.01]	0.45 [0.20, 1.01]
≥7.0	56	115	1.19 [0.85,1.66]	0.86 [0.59,1.26]	32	28	1.16 [0.66, 2.03]	1.20 [0.55, 2.60]
VT patients with unprovoked VT								
<6.1	534	2402	Ref	Ref	246	263	Ref	Ref
≥6.1& <7.0	38	92	1.34 [0.89,2.01]	1.13 [0.74,1.71]	21	10	1.15 [0.47,2.79]	0.83 [0.32, 2.12]
≥7.0	44	115	1.21 [0.83,1.76]	1.00 [0.67,1.48]	21	15	1.19 [0.52,2.74]	0.94 [0.37, 2.40]

* adjusted for sex and age
** adjusted for age, sex, BMI, statin use, estrogen use and CRP
*** adjusted for sex, age and matched by lifestyle
**** adjusted for age, sex, BMI, statin use, estrogen use and CRP, and matched by lifestyle

SUPPLEMENTAL TABLE 3. The association of fasting glucose levels categorized by the percentiles of the empirical fasting glucose distribution in the control population and the risk of VT

FG levels (mmol/l)	Patients (n=1888)	Controls (n=2531)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	Matched patients (n=869)	Matched controls (n=869)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
Total population								
<25th (<4.5)	483	610	Ref	Ref	212	202	Ref	Ref
25th -50th (4.5-4.8)	387	521	0.94 [0.78,1.12]	0.84 [0.69, 1.03]	182	186	0.93 [0.70, 1.23]	0.87 [0.60, 1.25]
50th-75th (4.8-5.2)	480	697	0.87 [0.73,1.03]	0.77 [0.63, 0.94]	224	245	0.86 [0.66, 1.14]	0.77 [0.54, 1.10]
75th-97.5th (5.2-6.6)	485	639	0.95 [0.80,1.14]	0.74 [0.61, 0.92]	222	216	0.96 [0.71, 1.30]	0.66 [0.44, 0.98]
≥97.5th (≥6.6)	53	64	1.04 [0.70,1.53]	0.73 [0.48,1.14]	29	20	1.35 [0.71,2.55]	1.05 [0.46,2.42]
Continuous variable	1888	2531	1.05 [0.98,1.13]	0.97 [0.89, 1.05]	869	869	1.11 [0.97,1.27]	1.08 [0.96, 1.22]
VT patients with provoked VT								
<25th (< 4.5)	377	610	Ref	Ref	164	135	Ref	Ref
25th -50th (4.5-4.8)	261	521	0.89 [0.73,1.09]	0.76 [0.60, 0.97]	131	136	0.85 [0.60,1.19]	0.84 [0.53, 1.32]
50th-75th (4.8-5.2)	324	697	0.91 [0.75,1.10]	0.78 [0.62, 0.98]	151	170	0.90 [0.65,1.27]	0.73 [0.46, 1.14]
75th-97.5th (5.2-6.6)	289	639	0.99 [0.81,1.22]	0.72 [0.57,0.93]	139	143	1.11 [0.76,1.62]	0.70 [0.41,1.17]
≥97.5th (≥6.6)	26	64	0.91 [0.56,1.48]	0.67 [0.39, 1.16]	16	17	0.93 [0.43, 2.04]	0.84 [0.30, 2.37]
Continuous variable	1277	2531	1.06 [0.98,1.15]	0.99 [0.90, 1.08]	601	601	1.12 [0.96, 1.31]	1.13 [0.98, 1.29]
VT patients with unprovoked VT								
<25th (< 4.5)	100	610	Ref	Ref	47	66	Ref	Ref
25th -50th (4.5-4.8)	122	521	1.17 [0.87,1.59]	1.05 [0.77, 1.43]	50	49	1.30 [0.65, 2.61]	1.19 [0.55, 2.56]
50th-75th (4.8-5.2)	151	697	0.90 [0.68,1.20]	0.80 [0.60, 1.08]	72	75	1.09 [0.57, 2.09]	1.05 [0.50 2.20]
75th-97.5th (5.2-6.6)	189	639	0.96 [0.72,1.28]	0.79 [0.58,1.06]	81	70	0.83 [0.42,1.63]	0.76 [0.36,1.61]
≥97.5th (≥6.6)	26	64	1.26 [0.74,2.14]	0.84 [0.48, 1.47]	13	3	1.88 [0.40, 8.83]	2.19 [0.34, 14.02]
Continuous variable	588	2531	1.02 [0.90,1.16]	0.92 [0.81, 1.06]	263	263	1.00 [0.73, 1.37]	0.98 [0.69, 1.38]

* adjusted for sex and age
** adjusted for age, sex, BMI, statin use, estrogen use and CRP
*** adjusted for sex, age and matched by lifestyle
**** adjusted for age, sex, BMI, statin use, estrogen use and CRP, and matched by lifestyle

SUPPLEMENTAL TABLE 4. Sensitivity analysis of taking the blood samples with the time interval between two and four hours, and fasting glucose were categorized by the percentiles of the empirical fasting glucose distribution in the controls

FG level (mmol/l)	Patients (n=1325)	Controls (n=1687)	Odds Ratio* (95% CI)	Adjusted Odds Ratio** (95% CI)	Matched patients (n=562)	Matched controls (n=562)	Odds Ratio*** (95% CI)	Adjusted Odds Ratio**** (95% CI)
Total population with all the patients								
<25th (<4.5)	338	414	Ref	Ref	138	127	Ref	Ref
25th -50th (4.5-4.8)	290	367	0.98 [0.79, 1.22]	0.84 [0.66, 1.08]	126	129	0.91 [0.64,1.29]	0.78 [0.50, 1.23]
50th-75th (4.8-5.2)	338	467	0.91 [0.74, 1.12]	0.79 [0.62, 1.00]	149	159	0.88 [0.63,1.23]	0.64 [0.41, 1.00]
75th-97.5th (5.2-6.6)	323	394	1.05 [0.84, 1.31]	0.77 [0.59, 0.99]	133	135	0.94 [0.64,1.37]	0.63 [0.38, 1.04]
≥97.5th (≥6.6)	36	45	1.02 [0.64,1.64]	0.64 [0.37,1.09]	16	12	1.26 [0.54,2.95]	1.41 [0.45,4.41]
Continuous variable	1325	1687	1.08 [0.99, 1.17]	0.98 [0.90, 1.08]	562	562	1.10 [0.95,1.28]	1.11 [0.97, 1.27]
VT patients with provoked VT								
<25th (<4.5)	263	414	Ref	Ref	102	87	Ref	Ref
25th -50th (4.5-4.8)	200	367	0.99 [0.78, 1.26]	0.82 [0.61, 1.10]	92	94	0.99 [0.65,1.50]	0.89 [0.50, 1.59]
50th-75th (4.8-5.2)	230	467	1.01 [0.80, 1.27]	0.83 [0.63, 1.11]	101	113	1.04 [0.68,1.57]	0.69 [0.39, 1.23]
75th-97.5th (5.2-6.6)	194	394	1.18 [0.92, 1.52]	0.80 [0.59, 1.09]	84	84	1.37 [0.84,2.24]	0.82 [0.42, 1.61]
≥97.5th (≥6.6)	18	45	0.99 [0.55,1.77]	0.62 [0.32,1.22]	8	9	1.18 [0.38,3.67]	1.99 [0.41,9.76]
Continuous variable	905	1687	1.11 [1.01, 1.22]	1.02 [0.92, 1.13]	387	387	1.19 [0.95,1.49]	1.18 [1.00, 1.41]
VT patients with unprovoked VT								
<25th (<4.5)	70	414	Ref	Ref	35	40	Ref	Ref
25th -50th (4.5-4.8)	86	367	1.09 [0.76,1.56]	0.94 [0.65, 1.37]	33	35	1.01 [0.44,2.31]	1.09 [0.43, 2.77]
50th-75th (4.8-5.2)	104	467	0.86 [0.61, 1.22]	0.76 [0.53, 1.09]	48	46	0.81 [0.37,1.76]	0.86 [0.35, 2.11]
75th-97.5th (5.2-6.6)	126	394	0.92 [0.65,1.31]	0.73 [0.50, 1.05]	49	49	0.49 [0.22,1.14]	0.57 [0.23, 1.41]
≥97.5th (≥6.6)	17	45	1.06 [0.55,2.01]	0.67 [0.34,1.33]	8	3	0.94 [0.18,5.00]	1.51 [0.21,11.06]
Continuous variable	403	1687	1.00 [0.86,1.16]	0.89 [0.75, 1.04]	173	173	0.85 [0.60,1.20]	0.88 [0.59, 1.29]

* adjusted for sex and age
** adjusted for age, sex, BMI, statin use, estrogen use and CRP
*** adjusted for sex, age and matched by lifestyle
**** adjusted for age, sex, BMI, statin use, estrogen use and CRP, and matched by lifestyle