PSYCHOPATHOLOGICAL CORRELATES AND PSYCHOSOCIAL FUNCTIONING IN CHILDREN AND ADOLESCENTS WITH SYNCOPE: A SYSTEMATIC REVIEW

Gaia Cuzzocrea, Andrea Fontana, Marta Mascanzoni, Francesco Manca, Riccardo Pecora, Lucrezia Trani, Cristiana Guido, Alberto Spalice, Paolo Versacci, Lucia Sideli, Vincenzo Caretti

Abstract

Objective: Syncope is defined as a spontaneous and transient loss of consciousness and postural tone due to brief and reversible cerebral hypoperfusion. This review aimed to summarize the research findings regarding the psychological correlates associated with pediatric syncope. Moreover, the study aimed to deepen the understanding of the relationship between psychological disorders and the onset of syncopal episodes in childhood, focusing on clinical features and different clinical classifications.

Method: A systematic review was carried out from inception to January 2023, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using the CINAHL Plus, APA PsycArticles, APA PsycInfo, MEDLINE, and Psychology and Behavioral Sciences Collection databases. The study search and selection were based on the Population Intervention Comparison Outcome Study Design (PICOS) strategy and the Quality Assessment was carried out using Critical Appraisal Skills Programme (CASP) scales. A combination of keywords related to a) syncope; b) psycho*; and c) child* (Subjects) was used. Studies concerning epilepsy-related syncope were excluded.

Results: Overall, 912 records were identified. After excluding non-English, non-original, and duplicate studies, 579 records were selected for the title screening, 88 for the abstract screening, 37 full-text articles were assessed for eligibility and a total of 14 were included. The Risk of Bias in the included studies was assessed and 78,6% of the studies satisfied robustness quality criteria. The findings highlighted that children and adolescents with syncope showed a higher rate of psychopathology as compared to the healthy and clinical controls. Furthermore, patients reported social withdrawal and poor quality of life.

Conclusions: The findings suggest that there is a robust relationship between psychopathology and syncope. Children and adolescents with syncope frequently report clinical symptoms related to emotional, relational, and psychosomatic dysregulation. Psychological assessment should be routinely included in the integrated care to identify potential targets for treatment and improve early differential diagnosis.

Key words: children, adolescents, syncope, psychopathology, systematic review

Corresponding author
Gaia Cuzzocrea, Ph.D Student. Department of Human Sciences, LUMSA University, Piazza delle Vaschette 101, 00193 Rome, Italy. E-mail: g.cuzzocrea1@lumsa.it

Gaia Cuzzocrea[a], Andrea Fontana[a*], Marta Mascanzoni[a*], Francesco Manca[a], Riccardo Pecora[a], Lucrezia Trani[a], Cristiana Guido[b,c], Alberto Spalice[b], Paolo Versacci[d], Lucia Sideli[a**], Vincenzo Caretti[a**]

[a] Department of Human Sciences, LUMSA University, Piazza delle Vaschette 101, 00193 Rome, Italy

[b] Pediatric Neurology Division, Department of Maternal Sciences, Sapienza University, Italy.

[c] Department of Developmental and Social Psychology, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy.

[d] Pediatric Cardiology, Department of Pediatrics, Obstetrics and Gynecology, Sapienza University of Rome, Rome, Italy.

[*]these authors equally contributed as second authors

[**]these authors equally contributed as last authors

Introduction

In the field of pediatric medicine, a complex situation arises when physical symptoms cannot be readily explained by conventional medical or organic factors. Indeed, certain physical symptoms in pediatric cases may elude clear medical or organic explanations, necessitating the adoption of diverse terminologies to

delineate these symptoms, including somatization, persistent somatic symptoms, and functional somatic symptoms (Dirkzwager & Verhaak, 2007). The literature highlights the common association of somatic symptoms with emotional and behavioural challenges, school absenteeism, and disruptions in social functioning (Rask et al., 2009).

Within this context, syncope is defined as an abrupt and temporary loss of consciousness (T-Loc) and postural muscle tone resulting from reduced blood flow to the brain. It is characterized by a swift onset, brief duration, and spontaneous recovery (Brignole et al., 2018). Syncope is common across the lifespan but has a particularly high incidence in adolescents, with a peak age of onset during puberty (~10–15 years) (Kanjwal & Calkins, 2015; Wieling et al., 2004;). At this age, the incidence of experiencing a syncopal episode before the end of the second decade is about 15% (L. Chen et al., 2007; Driscoll et al., 1997; Lai et al., 2010; Lewis & Dhala, 1999; McLeod, 2003; Ruckman, 1987; Scott, 1991; Strasberg et al., 1989; Wieling et al., 2004), with a female predominance (Bo et al., 2009; Wong & So, 2002).

One of the most significant pathogenic hypotheses for investigating the causes of syncope involves the regulation of the Autonomic Nervous System (ANS) (Brignole et al., 2000; Hainsworth, 1999). The ANS regulates the systemic blood pressure to maintain constant cerebral perfusion which tends to change due to physiological (e.g., postural variations) or emotional status (e.g., pain and fear) (Brignole et al., 2018; Hainsworth, 1999). Syncopal experiences can be categorized into three classifications: Neurally mediated (NMS), Cardiac, and Orthostatic Intolerance (Brignole et al., 2018; Moya & Sutton, 2009), while the remaining fainting experiences typically have a mixture of diagnoses, including psychogenic events, intoxications, and metabolic disorders (Brignole et al., 2018; Tanel & Walsh, 1997).

The NMS, otherwise known as vasovagal (VVS) or neurocardiogenic (NCS), or reflex syncope regards 61% to 80% of the cases in the pediatric age group (Lewis & Dhala, 1999; Soteriades et al., 2002; Tanel & Walsh, 1997) and refers to a heterogeneous group of diseases resulting from inappropriate cardiovascular reflexes (Dalton & Wang, 2017). The VVS or NCS reaction is characterized by hypotension (vasodilation) and reduction of heart rate (bradycardia or asystole) induced by several mechanisms. Physiologic states (e.g., prolonged standing or a sudden postural change) or strong emotional states (e.g., fear, blood phobia or pain) may trigger decreased systemic blood return to the heart that leads to cerebral hypoperfusion (Ayers & Lawrence, 2015; Brignole et al., 2000, 2018; Chen-Scarabelli & Scarabelli, 2004; Kolarczyk & Nowakowska, 2018; Van Dijk et al., 2014). Commonly, this mechanism involves decreased parasympathetic activity and increased sympathetic activity. By contrast, in NCS patients cerebral hypoperfusion triggers the Bezold-Jarisch reflex (Bechir et al., 2003; M. Y. Chen et al., 1989; Iwase et al., 2014; Mosqueda-Garcia et al., 2000; Pinna et al., 2015; Salo et al., 2007) which determines vagal activation and sympathetic withdrawal (Wallin & Sundlöf, 1982), leading to syncope (Salo et al., 2007). These abnormal alterations also depend on the stimulation of the sensory fibers of the cerebral cortex and the hypothalamus which are activated in several situations (Brignole et al., 2000, 2018). Generally, VVS occurs after consciousness alterations due to autonomic dysregulation (defined as prodromal symptoms) that also involve cardiopulmonary symptoms (such as

dyspnea, palpitation), gastrointestinal symptoms (such as indigestion, nausea, abdominal pain), and cerebral hypoperfusion symptoms (such as dizziness, vertigo, fatigue) (Dalton & Wang, 2017; Lee et al., 2013).

Cardiac syncope is the less common type of syncope, concerning 2% of the pediatric population, and is usually due to an underlying cardiac disease (Dalton & Wang, 2017; Yeh, 2015). Although in the adult population cardiac-originating syncope indicates a serious health risk, in the young population sudden cardiac death is extremely rare (Dalton & Wang, 2017). The causes of cardiac syncope can be classified as structural cardiovascular diseases or arrhythmia (Brignole et al., 2002, 2018). The first regards obstruction to cardiac output, including structural abnormalities and pulmonary hypertension. The second regards both bradyarrhythmia and tachyarrhythmia (such as sinus dysfunction), atrioventricular conduction disorders, hereditary syndromes (long QT syndrome, Brugada syndrome), malfunction of implantable devices (peacemaker, ICD), drug-induced proarrhythmia (Brignole et al., 2002). Patients may report overlap of both underlying cardiac causes (e.g., hypertrophic cardiomyopathy) (Dalton & Wang, 2017).

In cases of orthostatic syncope, individuals often experience presyncopal symptoms such as lightheadedness, dizziness, weakness, and blurred vision. Autonomic causes contributing to orthostatic syncope include various conditions (Brignole et al., 2002, 2018; Yang et al., 2013): (1) Classic Orthostatic Hypotension (OH) is characterized by a prolonged drop in blood pressure (BP) and an increase in total peripheral resistance and heart rate (HR) during the first three minutes after standing; (2) Initial Orthostatic Hypotension (OH) involves an immediate BP decrease within a few seconds of standing; (3) Delayed Orthostatic Hypotension (OH) manifests as a gradual and slow BP decrease without the presence of bradycardia, distinguishing it from Orthostatic Vasovagal Syncope (VVS); (4) Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by an elevated HR without a concurrent BP drop, setting it apart from Classic OH; (5) Orthostatic Vasovagal Syncope (Orthostatic VVS) displays a progressive vasovagal reflex, including vasodepressive and/or cardioinhibitory pathways, marked by a brief episode of decreased BP following prolonged standing, in contrast to Classic OH. Other factors that can trigger orthostatic syncope encompass conditions such as hypovolemia (e.g., anaemia), diabetes, and gastrointestinal diseases (e.g., diarrhoea).

Several fainting experiences, that imply a real or an apparently transient loss of consciousness, include symptoms that mimic syncope, such as seizures, psychogenic conditions, intoxications, metabolic disorders, drop attacks, hyperventilation syndrome, and breath-holding spells or unexplained syncopal symptoms (Brignole & Hamdan, 2012; L. Chen et al., 2006; Dalton & Wang, 2017; Linzar et al., Ventura et al., 2001). Psychogenic nonepileptic seizures (PNES) appear as episodic alterations in behaviour, movement, or arousal (Heyer et al., 2016; Hubsch et al., 2011), in which patients report a transient compromised or lost consciousness (Brignole et al., 2002). PNES resemble epileptic seizures, but with a psychological origin and without convulsions (positive motor signs), representing a functional neurological symptom disorder (Heyer et al., 2016; Hubsch et al., 2011). Similarly, psychogenic syncope (as coined by Grubb et al., 1992) also known as psychogenic non-syncopal collapse (PNSC) or psychogenic pseudo syncope (PPS) resembles NMS but without reflex syncope symptoms

such as hypotension and bradycardia (Blad et al., 2015; Raj et al., 2014; Tannemaat et al., 2013). PPS appears as episodic alterations in behaviour, movement, or arousal without apparent trigger and presyncope or prodromal symptoms (Lee et al., 2013). The most common type of psychogenic syncope in children is vasovagal syncope (Driscoll et al., 1997).

Syncope and psychological correlates

Literature suggests that syncope is associated with psychiatric disorders (Cohen et al., 2000; D'Antono et al., 2009; Kapoor et al., 1995; Kouakam et al., 2001, 2002; Lee et al., 2013; Linzer et al., 1992; McGrady et al., 2001). Serotoninergic mechanisms emerged as syncope reflex underlying causes and mediators (Flevari et al., 2009; Hainsworth, 2004), and Hainsworth (2004) reports that NCS and depression present common pathophysiologic features.

Several studies on the adult population found that patients with syncope show high levels of psychopathology (such as anxiety, depression, somatization, and mood disorders) (Cohen et al., 2000; D'Antono et al., 2009; Flint et al., 2009; Giada et al., 2005; Konig et al., 1992; Kouakam et al., 2002; Leftheriotis et al., 2008; McGrady et al., 2001; Ventura et al., 2001) and patients with mental health symptoms reported curred or past syncopal episodes (Bonadies et al., 2006; Leftheriotis et al., 2008; O'Hare et al., 2017). Furthermore, several studies suggest that children and adolescents with syncopal experiences exhibit more frequent comorbid psychopathological diseases, such as anxiety (Lee et al., 2013; Velasco-Benitez et al., 2022), depression (Byars et al., 2000; Ding et al., 2010) and sleep problems (Chan et al., 2022). Other studies investigated the relational features of patients with syncope and showed that children with VVS exhibit higher parental burden (Blount et al., 2004), social withdrawal (Byars et al., 2000) and poor quality of life (van Dijk et al., 2007). In a 2-year follow-up study, Hyphantis et al. (2012) showed an association between the number of syncopal episodes and depressive symptoms. Similarly, Alhuzaimi et al., (2018) found that patients with six or more syncopal episodes showed a higher rate of anxiety, depression and somatization disorder compared to patients with lesser syncopal episodes. Ayers & Lawrence (2015) reported that the predicting factor that confirms VVS diagnoses was the fear–pain stress emotion, despite negative HUTT responses.

Although a limited number of previously mentioned studies have explored the relationship between psychological conditions and syncopal experiences, the existing literature remains relatively scant. There is a compelling need for further investigation, specifically to elucidate whether psychological factors serve as causes, risk factors, or clinical consequences of syncope. Thus, the primary objective of this systematic review is to consolidate and analyze research findings on the psychological correlates in children and adolescents with syncopal experiences.

Moreover, we endeavour to gain a more profound understanding of the interplay between psychological disorders and the onset of syncopal episodes during childhood, taking into account clinical features and different clinical classifications. This undertaking highlights the necessity for a comprehensive review of the available literature to identify potential pathological mechanisms and clinical co-occurrences between syncope and psychological disorders in children and adolescents. This, in turn, can inform the development of preventive and therapeutic interventions to be incorporated into clinical practice, ultimately enhancing therapeutic procedures and identifying areas warranting further investigation.

Materials and methods

Search strategy and selection criteria

A systematic review of the literature on psychological factors of syncope in pediatric subjects was carried out, following the PRISMA guidelines (Page et al., 2020) using the CINAHL Plus with Full Text, APA PsycArticles, APA PsycInfo, MEDLINE, Psychology and Behavioral Sciences Collection databases.

The studies' search and selection were based on the Population Intervention Comparison Outcome Study Design (PICOS) strategy (see Supplementary Materials S1). Using the PICOS model, the search strategy is based on the identified population (P), intervention (I), control group (C), outcome (O), and study design (S) to clarify the initial step selection criteria and target.

The keyword syncope was selected and arranged in various combinations by the Boolean operator AND with psycho* OR depress* OR anxiet* OR phob* OR sleep OR insomnia OR mood OR "emotion* liability" OR "emotion* instability" OR disphor* OR "mood instability" OR "emotion* dysregulation" OR "affective dysregulation" OR ptsd OR "child* trauma" OR "child* advers*" OR "child* maltreat*" OR "child* abuse" OR stress OR attachment OR "parental bonding" OR "maternal stress" OR "parenting stress" OR dissociation. Epilepsy OR vaccin* OR immunization was excluded by the Boolean operator NOT. The keywords of the subjects section were selected with child* or adol* or teen* or ped*.

This systematic database search was conducted from inception to January 2023. We applied database filters to exclude duplicates and articles not published in the English language. Studies were included if a) they were published in English; b) they had a case-control, cross-sectional or cohort design; c) they were original articles; d) they had syncope as an outcome, including subclinical syncopal experiences (i.e. pre-syncope); e) they had population in pediatric age; f) they had psychological correlates (such as anxiety or depression symptoms, emotion dysregulation, sleep problems, poor quality of life, parental stress or abuse). Studies were excluded if a) they had a case report, technical report, proceedings, dissertation, book chapter, case series, archive, test validation, or review and meta-analysis; b) the age range of the population target was unclear or not specified; c) the outcomes were not correlated with psychological symptoms and involved only medical conditions; d) they were experimental studies (i.e. randomized controlled trial). The selection process includes several steps to analyze articles. The first step involved searching for the articles in the databases and filtering. The second step involved reading the titles and selecting appropriate records. Third, we conducted an abstract screening. Finally, we analyzed the full text of the eligible works.

Eligibility Criteria

We included all papers which provided data on psychological correlates of all types of pediatric syncope (e.g., NMS, cardiac, orthostatic, psychogenic). Syncope was defined as a fainting experience due to cerebral hypoperfusion, traumatic states, or orthostatic intolerance. The clinical population may include patients

of the pediatric unit's hospital and students of primary school who reported syncope or presyncope symptoms. Qualitative investigations were included for studies assessing the psychological correlates in subjects with syncope.

Identification of the studies

Seven reviewers (GC, MM, RP, LT, FM, AF, LS) independently reviewed the titles and five (GC, MM, RP, LT, FM) reviewed abstracts from potentially relevant papers. Two reviewers (GC, MM) independently reviewed the full texts. Any disagreements in paper eligibility were resolved through discussion with the senior authors (LS, VC).

Data extraction

For each eligible paper, data were independently extracted by two reviewers (GC, MM) and verified by a third (LS). Data extracted included: characteristics of participants including age, type of syncope, psychological correlates, method of assessing the presence of syncope and psychological diseases, and the relation between psychological outcomes and syncope.

Quality assessment of included studies for publication bias

we critically appraised each included paper using the CASP Case Control (CASP, 2018a) or the CASP modified Cross-Sectional (CASP, 2018b). Studies were defined as methodologically robust if they achieved a score above 8 corresponding to a score over 70% on the quality assessment scale (maximum score of 10 for case-control studies and 11 for cross-sectional studies). Each included paper was reviewed by one reviewer (GC) and verified by a second (MM). Any disagreements in appraisal scores were discussed and resolved by a third reviewer (LS).

Results

Search results

overall, 912 records were identified. After applying database filters, the records remained 812 using the function only English and 579 using the function without duplicates. 579 articles were selected for the title screening, and 88 for the abstract screening. 37 full-text articles were assessed for eligibility and a total of 14 were included in this review (see **figure 1**).

Figure 1. *PRISMA flow diagram*
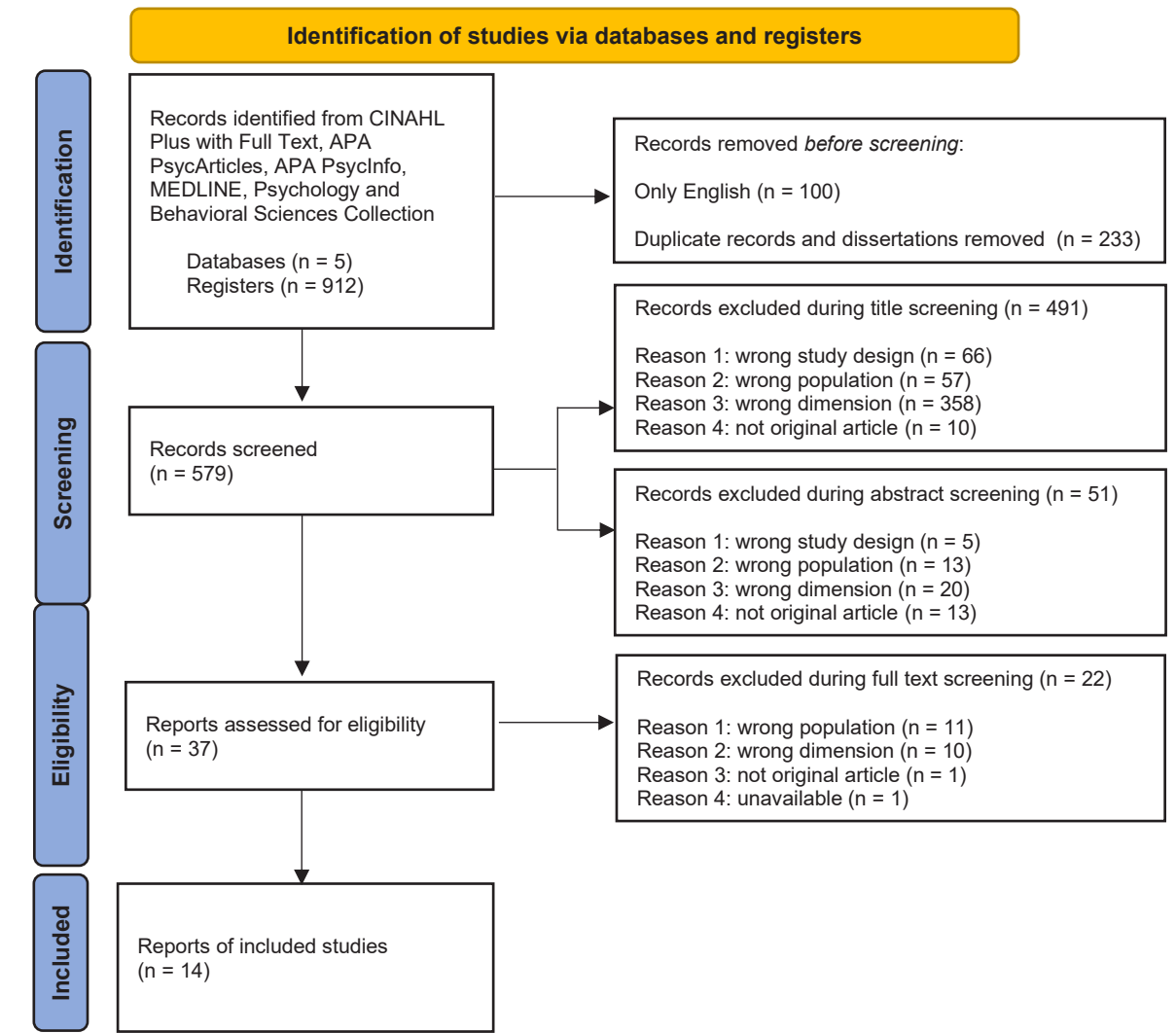
Study characteristics

Of these 14 papers, eight were case-control studies (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Kara & Doğan, 2021; Ojha et al., 2011); and seven were cross-sectional studies (Grimaldi Capitello et al., 2016; Kolarczyk et al., 2020; Lin et al., 2015; Massin et al., 2004; Qingyou et al., 2004; Wong & So, 2002).

The majority of the studies were carried out in the United States of America (n = 7) (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017, 2019; Hyphantis et al., 2012; Ojha et al., 2011; Heyer et al., 2018); three studies took place in China (Lin et al., 2015; Qingyou et al., 2004; Wong & So, 2002), and single studies in Turkey (Kara & Doğan, 2021), Italy (Grimaldi Capitello et al., 2016), Belgium (Massin et al., 2004), and Poland (Kolarczyk et al., 2020). The year of publication spanned from 2002 to 2021 with 21.4% (n=3) published in 2004 and 21.4% (n=3) in the last 5 years.

Most studies involved several clinical and control groups, as well as one or more case groups. Five studies (Anderson et al., 2012; Blount et al., 2004; Hyphantis et al., 2012; Kara & Doğan, 2021; Ojha et al., 2011) included healthy subjects as a control group; three studies (Heyer, 2017, 2019; Heyer et al., 2018) included two case groups with fainting experiences; only one study (Anderson et al., 2012) included participants with medical conditions (patients with diabetes, asthma, obesity, renal disease, and cardiac disorders) as a clinical control group. The total number of participants was 8132, with the prevalence of females (range 60% – 90%) and a mean age of 13.9. The participants of the control groups were 5648; the clinical control groups involved 857 patients, and the case groups comprised 1627 children and adolescents with fainting experiences, with 66.7% of females (n = 1101) and a mean age of 14.1 (range 3-25 years).

Of the 14 studies, 11 included head up tilt test (HUTT) evaluation for diagnosis of syncope (Blount et al., 2004; Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Kara & Doğan, 2021; Kolarczyk et al., 2020; Lin et al., 2015; Massin et al., 2004; Ojha et al., 2011; Qingyou et al., 2004); 11 included ECG (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Kara & Doğan, 2021; Kolarczyk et al., 2020; Lin et al., 2015; Massin et al., 2004; Qingyou et al., 2004); 7 performed EEG (Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Lin et al., 2015; Massin et al., 2004; Qingyou et al., 2004); 10 included historical and medical and psychiatric examination (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Kara & Doğan, 2021; Kolarczyk et al., 2020; Lin et al., 2015; Qingyou et al., 2004); 2 performed MRI (Hyphantis et al., 2012; Massin et al., 2004); 4 studies used holter 24h registration (Hyphantis et al., 2012; Kolarczyk et al., 2020; Lin et al., 2015; Massin et al., 2004); 5 performed blood pressure/ orthostatic blood pressure/ blood analysis (Heyer, 2019; Kara & Doğan, 2021; Kolarczyk et al., 2020; Massin et al., 2004; Qingyou et al., 2004); 3 performed ECHO (Kara & Doğan, 2021; Kolarczyk et al., 2020; Qingyou et al., 2004); 3 included CT (Kolarczyk et al., 2020; Massin et al., 2004; Qingyou et al., 2004) and only one study included toxicological analysis (Massin et al., 2004), clinical diagnosis (Grimaldi Capitello et al., 2016), self report measure (Wong & So, 2002); graded exercise testing (Anderson et al., 2012) and thoracic X-ray (Qingyou et al., 2004).

Pediatric patients with fainting reported 43% of syncope (n = 700) (Heyer et al., 2018; Heyer, 2019; Massin et al., 2004; Qingyou et al., 2004; Wong & So, 2002), 17.3% of PNSC (n = 281) (Heyer, 2017, 2019; Heyer et al., 2018), 12.7% of NCS (n = 206) (Blount et al., 2004; Grimaldi Capitello et al., 2016; Hyphantis et al., 2012), 10.7% of US (n = 174) (Lin et al., 2015), 9.4% of VVS (n = 153) (Anderson et al., 2012; Kara & Doğan, 2021; Kolarczyk et al., 2020), 3.7% of NMS (n = 60) (Heyer, 2017; Lee et al., 2013), and 3.3% of POTS (n = 53) (Ojha et al., 2011).

Overall, children and adolescents with fainting experiences referred anxiety (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017; Heyer et al., 2018; Kara & Doğan, 2021; Qingyou et al., 2004), depression (Anderson et al., 2012; Blount et al., 2004; Heyer, 2017, 2019; Heyer et al., 2018; Hyphantis et al., 2012; Kara & Doğan, 2021), fear (Kolarczyk et al., 2020; Lin et al., 2015; Qingyou et al., 2004; Wong & So, 2002), low quality of life (Anderson et al., 2012; Grimaldi Capitello et al., 2016), and sleep problems (Heyer, 2017; Ojha et al., 2011).

Methodological appraisal

Studies were evaluated for quality according to the Critical Appraisal Skills Programme (CASP, 2018a, 2018b) guidelines and tools. Overall, 78.6% (11/14) of the studies satisfied the criteria for robustness (see **tables 1** and **2**). Eight studies (57%) were assessed using the case-control study appraisal tool and the remaining six studies (43%) were assessed using the modified-cohort study appraisal tool.

The findings of the CASP appraisal tool (2018a, 2018b) indicated that control group recruitment was selected and followed an accurate method in most studies (62.5%, 5/8). Strengths included that the studies clearly explained the aim of the research and presented, according to Bradford Hill criteria (1965), the plausibility of results and the possibility of applying them to the local population. Syncopal diagnosis (outcome variable) was clearly explained and measured to minimize bias in most studies (92.8%, 13/14). Similarly, Psychological correlates (exposure variable) were accurately measured in the majority of the studies (57%), specifically the 50% of cross-sectional studies and the 62.5% of case-control studies, but some assessed them toward only history-taking or not standardized self-report measures. All the studies presented clinical implications for practice, except two cross-sectional studies (85.7%, 12/14). By contrast, limitations were observed in data analysis not being always clear, and results not being always accurately presented (e.g. some studies reported only percentages and not measures of estimate and precision) (21.43%, respectively 33.3% of cross-sectional studies and 12.5% of case-control studies). In addition, only a few studies (35.7%, 5/14) identified all the important confounding factors and took them into account in the design or the analysis (e.g. age). Specifically, the 83.3% of cross-sectional and the 50% of case-control studies did not identify all potential confounding factors.

Psychological correlates in children and adolescents with syncopal experiences

Existing literature suggests that children and adolescents who experience syncope often report symptoms of emotional, relational, and psychosomatic

Table 1. *Critical Appraisal Skills Programme Checklist for case-control studies*

Criterion	Anderson et al., 2012	Blount et al., 2004	Heyer et al., 2017	Heyer et al., 2018	Heyer, 2019	Hyphantis et al., 2012	Kara & Dogan, 2021	Ojha et al., 2011
1	√	√	√	√	√	√	√	√
2	√	N/C	√	√	√	√	√	√
3	√	√	√	√	√	√	√	√
4	√	X	√	X	√	√	√	X
5	N/C	√	√	√	X	√	√	X
6	X	√	X	√	X	√	√	X
7	√	√	√	√	√	√	√	X
8	√	√	√	√	√	√	√	√
9	√	√	√	√	√	√	√	√
10	√	√	√	√	√	√	√	√
Quality Judgement	robust	robust	robust	robust	robust	robust	robust	less robust

Note: √, - yes; X, no; N/C, Not Clear; Quality Judgement: less robust (0-6), robust (8-10)

Criteria:
1 "Did the study address a clearly focused issue?"
2 "Did the authors use an appropriate method to answer their question?"
3 Were the cases recruited in an acceptable way?
4 "Were the controls selected in an acceptable way?"
5 "Was the exposure accurately measured to minimise bias?"
6 "Have the authors taken account of the potential confounding factors in the design and/or in their analysis?
7 How precise are the results?
8 Do you believe the results?
9 "Can the results be applied to the local population?"
10 "Do the results of this study fit with other available evidence?"

Table 2. *Critical Appraisal Skills Programme Checklist for cross sectional studies*

Criterion	Grimaldi Capitello et al., 2016	Kolarczyk et al., 2020	Qingyou et al., 2004	Lin et al., 2015	Massin et al., 2004	Wong & So, 2002
1	√	√	√	√	√	√
2	√	√	√	√	√	√
3	√	X	√	√	X	X
4	√	√	√	√	√	X
5 a	X	X	X	X	X	√
5 b	X	X	X	X	X	X
6	√	√	X	√	√	X
7	√	√	√	√	√	√
8	√	√	√	√	√	√
9	√	√	√	√	√	√
10	√	√	√	N/C	√	X
Quality Judgement	robust	robust	robust	robust	robust	less robust

Note: √, - yes; X, no; N/C, Not Clear; Quality Judgement: less robust (0-7), robust (8-11)

Criteria:
1 "Did the study address a clearly focused issue?"
2 Was the sample recruited in an acceptable way?
3 Was the exposure accurately measured to minimise bias?
4 "Was the outcome accurately measured to minimise bias?"
5a "Have the authors identified all important confounding factors?"
5b Have they taken account of the confounding factors in the design and/or analysis?
6 How precise are the results?
7 Do you believe the results?
8 Can the results be applied to the local population?
9 Do the results of this study fit with other available evidence?
10 What are the implications of this study for practice?

dysregulation. Therefore, it is crucial to elucidate the relationship between fainting episodes and psychopathological factors to enhance early differential diagnosis and clinical care. While psychological correlates may be seen as potential factors contributing to the occurrence of syncope, it is also important to consider whether recurrent fainting events might be the primary trigger for the onset of psychiatric or psychological disorders.

Several authors investigated the role of anxiety, depression, sleep problems, poor quality of life, or parental/peer relationships linked to syncope, but research findings are still few and in some ways unclear to determine these relations. The role of psychological correlates exposure in the association with syncope has been investigated in our review in terms of psychopathology symptoms or history of psychopathology influencing the onset or the chronic fainting events. The majority of the studies included in this review are retrospectives, thus some of the clinical comorbidities are derived from the historical, medical, and psychiatric examination.

Anderson et al. (2012) indicated that patients with VVS presented clinical history of anxiety and depression disorders based on retrospective historical data (see **table 3**). Moreover, three case-control studies (Blount et al., 2004; Hyphantis et al., 2012; Kara & Doğan, 2021) assessed depression symptoms using the Children's Depression Inventory (CDI; Kovacs, 1985) and suggested that patients exhibited clinically significant depression compared to healthy controls. Furthermore, in a 2-year follow-up study, the data revealed a significant association between CDI scores and the number of syncopal episodes. Interestingly, during the follow-up period, depressive symptoms appeared to decrease (Hyphantis et al., 2012). Additionally, two case-control studies (Heyer, 2017; Heyer et al., 2018) employed the Patient-Reported Outcomes Measurement Information System (PROMIS; Irwin et al., 2010) to investigate psychological and psychiatric comorbidities in patients with psychogenic non-epileptic seizures (PNES) and a clinical control group of patients with syncope.

Compared to patients with syncope, patients with PNSC had higher self-ratings of sleep disturbances, more self-reported psychiatric symptoms, more psychiatric referrals, and more psychiatric diagnoses including anxiety, depression, PTSD, previous non-fainting conversion disorders, and eating disorders (Heyer, 2017). Patients with PNSC referred risks of self-harm and medically unexplained symptoms, including comorbid conversion disorders. Before diagnosis, some patients with PNSC (n=3) reported a history of suicidal ideation and conversion disorder (n=1), while others (n=8) developed suicidal thoughts or attempted suicide and developed new conversion disorders (n=12) including PNES (n=6) following diagnosis (Heyer et al., 2018). By contrast, none of the patients with syncope referred conversion disorder or suicidal ideation before the diagnosis, but only one had hospital admission for suicidal ideation during follow-up. These risks or new onset were not associated with depression scores, but only anxiety scores were related to patients' clinical course and differed between patients with and without suicidal ideation (Heyer et al., 2018).

In the diagnostic procedure, anxiety plays a significant role and could favour the onset of comorbid psychopathology. Several patients with atypical psychological symptoms underwent psychological evaluation to clarify the role of emotional stress as a prodromal feature of syncopal experiences. In the epidemiological study of syncope by Massin et al.

(2004), the most common diagnosis was NCS (n=181) but is interesting to note that some cases reported psychogenic syncope (n=8), associated with the recurrence of the syncopal occurrences and emotional stress as a significant predisposing factor. Five children with psychogenic syncope were treated in the long term for anxiety disorders, depression with a suicide attempt, hysteria, and conduct disturbance. Thirteen patients with NCS presented psychiatric disorders in the long term; following patients with depression (n=5 in which one with suicide attempt), severe school phobia (n=4), nervous anorexia (n=3), and hysteria (n=1).

Several studies underlined the incidence of psychiatric disorders in patients with syncope and reported the most common youth mental diseases. Generalized Anxiety Disorders, Depression, Panic, Tearfulness/crying, and Anger or Irritability could be predictive factors for syncope (Heyer, 2019; Kara & Doğan, 2021). Compared with controls, patients with VVS reported Major Depressive Disorder (n=10), Social Anxiety Disorders (n=9), Generalized Anxiety Disorders (n=9), Conversion Disorders (n=9) and Separation Anxiety Disorder (n=8) based on K-SADS-PL (Kaufman et al., 1997) outcome (Kara & Doğan, 2021). Three studies (Blount et al., 2004; Kolarczyk et al., 2020; Qingyou et al., 2004) investigated the differences between children diagnosed negative and those diagnosed positive for syncope depending on HUTT outcome. Sixteen children with positive HUTT showed fear-pain-stress emotions significantly greater compared to children with positive results of HUTT (n=8) (Kolarczyk et al., 2020). Children with Unexplained Syncope and a positive response at HUTT showed fear, anxiety, and emotional stress and these could be predisposing factors before syncope (Qingyou et al., 2004).

Compared to children with negative NCS, the number of physician visits for children with positive NCS was negatively associated with psychological symptoms. It is possible that for these children, visits to the physician were a potential source of relief and help for their disorder (Blount et al., 2004). The data also suggested that in their psychological functioning score, as measured by depressive, anxious and worry/oversensitivity symptoms, no significant difference was found.

Syncope also interferes with quality of life and normal daily social and academic activities for children. Patients with NCS showed worse relationships with their parents (Hyphantis et al., 2012) and significantly lower peer relationships (Heyer, 2017) compared with controls. Only one study (Wong & So, 2002) investigated the incidence of syncope in a random non-clinical population to quantify and examine syncopal experiences in youth using a self-report questionnaire to children in primary or secondary schools. Several students (n=121) reported experiencing at least one episode of syncope previously. The occurrence of syncope increased with older age. Students referred to fear as a psychological feature related to syncope. Fear is often identified as a prodromal factor associated with syncope, indeed Lin et al. (2015) investigated psychological fear in children using the Wong-Baker FACES scale (Garra et al., 2010) and showed a positive correlation with the tilt angle: patients reported the smallest psychological fear under 60° of tilt degrees. Two studies (Anderson et al., 2012; Grimaldi Capitello et al., 2016) assessed quality of life via PedsQL (Varni et al., 2001) and showed respectively that patients with VVS, compared both clinical and healthy controls, showed worse quality of life. Specifically, patients

presented significantly lower emotional and school functioning compared to healthy controls. Furthermore, internalizing problems on CBCL 6-18 (Achenbach & Rescorla, 2001) scores were significantly and negatively associated with the Psychosocial Health Score and Total Health Score (Grimaldi Capitello et al., 2016).

Only one study included in this review investigated patients with POTS (Ojha et al., 2011). Some of these patients (98%) reported one or more symptoms of sleep abnormality and other cases (32%) referred 3 episodes of syncope compared with clinical controls.

Discussion

This systematic review attempts to collect evidence on the relationship between psychological symptoms and syncopal experiences in children and adolescents. The findings suggest that children and adolescents who experience fainting episodes often report symptoms of emotional, relational, and psychosomatic dysregulation. Some studies explored the role of anxiety, depression, sleep problems, poor quality of life, and parental/peer relationships linked to syncope. However, the findings are still limited and not entirely clear in establishing these relationships.

The findings of this study also underline the role of psychological and psychopathological correlates on the onset or recurrence of fainting events were examined. The findings suggest that patients with syncopal experiences referred psychological symptoms, psychopathological or psychiatric diseases, and peer or parental relational impairment. Several studies (Heyer, 2019; Kara & Doğan, 2021; Kolarczyk et al., 2020; Massin et al., 2004; Qingyou et al., 2004) investigated the role of emotional stress as prodromal factors for syncope. The role of fear as a predisposing factor for syncope was described by several studies (Kolarczyk et al., 2020; Lin et al., 2015; Qingyou et al., 2004; Wong & So, 2002), and psychological fear was correlated with the tilt angle in patients with VVS (Lin et al., 2015).

Anxiety played a significant role in the diagnostic procedure and could contribute to the onset of comorbid psychopathology. Patients with VVS reported Social, Generalized, and Separation Anxiety Disorder (Kara & Doğan, 2021), addictionally patients with PNSC reported Panic, Tearfulness/crying, Anger or Irritability, and Depressed mood (Heyer, 2019). Notably, no study found an association between depression and prodromal symptoms of syncope or syncopal onsets, while anxiety was related to patients' clinical course, specifically for patients with suicidal ideation. Further studies (Anderson et al., 2012; Heyer, 2017; Massin et al., 2004) underlined the incidence of psychiatric disorders in patients with syncope and reported the most common youth mental diseases (such as PTSD, depression with a suicide attempt, conversion disorder, generalized, social and separation anxiety disorders).

According to ESC guidelines (Brignole et al., 2018), patients with PNSC, compared to patients with syncope, had more psychiatric diagnoses including anxiety, depression, PTSD, and eating disorders (Heyer, 2017; Heyer et al., 2018). Additional studies (Blount et al., 2004; Hyphantis et al., 2012; Kara & Doğan, 2021) suggested that patients referred clinically significant depression compared with healthy controls and that depression symptoms were positively associated with the number of syncopal episodes, but during the follow-up, the depressive symptoms were decreased (Hyphantis et al., 2012). It is important to consider these psychological correlates in the association with

syncope to better understand the underlying factors and provide appropriate clinical care. Monitoring the symptoms that precede and follow the diagnosis can be particularly meaningful in improving patient outcomes.

These findings underscore the potential influence of psychological factors on syncope and emphasize the significance of addressing mental health issues in individuals who suffer from fainting episodes. The data suggests a correlation between psychological symptoms such as anxiety, depression, conversion disorders, and sleep disturbances, and the occurrence of syncope. However, the current body of research remains limited in its ability to determine whether these psychological symptoms contribute to an increase in the severity and frequency of syncope or whether the relationship is the other way around.

Clinical implications and future directions

This systematic review underscores the need for future research to investigate the direction of the relationship between psychological symptoms or disturbances and syncopal experiences. Identifying syncope early and distinguishing it from other medical conditions and psychological disorders is crucial. The assessment of syncope should identify the main causes, excluding other factors (such as drug or alcohol intoxication), and stabilize the patient's condition (Dalton & Wang, 2017). The treatment of syncope depends on the patient's premorbid symptoms and the differential diagnosis of syncope. Patients with recurrent and chronic fainting experiences need treatment and should be taught pre-syncopal precautional technical or practical advice to avoid syncopal episodes (Sokoloski, 2001), such as adequate fluid and salt intake, and regular exercise (Schroeder et al., 2002).

Clarifying the relationship between pediatric syncope and psychological correlates could help healthcare providers offer psychological interventions to patients and their families, thus improving their overall well-being and psychological health. For example, young patients at risk for syncope could be advised to avoid potential triggers or be provided with tools to manage stress and anxiety effectively. Indeed, recognizing the psychological comorbidities associated with syncope can also lead to more effective treatment plans. This suggests enhancing studies on this subject and clarifying the different psychopathological comorbidities depending on the clinical features of syncope.

It is essential to clarify whether the relationship between the aforementioned symptoms follows a top-down pattern, where psychological symptoms contribute to the initiation of syncope experiences, or a bottom-up pattern, where the onset of syncope symptoms leads to the development of psychological symptoms. In this direction, future studies might examine the temporal relationship between the onset of syncope and the development of psychological symptoms to determine the direction of this relation. Understanding whether the syncopal event acts as a trigger for a psychopathological onset or vice versa if symptoms or psychopathological disorders lead to episodes of fainting (configuring themselves as conversion symptoms without organic causes) could benefit management and more effective rehabilitation treatments.

Our review also suggests that children and adolescents with syncope may experience relational difficulties, parental burden, and social withdrawal. First, children and adolescents with syncope episodes

Table 3. *Summary of the Characteristics and Findings of the Included Studies*

Authors, year, country	Sample Size	Study Design	Outcome - Type of measure of syncope	Exposure - psychological correlates	Measure of psychological correlates	Main findings	Quality score
Anderson et al., 2012, USA	n = 106 patients with VVS n = 300 patients with diabetes n = 162 patients with asthma n = 63 patients with obesity n = 82 patients with renal disease n = 250 patients with cardiac disorder n = 5480 HC	Case Control Study	Historical and physical examination, orthostatic vital sign measurement, ECG and graded exercise testing	Diagnosis of mental disorders, QOL and Emotional Functioning	Clinical records; Pediatric Quality of Life InventoryTM (PedsQLTM 4.0)	4% (4) of VVS patients reported history of anxiety disorders, and 1% (1) history of depressive disorder. The QOL domain Emotional functioning was significantly lower among patients with VVS (m = 68.9 (SD = 20.7)) compared to HC (79.3 (18.2), p < 0.001)), patients with asthma (72.9 (22.6), p < 0.05) and patients with renal disease (72.9 (22.6), p < 0.01)).	robust
Blount et al., 2004, USA	n = 36 patients with NCS n = 20 patients without NCS	Case Control Study	Historical and physical examination, ECG and HUTT.	Depression, Somatization, Anxiety, Worry-Oversensitivity Symptoms	The Child Depression Inventory (CDI); Revised Children's Manifest Anxiety Scale (RCMAS)	No significant differences between patients with NCS and without NCS were observed for depressive symptoms (6.0 (4.5) vs. 7.4 (7.4)), anxiety (9.9 (5.33 vs. (9.6 (6.3)), physiological anxiety (3.8 (2.7) vs. 4.1 (2.3)), or worry oversensitivity (4.1 (3.0 vs. (3.9 (3.2)). Among patients with NCS, the number of emergency room visits correlated with anxiety (rho = 0.43, p < 0 .05), worry–oversensitivity (rho = 0.59, p < 0.01), and depressive symptoms (rho = 0.39, p < 0.05).	robust
Grimaldi Capitello et al. 2016, Italy	N = 125 patients with NCS (n=63 adolescents and n=62 children)	Descriptive Cross Sectional Study	Clinical diagnosis	Quality of Life, Internalizing and Externalizing Problems	Child behaviour checklist for ages 6–18 (CBCL/6-18); PedsQL™	No significant correlation between recurrent syncope and internalizing/externalizing problems were observed. Internalizing problems were negatively connected with both total (r = -0.240, p < 0.01) and psychosocial quality of life (r = -0.240, p < 0.01).	robust
Heyer, 2017, USA	n = 60 patients with PNSC n = 60 patients with syncope	Case Control Study	Historical, medical and psychiatric examination, ECG, EEG and HUTT	Depressive and Anxiety Symptoms, Peer Relationships; Clinical diagnoses	Patient-Reported Outcomes Measurement Information System (PROMIS); Clinical Records	Patients with PNSC (M = 10.5 (SD = 7.7)) showed higher anxiety than patients with syncope (5.9 (5.8), p < 0.001)). Patients with PNSC (8.7 (8.3)) showed higher depression than patients with syncope (3.1 (5.0), p<0.001). Patients with PNSC (37 (12.3)) reported lower quality of peer relationships than patients with syncope (47.6 (7.9), p<0.001).	robust
Heyer et al., 2018, USA	n = 100 with PNSC n = 76 controls with tilt-induced syncope	Prospective Longitudinal Study	Historical, medical and psychiatric examination, ECG, EEG and HUTT	Depressive and Anxiety Symptoms; Clinical diagnoses	PROMIS	Immediate resolution occurred in 81 (44%) patients by 1 month, 72 (51%) by 6 months, 48 (52%) by 12 months, 48 (69%) after 12 months, and 26 (31%) still at follow-up. Patients with continued PNSC had higher anxiety scores than those with immediate resolution (p = 0.047). After diagnosis, visits to the emergency department decreased from 78.6% to 20.2% (p = 0.017); being taken in charge by a psychologist or psychiatrist increased from 26.2% to 76.2% (p < 0.001). Suicidal ideation was related to greater anxiety (p = 0.007).	robust

Table 3. *Continued*

Authors, year, country	Sample Size	Study Design	Outcome - Type of measure of syncope	Exposure - psychological correlates	Measure of psychological correlates	Main findings	Quality score
Heyer, 2019, USA	n = 121 patients with PNSC n = 121 patients with syncope	Case Control Study	Historical, medical and psychiatric examination, ECG, EEG, HUTT, heart rate and BP	Panic, Tearfulness/ crying, Anger or Irritability, Depressed mood symptoms	Standardized interviews for clinical information	29 (24%) patients with PNSC and 8 (6.6%) with syncope did not report or recall any psychological symptoms (p < 0.001). Among the 92 patients with PNSC who reported prodromal symptoms, 12 (13%) patients had one prodromal symptom, 28 (30.4%) had two, 34 (37%) had three and 18 (19.6%) had four or more. Among the 113 patients with syncope who reported prodromal symptoms, 12 (10.6%) had one, 50 (44.2%) had two, 43 (38.1%) had three and 8 (7.1%) had four or more. 9 (7.4%) prodromal symptoms reported by patients with PNSC and patients with syncope were Panic, Tearfulness/crying, Anger or Irritability, and Depressed mood. These symptoms were respectively 5 (4.1%) and 1 (0.8%) (p = 0.1); 4 (3.3%) and 0 (p = 0.04); 4 (3.3%) and 0 (p = 0.04); 2 (1.7%) and 0 (p = 0.16).	robust
Hyphantis et al., 2012, USA	n = 45 patients with NCS n = 45 HC	Case Control Longitudinal Study	Historical and physical examination, EEG, ECG, MRI, Holter 24h and HUTT	Depressive Symptoms, (Self-Esteem - Scholastic Competence, Social Acceptance, Athletic Competence, Physical Appearance, And Behavioral Conduct - Emotion and Behavior Problems: Hyperactivity Inattention, Emotional Symptoms, Conduct Problems, Peer Problems, Prosocial Behavior,Family Cohesion, Family Adaptability	Semi structured interview with children, parents, and teachers; CDI; Self-Perception Profile for Children (SPPC); Family Adaptability and Cohesion Scale-III (FACES-III)	Patients with NCS (M = 11.9 (SD = 7.7)) showed higher scores in CDI compared with controls (7.9 (5.9), p = 0.008); they also have a worse relationship with their parents (2.4 (0.7)) compared with HC (2.8 (0.6), p = 0.05). Patients showed clinically significant CDI results ($\chi2$ = 6.02, df = 1, p = 0,014). No significant differences between patients with NCS and HC in the Faces-III outcome. Specifically, in Family Cohesion (patients showed (4.6 (2.3)) similar scores to controls (5 (2) p = 0.361); and in Family Adaptability (p = 0.514), patients (4.0 (2.0) vs. controls (4.3 (1.8)). During the follow-up (T2): depressive symptoms were decreased in patients with NCS (p = 0.001). The number of NCS patients with CDI scores ≥15 decreased ($\chi2$ = 12.96, p = 0.001) from 16 of 45 (35.6%) to 1 of 36 (2.8%), being comparable ($\chi2$ = 0.41, p = 0.525) to controls (13.3% at T1 vs 18.4% at T2).	robust

Table 3. *Continued*

Authors, year, country	Sample Size	Study Design	Outcome - Type of measure of syncope	Exposure - psychological correlates	Measure of psychological correlates	Main findings	Quality score
Kara & Dogan, 2021, Turkey	n = 47 patients with VVS, n = 50 HC	Case-Control Study	Physical examination, Blood Pressure (BP), blood test, ECG, ECHO (for uncertain diagnosis) and HUTT	Depressive Disorders, Anxiety Disorders, Psychotic Disorders, Eating Disorders, Attention Deficit Hyperactivity Disorder and Tic Disorders	Kiddie-Sads-Present and Lifetime Version (K-SADS-PL); CDI; Child Anxiety Related Emotional Disorders (SCARED)	There were significant statistical differences in K-SADS-PL scores between HC and VVS patients. Specifically, Major Depressive Disorder (p = 0.003) was found in 10 (21.3%) patients and in one (2%) individual of the control group. In the case group, 9 patients (19.1), Social Anxiety Disorders (p = 0.001); Generalized Anxiety Disorders (p = 0.006) were found in 9 patients (19.1%) and in one (2%) individuals of the control group; Conversion Disorders (p = 0.001) were found in 9 (19.1%) patients, whereas Separation Anxiety Disorder (p = 0.002) was found in 8 (17%) people. Between the case (12.49 (7.17)) and control groups (7.58 (3.87)), there was a statistically significant difference in CDI total scores (p = 0.001). Between the case (28.34 (15.48)) and control groups (19.72 (10.71)), there was a statistically significant difference in SCARED scores (p = 0.002).	robust
Kolarczyk et al., 2020, Poland	N = 825 patients with syncope	Descriptive Cross Sectional Study	Historic and physical examination, orthostatic BP and standard 12 lead ECG. For a definite diagnosis or confirmation to the VVS: Holter 24h, laboratory test, x-ray examination and/or CT ECHO and HUTT.	Level of Fear-pain-stress Emotions examined during HUTT	Structured history taking	The study examined children with diagnosed syncope (N = 825) and included only children with diagnosed VVS (n = 109). The fear-pain-stress emotions (p = 0.02), evaluated during HUTT, were significantly greater in children with VVS and a negative result of HUTT (16 (32.6%), compared to children with VVS and a positive result of HUTT (8 (13.3%).	robust

Table 3. *Continued*

Authors, year, country	Sample Size	Study Design	Outcome - Type of measure of syncope	Exposure - psychological correlates	Measure of psychological correlates	Main findings	Quality score
Lin et al., 2015, China	N = 174 patients with US	Cross Sectional Study	Historical and physical examination, ECG, EEG, HUTT, Holter 24 h and blood Chemistries	Level of Psychological Fear examined during HUTT	Wong-Baker FACES scale	At various tilt degrees, there was a noticeable variation in the psychological fear. Between two tilt angles, fear was shown to be lowest at tilt degrees of 60° (p = 0.01). Psychological terror and tilt angle were found to have a positive rank correlation (rs = 0.445, p = 0.01). Of the entire sample (174), 62 reported (36%) VVS diagnosed during HUTT.	robust
Qingyou et al., 2004, China	N = 47 patients with US	Cross Sectional Study	Historical and physical examination, orthostatic BP, complete blood cell count, urinalysis, Blood electrolyte and glucose analysis, ECG, EEG ECHO, thoracic X-ray, CT and HUTT.	Anxiety and Fright, and Emotional Stress	NA	Children with a positive result of HUTT frequently did so under extended standing, fear and anxiety, and emotional stress (p = 0.004).	robust
Massin et al., 2004, Belgium	N = 226 patients with a primary complaint of syncope	Cross Sectional Study	ECG, Echocardiography, Holter (24 h), CT Scan, EEG, MRI, HUT, Blood glucose analysis, Electrolytes, Toxicologic analysis	NA	NA	Of the entire sample (N=226) 181 (80%) patients reported NCS; 21 (9%) patients reported neurologic problems; 8 patients had psychogenic problems (Hysteria/conversion, depression, panic attacks, breath-holding spells); 5 patients had cardiac problems; 4 patients had breath-holding spells; 4 patients an intoxication; 3 patients other causes. The psychogenic and cardiac categories were linked to the recurrence of the syncopal occurrences (p= 0.01 and p = 0.01, respectively). Long-term upright posture (p < 0.001) and conditions that increase the risk of NCS (such as a warm environment, concurrent illnesses, mild pain, hyperventilation, and so forth) (p < 0.001) were clearly associated with the NCS group. Before syncope, children with NCS were never supine. Psychogenic category and breath-holding periods were both linked to emotional stress (p =0.01).	robust

Table 3. *Continued*

Authors, year, country	Sample Size	Study Design	Outcome - Type of measure of syncope	Exposure - psychological correlates	Measure of psychological correlates	Main findings	Quality score
Ojha et al., 2011, USA	n = 53 patients with POTS n = 53 randomly chosen adult patients	Case Control Study	HUTT	Sleep abnormality	Ohio Dysautonomia Survey (ODYSA)	16/50 (32%) pediatric patients with POTS had more than 3 episodes of syncope compared with 14/47 (29.8%) adult patients (p = 0.80). 49/50 (98%) of pediatric patients had one or more symptoms of Sleep abnormality.	less robust
Wong & So, 2002, China	N = 2574 subjects n = 121 subjects who reported episodes of syncope	Cross Sectional Descriptive Study	Self-report questionnaire	Emotion, Fright	Self-report questionnaire	Of the entire sample (N = 2574), 121 subjects (4.7%) had experienced at least one episode of syncope lifetime. The prevalence increased with age (p < 0.001). The incidence of a first attack over the preceding 12 months was 1.7%. Emotion (9.1%) and fear (5.8%) were reported as psychological factors associated with syncope.	less robust

could need a better psychological assessment in compliance with the medical conditions linked to fainting. In addition of the traditional medication treatment (e.g. beta-blockers, fludrocortisone, alpha-adrenergic agonists, disopyramide, scopolamine, theophylline, serotonin-reuptake inhibitors) (Anderson et al., 2016; Kouakam et al., 1999; Sokoloski, 2001), it could be extremely important to promote psychological interventions forwarding better relationships with caregivers and peers, and emotion regulation (Sheldon et al., 2015). Second, creating support networks for patients and their families, such as support groups or educational resources, can be beneficial in addressing these challenges. For example, healthcare professionals could reassure and counsel patients about recognizing prodromes, and show appropriate postural maneuvers, teaching these to teachers and parents.

Thus, integrating psychological interventions alongside traditional medical treatments can help manage and prevent recurrent syncopal episodes. Additionally, research could explore the effectiveness of psychological interventions in reducing or, better, preventing syncope episodes and improving patients' psychological well-being. Therefore, it is recommended that future research employ longitudinal study designs. Such approaches would enable a comprehensive assessment of treatment outcomes and patient responses, which vary based on their reported coping mechanisms and personality functioning.

Consistent with the Polyvagal Theory (Porges, 2022), the ANS adapts responses to environmental demands, and in particular, to perceive situations of danger and threat or security. The syncopal experiences could be generated by fallacious neuroception (Porges, 2003): individuals perceive risk when instead in a secure environment and react to danger or risk with an extreme dysregulation that causes fainting. In this line, the syncope as a symptom could represent the effect of difficulty in processing stressful experiences, as well as the body that may preserve the mind from extreme suffering. In this sense, it is not the body that "betrays", but rather it is the body that "protects" against pain. Clarifying this association will contribute to an understanding of psychological correlates underlying syncopal experiences. Disruptions in neuroceptive processes may be reflective of an insecure attachment style, as noted by Porges (2011). Chronic relational failures with caregivers can significantly derail a child's developmental course, potentially leading to what van der Kolk (2005) identifies as developmental trauma. Furthermore, according to Bowlby's attachment theory (1988), such traumatic experiences could lead to the formation of insecure internal working models in children, evidenced by patterns of emotional withdrawal or an overreliance on caregivers. These maladaptive models contribute to emotional and autonomic dysregulation such as diminished vagal tone, heightened heart rate, and abnormal parasympathetic responses, which can predispose individuals to defensive responses like freezing or flight/fight reactions (Dale et al., 2022; Porges, 2011; Riordan et al., 2017). Thus, a syncopal episode, excluding organic dysfunction factors (e.g. cardiac syncope) and substance intoxication, could be the result of somatization processes in response to dysregulated psychological distress—a process possibly exacerbated by unresolved trauma and insecure attachment.

Consistent with previous literature and the findings of this review, pediatric syncope is associated with significant psychopathological distress, emotional dysregulation, and insecure attachment patterns (Bonadies et al., 2006; O'Hare et al., 2017). Given the integral role of family relationships in the development of children's social skills and self-regulation processes, a thorough exploration of family dynamics, attachment styles, and any potential history of traumatic experiences is crucial. Such factors could significantly influence both the diagnosis and the management of pediatric patients with syncope.

Limitations

There are several limitations in the current study. First, the small sample size does not allow the results to be generalized by referring to the general population experiencing syncopal episodes. Second, the absence of meta-analysis affects the generalizability of the findings and limits the ability to refer to strong conclusions. Third, the heterogeneity of outcomes and psychological assessment measures did not consent to explore potential factors as a clinical moderator or trigger (e.g., parental history of syncope, hereditary psychiatric disturbances, traumatic life experiences). Fourth, lack of longitudinal studies. Finally, the limited number of included studies regarding rigorous search and selection criteria and consequently the specificity of the topic and the sample did not provide numerous and strong evidence to investigate. However, the qualitative evaluation of the studies and the Risk of Bias investigation allows us to state that the selected studies, even if small, are robust and encourage us to underline the relationship between psychopathological symptoms and clinically documented fainting episodes.

Conclusions

This systematic review aims to collect evidence regarding the relationship between psychological symptoms and episodes of syncope in children and adolescents. Included studies suggest that children and adolescents who experience syncope frequently report clinical symptoms related to emotional, relational, and psychosomatic dysregulation. Specifically, patients refer to anxiety, depression, sleep problems, poor quality of life, and parental/peer relationship impairment.

This review also allows insights into the potential implications of the psychological correlates of pediatric syncope. Despite the limitations and the strict and rigid research and selection criteria of the study, it is possible to underline that there is a robust relationship between psychopathology and syncope. Future research could delve deeper into the bottom-up or top-down nature of the relationship between psychopathological symptoms and fainting experiences, so as to improve the effectiveness of treatments. Moreover, future studies could expand the investigation to family factors (e.g. syncopal or psychopathological inheritance, the course of pregnancy) or to developmental trauma, and emotional processing difficulties which could be valuable for new lines of early management. In this sense, syncope could be a symptom of traumatic conversion and in the absence of organic causes should be promoted psychotherapy treatments to reduce pharmacological treatments in developmental age.

Furthermore, healthcare professionals could improve early differential diagnosis, treatment, and therapeutic interventions, enhance the quality of life and support parental, scholastic and peer engagement for affected children and adolescents.

References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA school-age forms and profiles*. Department of Psychiatry, University of Vermont.

Alhuzaimi, A., Aljohar, A., Alhadi, A. N., Aljenedil, A., & Hersi, A. S. (2018). Psychiatric traits in patients with vasovagal and unexplained syncope. *International Journal of General Medicine*, 99-104. https://doi.org/10.2147%2FIJGM.S157335.

Anderson, J. B., Czosek, R. J., Knilans, T. K., & Marino, B. S. (2012). The effect of paediatric syncope on health-related quality of life. *Cardiology in the Young*, *22*(5), 583-588. https://doi.org/10.1017/s1047951112000133.

Anderson, J. B., Willis, M., Lancaster, H., Leonard, K., & Thomas, C. (2016). The evaluation and management of pediatric syncope. *Pediatric Neurology*, *55*, 6-13. https://doi.org/10.1016/j.pediatrneurol.2015.10.018

Ayers, M. D., & Lawrence, D. K. (2015). Near-infrared Spectroscopy to Assess Cerebral Perfusion during Head-up Tilt-table Test in Patients with Syncope. *Congenital Heart Disease*, *10*(4), 333-339. https://doi.org/10.1111/chd.12236.

Bechir, M., Binggeli, C., Corti, R., Chenevard, R., Spieker, L., Ruschitzka, F., Lüscher, T. F., & Noll, G. (2003). Dysfunctional baroreflex regulation of sympathetic nerve activity in patients with vasovagal syncope. *Circulation*, *107*(12),1620–1625. https://doi.org/10.1161/01.cir.0000056105.87040.2b.

Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The screen for child anxiety related emotional disorders (SCARED): Scale construction and psychometric characteristics. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(4), 545-553. https://doi.org/10.1097/00004583-199704000-00018.

Blad, H., Lamberts, R. J., Van Dijk, J. G., & Thijs, R. D. (2015). Tilt-induced vasovagal syncope and psychogenic pseudosyncope: overlapping clinical entities. *Neurology*, *85*(23), 2006-2010. https://doi.org/10.1212/wnl.0000000000002184.

Blount, R. L., Morris, J. A., Cheng, P. S., Campbell, R. M., & Brown, R. T. (2004). Parent and child psychological factors in pediatric syncope and other somatic symptoms. *Journal of consulting and clinical psychology*, *72*(4), 597. https://doi.org/10.1037/0022-006x.72.4.597.

Bo, I., Carano, N., Agnetti, A., Tchana, B., Allegri, V., Sommi, M., & Squarcia, U. (2009). Syncope in children and adolescents: a two-year experience at the Department of Paediatrics in Parma. *Acta Biomedical*, *80*(1), 36-41.

Bonadies, M., Di Trani, M., Solano, L., Tumbiolo, F., Piacentini, F., & Ammirati, F. (2006). Psychological characteristics of patients with vasovagal syncope: and observational study on sixty subjects. *Giornale Italiano di Cardiologia*, 7(4), 273-280.

Bowlby, J. (1988). *A secure base: Parent-child attachment and healthy human development*. Basic Books.

Brignole, M., & Hamdan, M. H. (2012). New concepts in the assessment of syncope. *Journal of the American College of Cardiology*, *59*(18), 1583-1591. https://doi.org/10.1016/j.jacc.2011.11.056.

Brignole, M., Alboni, P., & Benditt, D. (2002). Linee guida per la diagnosi e il trattamento della sincope. *Giornale Italiano di Cardiologia*, *5*, 1-54.

Brignole, M., Menozzi, C., Del Rosso, A., Costa, S., Gaggioli, G., Bottoni, N. A., Bartoli, P., & Sutton, R. (2000). New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification: Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge. *Europace*, *2*(1), 66-76. https://doi.org/10.1053/eupc.1999.0064.

Brignole, M., Moya, A., de Lange, F. J., Deharo, J. C., Elliott, P. M., Fanciulli, A., Fedorowski, A., Furlan, R., Kenny, R. A., Martín, A., Probst, V., Reed, M. J., Rice, C. P., Sutton, R., Ungar, A., & Van Dijk, J. G. (2018). Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. *European Heart Journal*, *39*(21), e43-e80. https://doi.org/10.1093/eurheartj/ehy071.

Byars, K. C., Brown, R. T., Campbell, R. M., & Hobbs, S. A. (2000). Psychological adjustment and coping in a population of children with recurrent syncope. *Journal of Developmental and Behavioral Pediatrics*, *21*(3), 189-197.

Chan, A., Gao, J., Houston, M., Willett, T., Farhadian, B., Silverman, M., Tran, P., Jaradeh, S., Thienemann, M., & Frankovich, J. (2022). Children With PANS May Manifest POTS. *Frontiers in Neurology*. *13*, 819636. https://doi.org/10.3389/fneur.2022.819636.

Chen, L., Yang, Y. Y., Wang, C., Wang, H. W., Tian, H., Zhang, Q. Y., Chen, J., Wang, Y., Kang, Y., Tang, C., & Du, J. B. (2006). A multi-center study of hemodynamic characteristics exhibited by children with unexplained syncope. *Chinese Medical journal*, *119*(24), 2062-2068.

Chen, L., Zhang, Q., Ingrid, S., Chen, J., Qin, J., & Du, J. (2007). Aetiologic and clinical characteristics of syncope in Chinese children. *Acta Paediatrica*, *96*(10), 1505-1510. https://doi.org/10.1111/j.1651-2227.2007.00446.x.

Chen, M. Y., Goldenberg, I. F., Milstein, S., Buetikofer, J., Almquist, A., Lesser, J., & Benditt, D. G. (1989). Cardiac electrophysiologic and hemodynamic correlates of neurally mediated syncope. *The American Journal of Cardiology*, *63*(1), 66-72. https://doi.org/10.1016/0002-9149(89)91077-1.

Chen-Scarabelli, C., & Scarabelli, T. M. (2004). Neurocardiogenic syncope. *British Medical Journal*, *329*(7461), 336-341. https://doi.org/10.1136/bmj.329.7461.336.

Cohen, T. J., Thayapran, N., Ibrahim, B., Quan, C., Quan, W., von zur Muhlen, F. (2000). An association between anxiety and neurocardiogenic syncope during head-up tilt table testing. *Pacing and Clinical Electrophysiology*, *23*(5), 837-841. https://doi.org/10.1111/j.1540-8159.2000.tb00852.x.

Critical Appraisal Skills Programme (2018a). CASP (Case Control Study) Checklist. 1-6. Available at: https://casp-uk.net/images/checklist/documents/CASP-Case-Control-Study-Checklist/CASP-Case-Control-Study-Checklist-2018-fillable-form.pdf. Accessed: 25 January 2023.

Critical Appraisal Skills Programme (2018b). CASP (Cohort Study modified Cross Sectional Study) Checklist. Available at: https://casp-uk.net/images/checklist/documents/CASP-Cohort-Study-Checklist/CASP-Cohort-Study-Checklist-2018_fillable_form.pdf. Accessed: 25 January 2023.

D'Antono, B., Dupuis, G., St-Jean, K., Lévesque, K., Nadeau, R., Guerra, P., Thibault, B., & Kus, T. (2009). Prospective evaluation of psychological distress and psychiatric morbidity in recurrent vasovagal and unexplained syncope. *Journal of psychosomatic research*, *67*(3), 213-222. https://doi.org/10.1016/j.jpsychores.2009.03.012.

Dale, L. P., Kolacz, J., Mazmanyan, J., Leon, K. G., Johonnot, K., Bossemeyer Biernacki, N., & Porges, S. W. (2022). Childhood maltreatment influences autonomic regulation and mental health in college students. *Frontiers in Psychiatry*, *13*, 841749. https://doi.org/10.3389/fpsyt.2022.841749.

Dalton, T., & Wang, N. E. (2017). Pediatric syncope: current status of diagnostic evaluation and management. *ReliasMedia*. *22*(5), 49-64.

Ding, Y. Y., Wang, C., Wu, L. J., Hu, C. Y., & Lin, P. (2010). Psychological factors of children with vasovagal syncope. *Journal of Applied Clinical Pediatrics*, *25*, 437-439.

Dirkzwager, A. J., & Verhaak, P. F. (2007). Patients with persistent medically unexplained symptoms in general

practice: characteristics and quality of care. *BMC Family Practice*, *8*(1), 1-10. https://doi.org/10.1186/1471-2296-8-33.

Driscoll, D. J., Jacobsen, S. J., Porter, C. B. J., & Wollan, P. C. (1997). Syncope in children and adolescents. *Journal of the American College of Cardiology*, *29*(5), 1039-1045. https://doi.org/10.1016/S0735-1097(97)00020-X.

Flevari, P., Leftheriotis, D., Komborozos, C., Fountoulaki, K., Dagres, N., Theodorakis, G., & Kremastinos, D. (2009). Recurrent vasovagal syncope: comparison between clomipramine and nitroglycerin as drug challenges during head-up tilt testing. *European Heart Journal*, *30*(18), 2249-2253. https://doi.org/10.1093/eurheartj/ehp255.

Flint, B., Baker, C., Freeston, M., & Newton, J. L. (2009). Level of psychosocial impairment predicts early response to treatment in vasovagal syncope. *Europace*, *11*(2), 231-236. https://doi.org/10.1093/europace/eun332.

Garra, G., Singer, A. J., Taira, B. R., Chohan, J., Cardoz, H., Chisena, E., & Thode, H. C. (2010). Validation of the Wong-Baker FACES pain rating scale in pediatric emergency department patients. *Academic Emergency Medicine*, *17*(1), 50-54. https://doi.org/10.1111/j.1553-2712.2009.00620.x.

Giada, F., Silvestri, I., Rossillo, A., Nicotera, P. G., Manzillo, G. F., & Raviele, A. (2005). Psychiatric profile, quality of life and risk of syncopal recurrence in patients with tilt-induced vasovagal syncope. *Europace*, *7*(5), 465-471. https://doi.org/10.1016/j.eupc.2005.05.008.

Grimaldi Capitello, T., Fiorilli, C., Placidi, S., Vallone, R., Drago, F., & Gentile, S. (2016). What factors influence parents' perception of the quality of life of children and adolescents with neurocardiogenic syncope?. *Health and Quality of Life Outcomes*, *14*(1), 1-9. https://doi.org/10.1186/s12955-016-0476-9.

Grubb, B. P., Gerard, G., Wolfe, D. A., Samoil, D., Davenport, C. W., Homan, R. W., & Temesy-Armos, P. (1992). Syncope and seizures of psychogenic origin: Identification with head-upright tilt table testing. *Clinical Cardiology*, *15*(11), 839-842. https://doi.org/10.1002/clc.4960151109.

Hainsworth, R. (1999). Syncope and fainting: classification and pathophysiological basis. In: Mathias, C.J., & Bannister, R. eds. *Autonomic Failure. A textbook of clinical disorders of the autonomic nervous system. Fourth Edition.* Oxford University Press, p.p. 428-436.

Hainsworth, R. (2004). Pathophysiology of syncope. *Clinical Autonomic Research*, *14*, i18-i24. https://doi.org/10.1007/s10286-004-1004-2.

Heyer, G. L. (2017). Youth with psychogenic non-syncopal collapse have more somatic and psychiatric symptoms and lower perceptions of peer relationships than youth with syncope. *Pediatric Neurology*, *79*, 34-39. https://doi.org/10.1016/j.pediatrneurol.2017.11.009.

Heyer, G. L. (2019). Atypical prodromal symptoms help to distinguish patients with psychogenic nonsyncopal collapse among youth referred for fainting. *Pediatric Neurology*, *95*, 67-72. https://doi.org/10.1016/j.pediatrneurol.2019.02.006.

Heyer, G. L., Albert, D. V., Weber, A., Gedela, S., & Vidaurre, J. (2016). Comparison of semiologies between tilt-induced psychogenic nonsyncopal collapse and psychogenic nonepileptic seizures. *Epilepsy & Behavior*, *62*, 171-175. https://doi.org/10.1016/j.yebeh.2016.06.027.

Heyer, G. L., Pabst, L. M., Kaucic, B. N., & Coley, T. A. (2018). Early outcomes in youth with psychogenic nonsyncopal collapse. *Neurology*, *91*(9), e850-e858. https://doi.org/10.1212/WNL.0000000000006098.

Hill, A. B. (1965). The environment and disease: association or causation?. *Proceedings of the Royal Society of Medicine*, *58*, 295–300.

Hubsch, C., Baumann, C., Hingray, C., Gospodaru, N., Vignal, J. P., Vespignani, H., & Maillard, L. (2011). Clinical classification of psychogenic non-epileptic seizures based on video-EEG analysis and automatic clustering. *Journal of Neurology, Neurosurgery & Psychiatry*, *82*(9), 955-960. https://doi.org/10.1136/jnnp.2010.235424.

Hyphantis, T. N., Pappas, A. I., Vlahos, A. P., Carvalho, A. F., Levenson, J. L., & Kolettis, T. M. (2012). Depressive symptoms and neurocardiogenic syncope in children: a 2-year prospective study. *Pediatrics*, *130*(5), 906-913. https://doi.org/10.1542/peds.2012-1379.

Irwin, D. E., Stucky, B., Langer, M. M., Thissen, D., DeWitt, E. M., Lai, J. S., Varni, J. W., Jeatts, K., & DeWalt, D. A. (2010). An item response analysis of the pediatric PROMIS anxiety and depressive symptoms scales. *Quality of Life Research*, *19*, 595-607. https://doi.org/10.1007/s11136-010-9619-3.

Iwase, S., Nishimura, N., & Mano, T. (2014). Role of sympathetic nerve activity in the process of fainting. *Frontiers in Physiology*, *5*, 343. https://doi.org/10.3389/fphys.2014.00343.

Kanjwal, K., & Calkins, H. (2015). Syncope in children and adolescents. *Cardiology Clinics*, *33*, 397–409. https://doi.org/10.1016/j.ccl.2015.04.008

Kapoor, W. N., Fortunato, M., Hanusa, B. H., & Schulberg, H. C. (1995). Psychiatric illnesses in patients with syncope. *The American Journal of Medicine*, *99*(5), 505-512. http://doi.org/10.1016/s0002-9343(99)80227-7.

Kara, A., & Doğan, M. T. (2021). The psychopathology, depression, and anxiety levels of children and adolescents with vasovagal syncope: a case-control study. *The Journal of Nervous and Mental Disease*, *209*(8), 547-551. http://doi.org/10.1097/NMD.0000000000001334.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(7), 980-988. http://doi.org/10.1097/00004583-199707000-00021.

Kolarczyk, E. B., Szydłowski, L., Skierska, A., & Markiewicz-Łoskot, G. (2020). The differences in the diagnostic profile in children with vasovagal syncope between the result of head-up tilt table test. *International Journal of Environmental Research and Public Health*, *17*(12), 4524. http://doi.org/10.3390/ijerph17124524.

Kolarczyk, E. B., & Nowakowska, E. (2018). The pathophysiology of vasovagal syncope. *Medical Science Pulse*, *4*, 49–53. http://doi.org/10.5604/01.3001.0012.7799.

Konig, D., Linzer, M., Pontinen, M., & Divine, G. W. (1992). Syncope in young adults: evidence for a combined medical and psychiatric approach. *Journal of Internal Medicine*, *232*, 169-176. http://doi.org/10.1111/j.1365-2796.1992.tb00567.x.

Kouakam, C., Lacroix, D., Klug, D., Baux, P., Marquié, C., & Kacet, S. (2002). Prevalence and prognostic significance of psychiatric disorders in patients evaluated for recurrent unexplained syncope. *The American Journal of Cardiology*, *89*(5), 530-535. http://doi.org/10.1016/s0002-9149(01)02292-5.

Kouakam, C., Lacroix, D., Vaksmann, G., Klug, D., Jarwe, M., Mairesse, G., Key, C., & Kacet, S. (1999). Determinants of Efficacy of Beta-Blocker Therapy in Patients with Asystole Induced During Head-up Tilt Testing. *Annals of Noninvasive Electrocardiology*, *4*(4), 377-384. https://doi.org/10.1111/j.1542-474X.1999.tb00226.x.

Kouakam, C., Vaksmann, G., Pachy, E., Lacroix, D., Rey, C., & Kacet, S. (2001). Long-term follow-up of children and adolescents with syncope; predictor of syncope recurrence. *European Heart Journal*, *22*(17), 1618-1625. http://doi.org/10.1053/euhj.2000.2577.

Kovacs, M. (1985). The Children's Depression Inventory (CDI). *Psychopharmacology bulletin, 21*(4), 995–998.

Lai, W. T., Chen, M. R., Lin, S. M., & Hwang, H. K. (2010).

Application of head-up tilt table testing in children. *Journal of the Formosan Medical Association*, *109*(9), 641-646. http://doi.org/10.1016/S0929-6646(10)60104-0.

Lee, S. H., Park, S. J., Byeon, K., On, Y. K., Yim, H. R., & Kim, J. S. (2013). Prevalence and clinical factors of anxiety and depression in neurally mediated and unexplained syncope. *Yonsei Medical Journal*, *54*(3), 583-589. http://doi.org/10.3349/ymj.2013.54.3.583.

Leftheriotis, D., Michopoulos, I., Flevari, P., Douzenis, A., Koborozos, C., Kostopoulou, A., Theodorakis, G. N., Lykouras, L., & Kremastinos, D. T. (2008). Minor psychiatric disorders and syncope: the role of psychopathology in the expression of vasovagal reflex. *Psychotherapy and Psychosomatics*, *77*(6), 372-376. http://doi.org/10.1159/000151517.

Lewis, D. A., & Dhala, A. (1999). Syncope in the pediatric patient: the cardiologist's perspective. *Pediatric Clinics of North America*, *46*(2), 205-219. http://doi.org/10.1016/s0031-3955(05)70113-9.

Lin, J., Wang, Y., Ochs, T., Tang, C., Du, J., & Jin, H. (2015). Tilt angles and positive response of head-up tilt test in children with orthostatic intolerance. *Cardiology in the Young*, *25*(1), 76-80. http://doi.org/10.1017/S1047951113001601.

Linzer, M., Varia, I., Pontinen, M., Divine, G. W., Grubb, B. P., & Estes-III, N. M. (1992). Medically unexplained syncope: relationship to psychiatric illness. *The American Journal of Medicine*, *92*(1), S18-S25. http://doi.org/10.1016/0002-9343(92)90132-u.

Massin, M. M., Bourguignont, A., Coremans, C., Comté, L., Lepage, P., & Gérard, P. (2004). Syncope in pediatric patients presenting to an emergency department. *The Journal of Pediatrics*, *145*(2), 223-228. http://doi.org/10.1016/j.jpeds.2004.01.048.

McGrady, A., Kern-buell, C. H. E. R. Y. L., Bush, E., Khuder, S., & Grubb, B. P. (2001). Psychological and physiological factors associated with tilt table testing for neurally mediated syncopal syndromes. *Pacing and Clinical Electrophysiology*, *24*(3), 296-301. http://doi.org/10.1046/j.1460-9592.2001.00296.x.

McLeod, K. A. (2003). Syncope in childhood. *Archives of Disease in Childhood*, *88*(4), 350-353. http://dx.doi.org/10.1136/adc.88.4.350.

Mosqueda-Garcia, R., Furlan, R., MD, J. T., & Fernandez-Violante, R. (2000). The elusive pathophysiology of neurally mediated syncope. *Circulation*, *102*(23), 2898-2906. https://doi.org/10.1161/01.cir.102.23.2898.

Moya, A., & Sutton, R. (2009). Guidelines for the diagnosis and management of syncope (version 2009): the Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). *European heart journal*, *30*(21), 2631-2671. https://doi.org/10.1093/eurheartj/ehp298.

Nowakowska, E., Morka, A., & Szydłowski, L. (2014). Syncope in children and adolescents as a sudden, transient, short-term and spontaneously reversible loss of consciousness caused by a decrease in cerebral perfusion. *Paediatrics and Family Medicine*, *10*(3), 234. https://doi.org/10.15557/PiMR.2014.0026.

O'Hare, C., McCrory, C., O'Leary, N., O'Brien, H., & Kenny, R. A. (2017). Childhood trauma and lifetime syncope burden among older adults. *Journal of Psychosomatic Research*, 97, 63-69. https://doi.org/10.1016/j.jpsychores.2017.03.019.

Ojha, A., Chelimsky, T. C., & Chelimsky, G. (2011). Comorbidities in pediatric patients with postural orthostatic tachycardia syndrome. *The Journal of Pediatrics*, *158*(1), 20-23. https://doi.org/10.1016/j.jpeds.2010.07.005.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Lo-der, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P., & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *British Medical Journal*, *372*(71), https://doi.org/10.1136/bmj.n71.

Pinna, G. D., Maestri, R., & La Rovere, M. T. (2015). Assessment of baroreflex sensitivity from spontaneous oscillations of blood pressure and heart rate: proven clinical value? *Physiological Measurement*, 36, 741–753. https://doi.org/10.1088/0967-3334/36/4/741.

Porges, S. W. (2022). Polyvagal theory: a science of safety. *Frontiers in integrative neuroscience*, *16*, 27. https://doi.org/10.3389/fnint.2022.871227.

Porges, S. W. (2011). *The polyvagal theory: Neurophysiological foundations of emotions, attachment, communication, and self-regulation (Norton series on interpersonal neurobiology)*. WW Norton & Company.

Porges, S. W. (2003). Social engagement and attachment: a phylogenetic perspective. *Annals of the New York Academy of Sciences*, *1008*(1), 31-47. https://doi.org/10.1196/annals.1301.004.

Qingyou, Z., Junbao, D., Jianjun, C., & Wanzhen, L. (2004). Association of clinical characteristics of unexplained syncope with the outcome of head-up tilt tests in children. *Pediatric Cardiology*, *25*, 360-364. https://doi.org/10.1007/s00246-003-0513-4.

Raj, V., Rowe, A. A., Fleisch, S. B., Paranjape, S. Y., Arain, A. M., & Nicolson, S. E. (2014). Psychogenic pseudosyncope: diagnosis and management. *Autonomic Neuroscience*, *184*, 66-72. https://doi.org/10.1016/j.autneu.2014.05.003.

Rask, C. U., Olsen, E. M., Elberling, H., Christensen, M. F., Ørnbøl, E., Fink, P., Thomsen, P. H., & Skovgaard, A. M. (2009). Functional somatic symptoms and associated impairment in 5–7-year-old children: the Copenhagen Child Cohort 2000. *European Journal of Epidemiology*, *24*(10), 625-634, https://doi.org/10.1007/s10654-009-9366-3.

Riordan, J. P., Blakeslee, A., & Levine, P. (2017). Toddler trauma: Somatic experiencing, attachment and the neurophysiology of dyadic completion. *International Journal of Neuropsychotherapy*, 5, 41–70. https://doi.org/10.12744/ijnpt.2017.1.0041-0069.

Ruckman, R. N. (1987). Cardiac causes of syncope. *Pediatrics in Review*, *9*(4), 101-108. https://doi.org/10.1542/pir.9-4-101.

Salo, L. M., Woods, R. L., Anderson, C. R., & McAllen, R. M. (2007). Nonuniformity in the von Bezold-Jarisch reflex. *The American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 293, R714–R720. https://doi.org/10.1152/ajpregu.00099.2007.

Schroeder, C., Bush, V. E., Norcliffe, L. J., Luft, F. C., Tank, J., Jordan, J., & Hainsworth, R. (2002). Water drinking acutely improves orthostatic tolerance in healthy subjects. *Circulation*, *106*(22), 2806-2811. https://doi.org/10.1161/01.cir.0000038921.64575.d0.

Scott, W. A. (1991). Evaluating the child with syncope. *Pediatric Annals*, *20*(7), 350-359. https://doi.org/10.3928/0090-4481-19910701-08.

Sheldon, R. S., Grubb-II, B. P., Olshansky, B., Shen, W. K., Calkins, H., Brignole, M., Raj, S. R., Krahn, A. D., Morillo, C. A., Stewart, J. M., Sutton, R., Sandroni, P., Friday, K. J., Hacuol, D. T., Cohen, M., Lau, D. H., Mayuga, K. A., Moak, J. P., Sandhu, R. K., & Kanjwal, K. (2015). 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart rhythm*, *12*(6), e41-e63. https://doi.org/10.1016/j.hrthm.2015.03.029.

Sokoloski, M. C. (2001). Evaluation and treatment of pediatric patients with neurocardiogenic syncope. *Progress in pediatric cardiology*, *13*(2), 127-131. https://doi.org/10.1016/s1058-9813(01)00095-9.

Soteriades, E. S., Evans, J. C., Larson, M. G., Chen, M. H., Chen,

L., Benjamin, E. J., & Levy, D. (2002). Incidence and prognosis of syncope. *New England Journal of Medicine*, *347*(12), 878-885. https://doi.org/10.1056/NEJMoa012407.

Strasberg, B., Sagie, A., Rechavia, E., Sclarovsky, S., & Agmon, J. (1989). The noninvasive evaluation of syncope of suspected cardiovascular origin. *American Heart Journal*, *117*(1), 160-163. https://doi.org/10.1016/0002-8703(89)90671-6.

Tanel, R. E., & Walsh, E. P. (1997). Syncope in the pediatric patient. *Cardiology Clinics*, *15*(2), 277-294. https://doi.org/10.1016/s0733-8651(05)70336-2.

Tannemaat, M. R., van Niekerk, J., Reijntjes, R. H., Thijs, R. D., Sutton, R., & van Dijk, J. G. (2013). The semiology of tilt-induced psychogenic pseudosyncope. *Neurology*, *81*(8), 752-758. https://doi.org/10.1212%2FWNL.0b013e3182a1aa88.

van der Kolk, B. A. (2005). Developmental trauma disorder: Toward a rational diagnosis for children with complex trauma histories. *Psychiatric Annals, 35*, 401–410.

van Dijk, N., Sprangers, M. A., Boer, K. R., Colman, N., Wieling, W., & Linzer, M. (2007). Quality of life within one year following presentation after transient loss of consciousness. *American Journal of Cardiology*, *100*(4), 672–676. https://doi.org/10.1016/j.amjcard.2007.03.085.

Van Dijk, J. G., Thijs, R. D., Van Zwet, E., Tannemaat, M. R., Van Niekerk, J., Benditt, D. G., & Wieling, W. (2014). The semiology of tilt-induced reflex syncope in relation to electroencephalographic changes. *Brain*, *137*(2), 576-585. https://doi.org/10.1093/brain/awt332.

Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical Care*, *39*(8), 800–812. https://doi.

org/10.1097/00005650-200108000-00006.

Velasco-Benitez, C. A., Falcon, A. C., Axelrod, C., & Saps, M. (2022). Prevalence of joint hypermobility, postural orthostatic tachycardia syndrome (POTS), and orthostatic hypotension in school-children. *Andes Pediatrica: Revista Chilena de Pediatria*, *93*(1), 53-58. https://doi.org/10.32641/andespediatr.v93i1.3755.

Ventura, R., Maas, R., Rüppel, R., Stuhr, U., Schuchert, A., Meinertz, T., & Nienaber, C. A. (2001). Psychiatric conditions in patients with recurrent unexplained syncope. *Europace*, *3*(4), 311-316. https://doi.org/10.1053/eupc.2001.0182.

Wallin, B. G., & Sundlöf, G. (1982). Sympathetic outflow to muscles during vasovagal syncope. *Journal of Autonomic Nervous System*, *6*, 287–291. https://doi.org/10.1016/0165-1838(82)90001-7.

Wieling, W., Ganzeboom, K. S., & Saul, J. P. (2004). Reflex syncope in children and adolescents. *Heart*, *90*(9), 1094-1100. https://doi.org/10.1136/hrt.2003.022996.

Wong, K. T., & So, L. Y. (2002). Syncope in children and adolescents of Hong Kong. *Journal of paediatrics and child health*, *38*(2), 196-198. https://doi.org/10.1046/j.1440-1754.2002.00780.x.

Yang, J., Zhu, L., Chen, S., Li, X., Zhang, Q., Zhang, F., Chen, L., Tang, C., Du, J., & Jin, H. (2013). Modified Calgary score in differential diagnosis between cardiac syncope and postural orthostatic tachycardia syndrome-associated syncope in children. *Cardiology in the Young*, *23*(3), 400-404. https://doi.org/10.1017/S1047951112001266.

Yeh, J. (2015). Syncope in children and adolescents. *Pediatric Annals*, *44*(12), e287-e291. https://doi.org/10.3928/00904481-20151113-01.