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Circadian, weekly, seasonal, and temperature-dependent patterns of syncope aetiology in patients at increased risk of cardiac syncope

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Aims It is unknown whether cardiac syncope, and possibly also other syncope aetiologies exhibit circadian, weekly, seasonal, and temperature-dependent patterns.

Methods and results We prospectively recorded the exact time, date, and outside temperature of syncope of patients >40 years old presenting with syncope to the emergency department in a diagnostic multicentre study. Two independent cardiologists/emergency physicians adjudicated the final diagnosis based on all information becoming available during clinical work-up including 1-year follow-up. Among 1230 patients, the adjudicated aetiology was cardiac in 14.6%, reflex in 39.2%, orthostatic in 25.7%, other non-cardiac in 9.7%, and unknown in 10.8% of patients. All syncope aetiologies occurred much more frequently during the day when compared with the night ($P < 0.01$). While reflex and orthostatic syncope showed a broad peak of prevalence with 80.9% of these events occurring between 4 am and 4 pm, cardiac syncope showed a narrow peak of prevalence with 70.1% of all events occurring between 8 am and 2 pm. A weekly pattern was present for most syncope aetiologies, with events occurring mainly from Monday to Friday ($P < 0.01$). Reflex syncope displayed a seasonal rhythm and was more common in winter ($P < 0.01$), while cardiac syncope stayed constant over the year. Syncope occurred most often when the outside temperature was coldest. Overall the patterns observed for cardiac syncope were similar to the patterns observed for its differential diagnosis.

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Conclusion Syncope aetiologies in patients >40 years old display circadian, weekly, seasonal, and temperature-dependent patterns. Unfortunately, these patterns do not allow to reliably differentiate cardiac syncope from other aetiologies.

Keywords Cardiac syncope • Circadian pattern • Weekly • Seasonal • Temperature • Diagnosis

What's new?

- It is unknown whether cardiac syncope, and possibly also other syncope aetiologies exhibit circadian, weekly, seasonal, and temperature-dependent patterns.
- This multicentre, international prospective diagnostic study shows that all syncope aetiologies are more common during the day and less common on the weekends.
- Patients with cardiac syncope present on the emergency department (ED) mainly between 8 am and 2 pm.
- Cardiac syncope does not seem to display any seasonal or temperature-dependent rhythm.
- Reflex and orthostatic syncope were less common during the summer and their incidence increase with decreasing outside temperature.
- These novel findings regarding circadian, weekly, seasonal, and temperature-dependent patterns may contribute to a better understanding of syncope pathophysiology as well to improved management strategies in the ED.

Introduction

Syncope is defined as a transient loss of consciousness attributable to global cerebral hypoperfusion, further characterized by rapid onset, brevity, and spontaneous recovery.[1] It is a common and challenging problem in the emergency department (ED).[2,3] In the United States, about 40% of patients with syncope are subsequently admitted for further investigation at an annual cost of $2.4 billion according to the Medicare database.[4] Early detection of the underlying aetiology is important for the initiation of risk-adjusted management including hospitalization, continuous rhythm monitoring, and specific treatments including pacemaker implantation, defibrillator implantation, coronary revascularization, and aortic valve replacement for cardiac syncope, and outpatient management with patient education and reassurance for most other aetiologies.[1]

In the ED, the ability of clinicians to rapidly identify the underlying cause of syncope is often limited by scant patient recall, absence of witnesses, the paroxysmal nature of cardiac arrhythmias, and time pressure. As a result, the aetiology of syncope remains unclear in up to 59% of patients after standard ED work-up.[5]

Circadian, weekly, seasonal, and temperature-dependent patterns have been observed for some cardiovascular events including cardiac arrhythmias, sudden cardiac death, and acute myocardial infarction (AMI).[6,7] Most of the events have been found to peak during the morning hours[8,9] in colder months,[6,7] and more commonly on Mondays.[7,10–12] Whether cardiac syncope or other syncope aetiologies exhibit similar patterns is largely unknown. Knowledge of such patterns could provide novel insights into the pathophysiology of syncope.

We, therefore, performed a large international diagnostic study to prospectively assess the presence of circadian, weekly, seasonal, and temperature-dependent patterns of cardiac syncope and other syncope aetiologies in patients older than 40 years old presenting with syncope to the ED.

Methods

Study design, setting, and selection of patients

*BA*sel Syncope *EvaL*uation Study (BASEL IX) is an ongoing prospective international diagnostic multicentre study enrolling patients presenting with syncope to the ED in thirteen hospitals in eight countries (Switzerland, Spain, Germany, Italy, Poland, New Zealand, Australia, and the United States) on three continents. The study is designed to contribute to improving the management of patients with syncope (ClinicalTrials.gov registry, number NCT01548352).[13] Patients aged more than 40 years presenting to the ED with syncope within the last 12 h were recruited, after written informed consent was obtained. The large time-window for recruitment enabled the enrolment of patients presenting to the ED during the night still in the next morning, as most participating institutions did not have research staff available during the night. The exact time of syncope was prospectively recorded. Patients were excluded if they presented to the ED later than 12 h after the syncopal event, if they did not lose consciousness, if a stroke, a hypoglycaemia, an alcohol intoxication or an epileptic crisis were diagnosed with certainty upon arrival on the ED and if patients had a haemoglobin levels <90 g/L.

For the analysis of the circadian 24 h-pattern, patients without documented time of syncope were excluded. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy (see Supplementary material online, *Appendix*), vouch for the data and analysis, wrote the paper, and decided to publish.

Clinical assessment, follow-up, and adjudicated final diagnosis

All patients underwent a clinical assessment that included standardized and detailed assessment of predefined details as listed in the Supplementary material online, *Appendix*.

Patients were contacted 6, 12, and 24 months after discharge and all available information was collected. To determine the final diagnosis for the index syncope in each patient, two independent cardiologists/emergency medicine experts reviewed all available medical records from the clinical data set and the study specific data set after at least 12 months of follow-up. In situations of diagnostic disagreement between adjudicators, cases were reviewed and adjudicated in conjunction with a third cardiologist. Predefined diagnostic categories for adjudication included cardiac syncope, reflex syncope, orthostatic syncope, other non-cardiac syncope, and unknown cause of syncope. Further details regarding the methods are available in the Supplementary material online, *Appendix*.

Time periods

Patients and witnesses were asked about the exact time at which the syncope occurred. The 24 h-day was divided into twelve 2-h periods for graphical representations and in four 6-h periods (8 am to 2 pm, 2 pm to 8 pm, 8 pm to 2 am, and 2 am to 8 am) for statistical analysis of the circadian pattern. Patients' characteristics, assessment of diagnostic uncertainty and logistic regressions were compared between two 12-hour periods, representing on the one hand the day (8 am to 8 pm) and on the other hand the night (8 pm to 8 am).

Weekly and seasonal pattern

The date of the event was recorded and matched to the corresponding weekday and season. Seasons were defined as 3-month periods according to the hemisphere the study centres are located in e.g. June, July, and August were defined as summer for the study centres in the Northern Hemisphere and as winter for the study centres in the Southern Hemisphere, while December, January, and February were defined as winter for the Northern Hemisphere and summer for the Southern Hemisphere.

Temperature data

Hourly meteorological data were purchased from a global weather simulation archive (MeteoBlue History+) for all centres and for the whole duration of the study.

Outcome measures

The primary objective of this study was to test the hypothesis that cardiac syncope displays a circadian, weekly, seasonal, and temperature-related pattern. Secondary objectives included the description of differences in patient characteristics as well as the assessment of diagnostic uncertainty regarding the diagnosis of cardiac syncope during the night and during the fall/winter time.

Statistical analysis

The frequency distributions of each aetiology per 6-h, day of the week, season, or temperature quintile were compared with a theoretical uniform occurrence (25% of total events per 6-h blocks or per season, 14.3% on each day of the week, 20% over each temperature quintile) by a χ^2 goodness-of-fit test to assess the presence of daily, weekly, or seasonal variations for each aetiology.

Theoretical homogenous occurrence ratios were calculated assuming a constant proportion of cardiac, vasovagal, and reflex syncope over the course of a day, a week and the four seasons. These theoretical occurrence ratios were then compared with the true occurrence ratios for every 2-h block of the day, every weekday, and every season using a binomial test.

All hourly temperatures recorded from the very first (05 November 2010) to the last patient (11 November 2015) available for analysis were divided into centre-specific quintiles (Supplementary material online, *Table S1*) to assess temperature intervals occurring with equal frequency during the time of observation at each centre.

Triggered by recent concerns that diagnostic uncertainty may be higher during the nights and winter time,[14,15] we quantified the early diagnostic uncertainty by asking the ED physician at 90 min to quantify on a visual analogue scale their impression of the likelihood for cardiac syncope. The lower the area under the receiver-operating characteristics curve (AUC) of clinical judgement for cardiac syncope, the higher the diagnostic uncertainty.

In order to assess the possible influence of patients baseline characteristics on the timing of cardiac syncope, we performed a logistic regression to assess the effect of predefined patient characteristics including age on the probability of an event happening either during the night or during spring or summer.

Continuous variables are presented as mean ± standard deviation when normally distributed and median with interquartile ranges when non-normally distributed. Categorical variables are expressed as numbers and percentages. Mann–Whitney *U*-test was applied for comparison of continuous variables. Categorical variables were compared by Pearson χ^2 test and Fisher's exact test.

All hypothesis testing was two-tailed and *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA) and the R statistical Software (MathSoft, Seattle, WA, USA).

Results

Patient characteristics

A total of 1230 patients, enrolled from November 2010 to November 2015, were eligible for the analysis of weekly and seasonal patterns and 1192 patients for the analysis of a circadian pattern (Supplementary material online, *Figure S1*). Median age was 70 years, 40% were women, cardiovascular risk factors and established cardiovascular disorders (hypertension in 61%, coronary artery disease in 22%) were common (*Table 1*). Accordingly, more than half of the patients were on cardiovascular medications. Most of syncopal events happened, while standing and more than a third were accompanied by at least one prodrome.

Patients with an nightly syncope (24.5%) were younger, had less often pre-existing coronary artery disease (CAD) and CAD risk factors and syncope in the sitting position or during exertion, but more often had syncope when standing up (orthostatic) or when standing. In addition, nightly syncope more often caused relevant injury (*Table 1*).

Patients with syncope during the spring or summer (43.4%) more often had a history of CAD as compared to patients having syncope during the fall or winter (Supplementary material online, *Table S2*).

Adjudicated final diagnosis

As defined by the adjudicated final diagnosis following one-year follow-up, 180/1230 patients (14.6%) had cardiac syncope, 482/1230 patients (39%) reflex (neurally-mediated) syncope, 316/1230 patients (25.7%) orthostatic hypotension, 119/1230 patients (9.7%) other non-cardiac causes of syncope, and 133/1230 patients (10.8%) had syncope of unknown aetiology.

Circadian pattern

Of the 1192 patients available for analysis, 292 (24.5%) had syncope during the night (8 pm to 8 am), and 900 (75.5%) had syncope during the day (8 am to 8 pm).

The adjudicated aetiologies of syncope showed pronounced daily 24-hourly patterns. Overall, all types of syncope occurred much more frequently during the day when compared with the night. However, the temporal distribution was not diagnostically uniform. While reflex and orthostatic syncope had a broad peak of prevalence (80.9% occurring between 4 am and 4 pm), cardiac syncope had a narrow prevalence distribution (70.1% occurred from 8 am to 2 pm) (*Figure 1A*, Supplementary material online, *Table S3*). Finally, although reflex syncope was the dominant aetiology during most 2 h-intervals,

Table 1 Baseline characteristics

	All patients ($n = 1192$)	Night ($n = 292$)	Day ($n = 900$)	*P*-value
Age (years), median (IQR)	70.0 (57.0–80.0)	63.0 (51.8–77.0)	73.0 (60.0–81.0)	<0.001
Female gender, *n* (%)	468 (39)	122 (42)	346 (38)	0.344
Characteristics of the syncope, *n* (%)				
Nausea/vomiting	334 (28)	103 (36)	231 (26)	0.002
Sweating	367 (32)	89 (32)	278 (32)	1.000
Pallor	294 (42)	54 (34)	240 (44)	0.035
Palpitations	86 (8)	27 (10)	59 (7)	0.146
Angina	85 (7)	21 (7)	64 (7)	1.000
Caused injury	165 (14)	59 (21)	106 (12)	<0.001
Position of the syncope, *n* (%)				
While lying	33 (3)	11 (4)	22 (2)	0.321
While sitting	455 (39)	72 (25)	383 (43)	<0.001
Orthostatic	159 (14)	62 (22)	97 (11)	<0.001
While standing	480 (41)	133 (46)	347 (39)	0.039
Exertion	121 (10)	18 (6)	103 (12)	0.012
Risk factors, *n* (%)				
Hypertension	720 (61)	147 (50)	573 (64)	<0.001
Hypercholesterolaemia	480 (42)	101 (35)	379 (44)	0.038
Diabetes	184 (15)	34 (12)	150 (17)	0.049
Smoking				0.723
Active smoker	209 (18)	48 (16)	161 (18)	0.601
Former smoker	398 (33)	94 (32)	304 (34)	0.619
History, *n* (%)				
Cerebrovascular disease	137 (12)	24 (8)	113 (13)	0.055
Chronic heart failure	134 (11)	27 (9)	107 (12)	0.256
Arrhythmia	250 (21)	54 (19)	196 (22)	0.273
Pacemaker	57 (5)	11 (4)	46 (5)	0.437
Coronary artery disease	267 (22)	43 (15)	224 (25)	<0.001
Previous DVT or PE	84 (7)	18 (6)	66 (8)	0.558
Previous MI	163 (14)	29 (10)	134 (15)	0.041
Previous stroke	99 (8)	16 (6)	83 (9)	0.062
Epilepsy	37 (3)	10 (3)	27 (3)	0.850
Chronic medication, *n* (%)				
ACEIs/ARBs	530 (44)	96 (33)	434 (48)	<0.001
Alphablocker	88 (7)	19 (7)	69 (8)	0.596
Antiarrhythmics Class I	44 (4)	10 (3)	34 (4)	0.921
Aspirin	368 (31)	66 (23)	302 (34)	0.001
Beta-blockers	384 (32)	75 (26)	309 (34)	0.007
Calcium antagonists	204 (17)	37 (13)	167 (19)	0.026
Digitalis	24 (2)	6 (2)	18 (2)	1.000
Diuretics	365 (31)	71 (24)	294 (33)	0.009

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; DVT, deep venous thrombosis; IQR, interquartile range; MI, myocardial infarction; PE, pulmonary embolism.

orthostatic syncope was dominant in the second half of the night. In comparison, cardiac syncope was very uncommon during the night (*Figure 1*, Supplementary material online, *Table S3*).

When compared with a uniform distribution of 25% of events per 6-h period to assess the homogeneity of incidence in absolute numbers, all syncope aetiologies showed unique temporal patterns (Supplementary material online, *Table S4*). The pattern of cardiac syncope was different from that of reflex syncope ($P = 0.04$) and that of orthostatic syncope was different from reflex syncope ($P = 0.04$) (Supplementary material online, *Table S5*).

When compared with a homogenous theoretical distribution over the course of the day, cardiac syncope was significantly more common than expected from 10 am to noon. Reflex syncope also happened more often than expected during the first part of the night, while orthostatic syncope predominated during the very early morning hours (*Figure 2*, Supplementary material online, *Table S6*).

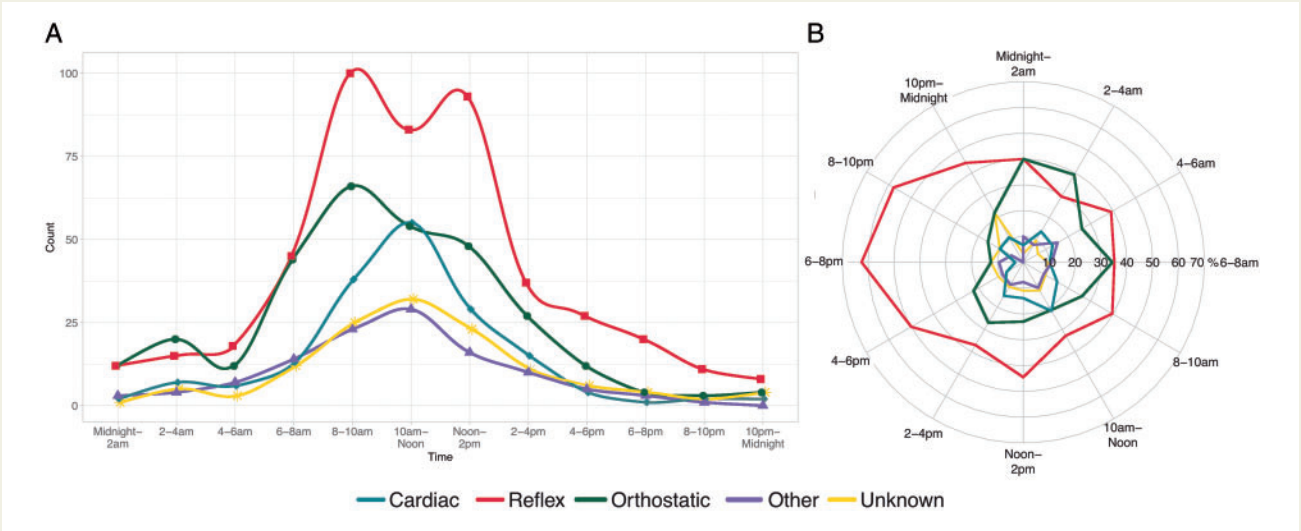

Figure 1 Circadian distribution of (*A*) the absolute numbers of events and (*B*) the percentage of events. A 24-h of a day are divided into 1- or 2-h periods, the lines represent the count or proportion of the different aetiologies at each time point.

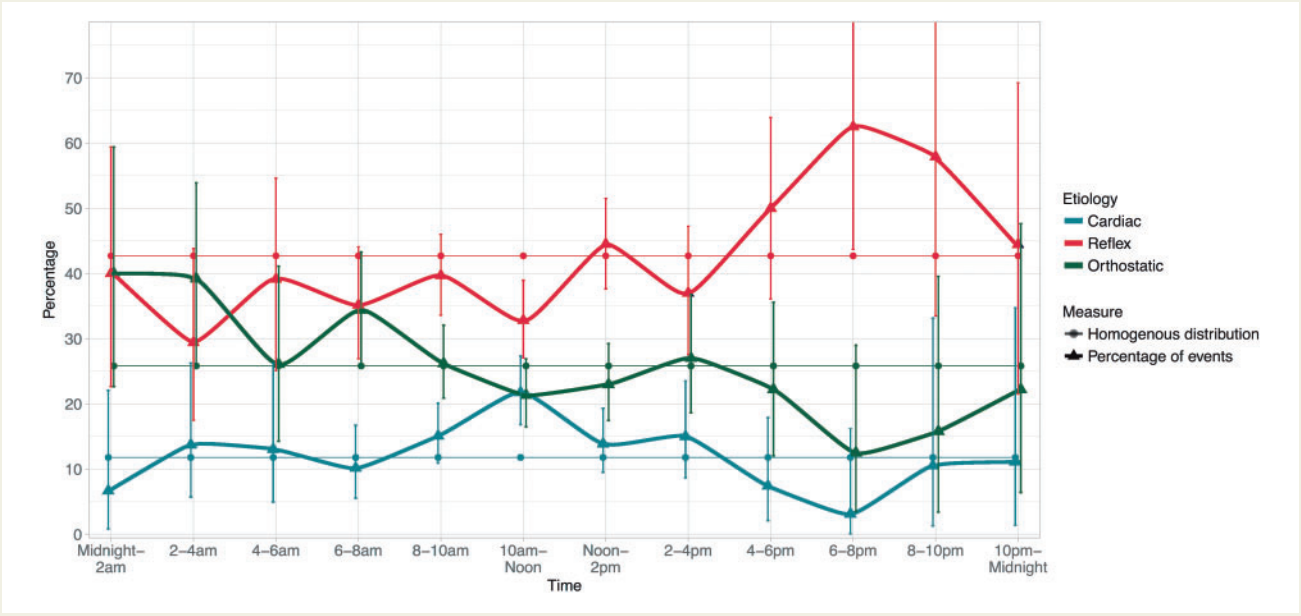

Figure 2 Distribution of the circadian true occurrence ratios compared with theoretical homogenous occurrence ratios.

Weekly pattern of syncope aetiology

Concerning the weekly pattern, 202 events (16.4%) occurred on Monday, 248 (20.2%) on Tuesday, 225 (18.3%) on Wednesday, 219 (17.9%) on Thursday, 204 (16.6%) on Friday, 56 (4.5%) on Saturday, and 76 (6.2%) on Sunday.

Accordingly, all the adjudicated aetiologies of syncope showed a significant weekly pattern, with more syncope happening during the week and less on the weekend (*Figure 3*, Supplementary material online, *Table S7*). This pattern was especially marked for syncope of reflex aetiologies. The proportion of the three main syncope aetiologies did not vary over the course of the week, except for reflex syncope on Sundays and orthostatic syncope on Mondays, which were both happening in a significantly higher proportion than other aetiologies on these days (*Figure 3*, Supplementary material online, *Table S8*).

Seasonal and temperature-related pattern of syncope aetiologies

Regarding seasonal pattern, 369 patients (30.0%) had syncope during the winter, 306 (24.9%) during the spring, 228 (18.5%) during the summer, and 327 (26.6%) during the fall.

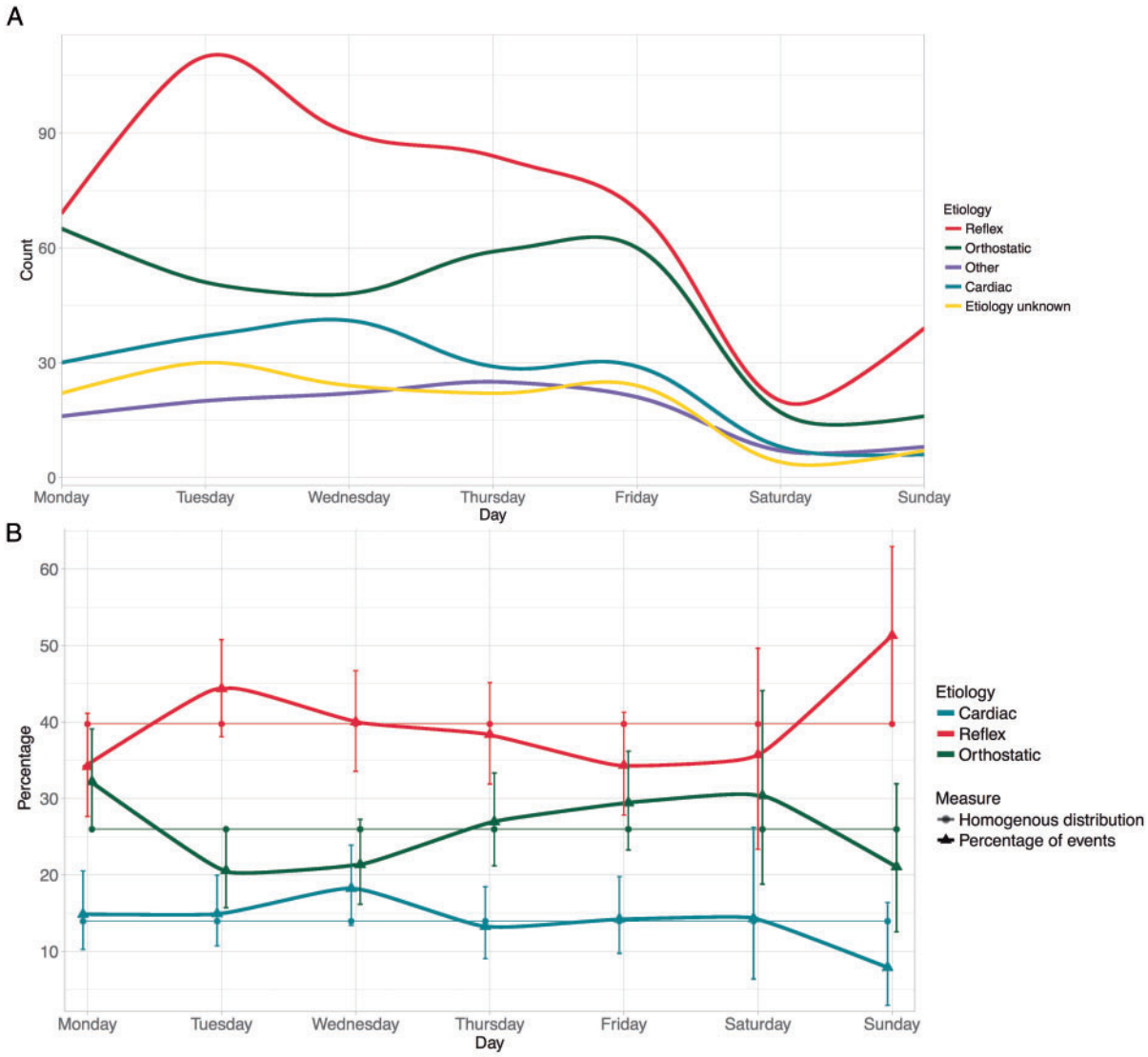

Figure 3 Weekly distribution of the absolute numbers of events (*A*) and of the true occurrence ratios compared with theoretical homogenous occurrence ratios (*B*) according to the different syncope aetiologies.

Accordingly, a significant seasonal pattern regarding absolute number of syncopal event presenting to the ED could only be observed for syncope of reflex aetiologies (*Figure 4*, Supplementary material online, *Table S9*). When considering the relative proportion of the different aetiologies (diagnostic perspective of the ED physician), the proportion of cardiac, reflex and orthostatic syncope was comparable between the seasons (*Figure 4*, Supplementary material online, *Table S10*). The higher incidence of reflex and orthostatic syncope during winter was conserved between centres with colder and centres with warmer seasons (Supplementary material online, *Figure S2*). In addition, differences among the different underlying cardiac aetiologies between the seasons did not reach statistical significance (Supplementary material online, *Figure S3*, *Table S11*).

Across all aetiologies, most syncope events occurred in the lowest temperature quintile. In addition, there were significantly less orthostatic syncope events in the 3rd, 4th, and 5th temperature quintile. Overall, the proportion of syncope aetiologies was similar in the temperature quintiles (*Figure 5*, Supplementary material online, *Table S12*).

Predictors for the circadian and seasonal pattern

Younger age, the absence of known cardiovascular disorders including CAD, diabetes mellitus, hypertension, hypercholesterolaemia, previous stroke or AMI, and renal dysfunction, the absence of certain cardiovascular therapies (antiarrhythmics and beta-blockers) and a lower Charlson comorbidity index were significant predictors of syncope occurring during the night in univariable logistic regression analysis (*Table 2*). When combined in a multivariable model, the only significant predictor for a syncope event occurring during the night was younger age.

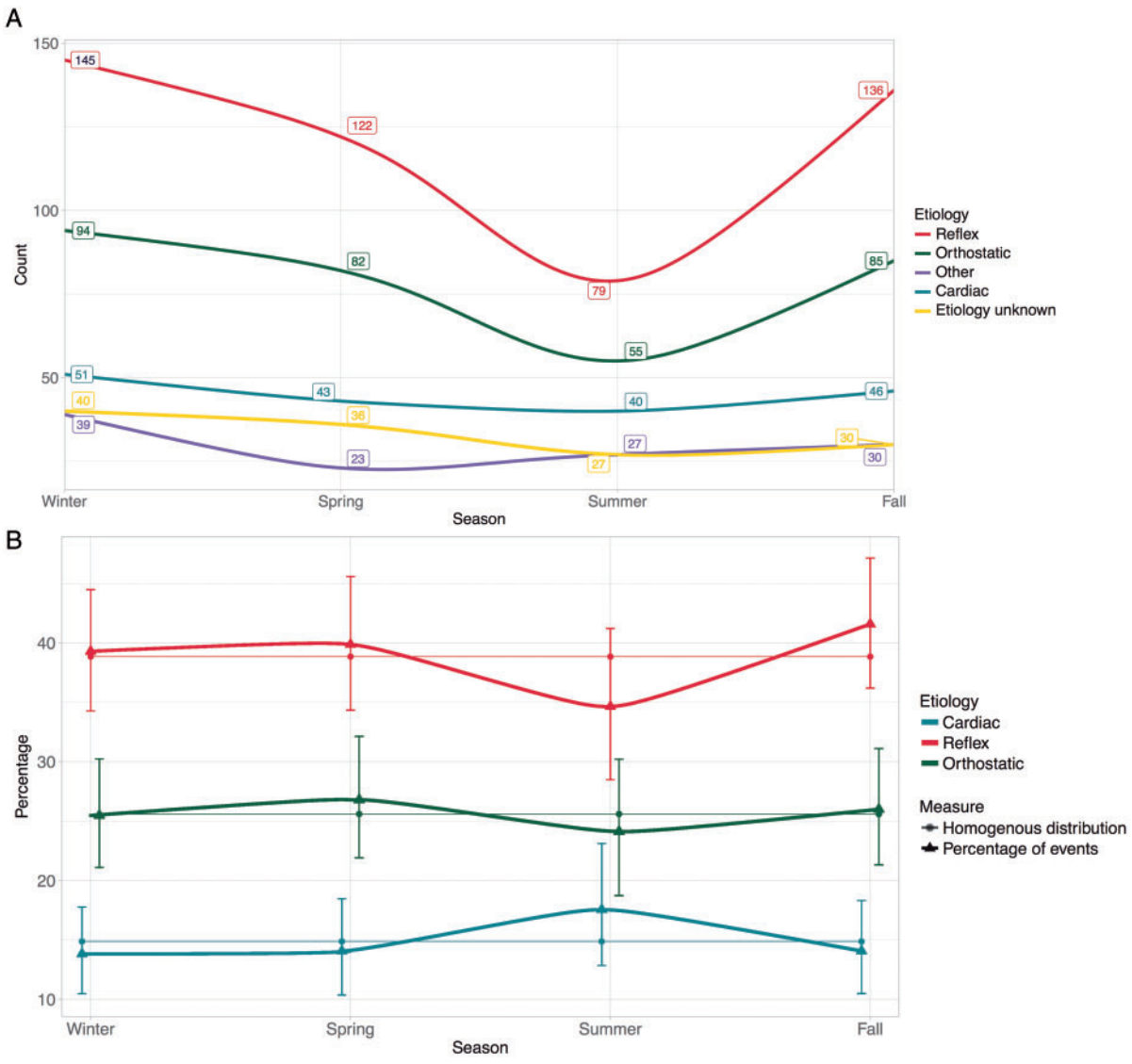

Figure 4 Seasonal distribution of the absolute numbers of events (*A*) and of the true occurrence ratios compared with theoretical homogenous occurrence ratios (*B*) according to the different syncope aetiologies.

In univariable regression, the only significant predictor for a syncope occurring during Spring or Summer was the presence of CAD (Supplementary material online, *Table S13*).

Diagnostic uncertainty of the emergency department physician

The AUC of the clinical judgement of the ED physician for the presence of cardiac syncope was 0.82 [95% confidence interval (CI) 0.73–0.91] during the night and 0.86 (95% CI 0.83–0.9) during the day (*Figure 6A*). Similarly, the AUC was 0.81 (95% CI 0.76–0.86) during the fall/winter and 0.9 (95% CI 0.86–0.93) during the spring/summer (*Figure 6B*). While the trend towards a higher early diagnostic uncertainty during the night was not significant ($P = 0.3$), a significant higher uncertainty could be observed during winter ($P = 0.01$).

Discussion

This large international diagnostic study was performed to test the hypothesis that syncope aetiologies exhibit a circadian, weekly, seasonal, and temperature-dependent pattern in patients older than 40 years old presenting to the ED. Documenting the existence of such patterns would contribute to substantially facilitating the early management of unselected patients presenting with syncope to the ED. The need for improving the care of patients with syncope seems highest for patients presenting during night shifts, which are recognized as particularly challenging tasks in the ED[14] or during winter, when ED crowding enormously limits physicians' time per patient and may even incite patients to leave without being seen.[15]

We report four major findings. First, all syncope aetiologies displayed a circardian rhythm, occurring more frequently during the day

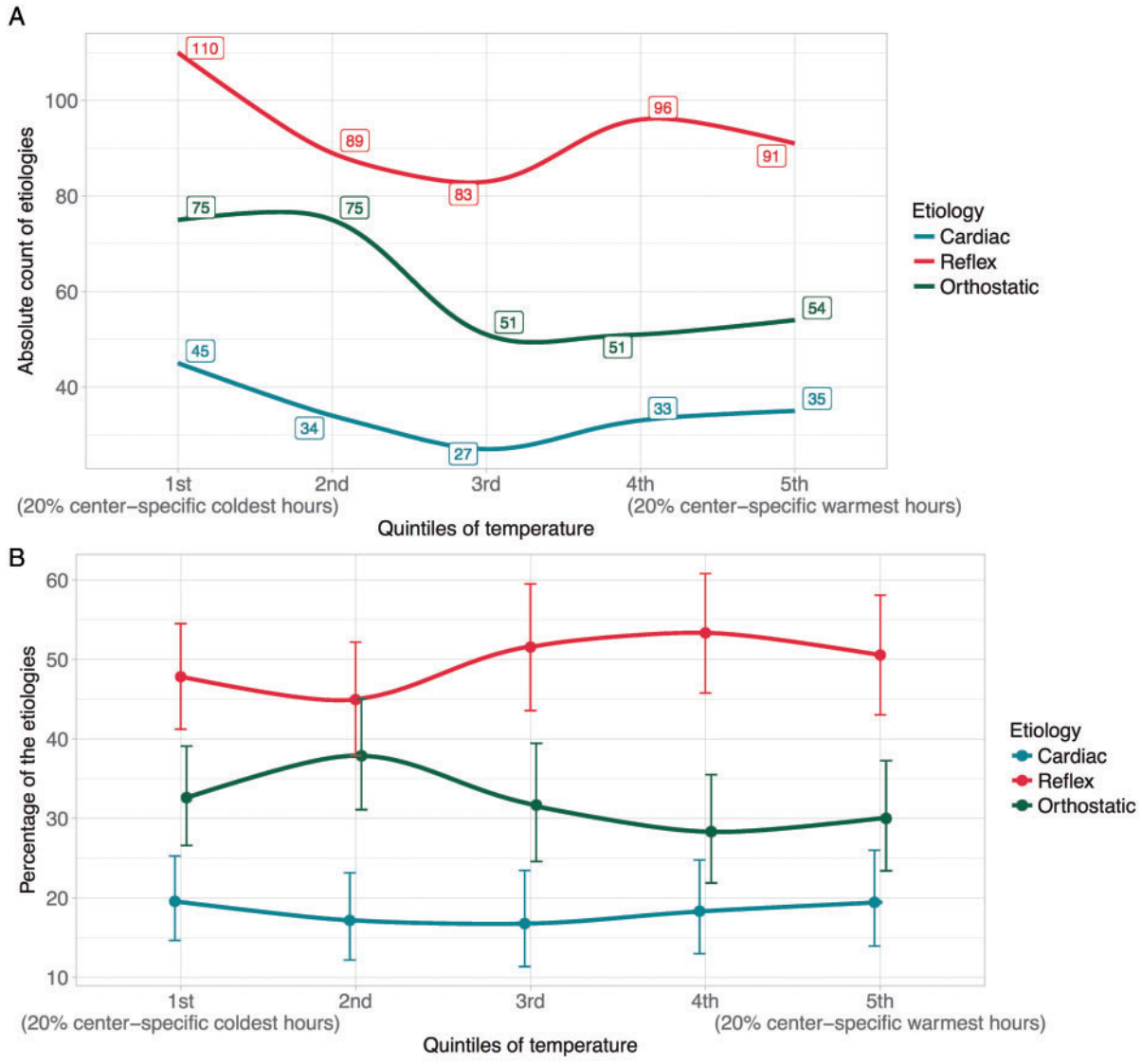

Figure 5 Distribution of the absolute numbers of events (*A*) and of the relative incidence (*B*) of the various syncope aetiologies according to centre-specific temperature quintiles.

(75%) when compared with the night. Reflex and orthostatic syncope were most common between 4 am and 4 pm, while cardiac syncope was most common during 8 am and 2 pm. Second, all syncope aetiologies displayed a weekly pattern, happening more frequently from Monday to Friday. A higher proportion of reflex syncope and orthostatic syncope are to expect on Sundays and Mondays, respectively. Third, while only reflex aetiology showed a significant seasonal variation and only orthostatic aetiology showed a temperature-dependent behaviour. All aetiologies happened most when the temperatures were the coldest. Fourth, significant differences in diagnostic uncertainty were observed during fall and winter, while the trend for higher diagnostic uncertainty during the night was not significant.

The findings of this study extend and corroborate previous pilot studies on syncope rhythms[1,3,16] as well as previous work establishing circadian,[6,7] weekly,[7,10–12] and seasonal patterns[6,7] for various cardiovascular events.

Several lines of evidence had supported the hypothesis of a higher incidence of cardiac syncope in the morning hours including reports on a higher incidence of sudden death, AMI, and stroke in the morning hours[6–9] and the circadian organization of the cardiovascular system. Synchronizing physiological functions to the natural 24 h light-dark cycle, for example by up-regulating body temperature and blood pressure before the time of awakening, anticipates to the demands of daytime activities.[8] Circadian rhythmicity has in addition been described for many cardiovascular traits: heart rate, sympathetic activity, vascular resistance, the renin-angiotensin-aldosteron system, prothrombotic tendency, platelet aggregability, and the fibrinolytic system.[17] As all these components and hormones possibly involved in the pathophysiology of cardiac syncope (e.g. epinephrine,

Table 2 Logistic regression: predictors for syncope occurring during the night

	Univariable logistic regression				Multivariable logistic regression			
	OR	95% CI (lower-upper)		*P*-value	OR	95% CI (lower-upper)		*P*-value
Age by 10 years increase	0.78	0.71	0.85	<0.01	0.84	0.76	0.93	0.01
DM	0.66	0.44	0.97	0.04	0.84	0.55	1.26	0.40
Hypertension	0.57	0.44	0.75	<0.01	0.8	0.59	1.09	0.15
Pacemaker	0.73	0.35	1.37	0.35				
History of arrhythmia	0.82	0.58	1.14	0.23				
Epilepsy	1.16	0.53	2.34	0.70				
CAD	0.52	0.36	0.74	<0.01	0.68	0.46	1	0.05
Antiarrhythmics	0.6	0.45	0.78	<0.01				
Hypercholesterolaemia	0.73	0.55	0.96	0.02				
History of stroke	0.57	0.32	0.97	0.05	0.77	0.42	1.32	0.36
History of AMI	0.63	0.41	0.95	0.03				
Charlson index	0.88	0.84	0.93	<0.01				
Presence of renal dysfunction	0.79	0.66	0.93	<0.01	0.96	0.79	1.16	0.69
Valvular disease	0.75	0.46	1.2	0.25				
Betablockers	0.66	0.49	0.89	<0.01				
Active smoker	0.9	0.63	1.28	0.51				
Congestive heart failure	0.76	0.48	1.16	0.22				

Charlson Comorbidity index is a score computed with age, diabetes mellitus, liver disease, solid tumour, AIDS (acquired immune deficiency syndrome), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction, peripheral vascular disease, cerebrovascular accident or transient ischaemic attack, dementia, hemiplegia, connective tissue disease, leukaemia, malignant lymphoma, and peptic ulcer disease. Significant predictors are highlighted.
AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

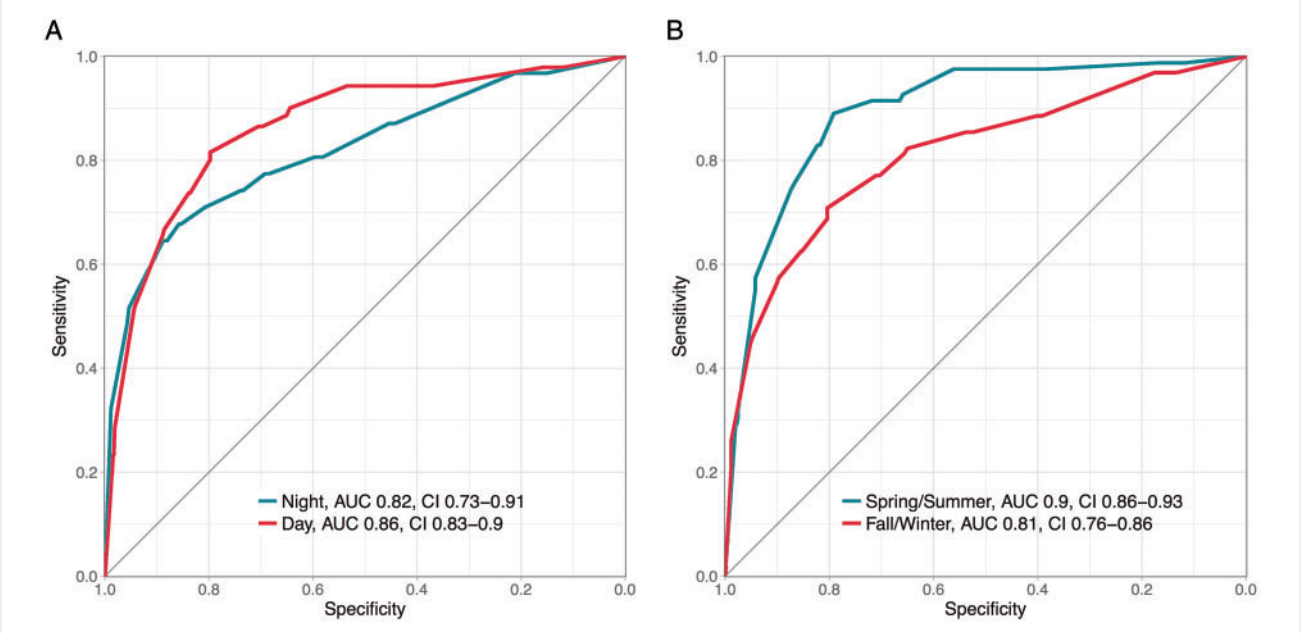

Figure 6 Analysis of early diagnostic uncertainty during the night (*A*) and during fall/winter (*B*). The early diagnostic uncertainty was characterized as the ability of the physician to estimate the risk for cardiac syncope within 90 min after ED presentation. The lower the AUC of clinical judgement, the higher the diagnostic uncertainty. AUC, area under the curve.

norepinephrine, renin, angiotensin, aldosterone, and cortisol) were shown to be higher during the morning hours,[8] and high level of physical activity and mental stress following awakening also may play an important role. These neurohumoral and hemodynamic factors increase oxygen demand and modify the electrical properties of the myocardium.[8,9,18] While this large diagnostic multicentre study documented that cardiac syncope in patients older than 40 years old displays a narrow distribution with 70% events occurring between 8 am and 2 pm, unexpectedly the circadian pattern of cardiac syncope overall was similar to that of the other syncope aetiologies. Accordingly, taking the time of occurrence into the diagnostic consideration does not seem to facilitate the early rule-out or rule-in of cardiac syncope in the ED to a clinically relevant extent.

Extending and corroborating previous pilot studies, this large multicentre study documented that also orthostatic and reflex syncope display a circadian pattern.[16] While the exploration of the exact mechanisms underlying these patterns goes beyond the scope of this study, regulation of blood pressure and heart rate as well as nocturnal polyuria and redistribution of body fluid may be involved.[16] The increase in reflex and orthostatic syncope in the early morning could be explained by patients waking up to go to the toilets and/or standing up. In addition, activities during specific times of the day as for instance a meal or an early afternoon nap may influence the circadian rhythm of different syncope aetiologies.

The lower level of physical and mental stress on the weekends, as well as possible higher reluctance to visit the ED on weekends when compared with weekdays may have contributed to the lower rate of syncope events on weekends. Sundays' specific activities such as going to church, prolonged standing or overindulgence may have contributed to the higher proportion of reflex syncope on Sundays. Increased orthostatic stress upon returning to work on Mondays could have contributed to the proportional increase of this aetiology on Monday. Unfortunately, taking the day of occurrence into the diagnostic consideration does not seem to facilitate the early rule-out or rule-in of cardiac syncope in the ED to a clinically relevant extent.

Previous studies suggested a higher incidence of life-threatening arrhythmias, AMI, and acute aortic dissection[19] during winter time, which is believed to be linked to climate variations, adaptations to temperature changes, air pressure, shorter duration of sunlight, and overindulgence around Christmas time[6,7]. In contrast, this study documented remarkable constant seasonal incidence of cardiac syncope with no correlation with outside temperature. This second observation is in line with previous studies indicating that the absolute outside temperature does not seem to play a major role in the incidence of cardiovascular events.[19] Therefore, also taking the season of occurrence or outside temperature into the diagnostic consideration does not seem to facilitate the diagnosis of cardiac syncope.

The higher incidence of reflex and orthostatic syncope in winter and within the lower quintiles of temperature may be related to the large and rapid difference between outside temperatures and inside temperatures and their associated stress to the circulation.[20] Future studies documenting the exact location of the syncopal event (inside vs. outside) are needed.

Accordingly, diagnostic protocols for cardiac syncope need to include thorough patient history, physical examination, cardiac biomarkers, electrocardiogram (ECG), and echocardiography, when there is suspicion of cardiac syncope, regardless of the time, weekday, season, and temperature of presentation. The detection of cardiac syncope has immediate consequences for patient management usually including the need for hospital admission, continuous ECG rhythm monitoring, cardiac pacemaker implantation in case of a bradyarrhythmic cause, cardioverter-defibrillator implantation in some cases of a tachyarrhythmic cause, and aortic valve replacement in case of severe aortic stenosis.

Major strengths of this study include the prospective assessment of the exact time of syncope, rigorous determination of the adjudicated final diagnosis, and the large number of patients enrolled on three continents, thus maximizing external validity.

The following limitations should be considered when interpreting the findings of the present study. First, we recruited patients presenting to the ED. Therefore, it is unknown whether our findings can be extrapolated to patients presenting to primary care. Second, we deliberately chose to only enroll patients age 40 or older as the differential diagnosis is much more difficult in these when compared with younger patients with predominantly vasovagal syncope. Accordingly, we cannot comment on possible circadian rhythms in very young patients with syncope. Third, we cannot comment on patients who present later than 12 h after symptom onset since these patients were excluded from our study. Fourth, despite using central adjudication based on 1-year follow-up, some patients may still have been misclassified. Fifth, we did not account for patients with a reversed sleep-wake routine (such as the patients engaged in night or rotating shift-work) nor did we assess their sleep quality, the presence of insomnia or sleep-disordered breathing, assess their travelling behaviour over the year or use of air-conditioning, all of which may distort circadian, seasonal and temperature-dependent patterns. Sixth, despite the presence of research personal 7 days a week in most enrolling EDs, less intense staffing with researchers in the ED may have contributed to the lower number of patients with syncope during weekends. Seventh, despite having a very large number of patients, three factors likely have been a barrier to even higher enrolment rate: While the first site started patient enrolment in 2010, most additional sites only became active in 2012 and beyond. While formally this study enrolled consecutive patients, the requirement to obtain informed consent and the fact that most enrolling sites did not have research staff available in the ED 24/7.

Conclusion

In conclusion, this large multicentre study showed that syncope aetiologies display important circadian, weekday, seasonal, and temperature-dependent patterns. Unfortunately, these patterns do not allow to reliably differentiate cardiac syncope from other aetiologies, and therefore, should not impact on the diagnostic protocol applied in the ED.

Supplementary material

Supplementary material is available at *Europace* online.

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