CHAPTER 9

Guideline based evaluation of syncope improves patient reported outcomes in secondary and tertiary settings

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Submitted

INTRODUCTION

Syncope is a transient loss of consciousness (TLOC) caused by global cerebral hypoperfusion, most commonly due to reflex mechanisms, orthostatic hypotension, or cardiac disease. Patients with TLOC report impaired health-related quality of life (HRQoL) compared with healthy populations,[1-6] with a burden comparable to New York Heart Association class II–III heart failure[5] and with increased physical and psychological morbidity. Recurrent TLOC affects patients in a similar manner as chronic disorders like rheumatoid arthritis or chronic low back pain,[7, 8] with persistent HRQoL impairment driven mainly by episode burden, comorbidity, and diagnostic uncertainty rather than the final etiological label alone.[2, 3, 7] Diagnostic uncertainty is particularly relevant in syncope care, where a recent in-depth analysis showed that many referred patients in secondary care remain undiagnosed or inaccurately diagnosed prior to referral to a syncope expert.[9, 10]

The burden of syncope can be quantified using syncope-specific patient-reported outcome measures (PROMs). The Syncope Functional Status Questionnaire (SFSQ) and the Impact of Syncope on HRQoL capture functional limitation, fear, emotional distress, and physical restriction, with good reliability, validity, and responsiveness across large TLOC populations.[8, 11] Previous studies have shown that episode frequency is inversely associated with HRQoL,[3, 5] and in reflex (or vasovagal) syncope, impairment may be similar to that seen in epilepsy[6] and other chronic disorders. Vasovagal syncope is the most common cause of non-head-trauma TLOC,[12-15] and management for syncope in general ranges from lifestyle measures and pharmacotherapy to more invasive therapy strategies like pacemaker or implantable cardioverter-defibrillator therapy in selected cardiac causes.[16] So far, treatment-related HRQoL effects have been examined in hospital-based cohorts,[2] and both syncope-specific and generic instruments have shown that anticipatory anxiety, activity restriction, loss of independence, and limitations in driving and work contribute to persistent impairment, increased healthcare use, and higher healthcare costs.[2, 7, 17]

Here, we investigated whether a structured guideline-based diagnostic approach to syncope, consisting of thorough history taking, physical examination, ECG, and active standing testing, was associated with changes in patient-reported outcomes in secondary and tertiary syncope units. We hypothesize that a structured approach results in similar improvement of patient reported outcomes, despite differences in patient case mix and referral patterns between those settings. We made use of a syncope specific instrument in all patients, complemented by a setting specific assessment of general health related quality of life.

MATERIALS AND METHODS

Study objective

This prospective observational cohort study examined patient reported outcomes specific for syncope and general HRQoL trajectories during follow-up after structured initial syncope evaluation and subsequent management in two distinct settings: secondary and tertiary SU. Data were obtained from three

non-academic general secondary care Dutch hospitals (HAGA, The Hague; Reinier de Graaf Gasthuis, Delft; Groene Hart Hospital, Gouda participating in the Haaglanden Syncope Unit database (Haaglanden: April 2015–December 2022). Data were further retrieved from a tertiary academic center with a dedicated syncope unit participating in the Fainting Assessment STudy database (F.A.ST, Amsterdam University Medical Center (AUMC), Amsterdam, the Netherlands: 2010–2012). All SUs were consistent with syncope-unit principles described in the European Heart Rhythm Association position statement.[18, 19] Both cohorts followed the same guideline based initial evaluation according to contemporary syncope guidelines.[20-22] We investigated disease-specific outcomes assessed with the SFSQ in both clinical settings (secondary and tertiary). Generic HRQoL was evaluated using the RAND-36-Item Health Survey (RAND-36) in the secondary care cohort. The Medical Outcomes Study 12-Item Short Form Health Survey (SF-12) was used in the tertiary academic cohort.[23-25] In addition, we examined the patient-level relationship between syncope-specific recovery and generic HRQoL change by assessing directional concordance and discordance between SDS and RAND-36/SF-12 changes from baseline to final follow-up.

Study population

All patients were ≥18 years old, who had experienced at least one episode of TLOC, and were able to complete the questionnaires, were referred to the syncope-unit by a general practitioner, or a medical specialist, from outpatient, hospital and emergency departments. Medical or neurological conditions precluding reliable questionnaire administration constituted exclusion criteria. Baseline demographic and clinical characteristics, including age, sex, total lifetime number of syncopal episodes, number of syncopal episodes in the preceding year, and presyncope, were prospectively collected.

Ethics

The study was approved by the Medical Ethics Review Committee Leiden–Den Haag–Delft (METC No. 18-061). All participants in the general hospital cohort provided written informed consent. For the academic center cohort (AUMC database), the METC waived the requirement for informed consent because the data were collected as part of routine clinical care (METC No. W12-172).

Syncope evaluation

In both secondary and tertiary settings, patients underwent guideline based initial syncope evaluation,[9, 20-22] comprising thorough history taking, physical examination, a 12-lead electrocardiogram (ECG), and an active standing test (AST)

Diagnostic classification and treatment

Diagnostic criteria were harmonized according to criteria now part of the European Society of Cardiology guideline (ESC),[9, 20-22] and diagnoses were assigned to prespecified categories, including reflex syncope, orthostatic hypotension,

cardiac syncope, epilepsy, functional syncope mimics, and unexplained TLOC. Treatment was guided by the working diagnosis and implemented according to guideline recommendations and clinical indication.

Primary analysis: Syncope specific patient reported outcomes and follow-up for both settings

The original "Linzer" SFSQ8 was collected in both settings at baseline assessment (Q0) and repeated at 3–6 months follow-up (Q6) and 12–18 months follow-up (Q18) (**Figure 1**).[8] Baseline SFSQ (Q0) was defined as the assessment obtained before specialist evaluation or disclosure of diagnostic conclusions, to minimize early changes in patient-reported outcomes related to diagnostic reassurance or the clinical encounter itself.[26-28]

The impairment score (IS) was defined as the percentage of applicable items 1–11 endorsed with a "yes" response, with not-applicable items excluded from the denominator. The original fear/worry score (FWS) was calculated as the mean of items 12–14 after linear rescaling to a 0–100 metric, with higher scores indicating greater syncope-specific burden. The Syncope Dysfunction Score (SDS) was calculated as the mean of the IS and FWS. The items assessing lack of control over health and low hope for a diagnosis were not incorporated into the SDS, but were analyzed separately as additional syncope-specific outcomes. Missing item responses were treated as missing before score calculation. Because the same SFSQ was available in both cohorts, syncope-specific outcomes were also examined in an additional pooled analysis across both settings, with higher scores indicating greater syncope-specific burden and lower scores indicating improvement.

Change-based SFSQ recovery quartiles

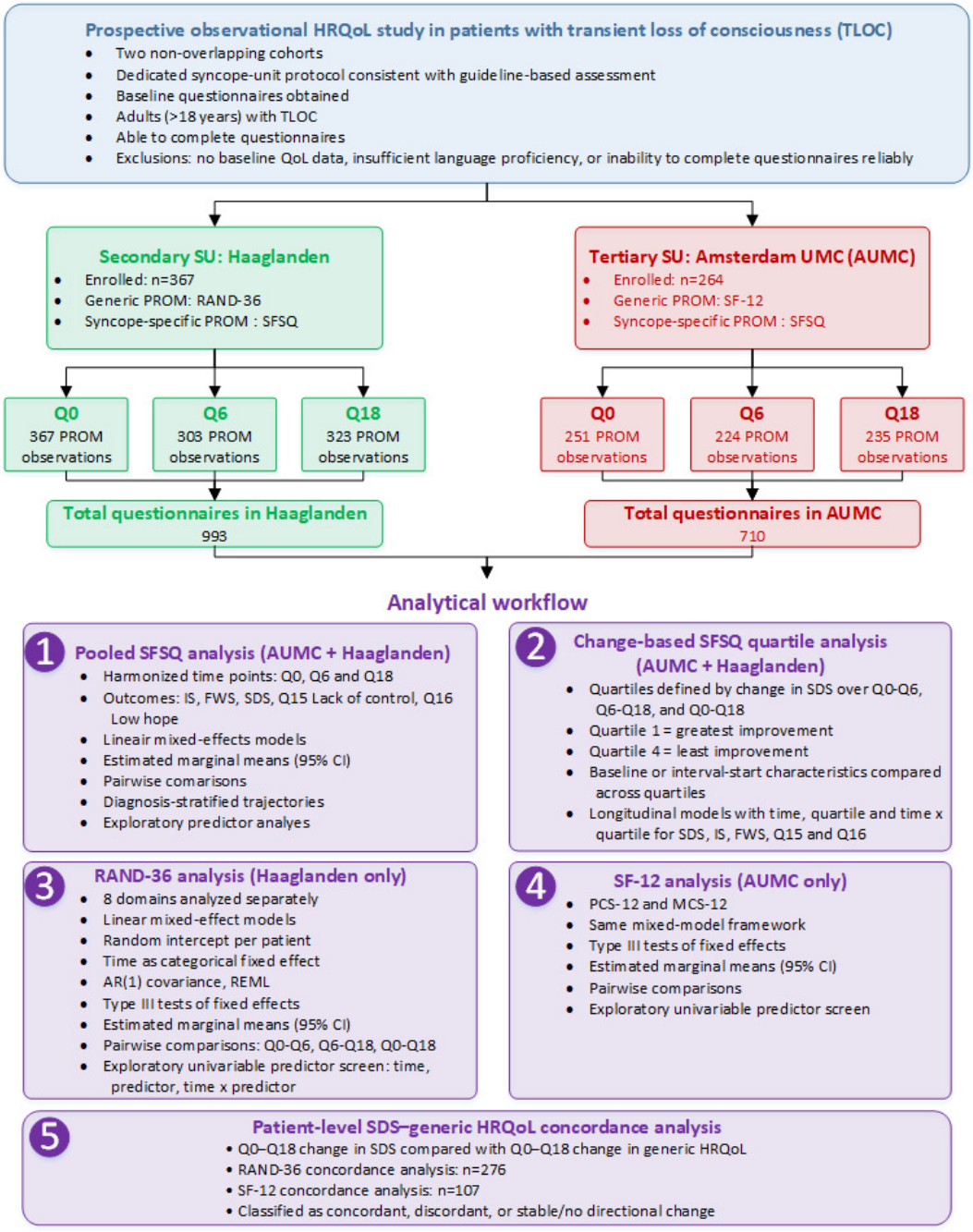
For the change-based SFSQ recovery analysis, interval-specific change in SDS was calculated for three predefined intervals: Q0–Q6, Q6–Q18, and Q0–Q18.

Change was calculated as SDS at the end of the interval minus SDS at the start of the interval; therefore, negative values indicated improvement. Patients were ranked according to interval-specific SDS change and divided into quartiles, with quartile 1 representing the greatest decrease in SDS and quartile 4 representing the smallest decrease or worsening. For the Q0–Q6, Q6–Q18, and Q0–Q18 recovery analyses, patient characteristics were compared across SDS recovery quartiles at the start of the corresponding interval, using Q0 for Q0–Q6 and Q0–Q18, and Q6 for Q6–Q18. These characteristics included age, sex, presyncope, recent syncope burden, total lifetime syncope burden, long-term absenteeism, and reduction in working hours. Cohort was also compared across recovery quartiles to assess whether quartile membership reflected differences between the secondary and tertiary care settings.

Patient-reported outcome measures

Because the two databases were developed independently, the available generic HRQoL instruments differed between cohorts. The RAND-36 was used in the secondary care cohort, and the SF-12 was used in the tertiary academic

Figure 1: Flowchart health related quality of life in patients with transient loss of consciousness.



Overview of cohort derivation, data sources, patient inclusion, harmonization of follow-up time points, and analytical workflow for generic and syncope-specific HRQoL outcomes. Abbreviations: AUMC = Amsterdam University Medical Center; HRQoL = health-related quality of life; RAND-36 = RAND 36-Item Health Survey; SF-12 = 12-Item Short Form Health Survey; SFSQ = Syncope Functional Status Questionnaire; TLOC = transient loss of consciousness.

cohort. Therefore, generic HRQoL was not pooled across settings but analysed separately for each cohort.

RAND-36 assessment for secondary care

The Dutch RAND-36[23] is a 36-item generic instrument comprising eight domains: physical functioning, physical role functioning, emotional role functioning, energy/fatigue, emotional well-being, social functioning, pain, and general health. Domain scores were calculated according to the instrument manual and linearly transformed to a 0–100 scale, with higher scores indicating better health and HRQoL. Domains that could not be scored validly because of missing item responses were coded as missing.[23]

SF-12 assessment for tertiary care

The SF-12[24, 25] is an abbreviated version of the SF-36. Two summary scores were derived: the Physical Component Summary score (PCS-12) and the Mental Component Summary score (MCS-12). Scores were calculated according to the standard "Ware" scoring algorithm. Where missing item responses prevented reliable calculation, the corresponding summary score was coded as missing. SF-12 scores were standardized to a mean of 50 and a standard deviation of 10 in the general population, with higher scores indicating better HRQoL.[25]

Patient-level concordance between syncope-specific and generic HRQoL change

To examine whether syncope-specific recovery paralleled generic HRQoL change, a descriptive patient-level concordance analysis was performed for Q0–Q18 change. SDS was used as the syncope-specific outcome, with a decrease indicating improvement. For RAND-36 domains and SF-12 PCS-12/MCS-12, an increase indicated improvement.

Patients with complete paired Q0 and Q18 data for SDS and the corresponding generic HRQoL score were classified as concordant when both measures changed in the same clinical direction, i.e. both indicated improvement or both indicated deterioration. They were classified as discordant when one measure indicated improvement and the other deterioration. Stable/no directional change was assigned when either score showed no change. No minimal important-difference threshold was applied.

Statistical analysis

Questionnaire data were collected in Castor EDC and analyzed using SPSS version 25.0. SFSQ data from both cohorts were merged into a harmonized longitudinal dataset. Before interpretation of the pooled SFSQ analyses, cohort-dependent differences were examined for each SFSQ outcome using linear mixed-effects models including time, cohort, and the time × cohort interaction. For SFSQ, models included the IS, FWS, SDS, lack of control over health, and low hope for obtaining a diagnosis. Because cohort-dependent differences were observed, cohort was included as a fixed effect in all subsequent pooled SFSQ models. Diagnosis-specific, predictor, and recovery-quartile analyses used interaction

terms for time with diagnostic group, predictor, or quartile, respectively (**Figure 1**).

RAND-36[23] and SF-12[24, 25] outcomes were analyzed separately by cohort. Longitudinal trajectories of SFSQ outcomes, RAND-36 domains, and SF-12 summary scores were analyzed using linear mixed-effects models[29] with a random intercept for patient, categorical time, an AR(1) covariance structure,[30] cohort as a fixed effect for pooled SFSQ models, and restricted maximum likelihood estimation. Global time effects were assessed using Type III tests and reported as estimated marginal means (EMM) with 95% confidence intervals and pairwise comparisons between Q0, Q6, and Q18.[31]

For recovery-quartile mixed models, separate interval-specific models were fitted for Q0–Q6, Q6–Q18, and Q0–Q18. These models included time, cohort, recovery quartile, and the time × recovery quartile interaction as fixed effects, with a random intercept for patient. Because each interval-specific recovery model contained only two time points, no AR(1) covariance structure was used for these models.

Continuous and categorical characteristics were compared across quartiles using Kruskal–Wallis and Pearson chi-square tests. Predictor and quartile analyses were exploratory, without correction for multiple testing. The patient-level concordance analysis was descriptive and reported as numbers and percentages within each generic HRQoL domain or summary score.

RESULTS

The baseline characteristics of the cohorts are shown in **Table 1**.

Syncope-specific SFSQ outcomes

Before interpretation of the pooled SFSQ analyses, cohort-dependent differences were examined between the Amsterdam University Medical Center (AUMC) and Haaglanden cohorts. This analysis included 1703 completed questionnaires: 710 from AUMC and 993 from Haaglanden. Questionnaire availability was 618/618 at Q0, 527/618 at Q6, and 558-618 at Q18. A significant cohort effect was observed for all SFSQ outcomes, indicating differences in absolute symptom burden between cohorts: IS, $F(1, 626.622)=59.934$, $p<0.001$; FWS, $F(1, 627.004)=33.232$, $p<0.001$; SDS, $F(1, 618.578)=63.356$, $p<0.001$; lack of control over health, $F(1, 611.225)=40.963$, $p<0.001$; and low hope for obtaining a diagnosis, $F(1, 630.831)=8.163$, $p=0.004$. Significant time × cohort interactions were observed for IS, $F(2, 713.229)=5.494$, $p=0.004$; FWS, $F(2, 818.425)=5.138$, $p=0.006$; and SDS, $F(2, 704.410)=5.800$, $p=0.003$, but not for lack of control over health, $F(2, 834.577)=1.353$, $p=0.259$, or low hope for obtaining a diagnosis, $F(2, 898.075)=2.055$, $p=0.129$. Subsequent pooled SFSQ models were therefore adjusted for cohort. Setting-specific SFSQ trajectories for general hospitals and the academic center are shown in **Supplementary Figure S1**.

For the cohort-adjusted pooled IS, the estimated mean decreased from 30.0 at Q0 to 24.0 at Q6 and 22.8 at Q18, with a significant overall effect of time ($F=16.65$; $p<0.001$). Pairwise comparisons showed significant differences between Q0 and Q6 and between Q0 and Q18 (both $p<0.001$), whereas Q6 and Q18 did not differ ($p=0.336$). For FWS, the EMM decreased from 40.0 at Q0 to 28.8 at Q6 and 24.6 at Q18 ($F=99.55$; $p<0.001$), and all pairwise comparisons were significant

Table 1 Baseline Characteristics

Variable	Secondary cohort (Haaglanden)	Tertiary cohort (AUMC)
Demographics		
N	367	264
Age, years, median (IQR)	66.0 (53.0–75.0)	50.5 (34.0–64.0)
Sex, male, n (%)	194 (52.9%)	122 (46.2%)
Living with partner / married, n (%)	239 (65.1%)	155 (58.7%)
Any children, n (%)	292 (79.6%)	177 (67.0%)
Syncope burden and clinical presentation		
Total syncopal episodes, median (IQR)	3 (2–6)	6 (3–20)
Syncopal episodes in the past year, median (IQR)	1 (1–2)	3 (1–6)
Pre-syncope, yes, n (%)	215 (58.9%)	203 (76.9%)
Self-reported duration of loss of consciousness ≤ 5 min (%)	326 (88,8%)	N/A
Self-reported duration of loss of consciousness > 5 min (%)	36 (9.8%)	N/A
Unclear/missing duration of loss of consciousness	5 (1.4%)	N/A
Prior diagnostic evaluation before referral		
Prior ECG, n (%)	130 (35.4%)	241 (91.3%)
Prior echocardiography, n (%)	15 (4.1%)	206 (78.0%)
Prior Holter monitoring, n (%)	32 (8.7%)	207 (78.4%)
Prior EEG, n (%)	20 (5.4%)	160 (60.6%)
Prior CT brain, n (%)	51 (13.9%)	97 (36.7%)
Prior exercise ECG, n (%)	8 (2.2%)	198 (75.0%)
Prior tilt-table testing, n (%)	4 (1.1%)	22 (8.3%)
Prior laboratory testing, n (%)	146 (39.8%)	164 (62.1%)
Prior ILR/PM/ICD-related evaluation, n (%)	0 (0.0%)	35 (13.3%)
Prior 24-hour blood pressure monitoring, n (%)	2 (0.5%)	96 (36.4%)
Diagnosis		
Reflex syncope, n (%)	143 (39.0%)	148 (56.1%)
Orthostatic hypotension, n (%)	71 (19.5%)	51 (19.3%)
Cardiac syncope, n (%)	96 (26.4%)	5 (1.9%)
Functional T-LOC, n (%)	8 (2.2%)	39 (14.8%)
Epilepsy, n (%)	13 (3.6%)	8 (3.0%)
Unexplained TLOC, n (%)	36 (9.9%)	8 (3.0%)
Other, n (%)	N/A	5 (1.9%)

Baseline demographic, clinical, diagnostic, therapeutic, electrocardiographic, laboratory, and echocardiographic characteristics of the two independent cohorts. Continuous and count variables are presented as median (interquartile range), and categorical variables as number (percentage). Percentages are based on valid cases. Variables unavailable in one database are shown as N/A. Abbreviations: BMI = body mass index; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; IQR = interquartile range; LV = left ventricular; LVEF = left ventricular ejection fraction; N/A = not available; PM = pacemaker; TLOC = transient loss of consciousness; TSH = thyroid-stimulating hormone.

(all p<0.001). The SDS decreased from 35.1 at Q0 to 27.4 at Q6 and 24.8 at Q18 (F=54.65; p<0.001). Differences were significant between Q0 and Q6 and between Q0 and Q18 (both p<0.001), and also between Q6 and Q18 (p=0.007) (**Figure 2 and Table 2**).

Figure 2: Longitudinal changes in pooled SFSQ impairment, fear/worry, and syncope dysfunction scores

Estimated marginal means with 95% confidence intervals for pooled SFSQ impairment score, fear/worry score, and Syncope Dysfunction Score across baseline, 3-6 months, and 12-18 months. Overall P values and pairwise comparisons are derived from linear mixed-effects models. Higher scores indicate greater syncope-specific burden. Abbreviations: SFSQ = Syncope Functional Status Questionnaire.

Diagnosis-specific and exploratory predictor analyses

In cohort-adjusted diagnosis-stratified analyses, time, diagnosis, and time × diagnosis interactions remained significant for IS, FWS, and SDS. For IS, the effects of time, diagnosis, and time × diagnosis were significant (time: F=8.76, p<0.001; diagnosis: F=11.95, p<0.001; time × diagnosis: F=1.88, p=0.026). Similar findings were observed for FWS (time: F=28.73, p<0.001; diagnosis: F=3.63, p=0.001; time × diagnosis: F=1.72, p=0.047) and SDS (time: F=20.76, p<0.001; diagnosis: F=9.54, p<0.001; time × diagnosis: F=2.12, p=0.009). Functional TLOC showed the highest SDS values across follow-up time points, whereas reflex syncope and cardiac syncope showed lower values (**Table 2 and Supplementary Figures S2 and S3**).

For the individual Linzer items, lack of control over health decreased from 42.5 at Q0 to 35.5 at Q6 and 33.8 at Q18. In the cohort-adjusted diagnosis-specific model, lack of control showed significant effects of time (F=8.48; p<0.001) and diagnosis (F=6.58; p<0.001), but no significant time × diagnosis interaction (F=1.06; p=0.388). Scores reflecting low hope for obtaining a diagnosis increased from 18.6 at Q0 to 31.3 at Q6 and 36.2 at Q18, with significant effects of time (F=13.23; p<0.001) and diagnosis (F=3.09; p=0.003), but no significant time × diagnosis interaction (F=1.11; p=0.343) (**Table 2**).

In exploratory cohort-adjusted pooled predictor analyses, significant time × predictor interactions were observed across several SFSQ outcomes, most consistently for age and total lifetime number of syncopal episodes. Recent syncope burden and presyncope also showed significant time × predictor interactions for selected outcomes, including IS, SDS, and lack of control over

Table 2 Summary of longitudinal SFSQ outcomes, diagnosis-specific models, item-level results, and significant exploratory predictor x time interactions

Section	Outcome	Predictor / component	Q0	Q6	Q18	Time effect	Diagnosis effect	Interaction / predictor × time F	Interaction / predictor × time p	Key finding(s)
A. Pooled time effects	IS	Overall time	30.0	24.0	22.8	F=16.65; p<0.001	—	—	—	Q0–Q6 and Q0–Q18 were significant; Q6–Q18 was not significant (p=0.336).
	FWS	Overall time	40.0	28.8	24.6	F=99.55; p<0.001	—	—	—	All pairwise comparisons were significant (all p<0.001).
	SDS	Overall time	35.1	27.4	24.8	F=54.65; p<0.001	—	—	—	Q0–Q6 and Q0–Q18 were significant (both p<0.001); Q6–Q18 was also significant (p=0.007).
B. Diagnosis-specific longitudinal models	IS	Time × diagnosis	—	—	—	F=8.76; p<0.001	F=11.95; p<0.001	F=1.88	p=0.026	Impairment differed by diagnostic group and showed diagnosis-specific longitudinal trajectories.
	FWS	Time × diagnosis	—	—	—	F=28.73; p<0.001	F=3.63; p=0.001	F=1.72	p=0.047	Fear/worry burden differed by diagnostic group, with modest but significant differences in trajectory.
	SDS	Time × diagnosis	—	—	—	F=20.76; p<0.001	F=9.54; p<0.001	F=2.12	p=0.009	Overall syncope-related dysfunction differed by diagnosis; functional TLOC showed the highest burden, whereas reflex and cardiac syncope showed lower values.
C. Individual Linzer items	LoC	Time × diagnosis	42.5	35.5	33.8	F=8.48; p<0.001	F=6.58; p<0.001	F=1.06	p=0.388	Perceived lack of control declined over follow-up, without evidence of diagnosis-specific trajectories.
	LH	Time × diagnosis	18.6	31.3	36.2	F=13.23; p<0.001	F=3.09; p=0.003	F=1.11	p=0.343	Low hope of obtaining a diagnosis increased over follow-up, without evidence of diagnosis-specific trajectories.
D. Significant exploratory predictor × time interactions	IS	Age	—	—	—	—	—	F(2,727.8) =7.03	p=0.001	Age shaped impairment trajectories.
	IS	Lifetime syncope burden	—	—	—	—	—	F(2,607.0) =3.84	p=0.022	Lifetime syncope burden shaped impairment trajectories.

	IS	Recent syncope burden	—	—	—	—	—	F(2,609.3) =3.28	p=0.038	Recent syncope burden shaped impairment trajectories.
	IS	Presyncope	—	—	—	—	—	F(2,707.0) =3.76	p=0.024	Presyncope shaped impairment trajectories.
	FWS	Age	—	—	—	—	—	F(2,861.5) =6.03	p=0.003	Older age was associated with lower fear/worry over time.
	FWS	Lifetime syncope burden	—	—	—	—	—	F(2,786.9) =4.85	p=0.008	Lifetime syncope burden shaped fear/worry trajectories.
	SDS	Age	—	—	—	—	—	F(2,720.9) =7.17	p=0.001	Age shaped SDS trajectories.
	SDS	Lifetime syncope burden	—	—	—	—	—	F(2,622.7) =6.54	p=0.002	Lifetime syncope burden shaped SDS trajectories.
	SDS	Recent syncope burden	—	—	—	—	—	F(2,689.1) =4.34	p=0.013	Recent syncope burden shaped SDS trajectories.
	SDS	Presyncope	—	—	—	—	—	F(2,694.7) =3.89	p=0.021	Presyncope shaped SDS trajectories.
	LoC	Age	—	—	—	—	—	F(2,876.2) =9.53	p<0.001	Age shaped perceived lack of control trajectories.
	LoC	Lifetime syncope burden	—	—	—	—	—	F(2,774.0) =3.73	p=0.025	Lifetime syncope burden shaped perceived lack of control trajectories.
	LoC	Recent syncope burden	—	—	—	—	—	F(2,830.3) =3.45	p=0.032	Recent syncope burden shaped perceived lack of control trajectories.
	LoC	Presyncope	—	—	—	—	—	F(2,825.8) =3.92	p=0.020	Presyncope shaped perceived lack of control trajectories.
	LH	Long-term absenteeism	—	—	—	—	—	F(30,246.7) =1.57	p=0.035	Long-term absenteeism shaped low hope trajectories.
	LH	Reduced working hours	—	—	—	—	—	F(19,279.6) =1.98	p=0.010	Reduced working hours shaped low hope trajectories.

Summary of longitudinal Syncope Functional Status Questionnaire analyses across Q0, Q6, and Q18. The table presents estimated scores where applicable, global time effects, diagnosis effects, time-by-diagnosis interactions, item-level results for lack of control over health and low hope of obtaining a diagnosis, and statistically significant exploratory predictor-by-time interactions. Values are estimated marginal means unless stated otherwise. Q0 indicates baseline; Q6, first follow-up assessment at 3–6 months; Q18, final follow-up assessment at 12–18 months. Higher SFSQ scores indicate greater syncope-specific burden. Higher LoC and LH scores indicate less favorable perceived control and diagnostic expectation, respectively. Section D reports statistically significant exploratory predictor × time interactions only and should not be interpreted as a complete overview of all tested predictors. Lifetime syncope burden refers to the total lifetime number of syncopal episodes; recent syncope burden refers to syncopal episodes in the preceding year. FWS = fear/worry score; FTLOC = functional transient loss of consciousness; IS = impairment score; LH = low hope of obtaining a diagnosis; LoC = lack of control over health; SDS = Syncope Dysfunction Score; SFSQ = Syncope Functional Status Questionnaire; TLOC = transient loss of consciousness.

health. For low hope for obtaining a diagnosis, significant interactions were observed only for long-term absenteeism and reduced working hours (**Table 2**).

Change-based SFSQ recovery quartiles

For the change-based SFSQ recovery quartile analysis, patients were ranked according to interval-specific change in SDS and divided into quartiles for Q0–Q6, Q6–Q18, and Q0–Q18. Start-interval characteristics and mixed-model results are shown in **Table 3**.

Across SDS recovery quartiles, syncope burden in the preceding year and total lifetime syncope burden differed significantly in all three follow-up intervals. For Q0–Q6, quartiles differed for syncope burden in the preceding year (p=0.026) and lifetime syncope burden (p=0.043), whereas cohort distribution did not differ significantly (p=0.307). For Q6–Q18, quartiles differed for cohort (p=0.023), sex (p=0.009), syncope burden in the preceding year (p=0.003), and lifetime syncope burden (p=0.018). For Q0–Q18, quartiles differed for age (p=0.030), sex (p=0.006), syncope burden in the preceding year (p<0.001), and lifetime syncope burden (p<0.001), with a borderline difference in cohort distribution (p=0.050). Presyncope, long-term absenteeism, and reduced working hours did not differ significantly across quartiles in any interval (**Table 3**).

In cohort-adjusted interval-specific mixed-effects models, SDS and FWS showed significant effects of time, recovery quartile, and time × recovery quartile interaction across all three intervals. IS and lack of control over health showed significant quartile and time × recovery quartile effects across all intervals, although the main effect of time was not significant for the Q6–Q18 interval for IS (p=0.403) or lack of control over health (p=0.318). For low hope for obtaining a diagnosis, the effect of time was significant across all intervals, whereas quartile and time × recovery quartile effects were significant only for Q0–Q6 (quartile: p=0.026; time × quartile: p=0.039) and not for Q6–Q18 or Q0–Q18 (**Table 3**).

Generic health-related quality of life in secondary care: RAND-36

The secondary care cohort consisted of 367 patients with RAND-36 data at baseline. Follow-up questionnaires were available in 82.6% (n=303) at Q6 and 88.0% (n=323) at Q18. Baseline characteristics and diagnostic distribution are shown in **Table 1**.

Across the eight RAND-36 domains, significant global time effects were observed in 4/8 domains, but not in the other 4 domains. Physical role functioning increased from 62.3 at Q0 to 70.6 at Q6 and 72.0 at Q18. Energy/fatigue increased from 59.9 at Q0 to 64.4 at Q6 and 64.8 at Q18. Emotional well-being increased from 74.1 at Q0 to 76.0 at Q6 and 76.7 at Q18. General health changed from 63.2 at Q0 to 62.2 at Q6 and 60.4 at Q18. Physical functioning, emotional role functioning, social functioning, and pain did not show significant global time effects. Estimated marginal mean trajectories and pairwise comparisons for all RAND-36 domains are shown in **Figure 3**.

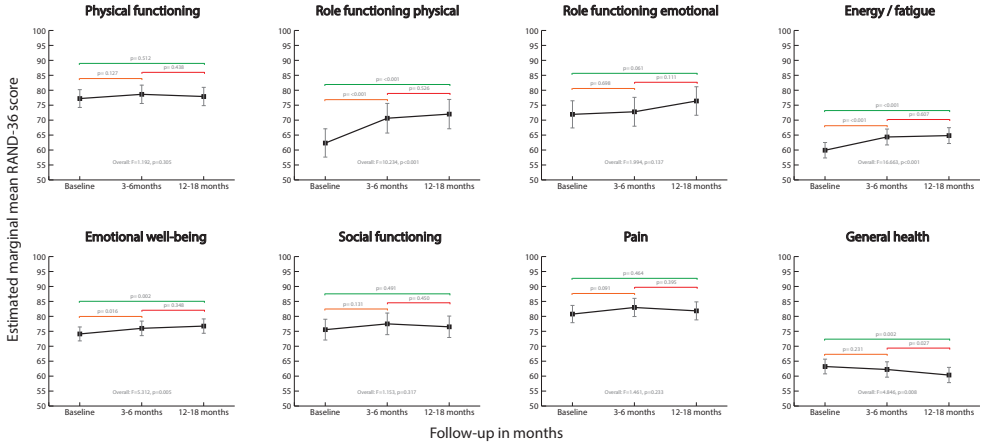
Exploratory RAND-36 predictor findings are summarized in **Supplementary Table S1 and Supplementary Figure S4**.

Table 3. Exploratory quartile-based responder analysis according to change in Syncope Dysfunction Score across three follow-up intervals

Panel A. Start-interval characteristics compared across quartiles of change in SDS				
Domain	**Characteristic**	**Q0–Q6 P=**	**Q6–Q18 P=**	**Q0–Q18 P=**
Clinical setting	Cohort	0.307	0.023	0.050
Demographics	Age	0.182	0.600	0.030
	Sex	0.251	0.009	0.006
Clinical profile	Presyncope	0.499	0.268	0.768
Syncope burden	Syncope burden in preceding year	0.026	0.003	<0.001
	Lifetime syncope burden	0.043	0.018	<0.001
Work participation	Long-term absenteeism	0.441	0.602	0.756
	Reduced working hours	0.658	0.499	0.683
Panel B. Type III tests from cohort-adjusted mixed models for SFSQ outcomes across quartiles of change in SDS				
Outcome	**Effect**	**Q0–Q6 P=**	**Q6–Q18 P=**	**Q0–Q18 P=**
SDS	Time	<0.001	<0.001	<0.001
	Quartile	<0.001	<0.001	<0.001
	Time × quartile	<0.001	<0.001	<0.001
IS	Time	<0.001	0.403	<0.001
	Quartile	<0.001	<0.001	<0.001
	Time × quartile	<0.001	<0.001	<0.001
FWS	Time	<0.001	<0.001	<0.001
	Quartile	<0.001	<0.001	<0.001
	Time × quartile	<0.001	<0.001	<0.001
Lack of control	Time	<0.001	0.318	<0.001
	Quartile	0.002	<0.001	<0.001
	Time × quartile	<0.001	<0.001	<0.001
Low hope for a diagnosis	Time	<0.001	0.007	<0.001
	Quartile	0.026	0.199	0.554
	Time × quartile	0.039	0.477	0.159

Exploratory analysis of quartiles of change in Syncope Dysfunction Score over Q0-Q6, Q6-Q18, and Q0-Q18. Panel A compares interval-start demographic and clinical characteristics across quartiles. Panel B shows Type III tests from mixed-effects models including time, quartile group, and time-by-quartile interaction. For Q0-Q6 and Q0-Q18 analyses, interval-start characteristics were assessed at Q0; for Q6-Q18 analyses, they were assessed at Q6. P values are uncorrected for multiple testing. Abbreviations: FWS = fear/worry score; IS = impairment score; Q0 = baseline; Q6 = 3-6 month follow-up; Q18 = 12-18 month follow-up; SDS = Syncope Dysfunction Score.

Figure 3: Longitudinal changes in RAND-36 domain scores



Estimated marginal means with 95% confidence intervals for the eight RAND-36 domains at baseline, 3-6 months, and 12-18 months in the general hospitals cohort. Overall P values are derived from linear mixed-effects models, and pairwise time comparisons are shown above each panel. Higher scores indicate better HRQoL. Abbreviations: RAND-36 = RAND 36-Item Health Survey.

Generic health-related quality of life in the tertiary setting: SF-12

The tertiary care cohort comprised 264 patients with SF-12 data at baseline. Follow-up questionnaires were available in 84.8% (n=224) at Q6 and 89.0% (n=235) at Q18. Baseline characteristics and diagnostic distribution are shown in **Table 1**.

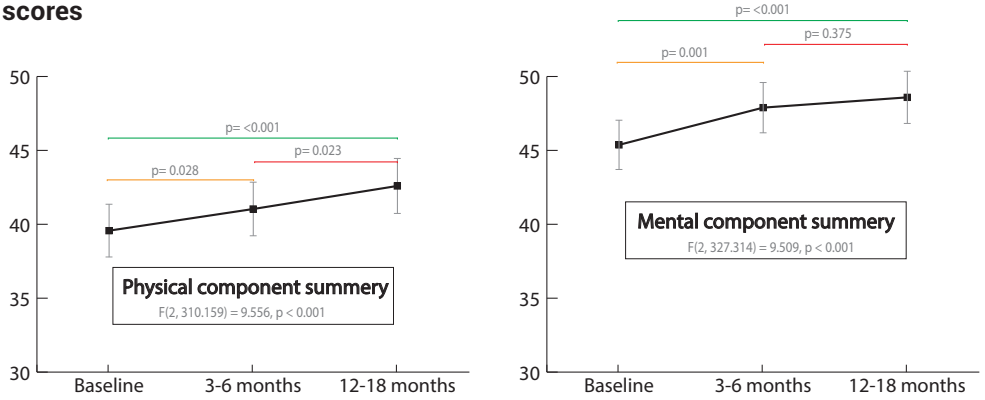
Significant global time effects were observed for both SF-12 summary scores. The estimated marginal mean PCS-12 score increased from 39.6 at Q0 to 41.0 at Q6 and 42.6 at Q18, with a significant overall effect of time (F=9.556; p<0.001). Pairwise comparisons were significant for Q0–Q6, Q6–Q18, and Q0–Q18. The estimated marginal mean MCS-12 score increased from 45.4 at Q0 to 47.9 at Q6 and 48.6 at Q18, with a significant overall effect of time (F=9.509; p<0.001). Pairwise comparisons were significant for Q0–Q6 and Q0–Q18, but not for Q6–Q18. Estimated marginal mean trajectories and pairwise comparisons for PCS-12 and MCS-12 are shown in **Figure 4**. Diagnosis-stratified PCS-12 and MCS-12 trajectories are shown in **Supplementary Figures S6 and S7**.

Exploratory SF-12 predictor findings are summarized in **Supplementary Table S3 and Supplementary Figure S5.**

Patient-level concordance between syncope-specific (SFSQ) and generic (RAND-36 and SF-12)

To examine the relationship between syncope-specific recovery and generic HRQoL change, Q0–Q18 directional changes in SDS and generic HRQoL scores were compared at patient level (**Table 4**). In the secondary-care cohort, 276 patients had complete paired Q0 and Q18 data for SDS and the corresponding RAND-36 domain. Across RAND-36 domains, SDS change was concordant with generic HRQoL change in 28.3% to 56.5% of patients, discordant in 12.0% to 34.1%, and stable/no directional change in 17.0% to 59.8%. Concordance was highest for energy/fatigue (156/276, 56.5%), emotional well-being (142/276, 51.4%), and

Figure 4: Longitudinal changes in SF-12 physical and mental component summary scores



Estimated marginal means with 95% confidence intervals for PCS-12 and MCS-12 at baseline, 3-6 months, and 12-18 months in the tertiary cohort. Overall P values are derived from linear mixed-effects models, and pairwise comparisons are shown above the plots. Higher scores indicate better health-related quality of life. Abbreviations: SF-12 = 12-Item Short Form Health Survey.

physical functioning (138/276, 50.0%). Discordance was most frequent for general health (94/276, 34.1%), emotional well-being (85/276, 30.8%), and pain (74/276, 26.8%). Stable/no directional change was most frequent for social functioning (165/276, 59.8%), role emotional (159/276, 57.6%), and role physical (145/276, 52.5%).

In the tertiary-care cohort, 107 patients had complete paired Q0 and Q18 data for SDS and the corresponding SF-12 summary score. SDS change was concordant with PCS-12 change in 60/107 patients (56.1%) and discordant in 39/107 patients (36.4%). For MCS-12, SDS change was concordant in 62/107 patients (57.9%) and discordant in 37/107 patients (34.6%). Stable/no directional change was observed in 8/107 patients (7.5%) for both PCS-12 and MCS-12.

DISCUSSION

The main finding of this prospective longitudinal study was that structured assessment of patients with syncope was followed by improvement in several clinically relevant aspects of syncope-specific burden and HRQoL, although recovery was not uniform across outcomes, cohorts, or patient subgroups. Improvement was most evident in the syncope specific SFSQ outcomes, but was also observed in the more generic SF-12 summary scores for tertiary care, and selected RAND-36 domains in secondary care.

Importantly, patient-level concordance analyses showed that syncope-specific recovery and generic HRQoL improvement frequently moved in the same clinical direction, but were not interchangeable. This supports the complementary use of syncope-specific and generic PROMs in longitudinal syncope care. The other important finding is that, SFSQ burden differed between the secondary and tertiary care cohorts, and significant time × cohort interactions were observed for IS, FWS, and SDS. Therefore, the pooled SFSQ findings should be interpreted as cohort-adjusted estimates across two clinically distinct settings rather than as evidence of identical recovery patterns. Nevertheless, the direction of change

Table 4. Patient-level concordance between syncope-specific and generic HRQoL change from Q0 to Q18

Instrument	Generic HRQoL measure	Complete paired cases, n	Concordant, n (%)	Discordant, n (%)	Stable/no directional change, n (%)
RAND-36	Physical functioning	276	138 (50.0)	68 (24.6)	70 (25.4)
RAND-36	Role physical	276	89 (32.2)	42 (15.2)	145 (52.5)
RAND-36	Role emotional	276	79 (28.6)	38 (13.8)	159 (57.6)
RAND-36	Energy/fatigue	276	156 (56.5)	73 (26.4)	47 (17.0)
RAND-36	Emotional well-being	276	142 (51.4)	85 (30.8)	49 (17.8)
RAND-36	Social functioning	276	78 (28.3)	33 (12.0)	165 (59.8)
RAND-36	Pain	276	114 (41.3)	74 (26.8)	88 (31.9)
RAND-36	General health	276	127 (46.0)	94 (34.1)	55 (19.9)
SF-12	PCS-12	107	60 (56.1)	39 (36.4)	8 (7.5)
SF-12	MCS-12	107	62 (57.9)	37 (34.6)	8 (7.5)

Patient-level Q0–Q18 directional change in Syncope Dysfunction Score was compared with directional change in generic HRQoL domains or summary scores. Concordant change indicates that SDS and the corresponding generic HRQoL measure changed in the same clinical direction, i.e. both indicated improvement or both indicated deterioration. Discordant change indicates opposite clinical directions, i.e. improvement in one measure and deterioration in the other. Stable/no directional change indicates that either SDS or the corresponding generic HRQoL measure showed no change. No minimal important-difference threshold was applied. Higher RAND-36 and SF-12 scores indicate better generic HRQoL, whereas lower SDS indicates lower syncope-specific burden. Abbreviations: HRQoL = health-related quality of life; MCS-12 = Mental Component Summary score of the SF-12; PCS-12 = Physical Component Summary score of the SF-12; Q0 = baseline assessment; Q18 = 12–18-month follow-up assessment; RAND-36 = RAND 36-Item Health Survey; SDS = Syncope Dysfunction Score; SF-12 = 12-Item Short Form Health Survey.

generally supported improvement in syncope-specific burden after structured evaluation and subsequent management.

Syncope-specific burden

Both setting-specific trajectories and the cohort-adjusted pooled SFSQ analysis showed a reduction in syncope-specific burden during follow-up. The largest improvements over time were observed for fear/worry and the SDS, suggesting that emotional and disease-specific burden may continue to improve beyond the early post-evaluation phase,[2, 26] perhaps because they become more

confident in how to manage it.

The different trajectories of lack of control over health and low hope for obtaining a diagnosis deserve separate interpretation. Lower lack-of-control scores suggest that patients felt more in control of their health during follow-up. In contrast, higher scores for low hope indicate less expectation of receiving a further diagnosis. This may reflect that, after completion of the main diagnostic pathway, patients no longer expected additional diagnostic clarification, despite experiencing greater control over their condition.

The IS improved mainly between baseline and early follow-up and then stabilised. This suggests that functional impairment may improve relatively early after structured evaluation, whereas fear and disease-specific concerns may improve more gradually.

Diagnosis-specific analyses showed that recovery was not uniform across diagnostic groups. Patients with functional syncope mimic had the highest syncope-specific burden, in keeping with previous literature showing poorer HRQoL and greater symptom burden in this group. Reflex syncope and cardiac syncope showed more favorable trajectories, although these findings should be interpreted in the context of case mix and subgroup size. Findings in smaller diagnostic groups, including epilepsy, should be interpreted cautiously because of limited numbers and clinical diversity.[6]

Change-based recovery patterns

The change-based SFSQ quartile analyses showed that recovery clustered into distinct patterns rather than following a uniform course. Because quartiles were defined by interval-specific change in SDS, these analyses should be interpreted as descriptive recovery-pattern analyses rather than independent prediction models.

Recent syncope burden and lifetime syncope burden were the most consistent differences between more favorable and less favorable recovery trajectories. This suggests that both recent event frequency and cumulative lifetime exposure may influence later functional recovery. Age and sex showed less consistent associations, suggesting that recovery patterns were mainly shaped by syncope burden rather than by demographic characteristics alone. Cohort distribution also differed across recovery quartiles for Q6–Q18 and was borderline different for Q0–Q18, indicating that recovery patterns partly reflected differences between the secondary and tertiary care settings. In contrast, low hope for obtaining a diagnosis showed less consistent time-by-quartile effects than the broader SFSQ outcomes, suggesting a more uniform course than broader disease-specific impairment.

Generic health-related quality of life in secondary care

RAND 36 domains related to daily functioning, vitality, and emotional well-being improved during follow-up, whereas general health declined despite a significant overall time effect. Physical functioning, emotional role functioning, social functioning, and pain did not show clear time-related change.

This pattern is clinically plausible. Daily functioning and emotional burden may respond to diagnostic clarification, education, reassurance, and treatment. In

contrast, general health reflects a broader and less easily modifiable perception of health, particularly in an older general hospital cohort with more comorbidity and cardiac diagnoses. Previous syncope studies support this pattern, showing that HRQoL may improve after presentation and evaluation, but not uniformly across all domains.[2, 23, 26, 32, 33]

Generic HRQoL in tertiary care

The two SF-12 summary scores followed different time courses. Mental HRQoL improved mainly during the first 6 months, whereas physical HRQoL improved more gradually, which may reflect early reduction of uncertainty followed by slower restoration of confidence and daily functioning.[2, 34]

Relationship between syncope-specific and generic HRQoL change

The patient-level concordance analysis strengthens the interpretation of these findings. Syncope-specific recovery and generic HRQoL improvement were related, but not identical. In both cohorts, a substantial proportion of patients showed concordant improvement or worsening, indicating that changes in syncope-specific burden often paralleled broader changes in perceived health. However, discordance was also common. This means that some patients improved in syncope-specific burden without parallel improvement in generic HRQoL, whereas others showed generic HRQoL improvement without comparable improvement in syncope-specific burden.

This distinction is clinically important. The SFSQ captures disease-specific aspects of recovery, including functional restriction, fear, worry, perceived control, and diagnostic expectation. Generic instruments such as RAND-36 and SF-12 capture broader physical, emotional, and social aspects of health that may also be influenced by age, comorbidity, functional reserve, and other non-syncope-related factors. Therefore, generic HRQoL instruments should not be interpreted as substitutes for syncope-specific PROMs. Conversely, syncope-specific improvement alone does not fully describe the patient's broader recovery. These findings support the combined use of disease-specific and generic PROMs when evaluating outcomes after structured syncope care.

Exploratory predictor findings

The exploratory predictor analyses showed that post-syncope HRQoL is affected by several factors rather than by one dominant predictor. The cohort-adjusted pooled SFSQ analyses most consistently pointed to burden-related variables, including age, lifetime syncope burden, recent syncope burden, and presyncope. On the other hand, RAND-36 and SF-12 findings varied across domains and summary scores. This variability further supports the interpretation that syncope-specific and generic HRQoL outcomes capture overlapping but distinct dimensions of recovery.

Because these analyses were exploratory, univariable, and not corrected for multiple testing, they should be interpreted as hypothesis-generating rather than confirmatory.

Strengths and limitations

The main strengths of this study are its prospective longitudinal design in two distinct care settings, repeated HRQoL measurements, and the use of syncope-specific PROMs as well as generic HRQoL questionnaires. Linear mixed-effects models allowed inclusion of all available observations, while use of the same SFSQ in both cohorts enabled pooled syncope-specific analyses. In addition, the patient-level concordance analysis directly examined how syncope-specific recovery related to generic HRQoL change, thereby clarifying the complementary role of disease-specific and generic outcome measures.

Several limitations should be considered. First, the observational design prevents causal conclusions. Improvements during follow-up cannot be attributed with certainty to structured diagnostic evaluation, or subsequent management separately.

Second, the predictor analyses were exploratory and univariable, and therefore did not account for overlap between predictors. Several diagnostic groups and categorical predictor strata were small, so subgroup-specific findings should be interpreted cautiously.

Third, generic HRQoL instruments differed between the two settings investigated. Although this reflected the independent design of the two cohorts and prevented direct pooling of RAND-36 and SF-12 outcomes, it also allowed assessment of whether syncope-specific improvement related to generic HRQoL change across two commonly used generic instruments. This was supported by the observed cohort effects and time × cohort interactions for several SFSQ outcomes. Although cohort adjustment reduced the influence of these differences on the pooled estimates, residual heterogeneity cannot be excluded.

CONCLUSION

Structured guideline-based diagnostic evaluation and subsequent management, was associated with improvement in syncope-specific, and generic HRQoL across general-hospital and tertiary-care settings. These findings support the clinical value of an integrated syncope-care pathway irrespective of the clinical setting, albeit that recovery is heterogeneous among individual patients and partly shaped by syncope burden and its functional consequences.

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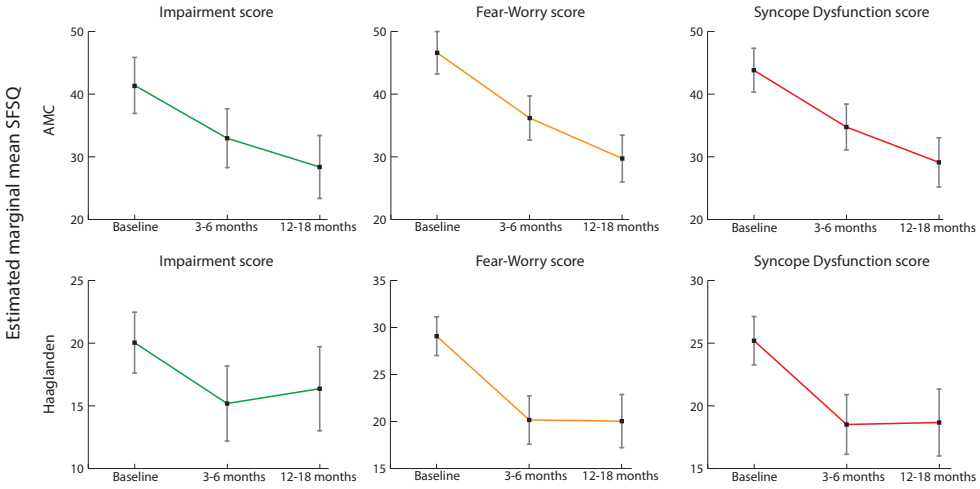
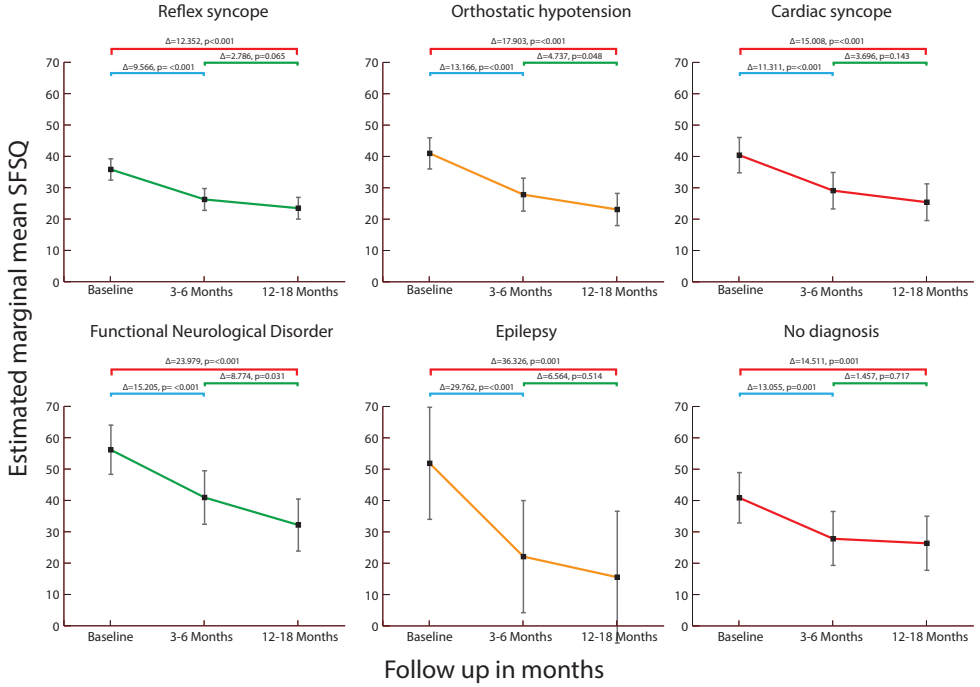
Supplementary Figure S1: Setting-specific longitudinal changes in SFSQ impairment, fear-worry and syncope dysfunction score



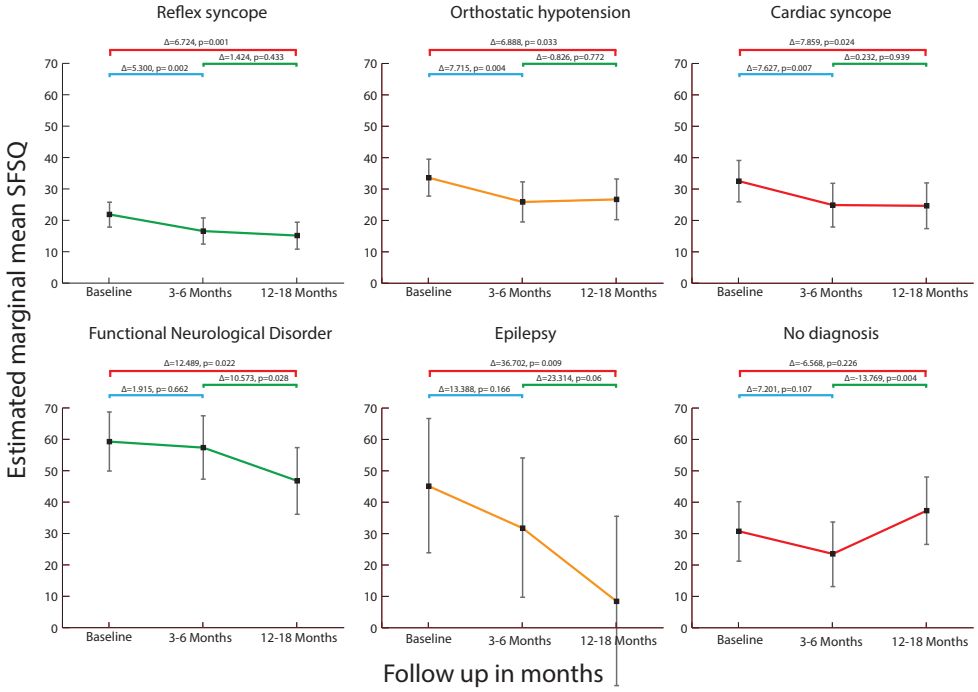
Estimated marginal means with 95% confidence intervals for SFSQ impairment score, fear/worry score, and Syncope Dysfunction Score across follow-up, shown separately for the secondary and tertiary hospitals cohorts. Higher scores indicate greater syncope-specific burden. Abbreviations: SFSQ = Syncope Functional Status Questionnaire.

Supplementary Figure S2: Diagnosis-specific longitudinal changes in SFSQ fear/ worry score



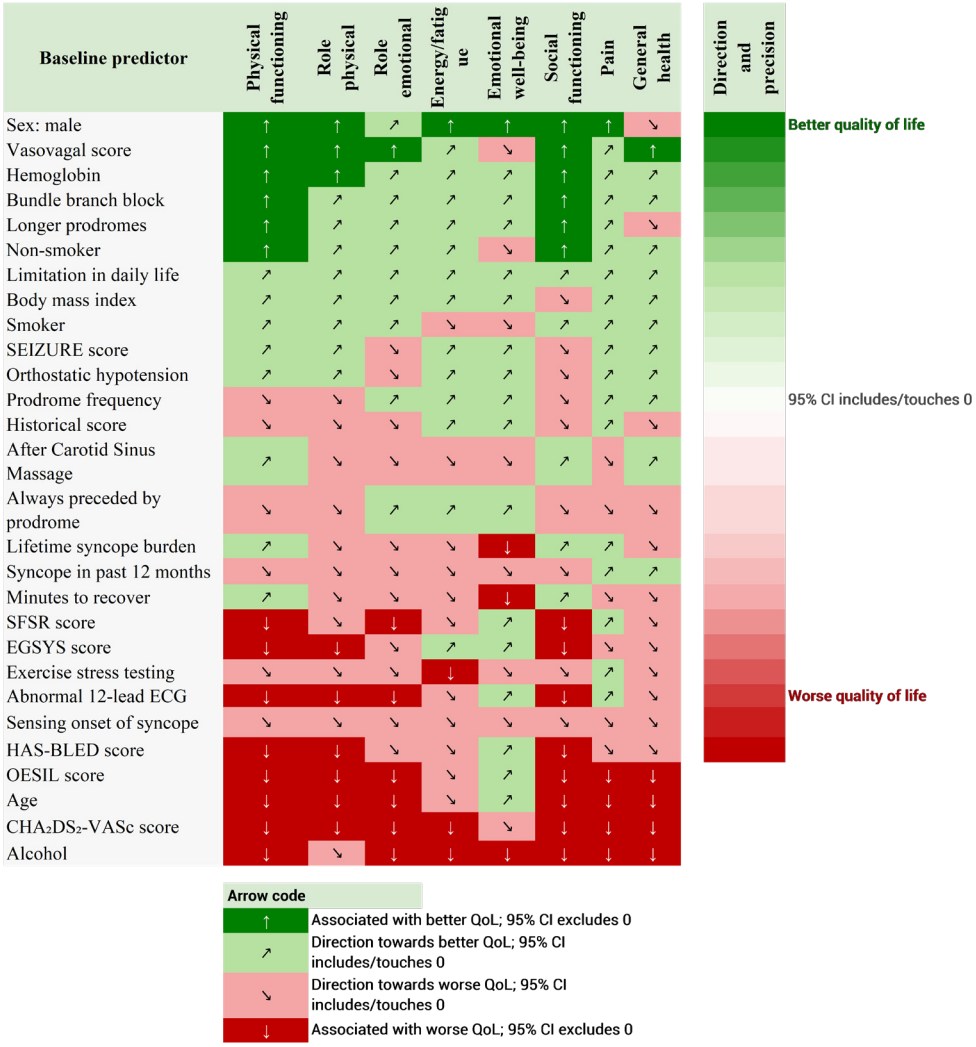
Estimated marginal means with 95% confidence intervals for the SFSQ fear/worry score across follow-up, stratified by final diagnosis. Pairwise time comparisons are shown within diagnostic groups. Higher scores indicate greater fear or worry related to syncope. Abbreviations: SFSQ = Syncope Functional Status Questionnaire.

Supplementary Figure S3: Diagnosis-specific longitudinal changes in SFSQ impairment score



Estimated marginal means with 95% confidence intervals for the SFSQ impairment score across follow-up, stratified by final diagnosis. Pairwise time comparisons are shown within diagnostic groups. Higher scores indicate greater syncope-related functional impairment. Abbreviations: SFSQ = Syncope Functional Status Questionnaire.

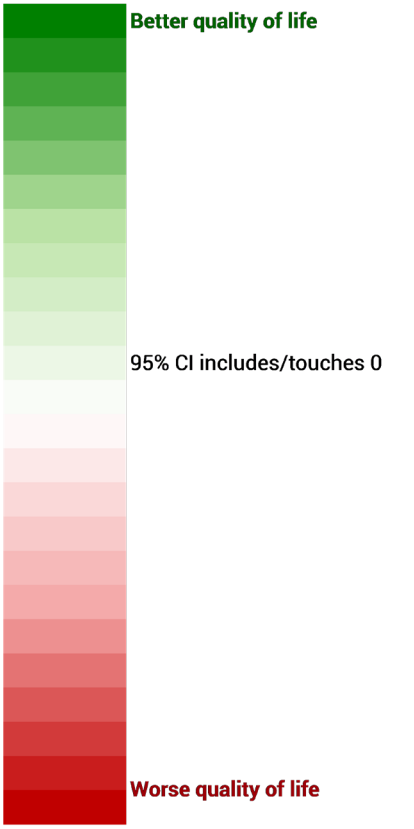
Supplementary Figure S4. Exploratory predictors of quality of life according to RAND-36 domains



Green arrows indicate predictors associated with better quality of life, whereas red arrows indicate predictors associated with worse quality of life. Vertical arrows indicate estimates with 95% confidence intervals excluding zero. Diagonal arrows indicate the direction of the point estimate when the 95% confidence interval included or touched zero.

Supplementary Figure S5. Exploratory predictors of SF-12 quality-of-life outcomes

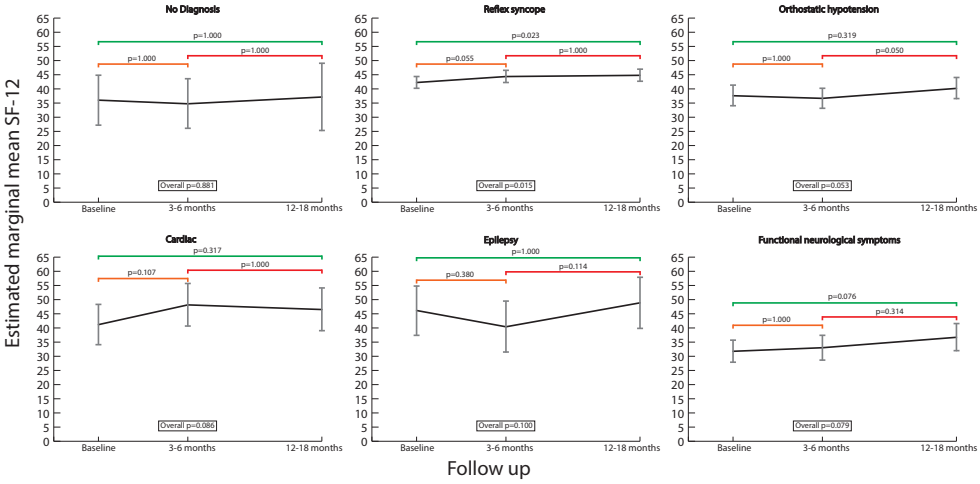
Baseline predictor	PCS-12	MCS-12
Sex (male vs female ref)	↑	↑
Work hours/week	↑	↑
Active stand OH positive	↗	↑
Syncope during Valsalva	↑	↗
Syncope forced insp/exp	↑	↗
Prior beta-blocker	↗	↗
Prior carotid duplex	↗	↗
Prior salt advice	↗	↗
Syncope on active stand	↗	↗
Syncope on tilt	↗	↗
Active stand IOH positive	↘	↗
Implantable loop recorder	↗	↘
Pre-syncope	↘	↗
Prior QoL issue	↗	↘
Prior catheterisation	↗	↘
Prior manoeuvres	↗	↘
Prior perfusion scan	↗	↘
Syncope during CSH	↘	↗
CSH positive	↘	↘
Medication stopped	↘	↘
Pacemaker implantation	↘	↘
Prior exercise advice	↘	↘
Syncope during manoeuvres	↘	↘
Syncope visits	↘	↘
Tilt test positive	↘	↘
Prior cardiac MRI	↓	↘
Syncopal episodes past year	↓	↘
Total syncopal episodes	↓	↘



Arrow code	
↑	Associated with better QoL; 95% CI excludes 0
↗	Direction towards better QoL; 95% CI includes/touches 0
↘	Direction towards worse QoL; 95% CI includes/touches 0
↓	Associated with worse QoL; 95% CI excludes 0

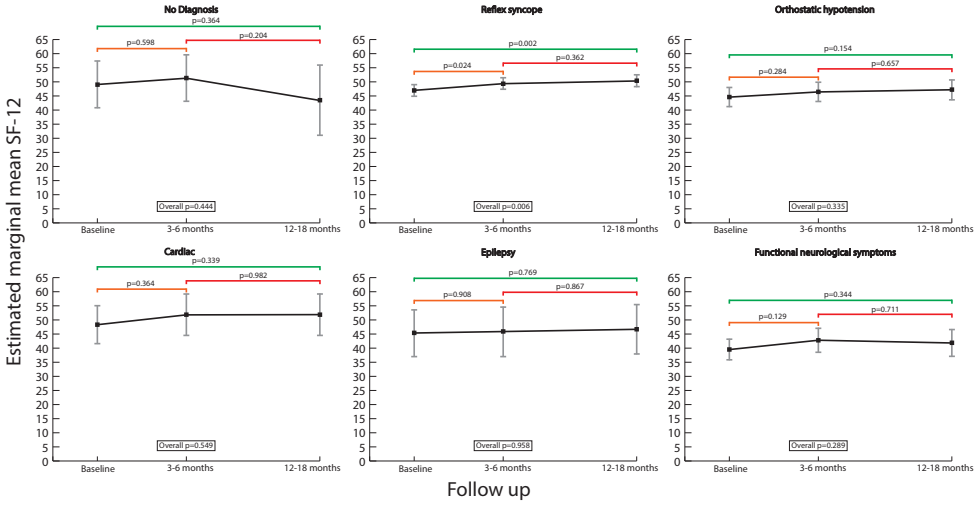
Green arrows indicate predictors associated with better quality of life, whereas red arrows indicate predictors associated with worse quality of life. Vertical arrows indicate estimates with 95% confidence intervals excluding zero. Diagonal arrows indicate the direction of the point estimate when the 95% confidence interval included or touched zero.

Supplementary Figure S6 Diagnosis-stratified longitudinal changes in SF-12 physical component summary score



Estimated marginal means with 95% confidence intervals for Physical component summary score across follow-up, stratified by final diagnosis in the tertiary cohort. Pairwise time comparisons are shown within diagnostic groups. Higher scores indicate better physical health-related quality of life. Abbreviations: SF-12 = 12-Item Short Form Health Survey.

Supplementary figure S7: Diagnosis-stratified longitudinal changes in SF-12 mental component summary score



Estimated marginal means with 95% confidence intervals for mental component summary score across follow-up, stratified by final diagnosis in the academic cohort. Pairwise time comparisons are shown within diagnostic groups. Higher scores indicate better mental health-related quality of life. Abbreviations: SF-12 = 12-Item Short Form Health Survey.

Supplementary Table S1. Summary of significant RAND-36 domain×predictor findings

Significant findings were defined as Type III P<0.05 in the definitive domain-specific mixed models. Counts are based on the supplied RAND-36 summary workbook. Unique significant combinations were calculated as main effects + time×predictor interactions − overlap.

RAND-36 domain	Main effects, n	Time×predictor interactions, n	Both main + interaction, n	Main only, n	Interaction only, n	Unique significant combinations, n	Significant main-effect predictors	Significant time×predictor interaction predictors
Physical functioning	28	14	10	18	4	32	No alcohol use; Always perceiving syncope coming; Marital status; CHA2DS2-VASc score; Prodrome duration; ECG PQ interval; ECG QTc interval; ECG axis; ECG heart rate; Normal ECG; ECG rhythm; EGSYS score; LVEF; Atrial dilatation; Atrial size; Diastolic dysfunction; Male sex; Weight; HAS-BLED score; Children; Hemoglobin; eGFR; Age; Height; OESIL score; SFSR score; Perceiving syncope coming; Vasovagal score	Bundle branch block; CHA2DS2-VASc score; ECG PQ interval; ECG QRS duration; EGSYS score; LVEF; Atrial dilatation; Atrial size; HAS-BLED score; TSH; eGFR; Age; OESIL score; Carotid sinus massage effect
Role physical	12	12	6	6	6	18	Syncope frequency; Limitations in daily life; CHA2DS2-VASc score; EGSYS score; Male sex; Weight; frequency syncope; Hemoglobin; Haematocrit; Age; Height; OESIL score	Marital status; CHA2DS2-VASc score; ECG PQ interval; ECG axis; EGSYS score; Weight; HAS-BLED score; eGFR; Age; Height; OESIL score; Vasovagal score
Role emotional	6	8	1	5	7	13	No alcohol use; Marital status; CHA2DS2-VASc score; Male sex; Height; Vasovagal score	Marital status; Duration of loss of consciousness; ECG PQ interval; ECG axis; EGSYS score; Diastolic dysfunction; Age; OESIL score
Energy/ fatigue	9	8	2	7	6	15	No alcohol use; Marital status; Recovery time; EGSYS score; Male sex; frequency syncope; T4; Age; Height	CHA2DS2-VASc score; EGSYS score; Atrial dilatation; HAS-BLED score; eGFR; Age; OESIL score; Vasovagal score

Emotional well-being	9	3	0	9	3	12	No alcohol use; Marital status; Recovery time; ECG QTc interval; Male sex; HAS-BLED score; frequency syncope; T4; Height	Bundle branch block; Abnormal exercise test; Carotid sinus massage effect
Social functioning	26	7	6	20	1	27	No alcohol use; Marital status; CHA2DS2-VASc score; Prodrome duration; ECG PQ interval; ECG QTc interval; ECG axis; ECG heart rate; Normal ECG; EGSYS score; LVEF; Atrial dilatation; Atrial size; Diastolic dysfunction; Male sex; Weight; HAS-BLED score; Children; Hemoglobin; eGFR; Age; Height; OESIL score; SFSR score; Perceiving syncope coming; Vasovagal score	Marital status; CHA2DS2-VASc score; EGSYS score; HAS-BLED score; Glucose; Age; OESIL score
Pain	11	7	2	9	5	16	Syncope frequency; No alcohol use; Limitations in daily life; CHA2DS2-VASc score; ECG heart rate; Male sex; Hemoglobin; T4; Height; SEIZURE score; Perceiving syncope coming	Syncope frequency; Always perceiving syncope coming; CHA2DS2-VASc score; Abnormal exercise test; eGFR; Age; OESIL score
General health	6	10	2	4	8	14	No alcohol use; CHA2DS2-VASc score; Atrial dilatation; eGFR; Height; OESIL score	Duration of loss of consciousness; ECG PQ interval; Diastolic dysfunction; eGFR; Glucose; Creatinine; Age; OESIL score; SEIZURE score; Vasovagal score
Total	107	69	29	78	40	147		

Overview of statistically significant exploratory predictor findings across the eight RAND-36 domains. Findings are classified as main effects, time-by-predictor interactions, overlap between both categories, main effects only, interaction effects only, and total unique significant domain-by-predictor combinations. Significance was based on uncorrected Type III P values <0.05. Abbreviations: RAND-36 = RAND 36-Item Health Survey.

Supplementary Table S2. Directional classification of significant RAND-36 main effects

RAND-36 domain	Direction	Predictor label	Beta (β)	95% CI	P value
Physical functioning	Higher RAND-36 score	Atrial dilatation	14,725	8.31 to 21.13	<0.001
		Bundle branch block	10,849	0.92 to 20.78	0.032
		Children	6,764	0.58 to 12.95	0.032
		Height	0,73	0.50 to 0.96	<0.001
		Hemoglobin	7,559	3.19 to 11.93	<0.001
		LVEF	1,223	0.72 to 1.72	<0.001
		Marital status	9,837	0.65 to 19.02	0.036
		Marital status	11,776	1.48 to 22.07	0.025
		Prodrome duration (seconds)	0,027	0.01 to 0.05	0.017
		Sex (Male)	10,473	5.58 to 15.37	<0.001
		Smoking	8,436	2.73 to 14.15	0.004
		Vasovagal score	2,838	1.82 to 3.86	<0.001
		Weight	0,28	0.11 to 0.45	0.002
		eGFR	0,398	0.21 to 0.58	<0.001
	Lower RAND-36 score	Age	-0,608	-0.75 to -0.47	<0.001
		Alcohol	-5,823	-10.80 to -0.85	0.022
		Atrial size	-0,576	-0.95 to -0.20	0.002
		CHA2DS2-VASc score	-7,892	-9.30 to -6.48	<0.001
		ECG PQ interval	-0,146	-0.23 to -0.06	0.001
		ECG QRS duration	-0,137	-0.27 to -0.00	0.043
		ECG QTc interval	-0,142	-0.25 to -0.03	0.011
		ECG heart rate	-0,202	-0.38 to -0.02	0.027
		EGSYS score	-2,215	-3.13 to -1.30	<0.001
		Glucose	-2,657	-4.91 to -0.40	0.021
		HAS-BLED score	-6,389	-8.44 to -4.34	<0.001
		Normal ECG	-9,118	-14.14 to -4.10	<0.001
		OESIL score	-9,895	-12.22 to -7.57	<0.001
		SFSR score	-8,436	-13.37 to -3.50	<0.001

Physical role functioning	Higher RAND-36 score	Atrial dilatation	14,392	3.06 to 25.72	0.013
		Height	0,978	0.57 to 1.39	<0.001
		Hematocrit	223,013	68.94 to 377.09	0.005
		Hemoglobin	13,277	5.51 to 21.04	<0.001
		Sex	13,321	4.72 to 21.92	0.002
		Vasovagal score	3,093	1.27 to 4.92	<0.001
		Weight	0,368	0.06 to 0.67	0.017
		eGFR	0,501	0.18 to 0.82	0.002
	Lower RAND-36 score	Age	-0,554	-0.80 to -0.30	<0.001
		CHA2DS2-VASc score	-8,211	-10.83 to -5.60	<0.001
		EGSYS score	-2,535	-4.15 to -0.92	0.002
		HAS-BLED score	-5,602	-9.24 to -1.97	0.003
		Normal ECG	-8,993	-17.79 to -0.19	0.045
		OESIL score	-9,803	-14.00 to -5.60	<0.001
Emotional role functioning	Higher RAND-36 score	Height	0,617	0.21 to 1.02	0.003
		Vasovagal score	2,6	0.83 to 4.37	0.004
		eGFR	0,339	0.02 to 0.65	0.035
	Lower RAND-36 score	Age	-0,338	-0.58 to -0.09	0.007
		Alcohol	-11,825	-20.19 to -3.46	0.006
		CHA2DS2-VASc score	-5,287	-7.85 to -2.72	<0.001
		ECG heart rate	-0,396	-0.70 to -0.09	0.010
		Normal ECG	-9,259	-17.76 to -0.76	0.033
		OESIL score	-6,617	-10.70 to -2.53	0.002
		SFSR score	-9,52	-17.89 to -1.15	0.026
Energy/fatigue	Higher RAND-36 score	Height	0,377	0.18 to 0.58	<0.001
		Sex	7,813	3.73 to 11.89	<0.001
	Lower RAND-36 score	Alcohol	-7,179	-11.28 to -3.08	<0.001
		CHA2DS2-VASc score	-2,349	-3.63 to -1.07	<0.001
		Exercise test abnormality	-10,143	-19.77 to -0.52	0.039
		Recovery time (minutes)	-0,004	-0.01 to -0.00	0.041

Emotional well-being	Higher RAND-36 score	Free T4	1,832	0.50 to 3.17	0.007
		Sex	5,289	1.71 to 8.87	0.004
	Lower RAND-36 score	Alcohol	-5,179	-8.78 to -1.58	0.005
		Lifetime syncope frequency	-0,057	-0.11 to -0.00	0.032
		Marital status	-10,425	-19.96 to -0.89	0.032
		Recovery time (minutes)	-0,004	-0.01 to -0.00	0.013
Social functioning	Higher RAND-36 score	Atrial dilatation	14,843	7.11 to 22.58	<0.001
		Bundle branch block	12,126	0.22 to 24.03	0.046
		Children	7,528	0.07 to 14.99	0.048
		Height	0,799	0.52 to 1.08	<0.001
		Hemoglobin	7,94	2.58 to 13.30	0.004
		LVEF	1,311	0.71 to 1.92	<0.001
		Prodrome duration (seconds)	0,031	0.00 to 0.06	0.025
		Sex	11,765	5.83 to 17.70	<0.001
		Smoking	9,96	3.07 to 16.85	0.005
		Vasovagal score	2,855	1.62 to 4.09	<0.001
		Weight	0,261	0.05 to 0.47	0.015
		eGFR	0,378	0.16 to 0.60	<0.001
	Lower RAND-36 score	Age	-0,628	-0.80 to -0.46	<0.001
		Alcohol	-6,062	-12.06 to -0.06	0.048
		Atrial size	-0,547	-1.00 to -0.10	0.018
		CHA2DS2-VASc score	-8,485	-10.21 to -6.76	<0.001
		ECG PQ interval	-0,155	-0.26 to -0.05	0.004
		ECG QTc interval	-0,152	-0.28 to -0.02	0.024
		EGSYS score	-2,369	-3.48 to -1.26	<0.001
		Glucose	-2,716	-5.43 to -0.00	0.050
		HAS-BLED score	-6,744	-9.22 to -4.26	<0.001
		Normal ECG	-10,239	-16.29 to -4.19	<0.001
		OESIL score	-10,403	-13.24 to -7.57	<0.001
		SFSR score	-9,189	-15.15 to -3.23	0.003

Pain	Higher RAND-36 score	Height	0,526	0.29 to 0.76	<0.001
		Sex	10,36	5.57 to 15.15	<0.001
		eGFR	0,229	0.06 to 0.40	0.010
	Lower RAND-36 score	Age	-0,202	-0.34 to -0.06	0.005
		Alcohol	-7,293	-12.16 to -2.43	0.003
		CHA2DS2-VASc score	-2,994	-4.49 to -1.50	<0.001
		ECG heart rate	-0,251	-0.43 to -0.08	0.005
		OESIL score	-2,763	-5.14 to -0.38	0.023
General health	Higher RAND-36 score	Atrial dilatation	5,208	0.08 to 10.34	0.047
		Vasovagal score	0,918	0.09 to 1.75	0.031
		eGFR	0,304	0.16 to 0.44	<0.001
	Lower RAND-36 score	Age	-0,15	-0.26 to -0.04	0.010
		Alcohol	-6,503	-10.42 to -2.58	0.001
		CHA2DS2-VASc score	-2,24	-3.45 to -1.03	<0.001
		Creatinine	-0,094	-0.16 to -0.02	0.008
		ECG PQ interval	-0,083	-0.15 to -0.01	0.021
		Glucose	-2,261	-3.99 to -0.53	0.011
		OESIL score	-3,008	-4.93 to -1.09	0.002
Total directional parameter-level estimates: 106					

Directional summary of significant main-effect estimates from the exploratory RAND-36 predictor analyses. Positive coefficients indicate associations with higher RAND-36 scores and therefore better domain-level health-related quality of life, whereas negative coefficients indicate lower RAND-36 scores and therefore worse domain-level health-related quality of life. Abbreviations: β = beta coefficient; CHA DS -VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischaemic attack/thromboembolism, vascular disease, age 65–74 years, and sex category score; CI = confidence interval; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EGSYS = Evaluation of Guidelines in Syncope Study score; Free T4 = free thyroxine; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly age, and concomitant drugs/alcohol score; LVEF = left ventricular ejection fraction; OESIL = Osservatorio Epidemiologico sulla Sincope nel Lazio score; PQ = atrioventricular conduction interval; QRS = ventricular depolarisation duration; QTc = corrected QT interval; RAND-36 = RAND 36-Item Health Survey; SFSR = San Francisco Syncope Rule.

Supplementary Table S3

Outcome	Effect category	Significant results	Predictors
PCS-12	Main effects	19/54	Work hours/week; work-related diagnosis; syncopal episodes in the previous year; hyperventilation-related testing; sex; total syncopal episodes; admission; referral diagnosis; short-term absenteeism; EEG testing; Holter monitoring; chest radiography; MRI; 24-hour monitoring; echocardiography; CT; perfusion imaging; syncope during Valsalva; syncope inducibility
PCS-12	Time × predictor interactions	4/54	Long-term absenteeism; EEG testing; Holter monitoring; pacemaker implantation
MCS-12	Main effects	9/54	Work hours/week; sex; long-term absenteeism; reduced working hours; work-related diagnosis; total syncopal episodes; syncopal episodes in the previous year; education level; number of syncope-related visits
MCS-12	Time × predictor interactions	7/54	Prior quality of life; ECG testing; echocardiography; 24-hour monitoring; psychosocial information; transient loss of consciousness while driving; family status

Summary of significant main effects and time-by-predictor interactions from exploratory univariable mixed-effects models for PCS-12 and MCS-12 in the tertiary cohort. Counts represent statistically significant findings based on uncorrected Type III P values <=0.05. Abbreviations: CT = computed tomography; ECG = 12-lead electrocardiography; EEG, =electroencephalography; MCS-12 = Mental Component Summary of the 12-Item Short Form Health Survey; MRI = magnetic resonance imaging; PCS-12 = Physical Component Summary of the 12-Item Short Form Health Survey; SF-12 = 12-Item Short Form Health Survey.