Lifetime prevalence and correlates of syncope in five ancestry groups. The HELIUS study

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ABSTRACT

Aim: To explore the lifetime prevalence and correlates of syncope in the general population.

Methods: Through stratified random sampling, we included 14,937 White-European, Asian, Turkish, Moroccan, and West-African ancestry adults (18–70 y) in the cross-sectional Healthy Life in an Urban Setting (HELIUS) population study. We assessed syncope history by ancestry, and the potential correlates body mass index (BMI), systolic/diastolic blood pressure (SBP/DBP), resting plasma activity of creatine kinase (CK), the ATP-generating enzyme that facilitates cardiovascular contractility and sodium retention, and in a subgroup, supine cardiac contractility (dP/dt), cardiac output (CO) and systemic vascular resistance (SVR).

Results: Mean age of the participants (39% men) was 43.3 y (SD 12.9). Lifetime prevalence of syncope in women/men was respectively (%), White-European 42/24; Asian 34/19; Moroccan 32/16; Turkish 30/17; and West-African 20/14. Mean age at first syncope was 24 y (SD 13). Participants with syncope history had lower SBP, DBP, BMI, CK, and modestly lower dP/dt and CO, but not SVR. In multivariable regression analysis, male sex (OR 0.52 [0.48 to 0.57]), West-African ancestry (0.59 [0.54 to 0.65]), and CK (0.56 [0.46 to 0.69]/log CK increase) were negatively associated with syncope.

Conclusion: This study indicates that West-African ancestry, male sex, and high activity of the pressor enzyme CK are associated with lower syncope prevalence. These findings may inform further studies on the hemodynamics of syncope.

1. Introduction

While subgroups in the population by ancestry are widely recognized to differ by cardiovascular risk, little is known about differences in syncope prevalence by ancestry. [1–3] Syncope is a transient loss of consciousness due to cerebral hypoperfusion, characterized by a rapid onset, short duration and spontaneous complete recovery. [1,2] A common reason for emergency department presentations, it is a presenting symptom rather than a disease entity. [1] About one in three adults report a history of syncope during their lifetime, with greater risk in the young, in women, and in persons with cardiac and pulmonary diseases or with autonomous dysfunction including after drug use. Reflex syncope, which includes vasovagal, situational, and carotid sinus syncope, is generally considered to be most common, representing around 60 % of all syncope presentations. Other conditions include orthostatic hypotension (around 15 %), arrhythmic syncope (10 %), and structural heart disease (5 %), with a distribution among these conditions dependent on age, sex, and comorbidities of the population studied. [1,2] Syncope in younger persons without cardiovascular risk factors or disease tends to be associated with a good prognosis. [1].

The pathophysiological hallmark of syncope is a rapid fall in systemic blood pressure thought to result from a decrease in cardiac output (CO), leading to insufficient cerebral perfusion pressure. [1,2,4,5] “Hypotensive susceptibility” is thought to be present in the majority of syncope cases. [4] Therefore, the ATP-regenerating enzyme creatine kinase (CK) that promotes cardiovascular hemodynamics and pressor responses, [6–11] may protect from syncope. CK is tightly bound near ATPases including myosin ATPase, Ca2+–ATPase and Na+/K+-ATPase, affecting smooth and striated muscle contractility as well as sodium retention. CK metabolically supports these ATPases through rapid in situ ATP generation from ADP and phosphocreatine, catalyzing the following reaction: [6–11]
Phosphocreatine + MgADP ↔ Creatine + MgATP.

CK is strongly associated with systemic arterial blood pressure—with up to 20 mm Hg systolic blood pressure increase per log CK increase driven by higher stroke volume (SV), CO, cardiac contractility (dp/dt), and systemic vascular resistance (SVR) as well as enhanced sodium retention and skeletal muscle contractility. [6-8,10,11] These factors may contribute to a reduced hypotensive tendency. Therefore, differences in tissue or resting plasma CK activity, observed to be relatively high in men, obese persons, persons with hypertension, and in persons of sub-Saharan African ancestry, [7-9,11] may lead to differences in syncope risk.

Incidental reports indicate syncope risk is possibly lower in persons of sub-Saharan African ancestry, [3] but population data are lacking. In a small, random population sample of 432 men and women of White-European ancestry, we found that CK was inversely associated with the lifetime prevalence of syncope, which occurred in 22 % of the participants within the high CK tertile vs 39 % in the low CK tertile (+73 %). [6] The implications of this study were limited due to the small sample size, the lack of diversity by ancestry, and the absence of hemodynamic data. [6] Therefore, in this study of five ancestry groups, we assessed the lifetime prevalence and correlates of syncope by ancestry, including whether CK is negatively associated with syncope history.

2. Methods

2.1. Ethics approval

The study complies with the Declaration of Helsinki and was approved by the local Ethical Review Board before data collection. Participants gave written informed consent prior to their inclusion.

2.2. Data collection

We examined participants of the cross-sectional Healthy Life in an Urban Setting (HELIUS) population study (data collection 2011–2015). Study details were published previously. [7,12] In brief, disproportionate stratified sampling (with oversampling by non-European ancestry and simple random sampling per ancestry group) was used to include comparable sample sizes of five ancestry subpopulations of non-institutionalized, non-pregnant, ambulant White-European, (South) Asian, Moroccan, Turkish, and West-African ancestry persons aged 18–70 y, living in Amsterdam, the Netherlands (Please see Online Supplement, Table S1). We used a dataset of 14,937 participants with data on syncope and resting CK (with a subgroup of 7876 participants for clinical hemodynamic evaluations, Supplement, Figure S1).

Clinical examinations included syncope history (participants were requested whether they ever “fainted”, defined as a sudden, brief loss of consciousness, followed by a spontaneous complete recovery), the age at first syncope, smoking (pack-years smoked), 12-month alcohol use, history of stroke, myocardial infarction, and/or revascularization, physical activity, self-reported heavy exercise in the past 3 days, demographic data, educational level, self-defined ancestry, physical examination (with measurements in duplo), and laboratory studies conducted in the early morning under fasting conditions. Education level was defined as “low” with elementary schooling or lower, lower vocational schooling or lower secondary schooling. Physical activity was expressed in minutes per week, assessed with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH), as reported in detail previously. [12] Participants were requested to refrain from smoking on the day of the physical examination. Sitting blood pressure was assessed by trained staff members after 5 min of rest, with an appropriately adjusted cuff on the left arm at heart level, using a validated automated digital device (Microlife WatchBP Home, Microlife AG, Widnau, Switzerland). Mean arterial pressure (MAP), heart rate, SVR, SV, CO, and dp/dt were measured in a substudy at selected study sites, independent of syncope status. After 5 min of rest in a stable supine position, beat-to-beat finger arterial pulse contour analysis was conducted with the validated, FDA-approved non-invasive Nexfin hemodynamic monitor (BMEYE BV, Amsterdam, the Netherlands). [7,13] Extended methods of the hemodynamic assessments are provided in the Supplement. Plasma CK was measured with an automated analyzer (Modular P, Roche/Hitachi Systems, Roche Diagnostics, Indianapolis, IN, USA) according to the procedure recommended by the International Federation of Clinical Chemistry. [7,8] Hypertension was defined as a blood pressure ≥ 140 mm Hg systolic or ≥ 90 diastolic or the self-reported use of antihypertensive drugs. Diabetes was defined as fasting glucose ≥ 7.0 mmol/L or self-reported use of antidiabetic drugs. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines to prepare this report.

2.3. Outcomes

Syncope by sex/ancestry groups was a predefined outcome of the HELIUS study, expecting a relatively high lifetime prevalence in White-Europeans and in women compared to West-African ancestry participants and men. [3,6] Furthermore, we expected CK to be inversely associated with (a history of) syncope in multivariable regression analysis as a secondary outcome. [6] Age-at-first-syncope before vs after the age of 40 y was a predefined subgroup analysis.

2.4. Sample size calculation

The probability of syncope at the mean value of the predictor variables was conservatively estimated at 0.25. Estimates by sex/ancestry were respectively 0.35 and 0.25 in White-European women and men; vs 0.25 and 0.20 in West-African ancestry women and men, [1,3,6] needing a sample size of least 326 in each group for women, and 1091 for men. Because of the strong independent association of CK with hemodynamics, [7] the sample size for multivariable binary logistic regression analysis was estimated based on a protective effect of CK for two levels of odds ratio (OR) of syncope, corresponding to an increase of one standard deviation (SD) from the mean value of CK (given the mean values of the remaining variables) at OR 0.7 (395 participants), and OR 0.8 (994 participants); with 2-tailed alpha 0.05 and 1 – beta 0.80 for all outcomes.

2.5. Statistical analysis

Lifetime syncope prevalence, defined as the proportion of individuals who reported at least one episode of syncope during their lives, was reported and analyzed in predefined subgroups by sex and ancestry using a chi-squared test for independence in contingency table analysis, followed by a post-test using cellwise adjusted residual statistics with Bonferroni-corrected alpha.

Potential correlates of syncope were first assessed through univariable analyses, using parametric or nonparametric estimates where relevant. We explored hemodynamic parameters by crude CK tertiles, and the correlation between syncope history and CK in deciles using Kendall’s tau. The univariable association between syncope and CK as a continuous measure (log transformed to the base of ten) was analyzed as a total group and by subgroups of hypertension status, age, sex, body mass index (BMI) strata (categories from < 18.18–24.9; 25–29.9 and ≥ 30 kg/m²), and West-African vs other ancestry (as the former group shows distinctly higher mean CK activity). [6-8,11] Relatively high CK in men, overweight or obese persons, and persons of West-African ancestry was reported to partially explain the association of these characteristics with hemodynamics. [7-9,11] As this may inflate the variances of the estimates of these parameters in multivariable regression analysis, we calculated Pearson’s correlation coefficient and partial correlations before modelling the multivariable association of predictors of syncope in binary logistic regression models using forced entry.

We included all clinically relevant variables in full models, retaining
3. Results

3.1. Prevalence of syncope by sex and ancestry

Questions on syncope history were answered by 14,804 out of 14,937 participants (>99 %) and 7807 out of 7876 in the hemodynamic substudy (>99 %). Lifetime prevalence of syncope in women/men was respectively, White-European 42/24; Asian 34/19; Moroccan 32/16; Turkish 30/17; and West-African 20/14 (Table 1, Fig. 1). Table 1 depicts clinical and hemodynamic characteristics of the participants by ancestry, Table 2 by syncope history, and Table S2 by sex. The lifetime prevalence of syncope in this sample (26 % [95 % CI, 25 to 27 %]), was not equally distributed in the population, with 31 % among women vs 18 % among men (mean difference 13 % [11 to 14 %]; χ²(1, N = 14804) = 293.18, p < 0.001).

3.2. Time-Related univariable analyses of syncope

Mean age-at-first-syncope was 24 (13) y. In women/men this was respectively, White-European 19/22 y; Asian 22/25 y; Moroccan 25/26 y; Turkish 24/25 y; and West-African 26/30 y. Between 3 and 5 % of the participants across ancestry groups reported the first syncope after the age of 40 y (Table 1). As expected, these participants were older than those with first syncope < 40 y, (55 y, SD 7 vs 40 y SD 13), and had a higher prevalence of diabetes (8.1 vs 2.7 %) and hypertension (44.4 vs 6.6 %).

Table 1

| Parameters* | Total† | European | Asian | Morrocan | Turkish | West-African |
|-------------|--------|----------|-------|----------|---------|-------------|
| N           | 14,804 | 3020     | 1962  | 2822     | 2627    | 4164        |
| Men, %      | 38.4   | 43.9     | 41.8  | 35.6     | 42.6    | 33.6        |
| Age, y      | 43.3 (12.9) | 45.3 (13.7) | 43.1 (12.8) | 39.7 (12.6) | 39.5 (11.7) | 46.1 (12.1) |
| Syncope, % (women/men) | 26.0 (31/18) | 34.0 (42/24) | 28.4 (35/19) | 27.4 (33/16) | 25.2 (33/17) | 18.5 (20/15) |
| 1st syncope > 40 y, % | 4.3 | 4.1 | 5.3 | 4.6 | 3.3 | 4.3 |
| Age 1st synope, y | 23.6 (13.1) | 20.1 (12.0) | 22.9 (13.4) | 25.3 (12.8) | 24.0 (11.9) | 26.8 (14.4) |
| Smoking, pack-years | 5.7 (14.3) | 8.3 (14.1) | 6.2 (20.4) | 3.0 (8.9) | 7.0 (13.8) | 4.6 (13.8) |
| Low education level, % | 42.2 | 16.2 | 43.5 | 47.6 | 55.0 | 48.8 |
| 12-mo Alcohol use, % | 49.7 | 91.3 | 58.2 | 7.0 | 22.3 | 60.9 |
| Physical activity (h/w) | 42 (28) | 46 (22) | 45 (28) | 38 (27) | 36 (28) | 45 (32) |
| History of stroke, % | 1.1 | 1.0 | 1.6 | 0.6 | 1.1 | 1.3 |
| History of MI, % | 0.7 | 0.2 | 1.2 | 0.4 | 1.4 | 0.6 |
| History of revasc., % | 1.6 | 0.5 | 1.9 | 1.8 | 2.4 | 1.6 |
| Prevalent CVD, % | 3.0 | 1.5 | 3.8 | 2.6 | 4.1 | 3.2 |
| BMI, kg/m² | 27.0 (5.3) | 24.6 (4.1) | 25.9 (4.8) | 27.4 (5.2) | 28.4 (5.6) | 27.9 (5.4) |
| SBP, mm Hg | 125.6 (17.4) | 124.0 (16.4) | 125.7 (17.6) | 120.8 (15.6) | 122.2 (15.5) | 132.0 (18.4) |
| DBP, mm Hg | 78.5 (10.8) | 77.3 (10.2) | 79.1 (10.5) | 74.6 (9.6) | 77.4 (10.0) | 82.5 (11.1) |
| Heart rate, bpm | 69.2 (17.5) | 66.1 (10.1) | 70.1 (10.1) | 69.4 (9.4) | 71.1 (9.7) | 69.0 (10.3) |
| Hypertension, % | 27.7 | 22.0 | 27.7 | 15.0 | 20.8 | 44.3 |
| Treated, † | 40.6 | 33.1 | 39.2 | 31.2 | 35.9 | 47.6 |
| Controlled, † | 44.0 (17.9) | 53.2 (17.6) | 39.2 (15.6) | 45.6 (14.2) | 55.1 (19.8) | 39.4 (18.7) |
| Diabetes, % | 4.8 | 1.8 | 7.2 | 4.8 | 3.8 | 6.6 |
| Total Chol., mmol/L | 5.0 (1.0) | 5.2 (1.1) | 5.1 (1.0) | 4.7 (0.9) | 4.9 (1.0) | 5.0 (1.0) |
| LDL-cholesterol | 3.1 (0.9) | 3.2 (1.0) | 3.3 (0.9) | 2.9 (0.8) | 3.1 (0.9) | 3.0 (0.9) |
| HDL-cholesterol | 1.4 (0.4) | 1.6 (0.4) | 1.3 (0.4) | 1.4 (0.3) | 1.3 (0.4) | 1.6 (0.4) |
| Triglycerides | 1.0 (0.7) | 1.0 (0.7) | 1.1 (0.8) | 1.0 (0.6) | 1.2 (0.9) | 0.8 (0.5) |
| eGFR | 103.7 (17.0) | 95.7 (15.0) | 99.2 (16.2) | 110.5 (14.3) | 108.2 (14.0) | 104.7 (18.9) |
| CK, IU/L | 129 (74) | 105 (54) | 125 (68) | 111 (62) | 105 (55) | 175 (86) |

Legend.
- Data are mean (SD) or percent; †Data are median, interquartile range; ‡Persons with data on syncope history, including persons of self-defined “other” ancestry (n = 209 resp. 131 in the hemodynamics substudy). Data are rounded to one decimal point, except for creatine kinase (CK), systemic vascular resistance (SVR), body surface area (BSA), and carditis index.; BMI, body mass index; bpm, beats per minute; CO, cardiac output; dP/dt, cardiac contractility; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation); h, hour; L(H)DL, low (high)-density lipoprotein; MAP, mean arterial pressure; MI, myocardial infarction; mo, month; Prevalent CVD, history of MI, stroke, and/or revascularization (revasc.); S(D)BP, systolic (diastolic) blood pressure; SV, stroke volume; w, week. Carditis index is adjusted for BSA. European refers to persons of white-European ancestry.
18.6 %). However, the prevalence of these comorbid conditions was comparable with participants > 40 y without a history of syncope (diabetes 7.9 %; hypertension 42.1 %). The median time since the first syncope was 15 y (interquartile range 6 to 28 y, n = 3757). We did not find evidence of syncope history recall bias by age (OR 0.99 [95 % CI, 0.99 to 0.99]).

3.3. Univariable predictors of syncope

The risk of syncope by univariable predictors is depicted in Fig. 2. Persons without a history of syncope showed higher values of (% of SD) current systolic blood pressure (+29 %), diastolic blood pressure (+28 %), BMI (+17 %), and CK (+31 %), and small increments in other hemodynamic parameters, including CO (+8%), but not SVR (Table 2).

The hemodynamic profile of lower systolic and diastolic blood pressure and modestly lower CO in participants with a history of syncope was consistent across subgroups of sex, age, and West-African vs other ancestry (data not shown).

Relatively high CK was observed in participants without syncope, in hypertensives, in men, in participants with a BMI ≥25, and in persons of West-African ancestry (Table S3, Figure S2). Hemodynamic parameters increased by CK tertiles (Figure S3, Panel A): mean SBP + 20 [19to21] mm Hg (+121 % SD); DBP + 13 [12to14] mm Hg (+116 % SD); SV + 6.8 [5.1 to 8.6] mL (+39 % SD); CO + 0.17 [0.05 to 0.30] mL/min (+14 % SD); dP/dt + 72 [40to103] mm Hg/s (+23 % SD), SVR + 87 [44to130] dyn⋅s/cm² (+20 % SD)/log CK increase. In an explorative univariable analysis, CK correlated negatively to syncope history (Table S3 and Figure S3 Panel B). A small number of participants (3 %, Table 1), had a history of CVD (stroke, MI or revascularization procedures), respectively 4 % of the participants with a history of syncope and 2.6 % of those without (Table 2). We accounted for this in the sensitivity analysis below.

3.4. Multivariable modeling of syncope

In multivariable binary logistic regression analysis, sex, ancestry and CK were independently associated with syncope, with OR of respectively 0.52 [0.48 to 0.57] (men), 0.59 [0.54 to 0.65] (West-African vs other ancestry), and 0.56 [0.46 to 0.69] (log CK), (Table S3). Hemodynamic parameters including blood pressure, lipid levels, glucose, and eGFR did not contribute to the model. When analyzed in subgroups by sex, outcomes were similar for men and women (OR syncope/log CK increase, 0.33 [0.24 to 0.47] in women; and 0.59 [0.38 to 0.92] in men).

Importantly, congruent with observations of high CK in persons of Sub-Saharan African ancestry and in men, CK partially accounted for the negative correlation of West-African ancestry (70 %) and men (43 %) with syncope. A sensitivity analysis to address this collinearity using partial least squares-discriminant analysis consequently identified log CK as leading in the multivariable classification function of “syncope” (vs “no syncope”): 0.47 – (0.12*Log CK) – (0.05 for West-African ancestry) + (0.05 for non-West-African ancestry) – (0.06 for men) + (0.06 for women) (Table S3). Excluding participants with CVD (n = 440) did not change the direction or the magnitude of the outcomes (Table S3).

Finally, to account for the factor time (time-to-first-syncope), we conducted multivariable time-to-event analyses (Figure S4). The relatively low syncope hazard in men, persons of West-African ancestry, and persons with high CK (reciprocally high in women, non-West-African ancestry and with low CK) was confirmed to be present at any given age-at-first-syncope (Table S4), with a hazard ratio of 1.83 [1.69 to 1.98] for women vs men, 0.64 [0.59 to 0.70] for West-African vs other ancestry, and between 0.33 [0.28 to 0.38] and 0.71 [0.59 to 0.85] for CK, depending on the model chosen. Please see the Supplement for details on Kaplan-Meier estimates (Table S4), Cox regression analyses (Table S5), and missing data analysis (Table S6 and Figure S5).

4. Discussion

To our knowledge, this is the first large population study on syncope with comparative epidemiological and clinical data by ancestry. We found a relatively high lifetime prevalence of syncope of White-Europeans compared to other ancestries, and of women compared to men of the same ancestry. Syncope risk was relatively high in white women, but not in African ancestry women, who had life-time prevalences comparable to white men. West-African ancestry men had the lowest lifetime syncope prevalence. These population data might aid in the triage of patients presenting with syncopeal transitory loss of consciousness.

With regard to the hemodynamic profile, participants with a history of syncope currently had a lower sitting systolic and diastolic blood pressure and supine MAP, with minor differences in other hemodynamic parameters, including marginally lower CO at rest. However, in multivariate analysis, only sex, ancestry, and CK were associated with a history of syncope, while relatively high CK in men and persons of African
ancestry partially accounted for the lower syncope prevalence in these groups. The findings were consistent across predefined subgroups and different statistical models, and present at any time to first syncope.

Hypotensive susceptibility is thought to be central to the pathophysiology of syncope. [1,2,4,5] With risk factors including low blood pressure, low BMI, decreased skeletal muscle tone and reduced circulatory volume, a hypotensive tendency is thought to contribute to the acute drop in CO that leads to syncope, [1,2,4,5] but the pathophysiology of “hypotensive susceptibility” remains unclear. [1,4,5,14]

CK is intimately involved in pressor responses and hypertension, as recently summarized. [6–8,11] Therefore, persons with relatively high CK may be at lower risk to develop hypotension and syncope. Resting plasma CK is relatively high in men and persons of West-African ancestry, with the lowest activity reported in women of White-European ancestry. [6–8,11] Plasma CK is the resultant of 3 main factors, release from tissues, lymphatic flow, and clearance by the liver. Physiological CK release by tissues is proportional to the intracellular CK activity pattern, which is biologically plausible as CK rapidly regenerates ATP from phosphocreatine, thereby metabolically supporting ATPases, including myosin ATPase, Ca\(^{2+}\)-ATPase and Na\(^+\)/K\(^+\)-ATPase, as involved in respectively the contractility of smooth and striated muscle, and sodium retention in the kidney. [6–8,10] In line with this, CK is strongly associated with contractility of isolated resistance arteries and with cardiovascular hemodynamic parameters (dp/dt, CO, SV, CO, SVR, and systolic and diastolic blood pressure). [6–8] Greater skeletal muscle contractility and enhanced intramuscular tension during standing may increase muscular blood flow; MI, myocardial infarction; mo, month; Prevalent CVD, history of MI, stroke, or and/or revascularization (revasc.); S(D)BP, systolic (diastolic) blood pressure; SV, stroke volume; w, week. Cardiac index is adjusted for BSA.

The inverse association between CK and syncope found in this study is biologically plausible as CK rapidly regenerates ATP from phosphocreatine, thereby metabolically supporting ATPases, including myosin ATPase, Ca\(^{2+}\)-ATPase and Na\(^+\)/K\(^+\)-ATPase, as involved in respectively the contractility of smooth and striated muscle, and sodium retention in the kidney. [6–8,10] In line with this, CK is strongly associated with contractility of isolated resistance arteries and with cardiovascular hemodynamic parameters (dp/dt, CO, SV, CO, SVR, and systolic and diastolic blood pressure). [6–8] Greater skeletal muscle contractility and enhanced intramuscular tension during standing may increase muscularovenous return and add to reduce syncope with high CK (Table S7 and Figure S6). [6,8,15] In addition, physical activity substantially modifies baroreflex activity, which may affect muscle tone and susceptibility to syncope. [2,4] We previously reported an association between (low) plasma CK and syncope in a small sample of White-Europeans. [6] Such association has also been reported in children. [16] This large study replicates these findings in a large population sample across sex/ancestry groups and BMI strata, in accord with earlier findings that CK is involved in generating and maintaining arterial blood pressure. [6–8,11]

There are no previous population data on syncope except for persons of white-European ancestry. The main strength of this study is the presentation of unique, extensive demographic and non-invasive hemodynamic data by syncope history in five different ancestries, using a large,
random population sample. These data importantly indicate that the prevalence of syncope is high in white-Europeans compared to other ancestry groups. Furthermore, syncope history is strongly associated with (low) CK, the enzyme that promotes cardiovascular contractility, sodium retention and blood pressure increase. These important population data may further studies on the pathophysiology of syncope, as orthostatic intolerance is still poorly understood. [2].

However, several limitations apply to the presented data. First, we oversampled non-European ancestry groups to achieve equal sample sizes by ancestry, thus the results reflect population estimates by ancestry. Furthermore, we did not collect data in citizens older than 70 y. Therefore, the prevalence estimates are not based on completed life-courses. Although recall bias cannot be excluded, such bias would unlikely explain the observed differences in syncope by sex, ancestry and CK. The modestly lower supine CO observed with syncope history is in line with hemodynamic changes seen during acute syncope, as well as with a history of (recurrent) syncope. [1,2,17] Still, the absolute differences found in our study in hemodynamic parameters by syncope history in the resting supine position were relatively small. Assessment of a large population at rest rather than during stressed or acute dynamic conditions is a further limitation of our study design. We did not collect data on subtypes of syncope, recurrent syncope, or seizures. While most cases of syncope in the general population are thought to be reflex syncope or orthostatic hypotension, [1–5,14] our data may partly reflect seizures and cardiac abnormalities. Syncope due to cardiac or other conditions with high mortality is evidently underrepresented. Supplementary studies are needed to address specific (non-reflex) causes of syncope by ancestry, in particular with high cardiovascular risk, a history of CVD, or relatively high age-at-first-syncope, a subgroup which might have different cardiac and hemodynamic characteristics.

This study suggests that resting plasma CK is a pathophysiologically relevant biomarker of CK-dependent mechanisms, which may reduce syncope risk through different pathways (Table S7). [7,8] However, it is important to note that although the effects of CK on cardiovascular and skeletal muscle energy metabolism and contractility have been firmly established, [8,10] the cross-sectional design of this study precludes causal inferences. Another limitation is that we did not assess

### Table 3
The Association between CK and Syncope in Subgroups.

| Category          | n    | CK, IU/L | Syncope (%) | OR Syncope/Log CK |
|-------------------|------|----------|-------------|-------------------|
| **Incl. all**     | 14,804 | 129      | 26.0        | 0.24 (0.20 to 0.29) |
| BMI < 18.5 vs ≥ 18.5 to 30 | 10,705 | 121      | 28.0        | 0.27 (0.22 to 0.33) |
| **Ancestry strata** |      |          |             |                   |
| European          | 3020  | 105      | 34.0        | 0.40 (0.27 to 0.61) |
| Asian             | 1962  | 125      | 28.4        | 0.38 (0.23 to 0.62) |
| Moroccan          | 2822  | 110      | 28.7        | 0.41 (0.17 to 0.83) |
| Turkish           | 2627  | 105      | 25.2        | 0.37 (0.23 to 0.60) |
| West-African      | 4164  | 175      | 18.5        | 0.25 (0.17 to 0.36) |
| **Sex groups**    |      |          |             |                   |
| Women             | 9077  | 112      | 30.9        | 0.26 (0.21 to 0.33) |
| Men               | 5727  | 155      | 18.2        | 0.59 (0.43 to 0.80) |
| **Age groups**    |      |          |             |                   |
| ≤ 40 y            | 5954  | 122      | 28.8        | 0.22 (0.17 to 0.29) |
| > 40 y            | 8850  | 134      | 24.1        | 0.27 (0.21 to 0.34) |
| **Body mass index** |      |          |             |                   |
| < 25 kg/m²        | 5922  | 117      | 30.5        | 0.25 (0.19 to 0.33) |
| ≥ 25 kg/m²        | 8871  | 137      | 23.0        | 0.27 (0.21 to 0.34) |

**Legend.** OR Syncope/Log CK, odds ratio of syncope vs no syncope per log CK increase. *All participants with resting CK and syncope data. | Systolic (SBP) < 140 and diastolic blood pressure (DBP) < 90 without antihypertensive drug use; | SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or use of antihypertensive drugs | Excluding those of self-defined “other” ancestry (n = 209). | [11] participants had missing body mass index data. CK, creatine kinase.

Fig. 2. Univariable Predictors of Syncope | BMI, body mass index; CK, creatine kinase; CO, cardiac output; dP/dt, cardiac contractility; SV, stroke volume; RR, relative risk; SVR, systemic vascular resistance; Ancestry, West-African vs all others; and vs White-European, Asian and Mediterranean (Turkish and Moroccan). Hemodynamic parameters (n = 7876) and CK (n = 14 804) are discretized into Tertile 3 (high) vs Tertile 1 (low).
isoenzymes. CK-MB (%) might be elevated in acute syncope due to myocardial injury, [1] but we did not include participants who needed acute care. This isoenzyme fraction is normal in healthy persons with high constitutive CK. [8] However, the results should be interpreted with caution, as CK might be increased in various cardiac and non-cardiac conditions. [8] Therefore, when assessing a patient with syncope, different possible causes of CK elevation should be taken into account. Finally, we used plasma CK in the absence of recent exercise or tissue damage as proxy intracellular CK activity, a validated yet indirect measure. [6–8,11] We did not take habitual exercise into account. In addition, particularly after heavy exercise, exercise-induced CK may last longer than 3 days, and this tends to affect men more than women. [7,8] Hence, despite 3 days of rest, relatively high exercise-induced CK levels occur more often in men. This might have “diluted” the association with cardiovascular function. [7,8].

Provocation studies with tilt testing combined with assessments of skeletal muscle mass and tension, and CK assessed in plasma after rest or more precisely with skeletal muscle 31P magnetic resonance spectroscopy, might help clarify the role of this ATP generating pressor enzyme in “hypotensive susceptibility”. As a proof of principle, increasing the flux through the CK reaction might be tried to alleviate hypotensive susceptibility and (recurrent) syncope.

In conclusion, taking the limitations of the cross-sectional design into account, the presented data indicate that the lifetime prevalence of syncope is relatively high in White-Europeans, particularly in younger women, with a nearly threefold lower occurrence in men of West-African ancestry. We found lower blood pressure levels and modestly lower cardiac output in participants with a history of syncope. Female sex, non-African ancestry, and low activity of the pressor enzyme CK were significantly associated with a history of syncope in multivariable analysis. Clinical studies may further elucidate the concept of hypotensive susceptibility and the potential role of molecular motors and cellular energy metabolism in the large differences in syncope risk observed in men and women of different ancestry groups.

Availability of data and material.

Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the HELIUS Study, Department of Public Health, Amsterdam UMC, P.O. Box 22700, Amsterdam, the Netherlands.

Authors’ contributions and consent for publication: LMB, GvM, and BvdB contributed to the design of the HELIUS study. LMB designed the syncope and CK substudy, conducted the analyses and drafted the manuscript with tables and figures. All authors critically reviewed the manuscript and approved the final text for publication.

Study registration number: n.a.

Competing interests: LMB is an inventor on patent WO/2012/138226, an “open” non-restrictive patent request filed and published as “prior art” to protect the freedom of researchers to operate and share their innovative ideas on CK and CK inhibition without license or payment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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