Original Article

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Low-blood pressure phenotype underpins the tendency to reflex syncope

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Background: We hypothesized that cardiovascular physiology differs in reflex syncope patients compared with the general population, predisposing such individuals to vasovagal reflex.

Methods: In this multicohort cross-sectional study, we compared aggregate data of resting SBP, DBP, pulse pressure (PP) and heart rate (HR), collected from six community-based cohort studies (64 968 observations) with those from six databases of reflex syncope patients (6516 observations), subdivided by age decades and sex.

Results: Overall, in male individuals with reflex syncope, SBP (−3.4 mmHg) and PP (−9.2 mmHg) were lower and DBP (+2.8 mmHg) and HR (+5.1 bpm) were higher than in the general population; the difference in SBP was higher at ages above 60 years. In female individuals, PP (−6.0 mmHg) was lower and DBP (+4.7 mmHg) and HR (+4.5 bpm) were higher than in the general population; differences in SBP were less pronounced, becoming evident only above 60 years. Compared with male individuals, SBP in female individuals exhibited slower increase until age 40 years, and then demonstrated steeper increase that continued throughout remaining life.

Conclusion: The patients prone to reflex syncope demonstrate a different resting cardiovascular haemodynamic profile as compared with a general population, characterized by lower SBP and PP, reflecting reduced venous return and lower stroke volume, and a higher HR and DBP, suggesting the activation of compensatory mechanisms. Our data contribute to a better understanding why some individuals with similar demographic characteristics develop reflex syncope and others do not.

Video abstract: http://links.lww.com/HJH/B580.

Keywords: autonomic nervous system, blood pressure, heart rate, hemodynamics, population, reflex syncope, syncope

Abbreviations: BP, blood pressure; HR, heart rate; MAP, mean blood pressure; PP, pulse pressure

INTRODUCTION

The 2018 ESC guidelines on syncope [1] introduced the concept of 'low blood pressure (BP) phenotype' as a mix of clinical and investigational findings that identify those patients in whom a low BP plays a role in causing reflex (neurally mediated) syncope. For example, the patients with persistent low BP [2–4] and those who show a hypotensive susceptibility on tilt testing [5] seem to satisfy the criteria for low BP phenotype. Being only a concept, the guidelines were unable to define more precisely low-BP phenotype. Supine resting BP values have been given little importance in the literature of reflex syncope. Several trials even omitted reporting supine BP values among the baseline clinical characteristics. Among those trials that reported baseline BP values, a comparison with the general population was hampered by the fact that BP is highly age-dependent and sex- dependent, which makes the population of such trials underpowered for these purposes.

On the assumption that cardiovascular physiology may fundamentally differ in patients with reflex syncope compared with individuals from a general population, an age-specific and sex-specific analysis of existing data could offer new insights, improve our understanding of the mechanism of reflex syncope and help to characterize the low-BP phenotype.

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METHOD

We compared resting BP and heart rate (HR) measures collected from six databases of patients affected by certain or likely reflex syncope (6516 observations) [6–13] with those collected in six community-based cohort studies of general population (64 968 observations)[14–19]. Both syncope and general population studies were undertaken in the years 1998–2019 and were analyzed between December 2019 and April 2020.

The principal investigators of each included study were asked to calculate the average and the standard deviation of the baseline values of BP and HR subdivided by age decade and sex from his/her respective database unless the data were already available in the literature. In addition to SBP, DBP and HR, the variables of interest included pulse pressure (PP) and mean arterial pressure (MAP). These indices were calculated using the following formulae: $PP = SBP - DBP$ and $MAP = DBP + (1/3)PP$.

The diagnosis of definite or likely reflex (neurally mediated) syncope was made according to the presence of the clinical features of reflex syncope, the exclusion of competing diagnoses (especially orthostatic hypotension) and, eventually, confirmed by cardiovascular autonomic investigations. The patients had syncope of sufficient severity to require assessment in a specialized syncope clinic. All included studies have been approved by ethics committees of their respective study sites.

Statistical analysis

In the absence of previous data from the literature, we assumed, as biologically relevant, a minimum mean difference of 2 mmHg in SBP between the syncope group and the general population group. We calculated that 250 patients with syncope and 2500 individuals from the general population for each age decade would have a power to detect a difference of 2 mmHg with a two-sided alpha error of 0.10 and a beta error of 0.20. Thus, the minimum size of an age decade group was set to 2000, and for general population to 20,000.

Continuous variables were expressed as means ± SD and categorical data as frequencies and proportions. In order to evaluate the relationship of population type (general population and syncope), sex, age decade with BP and HR, we employed the Generalized Estimating Equation (GEE) models, which take into account the clustering effect because of correlation among estimates within a study. Moreover, we weighted each available mean estimate for the corresponding sample size. The model included four groups of patients according to the sex and population type (syncope or general population): male individuals and syncope (MSyn); male individuals and general population (MGP); female individuals and syncope (FSyn); female individuals and general population (FGP). Age decade was included as a continuous variable. To take into account the potential modifying effect of age on the association among groups and BP/HR levels, we included an interaction term between age and groups. The group-specific least square means [and their 95% confidence interval (95% CI)], adjusted for age decade were estimated. The following contrasts of least square means were performed: MSyn vs. MGP, FSyn vs. FGP to underline differences among population types in male and female individuals. Moreover, we considered further three comparisons; the first two (separately for sex) related to differences in trend of BP/HR levels through age decades among syncope and general population groups and the third related only to syncope patients for differences in trend of BP/HR levels through age decades among male and female individuals.

A sensitivity analysis was performed considering only the three cross-sectional consecutive series (intervention trials excluded), in order to verify the independence of findings from the potential selection biases of trials.

Finally, we evaluated the potential effect of hypertension prevalence as a confounder verifying if the relationship between age and prevalence of hypertension changes as a function of population type. We modelled the prevalence of hypertension, available only at study level, as a function of average age and population type as well as their interaction.

All analyses were performed using the Statistical Analysis System Software (version 9.4; SAS Institute, Cary, North Carolina, USA). Statistical significance was set at the 0.05 level. All P values were two-sided.

RESULTS

The features of the databases of patients affected by certain or likely reflex syncope and of the community-based cohort studies of general population are described in detail in the eTable S1, http://links.lww.com/HJH/B581 and eTable S2, http://links.lww.com/HJH/B581. There were 44 and 45% male individuals, respectively, with ages spanning from the second to the ninth decade of life. Antihypertensive therapy rate was correlated with the respective average age of the studies ($P = 0.03$). The interaction between age, prevalence of hypertension and study groups was assessed by a sensitivity analysis (eFigure S1, http://links.lww.com/HJH/B581) that showed a similar effect of hypertension on the syncope group and the general population, $P = 0.89$.

The comparison of SBP, DBP and HR per age decade and sex between syncope patients and individuals from the general population is displayed in Table 1. Overall, in male individuals with reflex syncope, SBP (−3.4 mmHg) and PP (−9.2 mmHg) were lower and DBP (+2.8 mmHg) and HR (+5.1 bpm) were higher than in the general population; the difference in SBP was higher at ages above 60 years (Fig. 1). In female individuals, PP (−6.0 mmHg) was lower and DBP (+4.7 mmHg) and HR (+4.5 bpm) were higher than in the general population; differences in SBP were less pronounced, becoming evident only above 60 years (Fig. 1). In contrast, there was no decrease in MAP in syncope patients compared with the general population either in male individuals (93.0 vs. 92.5 mmHg, respectively) and in female individuals (91.4 mmHg vs. 89.0 mmHg, respectively).

A sensitivity analysis limited to the three cross-sectional studies (intervention trials excluded) showed similar results (eTable S3, http://links.lww.com/HJH/B581 and eFigure S2, http://links.lww.com/HJH/B581).

TABLE 1. Overall results

	Syncope				General population				*P* value
	Number of patiens	Observed mean	LS adjusted mean	95% CI	Number of patients	Observed mean	LS adjusted mean	95% CI	
Males									
SBP (mmHg)	2855	128.1	126.7	124.0–129.3	29 424	131.5	131.8	129.3–134.2	0.006
DBP (mmHg)	2426	77.7	77.4	75.0–79.7	29 424	74.9	75.3	73.9–76.6	0.14
Pulse pressure (mmHg)	2425	48.8	49.0	44.9–53.1	29 424	58.0	56.2	54.1–58.2	0.002
Mean arterial pressure (mmHg)	2425	93.0	93.7	92.0–95.4	29 424	92.5	93.7	92.4–95.5	0.81
Heart rate (bpm)	2020	67.7	67.9	66.5–69.3	9493	62.6	62.7	60.4–64.9	0.0001
Females									
SBP (mmHg)	3661	127.2	125.9	122.1–129.8	35 554	125.7	127.5	125.1–129.9	0.50
DBP (mmHg)	2961	75.7	74.9	73.9–75.8	35 544	71.0	71.3	70.3–72.4	0.0001
Pulse pressure (mmHg)	2960	50.2	51.3	46.3–56.2	35 544	56.2	55.5	52.2–58.8	0.16
Mean arterial pressure (mmHg)	2960	91.4	92.0	90.7–93.2	35 544	89.0	89.8	89.4–90.2	0.001
Heart rate (bpm)	2428	70.2	70.5	69.6–71.5	11 576	65.7	65.0	62.3–67.6	0.0001

Observed and least square-adjusted supine BP and HR in patients with reflex syncope: comparison with general population. The group-specific least square means (and their 95% confidence interval [95% CI]), adjusted for age decade were estimated. CI, confidence interval; LS, least square.

The comparison between male and female individuals in the syncope group showed a different pattern of incremental SBP elevation from childhood through older age. Figure 2 displays changes in SBP levels by decades in ascending order. Compared with male individuals, female individuals had lower SBP at very young age (<20 years) and exhibited a slower increase until the age of 40 and then a steeper increase that continued throughout the rest of life. Therefore, female individuals had lower SBP values than male individuals until the age of 40 years and higher values above the age of 60 years. This different pattern is correlated with the males/female ratio calculated at each decade, with male individuals constituting one-third of the syncope population until the age of 40 years and approximately one half after that age. The patterns of incremental SBP elevation in the general population, stratified by sex, and their comparisons with the syncope group, are shown in the eFigure S3, http://links.lww.com/HJH/B581.

DISCUSSION

The data presented here for the first time provide evidence that BP and HR in patients with reflex syncope differ from the general population. In this multicohort cross-sectional analysis, male patients diagnosed with reflex syncope showed lower SBP but higher DBP and higher HR compared with population-derived controls. These differences were similar in female individuals, but lower SBP became evident only over 60 years. According to SBP and DBP alterations, PP was consistently reduced over decades of life in individuals prone to reflex syncope.

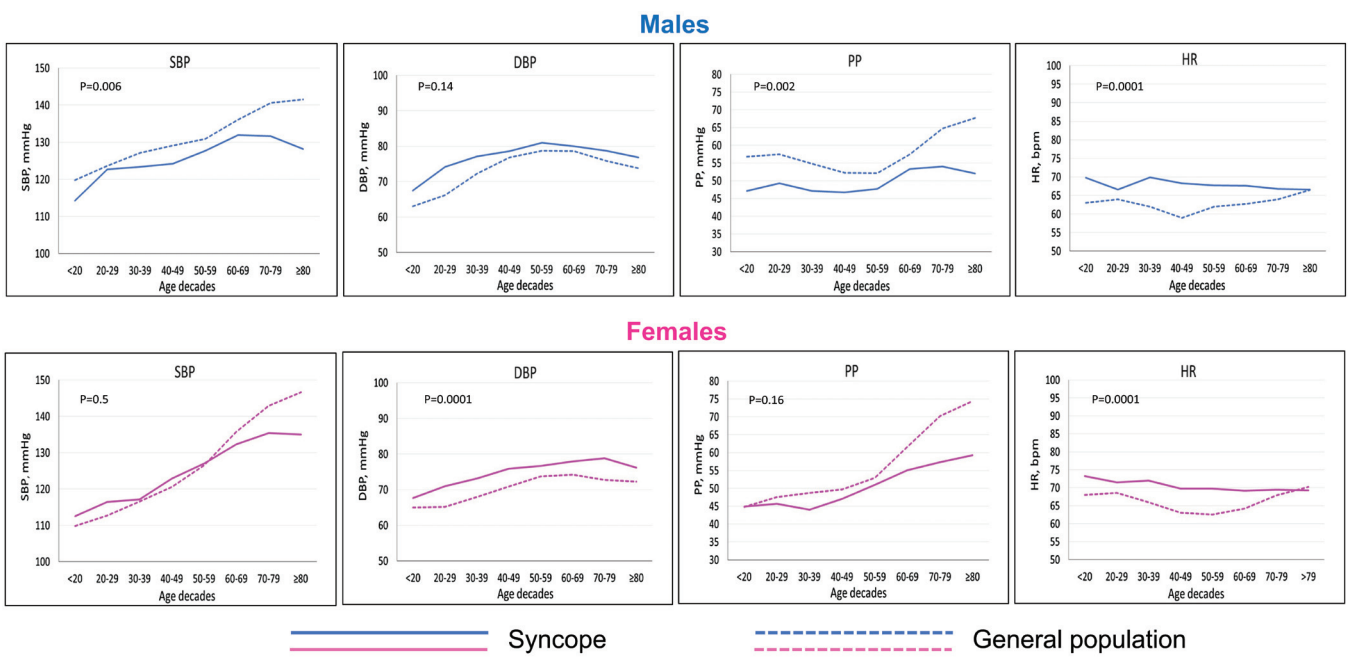

FIGURE 1 Different hemodynamic profiles of SBP, DBP, pulse pressure (PP), and heart rate in beats per minute (bpm) in male and female individuals with reflex syncope and in the general population. Data are shown over the different decades, throughout the lifespan.

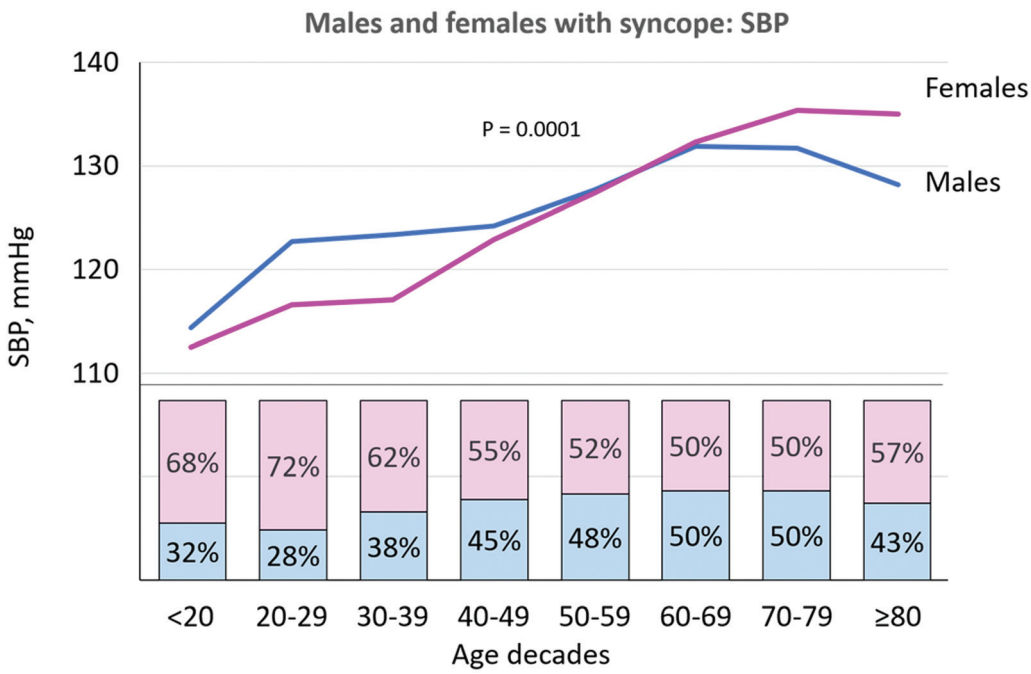

FIGURE 2 Comparison between sex in patients with reflex syncope. The upper part shows the patterns of incremental SBP elevation from youth in male and female individuals. Data are shown over the different decades, throughout the lifespan. SBP increases progressively with age. Compared with men, women exhibit a slower increase until the age of 40 years and then a steeper increase that continues throughout the rest of life. SBP declines in men after the age of 60 years. A significant interaction of sex with age is present ($P = 0.0001$). The lower part of the figure shows the male/female ratio of reflex syncope per age decade. The relative rate of syncope in men and women is related to their SBP until the sixth decade. The slightly higher rate of women at ages at least 80 years is likely because of the higher census prevalence of womrn in those ages. Chi-square test for trends: $P = 0.0001$.

The above findings thus suggest that different haemodynamic features are already evident in basal conditions and underpin the tendency to reflex syncope. Our interpretation is that a reduced venous return and stroke volume, that is reflected by lower SBP and PP, is already present in basal conditions and constitutes the pathophysiological primary mechanisms of patients prone to reflex syncope (Fig. 3). Assuming that aortic compliance in reflex syncope patients is not different from age-matched and sex-matched general population, PP can be seen as an indirect estimate of stroke volume. These findings are consistent with those of Weissler *et al.* [20] who demonstrated that an acute reduction in central blood volume and cardiac output critically contributed to vasovagal reflex initiation. The reduced venous return and stroke volume is accompanied by compensatory increases in HR and DBP, the latter reflecting increased peripheral vascular resistance. According to this interpretation, patients with reflex syncope may be characterized by a reduced ability to counter-regulate reduced stroke volume also in basal conditions, and such an inability may translate into a 'low BP phenotype'. The higher HR and DBP in female individuals below the age of 60 years are most likely able to compensate fully for the haemodynamic changes on standing, and to preserve SBP levels ('masked' low-BP phenotype). Such a reduced compensatory capacity predisposes to intolerance to orthostatic stress [21]. A generally preserved cardiovascular homeostasis, aimed at maintaining brain perfusion, is reflected by the lack of difference in MAP among all groups. This result, however, is achieved at the expense of chronic compensatory mechanisms. Reflex syncope occurs when orthostatic stress or other typical triggers overcome the capacity of these adaptive mechanisms, leadings to a decrease in MAP and a reduced blood supply to the brain.

In case of vasovagal reflex activation, blood is predominantly pooled in the splanchnic capacitance vessels, which, when the patient is placed supine, empty into the right heart through the inferior vena cava restoring normal cardiac output [22]. Neuroendocrine studies performed recently revealed that the phase of presyncopal circulatory instability is accompanied by a distinct epinephrine and vasopressin surge [21,23]. Hypothetically, this pronounced neuroendocrine response to orthostatic challenge could be evoked by haemodynamic instability and would be secondary to reduced cardiac filling and hypotensive tendency detected by central and arterial baroreceptors. The results of our study thus suggest that low basal SBP might be an important factor facilitating initiation of the neuroendocrine cascade and vasovagal reflex, implying that the different basal haemodynamics existing in those prone to syncope underpin its occurrence.

There are various possible explanations for this specific cardiovascular profile among patients with reflex syncope. First, these individuals may have lower circulating blood volume or tendency to blood pooling in splanchnic and other subdiaphragmatic regions [4,21,24]. Female individuals, having lower blood volume in general and less skeletal mass, showed, on average, higher HR, supporting the lower blood volume-hypothesis. Second, the baroreceptors may be chronically reset to a lower mean arterial pressure in syncope patients. In spite of this, it has been demonstrated that baroreceptor sensitivity is elevated in reflex syncope patients, which could explain more pronounced changes in sympathetic ouflow and higher DBP and HR responses to

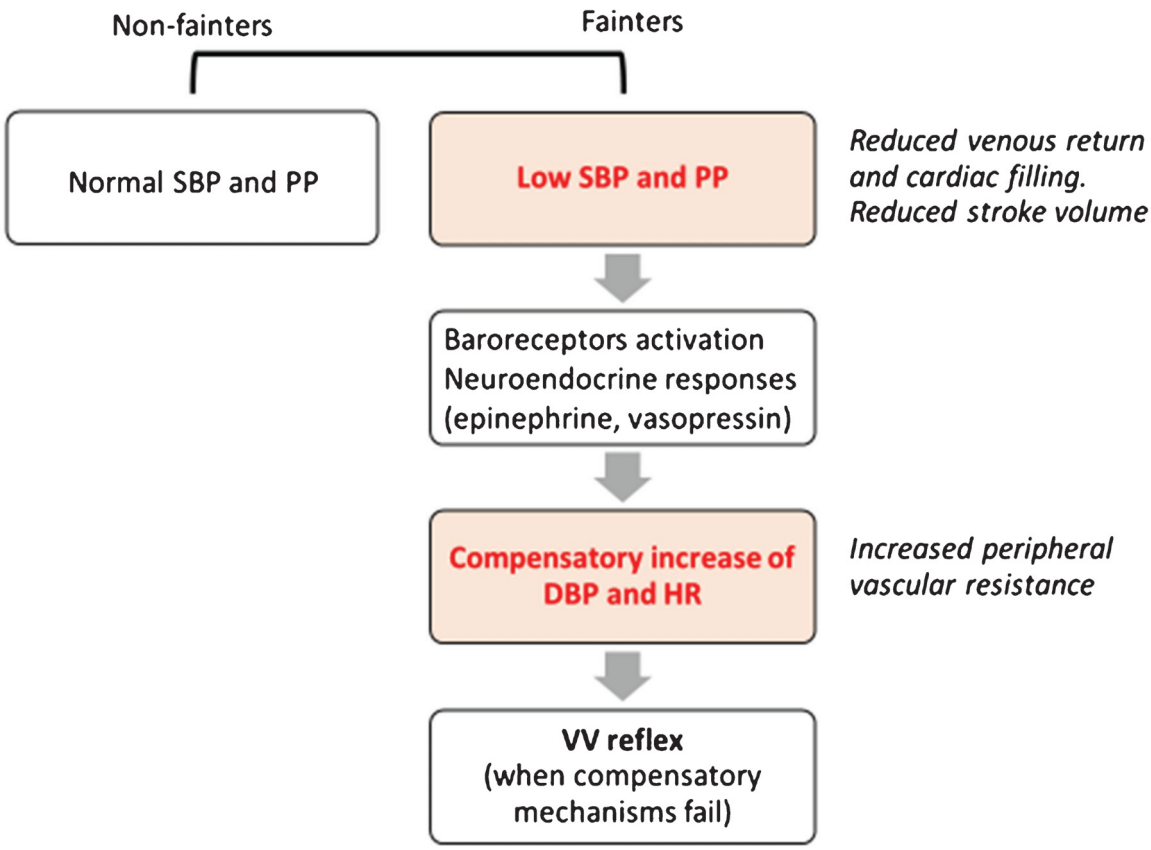

FIGURE 3 The haemodynamic cascade of orthostatic vasovagal syncope (see text for explanation). HR, heart rate; VV, vasovagal.

orthostatic challenge as a consequence of their 'syncope-prone status' [25]. Third, changes in neuroendocrine status, including baseline catecholamine levels and clearance, as well as differences in cardiovascular receptor density and reactivity, may promote a low BP phenotype in patients prone to syncope [2–4]. Further, supressed chronotropic response and reduction in HR difference between syncope and control group in advanced age might explain the increase in relative SBP difference between these groups as shown in Fig. 1. A role for hereditary factors seems likely but, as yet, they have not been sufficiently explored.

In this study, some 25–30% of all included individuals declared taking antihypertensive drugs. It may be argued that antihypertensive treatment, which is common in later life, may have contributed to the distinctly lower SBP observed among patients older than 60 years. As antihypertensive treatment was balanced between syncope and general population cohorts without potential confounding effect (eFigure S1, http://links.lww.com/HJH/B581), the possible role of higher antihypertensive drug use in explaining lower SBP in the syncope population is unlikely.

Female individuals exhibited lower absolute values and lesser increment in SBP than men until the age of 40 years. The lower SBP levels might explain why female individuals are more susceptible to syncope than males at younger age (Fig. 2). In this context, the hormonal changes following puberty in female individuals, promoting vasodilation, excessive splanchnic pooling and decreased plasma volume, may offer an explanations [26]. Moreover, important anatomical differences between sexes cannot be ignored: women compared with men have not only smaller total body size but also smaller organs, including the heart and vascular beds. Finally, gut and adipose tissue have different susceptibility to pooling and their relative amounts differ between men and women [26].

The different lifetime BP profile observed in patients with reflex syncope as compared with the general population, in both male and female individuals offers additional insights. Syncope patients showed a lower than expected age-related BP increase compared with a general population, in particular for men above 60 years, and women above 40 years (eFigure S3, http://links.lww.com/HJH/B581). It is well known from epidemiological studies [1] that the incidence of syncope is bimodal, showing a high prevalence in patients aged 10–30 years, being less common in adults and peaking again after age 60 years. Our results might offer an explanation for this pattern. Syncope is more frequent when SBP has a low absolute value or is lower than in the general population. Conversely, syncope is less frequent in the middle age, when SBP of syncopal patients is in the same range as that of the general population (eFigure S3, http://links.lww.com/HJH/B581).

Limitations

We have to acknowledge some limitations of our study. First of all, since only aggregate data were available, the relationship between a specific individual characteristic and a syncopal event could not be addressed. Thus, the present

study should be considered as hypothesis-generating, and, although providing data from a very large number of individuals, cannot draw firm conclusions.

Our study also has other limitations. Differences in the years of recruitment of individuals, differences in methods for assessing BP, heterogeneity existing between and within-cohort study settings may have affected our results (eTable S1, http://links.lww.com/HJH/B581). Information regarding associated risk factors for syncope, for example, BMI is lacking. Interpretation of PP differences should be made with caution as PP is affected by both stroke volume and vascular properties. In absence of data, we assumed that aortic compliance in reflex syncope patients is not different from age-matched and sex-matched general population individuals.

Given the heterogeneity of the cohorts considered in our study, we cannot completely exclude a bias in selecting syncope patients and controls. However, this is unlikely because of the very large population and broad age range of both patients (randomly sampled by referral) and of the general population. In order to increase the generalizability of results, we performed a sensitivity analysis, in which we included in the syncope group the results from the three cross-sectional databases while excluding the data derived from the three clinical trials (eTable S3, http://links.lww.com/HJH/B581 and eFigure S2, http://links.lww.com/HJH/B581).

A similar percentage of individuals in both groups were taking antihypertensive drugs (eTable S1, http://links.lww.com/HJH/B581). The lack of individual data prevented us from determining possible differences in the the type and dosage of drugs used.

Finally, we have been unable to determine the proportion of individuals in the control group who had a history of syncope. From epidemiological studies, we can estimate the prevalence of syncope to be approximately 25–30% in the general population, and in most cases, because of reflex mechanisms [1]. Hypothetically, if these individuals were excluded, the difference in BP and HR between syncope group and control population would, most likely, be even greater..

In conclusion, the different life-course of blood pressure and heart rate profile that we observed in patients with reflex syncope compared with a general population identifies a specific cardiovascular profile, that is. lower SBP and PP with higher heart rate and DBP in patients with reflex syncope as compared with controls. These findings represent novel information, which contributes to our understanding of the mechanism of reflex syncope, suggesting a primary role of cardiovascular haemodynamic differences underpinning reflex syncope, which should thus not be considered a readily dismissed neurological phenomenon [27]. Our study might provide explanation why some individuals with similar demographic characteristics develop reflex syncope and others not, which should be confirmed by additional studies.

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Conflicts of interest

There are no conflicts of interest.

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