

INCIDENCE AND PROGNOSIS OF SYNCOPE

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ABSTRACT

Background Little is known about the epidemiology and prognosis of syncope in the general population.

Methods We evaluated the incidence, specific causes, and prognosis of syncope among women and men participating in the Framingham Heart Study from 1971 to 1998.

Results Of 7814 study participants followed for an average of 17 years, 822 reported syncope. The incidence of a first report of syncope was 6.2 per 1000 person-years. The most frequently identified causes were vasovagal (21.2 percent), cardiac (9.5 percent), and orthostatic (9.4 percent); for 36.6 percent the cause was unknown. The multivariable-adjusted hazard ratios among participants with syncope from any cause, as compared with those who did not have syncope, were 1.31 (95 percent confidence interval, 1.14 to 1.51) for death from any cause, 1.27 (95 percent confidence interval, 0.99 to 1.64) for myocardial infarction or death from coronary heart disease, and 1.06 (95 percent confidence interval, 0.77 to 1.45) for fatal or nonfatal stroke. The corresponding hazard ratios among participants with cardiac syncope were 2.01 (95 percent confidence interval, 1.48 to 2.73), 2.66 (95 percent confidence interval, 1.69 to 4.19), and 2.01 (95 percent confidence interval, 1.06 to 3.80). Participants with syncope of unknown cause and those with neurologic syncope had increased risks of death from any cause, with multivariable-adjusted hazard ratios of 1.32 (95 percent confidence interval, 1.09 to 1.60) and 1.54 (95 percent confidence interval, 1.12 to 2.12), respectively. There was no increased risk of cardiovascular morbidity or mortality associated with vasovagal (including orthostatic and medication-related) syncope.

Conclusions Persons with cardiac syncope are at increased risk for death from any cause and cardiovascular events, and persons with syncope of unknown cause are at increased risk for death from any cause. Vasovagal syncope appears to have a benign prognosis. (N Engl J Med 2002;347:878-85.)

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SYNCOPE, defined as a sudden loss of consciousness associated with the inability to maintain postural tone, followed by spontaneous recovery, is relatively common. However, the epidemiology and prognosis of syncope in the community have not been well described. Data are limited on the cumulative incidence^{1,2} and lifetime prevalence³⁻⁷ of syncope.

Although syncope has many possible causes, several studies have used three categories of cause — cardiac, noncardiac, and unknown — to examine the prognosis of syncope prospectively.⁸ Previous studies of syncope were conducted in emergency departments,⁹⁻¹² in general hospitals,¹³⁻¹⁷ and among highly selected subgroups of patients with syncope of unknown cause.¹⁸⁻²⁷ Little is known about the prognosis of syncope due to specific causes in the general population. We conducted a study to evaluate the incidence and prognosis of syncope due to specific causes among participants in the Framingham Heart Study.

METHODS

Study Sample

The study sample consisted of participants in the original Framingham Heart Study and in the Framingham Offspring Study who underwent routine clinical examinations between 1971 and 1998. The details of the study design and selection criteria have been described elsewhere.^{28,29} We examined all reports of syncope in study participants undergoing a qualifying clinical examination. Syncope reports were coded as “yes,” “no,” or “maybe.” A committee of physicians reviewed all episodes coded as “maybe.” Possible episodes of syncope were coded as definite only if the participant’s chart contained additional medical information confirming a syncopal event that had not been available at the time of the initial clinical evaluation. We excluded 120 equivocal reports of syncope, 101 reports of syncope from participants who had not had an examination within four years before the index report (to minimize possible recall bias), 47 reports of syncope due to head trauma, and 7 reports of syncope with incomplete records. All participants undergoing examination in the Framingham Heart Study provided written informed consent; the content and procedures of the examinations were reviewed and approved by the institutional review board of Boston Medical Center.

Incidence

The overall incidence rate of syncope and the incidence rates for syncope with specific causes were calculated by dividing the number of participants with syncope by the total number of person-years of follow-up in each subgroup. For the calculation of incidence rates in different age groups, we categorized participants according to their age halfway between the time of the clinical examination preceding the report of syncope and the time of the index examination for syncope. We calculated the cumulative in-

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cidence by assuming a constant incidence over time, using the following formula:

$$\text{cumulative incidence} = 1 - e^{-I\Delta t},$$

where e is the natural logarithm constant (2.718), I denotes the incidence rate, and Δt denotes the duration of follow-up.

Causes of Syncope

The cause of syncope was assigned according to a clinical diagnosis made by two physicians (an internist and a cardiologist) on the basis of documentation provided by the examining Framingham Heart Study physician and information obtained during routine clinic visits from the medical history, physical examination, and electrocardiographic examination. In addition, the physicians reviewed all available hospital and outpatient medical records pertaining to each instance of syncope. Generally, the discharge diagnosis was used for participants evaluated at an outside hospital, as long as this diagnosis was supported by associated records. For other participants, the diagnosis of the examining Framingham Heart Study physician was used. If a cardiovascular cause was suspected, a second evaluation was performed by another Framingham Heart Study physician. If these evaluations did not agree, the physician reviewers evaluated available data to assign a cause.

Reports of syncope were classified into eight categories according to cause: cardiac cause (including ischemia and arrhythmias), unknown cause, stroke or transient ischemic attack, seizure disorder, vasovagal cause, orthostatic cause, medication, and other, infrequent causes (including cough syncope, micturition syncope, and situational syncope). These eight categories were reduced to four etiologic categories for the outcome analysis: cardiac cause, unknown cause, neurologic cause (including syncope due to stroke, transient ischemic attack, and seizure), and vasovagal or other cause (including vasovagal syncope, orthostatic syncope, medication-induced syncope, and syncope due to other identified causes). Secondary analyses were also performed after we excluded syncope due to seizure from the category of neurologic syncope. When a participant did not seek medical attention for syncope and the history, physical examination, and electrocardiographic findings were not indicative of any of the specific causes, the cause was classified as unknown. The physicians who confirmed the diagnoses of syncope and assigned the causes were unaware of subsequent outcomes.

Recurrence of Syncope

The first episode of syncope reported by a participant during a clinical examination was treated as the first syncopal event. If more than one syncopal event was reported between clinic visits, we counted only one episode of syncope. Episodes reported at subsequent clinical examinations were considered recurrences of syncope.

End Points

The participants in the follow-up sample were followed for up to 25 years. A prospective cohort design was used to study three outcomes in relation to syncope: death from any cause, myocardial infarction or death from coronary heart disease (which included both sudden and nonsudden death from coronary heart disease), and fatal or nonfatal stroke. All outcome events were reviewed with the use of all pertinent available medical records and adjudicated on the basis of previously published criteria.³⁰ Data from 95 participants who reported syncope during their last index examination were excluded from the outcome analysis, because no follow-up data were available for them. For each participant with syncope, we randomly selected two participants without syncope who underwent clinical examination at the Framingham Heart Study clinic during the same examination cycle, matched according to age and sex.

Statistical Analysis

All statistical analyses were performed with SAS software (version 6.12).³¹ The age-, sex-, and category-specific incidence rates of syn-

cope were computed. The survival rates among participants with syncope due to specific causes were examined with Kaplan–Meier survival curves.³² Age- and multivariable-adjusted Cox proportional-hazard regression models³³ were used to analyze the risk of each outcome of interest among participants with cause-specific syncope (four etiologic categories) as compared with participants without syncope. We evaluated the outcomes of interest by using dummy variables for each of the four etiologic categories. Multivariable models were adjusted for age, sex, presence or absence of a history of cardiovascular disease (myocardial infarction, coronary heart disease, stroke or transient ischemic attack, congestive heart failure, atrial fibrillation, and intermittent claudication), smoking status, presence or absence of hypertension, systolic blood pressure, presence or absence of diabetes, total cholesterol level, heart rate, and use or nonuse of cardiac medication, including antihypertensive medications. Hypertension was a dichotomous variable defined as a systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or current use of antihypertensive medication. The presence or absence of a history of cardiovascular disease, smoking status, presence or absence of diabetes, use or nonuse of cardiac medication, and normal or elevated total cholesterol level (with an elevated level defined as at least 200 mg per deciliter [5.2 mmol per liter]) were also included in the model as dichotomous variables. Age, systolic blood pressure, and heart rate were included as continuous variables.

RESULTS

We followed 7814 participants (3563 men and 4251 women) for an average of 17.0 years (median, 19.1; interquartile range, 10.6 to 23.6) during 133,164 person-years of follow-up. The participants had a mean (\pm SD) age of 51.1 ± 14.4 years (range, 20 to 96). A total of 822 participants (348 men and 474 women; mean age, 65.8 years) reported syncope. After excluding participants without follow-up (those whose first episode of syncope was reported at the last index examination), we included 727 participants in the outcome analysis.

Incidence

The overall incidence rate of a first report of syncope was 6.2 per 1000 person-years. The incidence rates increased with age, with a sharp rise at 70 years (Fig. 1). The age-adjusted incidence was 7.2 per 1000 person-years among both men and women. The age-adjusted incidence rate among participants with cardiovascular disease was nearly twice that among participants without cardiovascular disease (10.6 vs. 6.4 per 1000 person-years). The incidence rates of first reports of cardiac syncope, syncope of unknown cause, syncope due to stroke or transient ischemic attack, syncope due to seizure, vasovagal syncope, orthostatic syncope, medication-induced syncope, and syncope of other causes were 0.59, 2.26, 0.26, 0.30, 1.31, 0.58, 0.42, and 0.47 per 1000 person-years, respectively. Assuming a constant incidence rate over time, we calculated a 10-year cumulative incidence of syncope of 6 percent.

Causes of Syncope

The distributions of causes in men and women, respectively, were as follows: cardiac causes (13.2 per

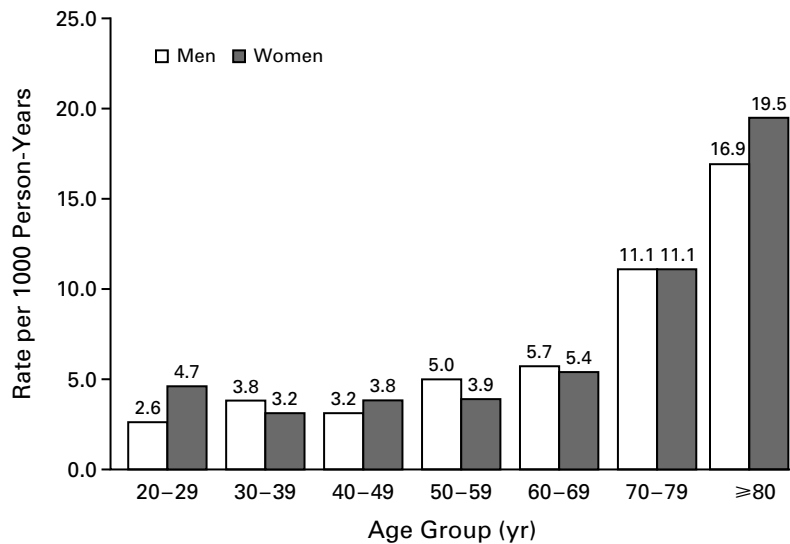


Figure 1. Incidence Rates of Syncope According to Age and Sex.

The incidence rates of syncope per 1000 person-years of follow-up increased with age among both men and women. The increase in the incidence rate was steeper starting at the age of 70 years. Syncope rates were similar among men and women.

cent and 6.7 percent), unknown cause (31.0 percent and 40.7 percent), stroke or transient ischemic attack (4.3 percent and 4.0 percent), seizure disorder (7.2 percent and 3.2 percent), vasovagal cause (19.8 percent and 22.2 percent), orthostatic cause (8.6 percent and 9.9 percent), medication (6.3 percent and 7.2 percent), and other causes (9.5 percent and 6.1 percent). The causes of syncope according to cardiovascular disease status at base line are shown in Table 1. Overall, 56 percent of participants with a syncopal episode reported seeing a doctor or visiting a hospital for evaluation.

Recurrence of Syncope

Five hundred seventy participants (78.4 percent) reported only one episode of syncope. One hundred fifty-seven participants (21.6 percent) reported one or more recurrences of syncope (17.6 percent reported one recurrence, 3.3 percent two recurrences, and 0.7 percent three or more recurrences). The rate of recurrence among participants with a history of syncope was higher than the incidence of a first episode of syncope among those without such a history (multivariable-adjusted hazard ratio, 23.2; 95 percent confidence interval, 14.2 to 37.9). The risk of recurrence was especially high among participants with cardiac syncope (multivariable-adjusted hazard ratio, 30.0; 95 percent confidence interval, 14.9 to 60.3).

Follow-up

The characteristics of the 2181 study participants who were eligible for follow-up are shown in Table 2. As compared with those without syncope, participants with syncope of any cause, and in particular those with cardiac syncope, were more likely to have a history of coronary artery disease or cerebrovascular disease and to take cardiac or antihypertensive medications. During a mean follow-up of 8.6 years (median, 7.7), there were 847 deaths from all causes, 263 myocardial infarctions or deaths from coronary heart disease, and 178 fatal or nonfatal strokes.

Participants with cardiac syncope had lower survival than those without syncope, as shown by Kaplan-Meier survival curves (Fig. 2). Multivariable-adjusted Cox proportional-hazard regression models showed that the risk of death was increased by 31 percent among all participants with syncope and was doubled among participants with cardiac syncope, as compared with those without syncope. Syncope of unknown cause and neurologic syncope were associated with an increased risk of death from any cause, and neurologic syncope was also associated with a three-fold risk of stroke (Table 3). Vasovagal syncope (including orthostatic syncope, medication-related syncope, and syncope due to other, infrequent causes) was not associated with an increased risk of any of the major outcomes.

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TABLE 1. CAUSES OF SYNCOPE ACCORDING TO SEX AND THE PRESENCE OR ABSENCE OF CARDIOVASCULAR DISEASE AT BASE LINE.

CAUSE	CARDIOVASCULAR DISEASE ABSENT (N=599)		CARDIOVASCULAR DISEASE PRESENT (N=223)		TOTAL SAMPLE (N=822)
	MEN (N=232)	WOMEN (N=367)	MEN (N=116)	WOMEN (N=107)	
	percent of subjects				
Cardiac	6.5	3.8	26.7	16.8	9.5
Unknown*	31.0	41.7	31.0	37.4	36.6
Stroke or transient ischemic attack	1.7	2.5	9.5	9.4	4.1
Seizure	7.3	3.3	6.9	2.8	4.9
Vasovagal	24.1	24.5	11.2	14.0	21.2
Orthostatic	9.5	10.9	6.9	6.5	9.4
Medication	7.3	6.5	4.3	9.4	6.8
Other†	13.0	6.8	3.5	3.7	7.5

*When a participant did not seek medical attention for syncope and the history, physical examination, and electrocardiographic findings were not consistent with any of the specific causes, the cause was considered to be unknown.

†Cough syncope, micturition syncope, and situational syncope were included in the category of other causes.

TABLE 2. CHARACTERISTICS OF THE FOLLOW-UP SAMPLE.

CHARACTERISTIC	PARTICIPANTS WITH SYNCOPE				TOTAL (N=727)	PARTICIPANTS WITHOUT SYNCOPE (N=1454)
	CARDIAC CAUSE (N=71)*	UNKNOWN CAUSE (N=272)	NEUROLOGIC CAUSE (N=72)	VASOVAGAL OR OTHER CAUSE (N=312)†		
Mean age (yr)	71.1	68.5	67.2	62.2	65.9	65.9
Female sex (%)	40.9	65.1	44.4	58.0	57.6	57.6
Smoking (%)	16.9	18.4	34.7	20.8	20.9	18.2
Hypertension (%)	78.9	63.6	52.8	53.9	59.8	57.8
Diabetes (%)	7.0	4.4	9.7	6.7	6.2	6.9
Mean body-mass index‡	26.2	26.0	25.4	25.9	25.9	26.3
History of myocardial infarction or coronary heart disease (%)	36.6	9.6	11.1	5.8	10.7	7.6
History of stroke or transient ischemic attack (%)	11.3	8.8	38.9	6.1	10.9	5.0
Use of antihypertensive medications (%)	60.6	45.6	38.9	36.2	42.4	36.1
Use of other cardiac medications (%)	49.3	18.4	18.1	14.1	19.5	11.8
History of atrial fibrillation (%)	18.3	7.0	11.1	3.5	7.0	3.8
Intraventricular heart block (%)	18.3	5.9	8.3	6.7	7.7	6.3

*Cardiac syncope was attributed to arrhythmia in 36 participants (50.7 percent), myocardial ischemia or infarction in 22 (31.0 percent), cardiac arrest in 6 (8.5 percent), aortic stenosis or other valvular disease in 5 (7.0 percent), hypertensive crisis in 1, and carotid-sinus syncope in 1.

†This category includes vasovagal, orthostatic, medication-induced, and other, infrequent causes of syncope.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

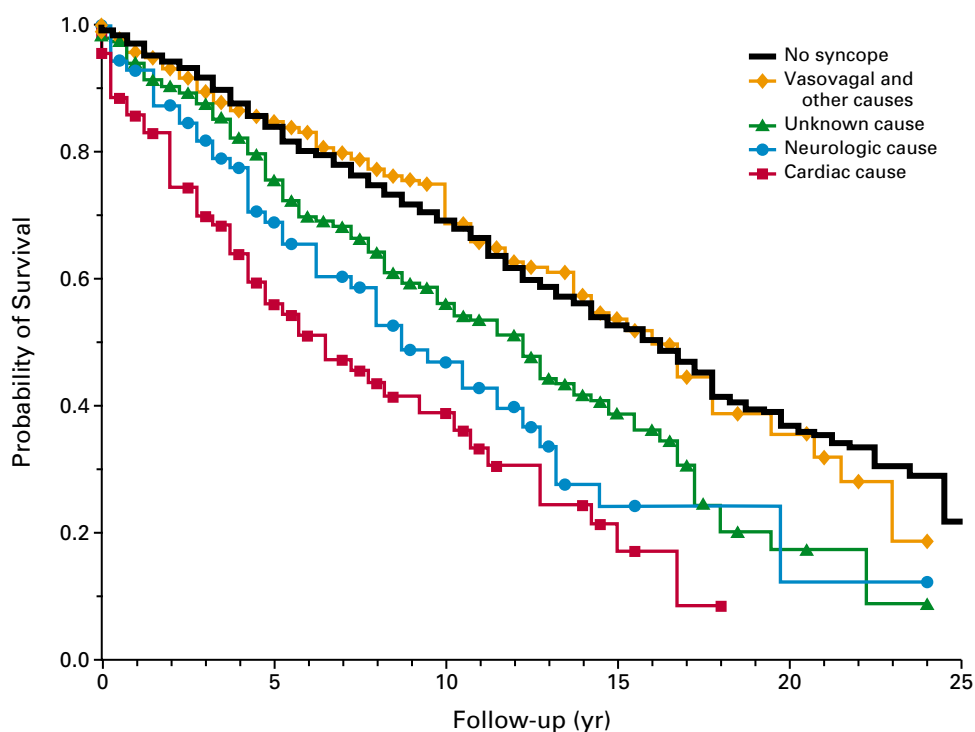


Figure 2. Overall Survival of Participants with Syncope, According to Cause, and Participants without Syncope.

$P < 0.001$ for the comparison between participants with and those without syncope. The category “Vasovagal and other causes” includes vasovagal, orthostatic, medication-induced, and other, infrequent causes of syncope.

Secondary analyses were also performed to examine the relations of cause-specific syncope to the outcomes of interest after exclusion of data from 40 participants who had syncope due to seizures. The findings were similar to the results shown in Table 3, except that the association between neurologic syncope and death from any cause was no longer statistically significant (hazard ratio, 1.24; 95 percent confidence interval, 0.81 to 1.89).

Because cardiac syncope might have been preferentially diagnosed in participants with syncope who were already known to have cardiovascular disease, we also performed secondary analyses stratified according to the presence or absence of known cardiovascular disease. The results were similar in the two groups (data not shown). In addition, to address the possibility that syncope of unknown cause might have been associated with poor outcomes because persons with this diagnosis received a different level of medical care, we performed analyses stratified according to whether the participant sought or did not seek medical care for the syncopal event (130 and 131 participants, respectively). The data from 11 participants were excluded

from this analysis because information on whether they sought medical care was not available. As compared with participants without syncope, participants with this diagnosis who sought medical care had a higher risk of death from any cause (multivariable-adjusted hazard ratio, 1.47; 95 percent confidence interval, 1.14 to 1.90), although their risk of myocardial infarction or death from coronary heart disease was not significantly elevated (adjusted hazard ratio, 1.07; 95 percent confidence interval, 0.63 to 1.83). Participants with syncope of unknown cause who did not seek medical care had a higher risk of myocardial infarction or death from coronary heart disease (adjusted hazard ratio, 1.60; 95 percent confidence interval, 1.04 to 2.48), but their risk of death from any cause was not significantly elevated (adjusted hazard ratio, 1.23; 95 percent confidence interval, 0.94 to 1.60).

DISCUSSION

In this population-based study, we found a similar incidence of syncope in men and women. The incidence was almost doubled in participants with a history of cardiovascular disease. Mortality was about 30

TABLE 3. HAZARD RATIOS FOR THE OUTCOMES OF INTEREST IN PARTICIPANTS WITH SYNCOPE AS COMPARED WITH PARTICIPANTS WITHOUT SYNCOPE.

CAUSE OF SYNCOPE	HAZARD RATIO (95% CONFIDENCE INTERVAL)	
	ADJUSTED FOR AGE AND SEX	MULTIVARIABLE- ADJUSTED*
Any cause		
Death from any cause	1.43 (1.25–1.64)†	1.31 (1.14–1.51)†
Myocardial infarction or death from coronary heart disease	1.47 (1.15–1.88)‡	1.27 (0.99–1.64)
Fatal or nonfatal stroke	1.19 (0.87–1.62)	1.06 (0.77–1.45)
Cardiac		
Death from any cause	2.41 (1.78–3.26)†	2.01 (1.48–2.73)†
Myocardial infarction or death from coronary heart disease	3.56 (2.29–5.55)†	2.66 (1.69–4.19)†
Fatal or nonfatal stroke	2.67 (1.43–4.98)‡	2.01 (1.06–3.80)§
Unknown		
Death from any cause	1.36 (1.13–1.65)‡	1.32 (1.09–1.60)‡
Myocardial infarction or death from coronary heart disease	1.43 (1.00–2.03)§	1.31 (0.92–1.86)
Fatal or nonfatal stroke	0.72 (0.43–1.22)	0.66 (0.39–1.11)
Neurologic (including seizure)		
Death from any cause	1.98 (1.45–2.72)†	1.54 (1.12–2.12)‡
Myocardial infarction or death from coronary heart disease	1.02 (0.48–2.17)	0.79 (0.37–1.69)
Fatal or nonfatal stroke	3.12 (1.82–5.36)†	2.96 (1.69–5.18)†
Vasovagal or other¶		
Death from any cause	1.17 (0.95–1.44)	1.08 (0.88–1.34)
Myocardial infarction or death from coronary heart disease	1.16 (0.80–1.68)	1.03 (0.71–1.49)
Fatal or nonfatal stroke	0.93 (0.57–1.52)	0.87 (0.54–1.42)

*The values are 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).

†P<0.001.

‡P<0.01.

§P<0.05.

¶This category includes vasovagal, orthostatic, medication-induced, and other, infrequent causes of syncope.

percent higher among all participants with syncope and among those with syncope of unknown cause than among those without syncope; this increase was due largely to an increased risk of death from myocardial infarction or coronary heart disease. Cardiac syncope doubled the risk of death from any cause and increased the risk of fatal and nonfatal cardiovascular events. Neurologic syncope was associated with an increased risk of death from any cause and an increased risk of stroke.

Although the incidence of syncope rose sharply with advancing age, the age-specific annual incidence of syncope for those above 80 years of age in our study (about 2 percent) was considerably lower than that reported by Lipsitz et al. (6 percent) in an elderly institutionalized population (mean age, 87 years).¹ Overall, 37 percent of syncopal events in our sample were due to unknown causes. The distribution of causes of syncope that we observed is similar to that reported elsewhere.^{34,35} For example, Linzer et al. reported that, on average, 34 percent of syncopal episodes could not be assigned to an etiologic category after a standard evaluation with a detailed history taking, physical examination, and electrocardiography.³⁶

Our findings are consistent with those of Kapoor¹⁵ in suggesting that cardiac syncope is associated with increased risks of premature death and cardiovascular events. Whether or not there was a history of cardiovascular disease, we found that participants with a diagnosis of cardiac syncope were more likely to have a poor outcome than those without syncope.

Several other studies have evaluated the outcome of syncope of unknown cause.^{18–27} The results suggested that among subjects with syncope that was initially classified as being of unknown cause and that was later found to have a cardiac cause, the risk of death was higher than in the general population. Electrophysiological studies and electrocardiographic monitoring in highly selected subgroups of patients^{37–41} have suggested that 45 to 80 percent of cases of syncope classified as being of unknown cause could be assigned a cardiac cause. It is likely that many participants in our study with syncope of unknown cause had unrecognized cardiac syncope, with its attendant risk of an adverse outcome.

Participants with syncope of neurologic cause had more than twice as high a risk of fatal or nonfatal stroke as subjects without syncope. The increased risk

is probably attributable to a high risk of stroke, often recurrent, in participants with neurologic syncope who had preexisting cerebrovascular disease.

Among participants with syncope of identified cause, by far the largest subgroup consisted of those with syncope of vasovagal or other causes, including orthostatic and medication-induced syncope. Among these participants we found no increase in the risk of death from any cause or in the risk of myocardial infarction or death from coronary heart disease, in comparison to those without syncope, even though the statistical power to detect such increases was high (96 percent power to detect a 50 percent increase in the risk of death from any cause; 84 percent power to detect a 75 percent increase in the risk of myocardial infarction or death from coronary heart disease).

This study involved a population-based sample free of selection bias and an extensive period of follow-up. However, some limitations should be noted. We attempted to minimize misclassification of participants according to whether or not they had previously had an episode of syncope by excluding those who had not undergone a clinical examination within four years before an examination at which they reported syncope. However, a four-year interval may constitute a long recall period, especially for older patients. Differential recall bias is unlikely to have affected our findings, because our prospective cohort design ensured that exposures were ascertained before the outcomes. Problems with recall, however, may have contributed to underestimation of the incidence of syncope and hazard ratios for adverse outcomes associated with this diagnosis.⁴²

Another concern is possible misclassification of participants according to etiologic categories of syncope.⁴³ Although we did not develop explicit criteria for confirming a given cause of syncope, we sought to minimize misclassification by having diagnoses assigned by the consensus of two physician reviewers, unaware of the study outcomes, who reviewed all related outside records and Framingham Heart Study examination records. The presence of other risk factors for cardiovascular disease or the presence of cardiovascular disease may have contributed to cardiovascular risk among participants with syncope, but our findings persisted after we adjusted for these factors in multivariable models and in secondary analyses stratified according to the presence or absence of known cardiovascular disease. Finally, our study sample consisted almost entirely of middle-aged and older white men and women, and thus the results may not be generalizable to other populations.

Our findings suggest that persons with cardiac syncope constitute a high-risk group predisposed to morbidity and premature mortality from cardiovascular disease who should be monitored closely. Persons with

syncope of unknown cause appear to constitute a mixed group at increased risk for death; this result suggests that further diagnostic testing may be warranted in these patients. The increased risk of stroke in participants with neurologic syncope may be attributable to preexisting cerebrovascular disease. Our results also provide reassurance that vasovagal syncope has a benign prognosis.

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