Fabrizio Ricci ORCID iD: 0000-0002-7427-0658

Prognostic significance of non-cardiac syncope in the general population: a systematic review and meta-analysis

Fabrizio Ricci[1,5], MD, Richard Sutton[2], DSc, MB, BS, Stefano Palermi[3], MD, Claudio Tana[4], MD, Giulia Renda[3], MD, PhD, Sabina Gallina[3], MD, Olle Melander[5], MD, PhD, Raffaele De Caterina[3], MD, PhD, and Artur Fedorowski[5,6*], MD, PhD

[1]Institute for Advanced Biomedical Technologies, Department of Neuroscience and Imaging and Clinical Sciences, G. d'Annunzio University, Chieti, Italy
[2]National Heart and Lung Institute, Imperial College, Hammersmith Hospital Campus, Ducane Road, London W12 0NN, UK
[3]Institute of Cardiology, Department of Neuroscience, Imaging and Clinical Sciences, and Center of Excellence on Aging, CeSI-Met, G. d'Annunzio University, Chieti, Italy
[4]Internal Medicine and Critical Subacute Care Unit, Medicine Geriatric-Rehabilitation Department, University-Hospital of Parma, Parma, Italy
[5]Department of Clinical Sciences, Lund University, Clinical Research Center, Skåne University Hospital, Malmö 205-02, Sweden
[6]Department of Cardiology, Skåne University Hospital, Malmö 205-02, Sweden

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***Corresponding author:** Artur Fedorowski, MD, Assoc. Prof; Dept. of Cardiology, Jan Waldenströms gata 14, Skåne University Hospital, 214 28 Malmö, Sweden. Fax: +46 40 33 62 25, Phone: +46 40 33 10 00. Email: artur.fedorowski@med.lu.se

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Abstract

Introduction. Cardiac syncope heralds significantly higher mortality compared with syncope due to non-cardiac causes or unknown etiology, commonly considered a benign event. A few epidemiologic studies have examined the outcome of non-cardiac/unexplained syncope comparing individuals with and without syncope, but with controversial results. We performed a systematic review and meta-analysis to clarify whether history of non-cardiac/unexplained syncope is associated with increased all-cause mortality in the general population.

Methods and Results. Our systematic review of the literature published between January 1st, 1966, and March 31st, 2018 sought prospective, observational, cohort studies reporting summary-level outcome data about all-cause mortality in subjects with history of non-cardiac/unexplained syncope compared with syncope-free participants. Adjusted hazard ratios were pooled through inverse variance random-effect meta-analysis to compute the summary effect size. Meta-regression models were performed to explore the effect of age, cardiovascular risk factors or other potential confounders on the measured effect size. We identified 4 studies including 287,382 individuals (51.6% men; age, 64±12 years): 38,843 with history of non-cardiac/unexplained syncope and 248,539 without history of syncope. The average follow-up was 4.4 years. History of non-cardiac/unexplained syncope was associated with higher all-cause mortality (pooled adjusted hazard ratio 1.13; 95%CI:1.05-1.23). Meta-regression analysis showed a stronger positive relationship proportional to aging and increasing prevalence of diabetes and hypertension.

Conclusion. This study-level meta-analysis showed that among older, diabetic and/or hypertensive individuals, history of non-cardiac/unexplained syncope,

even in the absence of an obvious cardiac etiology, is associated with higher all-cause mortality.

Keywords: all-cause mortality; meta-analysis; cardiovascular autonomic dysfunction; orthostatic hypotension; neutrally-mediated syncope.

Introduction

Previous studies have shown that cardiac etiology of syncope herald significantly higher risk of all-cause and sudden death rates compared with patients in whom syncope is due to non-cardiac causes or unknown etiology(1-3), which are much more common than cardiac causes and typically considered to be benign(4). Others have claimed that prognosis is largely determined by the underlying comorbidities, with or without cardiac etiology(5), and have even questioned the impact of any syncope subtype on survival(6). Moreover, most previous studies investigated the outcomes of syncope per se, typically in the setting of emergency department(7), rather than comparing individuals with and without a history of syncope, and the latter are very sparse(4).

Hence, in this systematic review and meta-analysis of prospective cohort studies, we aimed to explore the long-term prognosis of non-cardiac/unexplained syncope in the general population, after the exclusion of patients with a definite diagnosis of cardiac syncope.

Methods

Search strategy and study selection criteria.

This meta-analysis was planned, conducted, and reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Medline and Embase databases, the Clinical Trials Registry (www.clinicaltrials.gov), as well as abstracts from major cardiological and neurological societies' meetings were searched for potentially relevant articles using the search terms ((syncope OR vasovagal OR neurally-mediated OR loss of consciousness OR faint OR lipothymia)) AND ((follow OR cohort OR mortality OR prognosis OR outcome OR death)). Websites, including the-heart.org, escardio.org and ResearchGate, as well as reference lists of all identified articles, including hand-searching of reviews and previous meta-analyses, were also appraised for additional relevant studies.

The search was performed for the period January 1, 1966, through December 31, 2017.

Studies were included for analysis if they met the following criteria: (i) published as a full-length article; (ii) English language; (iii) including >100 individuals with a history of non-cardiac or unexplained syncope; (iv) with age ≥18-years; (v) with ≥1-year follow-up; and (vi) reporting all-cause mortality of both individuals with and without non-cardiac/unexplained syncope, regardless of the site of presentation, i.e. inpatient or outpatient.

Data Extraction and Quality Assessment

Two authors (F.R. and S.P.) performed the screening of titles and abstracts, reviewed full-text articles, and determined their eligibility. The remaining authors acted as reviewers not blinded to the full texts of articles in consideration. Divergences were solved by consensus and/or involving the review by another author (R.S.).

We included 4 longitudinal studies with non-matched control groups reporting on the long-term all-cause mortality outcome of patients with a first-time episode of non-cardiac/unexplained syncope. Two investigators (F.R. and C.T.)

independently abstracted summary-level data (i.e. baseline characteristics, the number of events in each group and the adjusted summary statistic) reported in original publications, using standardized data extraction. Syncope definition and case ascertainment across different selected studies are detailed in Table 1. Two investigators (S.P and G.R) appraised the internal validity of included observational studies using of the Newcastle-Ottawa Scale. This scale awards 1 up to 9 stars judging each study in three main categories, i.e., selection of study group, comparability, and ascertainment of the outcome of interest. Divergences were solved by consensus and/or involving the review by another author (R.S.).

As we intended to use anonymized data from previous studies, the acceptance of Regional Ethical Review Board was not required, and the included studies were examined whether the Institutional Review Board clearance was obtained.

Statistical Analysis

The primary outcome was all-cause mortality. Outcome data were extracted as adjusted hazard ratios (HR) and 95% confidence intervals (CI) for and pooled in a random-effect, generic inverse variance meta-analysis in order to compute the summary effect size. Each study estimate of the relative condition was given a weight that was equal to the inverse of the variance of the effect estimate, i.e., 1 divided by the squared SEM.

Heterogeneity of the effect across studies was assessed by means of the Cochrane Q chi^2 and I^2 statistics. Lack of homogeneity was considered for Cochrane Q chi^2 test $P \leq 0.10$ and/or for an I^2 statistics $\geq 50\%$. When heterogeneity was judged significant, the pooled RR was calculated through the analysis of variance between studies with the 'method of moments' or the Der Simonian and Laird method for random effects. We computed the z-statistic for

each clinical outcome, and considered results statistically significant at a P<0.05 level.

We performed a leave-one-out sensitivity analysis, for each endpoint of interest, to evaluate the robustness of the results and the impact of each study on the summary estimate of effect; pooled estimates were recalculated multiple times, using a random effects model, each time with the removal of a single study from the baseline group. The likelihood of publication bias was visually assessed by generating a funnel plot, and evaluation by the Egger's test of intercept: here, a P<0.10 was considered as indicative of significant asymmetry. We also performed the non-parametric 'trim-and-fill' procedure that would adjust for funnel plot asymmetry by generating hypothetical missing studies. To investigate possible sources of heterogeneity among studies, univariate meta-regression analysis using a mixed-effects model to assess the effect of study-level selected variables [sample size, age, sex, diabetes, hypertension, prevalent cardiovascular disease, and follow-up duration] was also performed.

Statistical analyses were made using the Review Manager software package (RevMan version 5.3 for OSX, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008, Copenhagen, Denmark), Open MetaAnalyst (version for OSX, Brown University School of Public Health Providence, RI, USA), and STATA 11.0 version (STATA, College Station, TX, USA).

Results

Of 6590 citations identified and 96 potentially relevant articles retrieved, we included 4 studies (3, 8-10), based on 4 unique cohorts from 3 different countries (1 from the US, 1 from Denmark and 2 from Sweden), for an overall population of 287 296 individuals (51.6% men; age, 64.5±12.4 years), including 38,757 subjects with a history of non-cardiac/unexplained syncope and 248,539 non-

randomized controls (Figure 1). The average follow-up after the first-syncopal event was 4.4 years. The overall quality of studies was high, with 1 study scoring 7 stars and 3 studies scoring 9 stars (Newcastle-Ottawa Scale). The main characteristics of the included studies are summarized in Table 1.

Compared with non-randomized controls, a history of non-cardiac or unexplained syncope was associated with a 13% increase in all-cause mortality (pooled adjusted HR: 1.13; 95%CI 1.05-1.23) (Figure 2).

Publication bias, or “small study effect”, was excluded by both visual inspection of the funnel plot and Egger’s test of intercept (Figure S1). Furthermore, the non-parametric ‘trim-and-fill’ procedure could not impute any ‘missing’ study.

‘Leave-one-out’ sensitivity analysis showed that no single study significantly affected the pooled aHR for all-cause mortality (Table 2).

Heterogeneity was moderate, but significant (I^2>50%; P<0.10). The univariate meta-regression analysis showed that the effect of non-cardiac/unexplained syncope on mortality was higher with increasing age, and growing prevalence of diabetes and hypertension (Table 3).

The four included studies were accepted by the appropriate Institutional Review Board at the main study site and the informed consent was obtained by the investigators for the US and two Swedish studies, whereas the Danish study was accepted by the Danish Data Protection Agency as the ethical approval is not required for registry-based studies in Denmark. All patient-related data used for the meta-analysis were anonymized.

Discussion

This meta-analysis provides evidence that history of non-cardiac syncope is associated with a moderate but significantly increased all-cause mortality. The

association is stronger in older, diabetic and hypertensive individuals, regardless of whether structural cardiovascular disease was present or not.

Syncope is a not a specific diagnosis, it is only a symptom. According to the International Classification of Diseases, 10th Revision (ICD-10), the diagnosis of syncope (R55.9) belongs to the group of “general symptoms and signs”, such as headache or pain, without reference to the possible etiology. The diagnostic code is often used as a synonym for vasovagal syncope, which represents about 60-70% of all syncopal attacks(11). However, the same code may be used for unexplained syncope, syncope with underlying autonomic failure or orthostatic hypotension (OH), or psychogenic attacks. Unexplained syncope may also represent a clinical manifestation of an unrecognized or paroxysmal cardiovascular disorder, such as pulmonary embolism(12) or cardiac arrhythmia(13). Although the ICD-10 diagnostic code for syncope demonstrates a very high positive accuracy for an actual syncopal event(14), the role of a vasovagal reflex in the assessed event is not always obvious. Indeed, a vasovagal reflex-related etiology is frequently inferred by exclusion method, i.e., by absence of cardiac or autonomic nervous system (ANS) disease. It may be further confirmed by a typical history of past attacks, triggers and prodromes(15). However, some expertise is usually needed to identify reflex syncope adequately; and it should be borne in mind that ANS disorders, such as OH and postural orthostatic tachycardia syndrome may mimic events caused by an isolated reflex syncope. Thus, the diagnostic code R55.9, although highly specific for loss of consciousness due to cerebral hypoperfusion, does not offer any specific information about its etiology. As administrative discharge codes are widely used in epidemiology, the ICD-10 code R55.9 should probably be revised

in order to offer specific sub-codes and proper discrimination of syncope etiologies.

After exclusion of cardiac syncope, the potential role of prevalent CV disease in a recent syncopal episode may have been radically reduced, but not totally excluded for the reasons mentioned above. Hence, patients with prevalent CVD and unexplained syncope should be considered at high-risk, and need early hospital evaluation, including ECG telemetry and, possibly, cardiac imaging(15), especially those who are older, have diabetes or hypertension.

Traditionally, patients diagnosed with non-cardiac syncope have been seen as a group with benign prognosis, especially at younger age, although, notably, unexplained syncope heralded moderately increased risk of premature death compared with syncope-free individuals in the general population(3). Later reports have questioned this view, as hospital discharge with a diagnosis of non-specific syncope (R55.9) in the absence of obvious CVD indicated a higher mortality and a higher risk of incident CVD in independent populations(8, 10). When searching for previous studies with a first diagnosis of non-cardiac syncope as a discriminating factor, it appeared that surprisingly little has been written on this topic. In fact, only 4 studies reported on non-specific syncope and subsequent mortality in a longitudinal manner, having background population as a control group. Interestingly, all these studies, independent of each other, indicate a very similar increase in mortality mediated by the history of unexplained syncope, regardless of whether the episode was self-reported (Framingham Study) or based on the hospital discharge diagnosis (the other three studies).

The average 10-15% increase in all-cause mortality conferred by non-cardiac syncope deserves specific comment. For this, there are some possible

explanations. First, patients who were diagnosed with syncope without concurrent CVD may have been underdiagnosed, or an intermittent CVD, such as arrhythmia, may have been unrecognized. Clinicians involved may have been confident that the diagnostic work-up efficiently excluded everything of importance for a specific pathological diagnosis. This is typically done with the use of telemetry, echocardiography, exercise ECG, and coronary angiography, or with orthostatic blood pressure measurements and head-up tilt testing. However, if the required methods for any very specific diagnosis, such as pulmonary embolism, are not applied(12), or, in the scenario of paroxysmal disorders such as atrioventricular block(16), the true etiology of syncope associated with potential increased mortality may easily be missed. Second, the non-specific diagnosis of syncope may herald higher risk of vehicle accidents(17), and also a history of vasovagal syncope may indicate a higher likelihood of coronary events later in life, although the pathophysiological mechanisms are not well understood. Third, syncope due to autonomic dysfunction and OH, which may have been unrecognized during the primary assessment of syncope, confers a higher risk of death, as shown in previous studies (18, 19). Thus, a “syncope” diagnosis might not reveal OH and its associated increased risk of death.

A possible solution to this problem has been presented by an Italian group, where a systematic approach to unexplained syncope in patients above 40 years of age resulted in pacemaker implantation in about half, with subsequent resolution of syncopal episodes(20). On the other hand, there is a huge gap in knowledge of whether syncope apparently due to vasovagal reflex or OH, especially in older, diabetic or hypertensive patients, should stimulate a more proactive approach to cardiac risk assessment. This approach could include

long-term invasive cardiac monitoring, the application of specific and otherwise rarely used diagnostic modalities, and, finally, prophylactic measures.

Study limitations

We acknowledge some limitations requiring attention. Firstly, our analysis was based on aggregate summary-level data abstracted from original publications, but not on individual patient-level data. This prevented us from conducting in-depth subgroup or multivariate meta-regression analyses.

Secondly, unexplained and non-cardiac syncope have been combined as one entity, though they may have significantly different risks of mortality. However, the diagnostic code R55.9 classification and lack of clinical data about systematic diagnostic work-up prior to ICD coding prevented us from segregating these two groups.

Thirdly, we found a significant statistical heterogeneity, possibly affecting the robustness of the results; nonetheless, we applied a rigorous statistical approach to explain heterogeneity and detected those study variables, particularly age, hypertension and diabetes, representing a possible source of the observed variability.

Finally, the absence of CVD in the various studies was commonly only evaluated at one single time point, so that recurrence of syncope and incident CVD were not accounted as possible additional confounding factors and/or effect modifiers.

Conclusion

This study-level meta-analysis showed that among older, diabetic and/or hypertensive individuals, history of non-cardiac/unexplained syncope, even in the absence of an obvious cardiac etiology, is associated with higher all-cause mortality. We suggest that in non-cardiac/unexplained syncope, especially older, diabetic or hypertensive patients, a more proactive approach to cardiovascular

risk assessment, including the use of long-term minimally-invasive cardiac monitoring and other specific investigations, via syncope unit referral, may offer prophylactic measures and ultimately a reduction in this now identified mortality.

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Contributors: FR, SP, AF, RS had full access to all the data in the study and take responsibility of the data and accuracy of the data analysis. CT, GR, OM, RS, RDC, SG contributed to the study concept and design. FR, SP, CT, AF contributed to the acquisition of data. All authors analysed and interpreted the data. AF was the study supervisor. FR and SP did the statistical analysis. FR, RS, AF and RDC drafted the manuscript with critical revision for important intellectual content from all authors.

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Figures.

Figure 1. Flow chart showing the process of study selection.

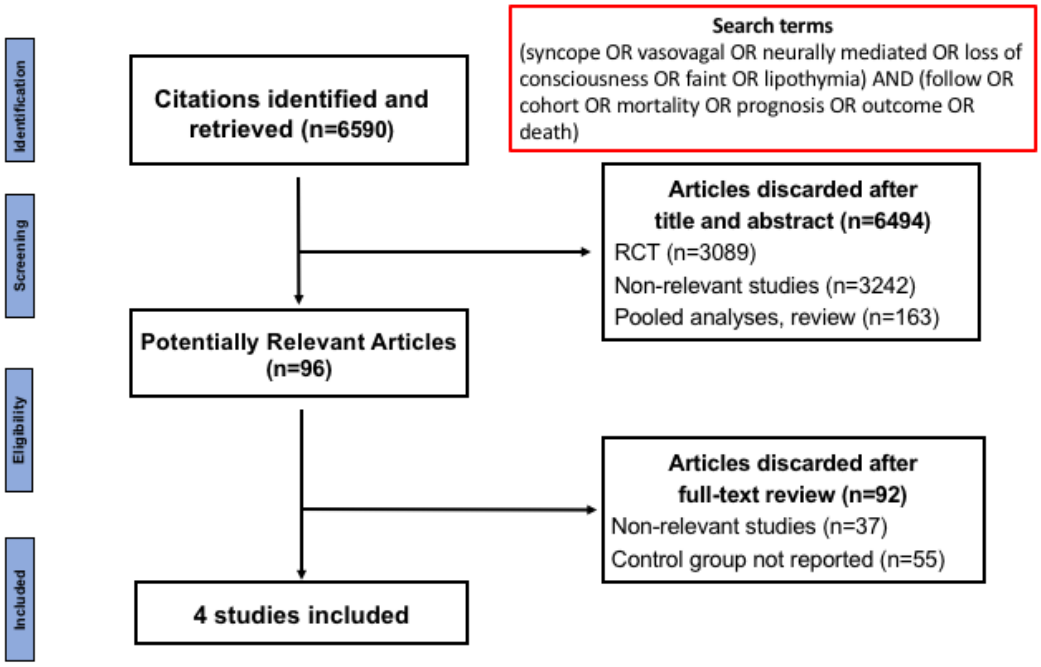

Figure 2. All-cause mortality in patients with and without history of non-cardiac syncope in the general population. FHS(3): hazard ratio adjusted for age, sex, smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, total cholesterol level, heart rate, reported use or nonuse of cardiac medications (including antihypertensive medications), and presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke, congestive heart failure, atrial fibrillation, and intermittent claudication). DNPR(10): hazard ratio adjusted

for age, sex, comorbidities (hypertension, ischemic heart disease, cerebral vascular disease, previous myocardial infarction. cardiac conduction disorders, cardiac arrhythmia, previous atrial fibrillation, heart failure or pulmonary edema, diabetes, acute or chronic renal failure, COPD, cancer, liver disease) and concomitant pharmacotherapy. MPP(9): hazard ratio adjusted for age, sex, BMI, smoking, hypertension, diabetes, triglycerides, total cholesterol, history of cancer, atrial fibrillation, glomerular filtration rate, orthostatic hypotension, antihypertensive medications. MDC(8): hazard ratio adjusted for age, sex, BMI, smoking, diabetes, use of hypolipidaemic agents, systolic blood pressure, antihypertensive medications. DNPR, Danish National Patient Register; FHS, Framingham, Framingham Heart Study; MDCS, Malmö Diet and Cancer Study; MPP, Malmö Preventive Project; CI=confidence interval; IV=inverse variance; SE=standard error.

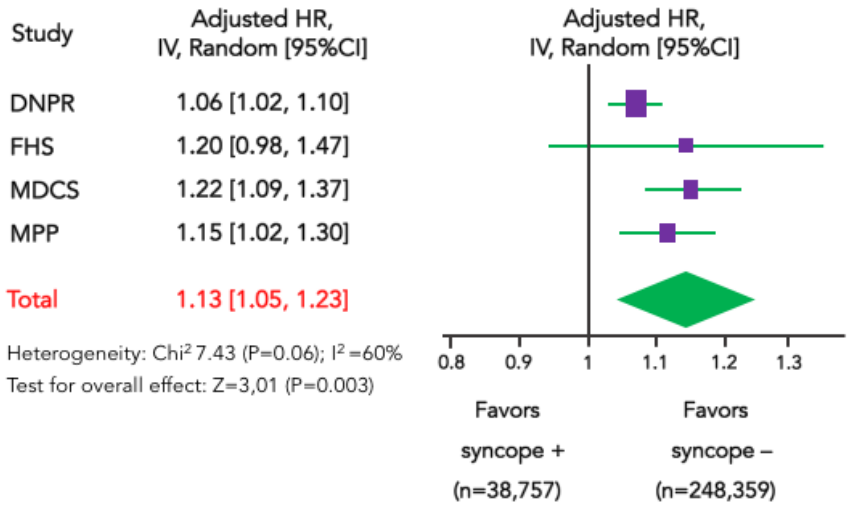

Table 1. Baseline characteristics of the included studies.

Author, year (study cohort)	Country	Study Design	Syncope (total sample size) N(n)	Follow-up overall/ after syncope (years)	Mean age at index event	Male sex (%)	CVD (%)	DM (%)	HTN (%)	Syncope definition	Study quality
Soteriades, 2002 (FHS)	U.S.	Population-based prospective cohort study with non-randomised control group	584 (2,038)	17/8.3	66	42	27	6.5	57.9	Unknown aetiology and vaso-vagal syncope (including orthostatic, medication-related and syncope due to other, infrequent causes)	7
Ruwald, 2013 (DNPR)	Denmark	Population-based prospective cohort study with non-randomised control group	37,017 (222,102)	4.5/4.5	48.5	53	0	2.5	7.9	First-time hospitalisation or ED visit for syncope when classified as the primary discharge diagnosis (ICD-10 code R55.9)	9

Ricci, 2017 (MPP)	Sweden	Population-based prospective cohort study with non-randomised control group	632 (32,628)	26.6/2.0	72	68	0	5.7	51.6	First-time hospitalisation syncope based on primary or main secondary discharge diagnoses according to the ICD-9/10 system (ICD-9 code 780.2 and ICD-10 code R55.9)	9
Yasa, 2017 (MDCS)	Sweden	Population-based prospective cohort study with non-randomised control group	524 (30,528)	15/2.7	74	40	0	3.5	61.4	First-time hospitalisation syncope based on primary or main secondary discharge diagnoses according to the ICD-9/10 system (ICD-9 code 780.2 and ICD-10 code R55.9)	9

CVD=cardiovascular disease; DM=diabetes mellitus; DNPR=Danish National Patient Register; HTN=hypertension; ICD=International Classification of Disease; MDC=Malmö Diet and Cancer Study; MPP=Malmö Preventive Project.

Table 2. Leave-one-out sensitivity analysis

Study cohort	Adjusted hazard ratio (95%CI)
Omitting FHS	1.13 (1.03-1.23)
Omitting DNPR	1.19 (1.10-1.27)
Omitting MPP	1.14 (1.01-1.26)
Omitting MDCS	1.10 (1.02-1.17)
Overall	**1.13 (1.05-1.23)**

DNPR=Danish National Patient Register; FHS=Framingham Heart Study; MDC=Malmö Diet and Cancer Study; MPP=Malmö Preventive Project

Table 3. Univariable meta-regression analysis: impact of study-level covariates on the association between syncope and all-cause death.

Study covariate	All-cause mortality		
	Coefficient	95%CI	p-value
Mean age (years)	0.005	0.001-0.009	**0.008**
Diabetes (%)	0.036	0.001-0.070	**0.041**
Male sex (%)	0.002	-0.006-0.009	0.680
Hypertension (%)	0.003	0.001-0.005	**0.006**
Previous CVD (%)	0.003	-0.006-0.012	0.498
Mean follow-up (years)	-0.006	-0.046-0.034	0.770

CI=confidence interval; CVD=cardiovascular disease