Heritability of social anxiety disorder: a systematic review of methodological designs

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Abstract

Background: The investigation of heritability stands out as an important means to establish the weight of genetic and environmental factors in the development of social anxiety disorder. **Objective:** This study aims to make a critical review of methodological designs used in the investigation of the social anxiety disorder (SAD) heritability. **Methods:** We reviewed 31 research articles published until October 2015 and found through the electronic search bases PubMed, Web of Science, and Scopus and manual searches in the reference lists of the selected references. Most of the investigations involved adult samples and twins to assess heritability. **Results:** There was great variability in the screening and diagnostic instruments used in the studies, leading to different outcomes. Structural equation models proved to be the most adequate to assess SAD heritability, allowing better estimates of this aspect of the disorder. SAD heritability rates varied between 13% and 76% in the articles reviewed. **Discussion:** We discuss methodological aspects that may affect the quality and the development of improved studies to investigate SAD heritability such as sample size, quality of screening instruments, and use of diagnostic interviews. More homogeneous investigations involving larger samples and standardized instruments and methods are desirable and opportune.

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Keywords: Social anxiety disorder, heritability, genetics, methodological design, social phobia.

Introduction

Social anxiety disorder (SAD) or social phobia is an anxiety disorder characterized by the presence of fear and anxiety in social situations, associated with the avoidance of such situations or significant personal distress that affect daily life. The prevalence of SAD has been estimated between 7%-12%[1,2], causing impairment in the life of diagnosed individuals[3] and direct and indirect costs to health systems[4].

The current model of the development and maintenance of SAD holds that multiple factors interact at specific moments and circumstances for the disorder to occur[5]. This interaction model combines both genetic factors, such as polymorphisms[6] and temperament[7], and environmental factors including the perception of family environment[8] and parental conflicts[9]. However, despite the existence of studies in this field, it is not yet possible to determine the specific contribution of each factor for the development of SAD. Therefore, the investigation of heritability stands out as an important means to establish the weight of genetic and environmental factors in the development of disorders, and different methodological designs can be used for this purpose.

In one methodological approach, heritability can be assessed by the chance that one relative will have the disorder, given the diagnosis of a patient, compared to a volunteer without the disorder (odds ratio). In this case, the participation of several relatives is required for each participant, divided according to the degree of genetic similarity (*e.g.*: 50% genetic similarity for first-degree relatives, 25% for second-degree relatives, 12.5 for third-degree relatives, and zero for spouses and adopted siblings). In this study design, the comparison of odds ratios (relative risk) for each degree of genetic similarity indicates the importance of genetic factors, whereas the analysis of relatives with no genetic similarity allows the observation of environmental factors. However, this design makes it difficult to determine the specific weight of genetic and environmental factors, since it is impossible to establish which environmental factors are social/shared or individual, as well as whether any genetic factors associated with the disorder are related to additive effects or dominant alleles.

Another method to assess heritability involves the participation of twins. In these studies, the genetic similarity between monozygotic (MZ) and dizygotic (DZ) twins is used to determine shared elements, since MZ twins virtually share 100% of their genes, while DZ twins share around half of their genes. It is also possible to explore gender differences in this type of investigation given the different gender-related experiences of the twins. Studies involving twins allow a more accurate determination of the factors that influence a given disorder, which are observed according to four possible outcomes: additive genetic effects, genetic effects resulting from dominant or non-additive alleles, familial or shared environmental effects (*e.g.*: parental conflict), and environmental effects that are not shared by individuals (*e.g.*: perception of family environment).

In research with twins, heritability can be assessed through types of analyses. The first involves the correlations of a given disorder indicator (diagnosis, interview, instrument) between MZ and DZ twins. In this approach, differences indicate additive genetic effects (A), which can be considered dominant (D) if the correlation in MZ twins is at least twice as that of DZ twins. In another type of analysis, the factors are explored in structural equation models that indicate the model that best fits the sample data (*e.g.*: a model considering only additive genetic effects and environmental factors that are not shared; or another model that will also contemplate shared environmental factors) and the estimated explained percentage for each factor.

In respect to SAD, a meta-analysis[10] estimated the heritability of the disorder as ranging between 20%-40%. This result, however, refers to a group comprising individuals with SAD, specific phobia, and agoraphobia, and does not specify the heritability of each disorder. A more recent review estimated the heritability of SAD between 27%-56%[11], but it included only studies with twins and which described precise estimates of variance explained by genetic factors.

Despite these efforts and as far as we know, no study to date made a comprehensive assessment of investigations on the heritability

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of SAD that used different methodological designs. Therefore, the objective of our study was to review articles dealing with the heritability of SAD with an emphasis on their methodological design and to provide directions for future research.

Method

Systematic searches were performed using the online databases PubMed, Web of Science, and Scopus for articles published until October 2015 using the following search terms: "social phobia AND genetics", "social phobia AND heritability", "social anxiety AND genetics", and "social anxiety AND heritability". The reference lists of articles found through the electronic databases and other review articles were hand-searched for additional references.

We included articles that described any measure or SAD heritability as an outcome. Animal studies, studies on genetic polymorphisms related to SAD, articles with no specific SAD heritability data, letters to the editor, editorials, book chapters, and review articles were not included in this review.

From each selected article, the following data were extracted whenever possible: (I) origin of the study sample; (II) country; (III) sample size; (IV) instruments used for the screening or diagnosis of SAD; (V) method of data analysis; (VI) primary outcome; (VII) correlation values between MZ and DZ twins; (VIII) genetic model; and (IX) values of additive genetic effects (A), shared environmental effects (C), and environmental effects (E). The data of the different articles were than assessed conjointly based on these categories. In addition, the studies were assessed according to the criteria of the STROBE initiative[12], which consist of a list of 22 items that assess the methodological quality of scientific articles.

Results

A total of 888 articles were found through the electronic searches. After a selection based on the inclusion and exclusion criteria, 28 articles were included in the review. Three other articles were found through the reference lists of selected articles and were also included in the review. Therefore, this review comprises the data of 31 articles. Details of the search and selection procedures are presented in Figure 1.

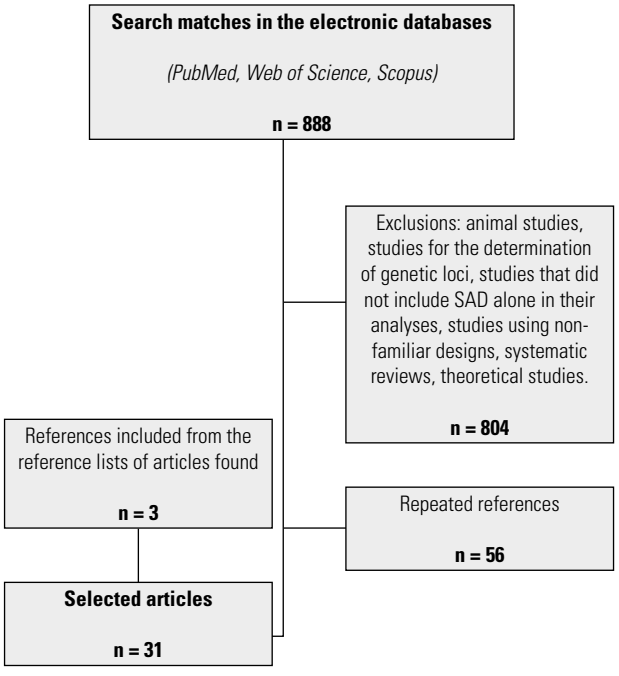

Figure 1. Flowchart showing the steps of the search and selection of articles for the review.

Table 1 presents the data of each article included in the review. From the studies selected, 21 (67.75%) recruited twins, and only one of these included volunteers recruited through community ads. Thus, 20 (95.23%) of the studies involving twins used public or private medical records, where data on the twin pairs were available since their birth until the data collection. In respect to the origin of articles included in this review, 19 (61.3%) were from Europe, 9 (29.03%) were from North America, and 2 (6.4%) came from Oceania. One study involved samples from two continents (Europe and Oceania).

Concerning the age range of participants, 17 studies (54.83%) involved adult samples and 12 studies (38.7%) involved children and adolescents. Two longitudinal studies collected data from participants at different age ranges, including periods of childhood, adolescence, and adult life. In general, the instruments used to measure symptoms or diagnose SAD varied widely across the studies. Despite this variation, self-report instruments were used as the only measure of SAD symptoms in 13 studies (41.93%). Thus, whereas some of the studies reviewed used well-established measures for the assessment of SAD (*e.g.*, Social Phobia Inventory[13]), others used sets of items taken from assessment instruments (*e.g.*[14]). Interviews were used as the only diagnostic instrument in 11 studies (35.48%) and structured interviews as the Structured Clinical Interview for DSM-IV (SCID)[15] and the Composite International Diagnostic Interview (CIDI)[16] were the most common among these. Two investigations (6.4%) used only medical records to establish diagnosis, with no procedures included to confirm the criteria applied or the accuracy of diagnosis during the period of the study. Other studies used more than one type of instrument to assess symptoms or diagnosis due to different profiles of their participants. In these studies, cases and controls were assessed with diagnostic interviews (three studies) or self-report instruments (two studies), whereas relatives (parents, siblings, uncles and grandparents) were assessed through previous diagnostic records or assessments by their health networks.

The studies included in this review also differed significantly in respect to methods of data analysis and the outcomes derived from these analyses. Among all the articles selected, 14 (45.16%) analyzed correlations between the twins in their samples, using the correlations between monozygotic and dizygotic siblings as outcomes, and also provided models and heritability estimates as outcomes based on structural equations. Two studies assessed only correlation differences between twins, while five others reported only heritability estimates based on structural equation models. Five of the articles reviewed analyzed the odds ratios for SAD in relatives of participants diagnosed with the disorder and presented as outcomes the differences between the degrees of relatedness, including that of twins, considering cases and controls. In addition, two studies reported heritability estimates obtained from structural equation models together with odds ratios for relatives of affected patients, and only one study provided heritability estimates based on the difference of correlations between siblings and half-siblings together with odds ratios. The investigation by Stein *et al.*[17] used factorial analysis to assess the extent to which the degree of consanguinity of SAD patients explained SAD symptoms in relatives, presenting as their outcome the variance explained by consanguinity relative to other factors. Finally, the study by Li *et al.*[18] assessed the incidence of SAD in siblings of patients diagnosed with anxiety disorders, presenting the standardized index ratio as outcome.

All the articles included in this review had satisfactory methodological quality, fulfilling at least 15 (68%) of the STROBE assessment items[12]. Additionally, 17 articles (55%) fulfilled more than 80% of the methodological recommendations of that initiative. Conversely, none of the studies included followed all the guidelines of the STROBE. The mains items that were not fulfilled by the studies reviewed here refer to the absence of information on sample size calculations and efforts to reduce possible biases.

Table 1. Population, number of participants, age of participants, instruments used to assess SAD, data analysis method, outcome and items fulfilled of STROBE of each study included

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Coelho *et al.*, 2007[21]	UK/Outpatients	37 SAD 22 GAD 15 SAD + GAD 60 HC 403 Relatives	Cases: 32.1 (3.77) Relatives: 47.4 (14.98)	SCID. Diagnosis of relatives based on information provided by cases/ controls	OR Case X Relative	OR SAD X SAD = 3.38 (1.25-9.16); SAD X Comorbidity OR (SAD-GAD) = 3.50 (0.98-12.55); Comorbidity OR (SAD-GAD) X TAS = 7.01 (0.82-60.23); Comorbidity OR X Comorbidity = 17.34 (1.96-153.62)	19 (86%)
Czajkowski *et al.*, 2011[22]	Norway/Twins (medical record services)	446 P Mz F; 264 P Dz F; 10 I	28.1	CIDI	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Eley *et al.*, 2003[23]	UK/Twins (medical record services)	723 P Mz M; 769 P Dz M; 818 P Mz F; 760 P Dz F; 1494 P Dz O	4	16-item questionnaire on anxiety-related behaviors	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Eley *et al.*, 2008[24]	UK/Twins (medical record services)	T0: 754 P Mz M; 783 P Dz M; 845 P Mz F; 768 P Dz F; 1512 P Dz O; T1: 120 P Mz M; 133 P Mz F; 138 P Dz M; 136 P Dz F; 327 P Dz O	T0: 4 T1: 6	T0 Anxiety Related Behaviors Questionnaire. T1 Anxiety Disorders Interview Schedule for Children and Parents	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Hallett *et al.*, 2009[14]	UK/Twins (medical record services)	T0 1205 P Mz M; 1118 P Dz M; 1370 P Mz F; 1219 P Dz F; 2255 P Dz O; T1: 538 P Mz M; 674 P Dz M; 503 P Mz F; 557 P Dz F; 1004 P Dz O	T0: 7 T1: 9	25 items taken from other instruments	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Hallett *et al.*, 2012[25]	UK/Twins (medical record services)	T0: 1232 P Mz M; 1164 P Dz M; 1375 P Mz F; 1230 P Dz F; 2310 P DzO; T1: 1069P Mz M; 1044 P Dz M; 1195 P Mz F; 1054 P Dz F; 2064 P Dz O	T0: 7 T1: 9	22 items taken from other instruments	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	18 (82%)
Hettema *et al.*, 2005[26]	USA/Community sample	2156 P F; 2939 P M	_	Diagnostic interviews based on DSM = III-R criteria	Structural Equation Models	Heritability estimates	17 (77%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Hettema *et al.*, 2006[27]	USA/Twins (medical record services)	679 P Mz F; 467 P Dz F; 869 P Mz M; 653 P Dz M; 1429 P Dz O; 125 I Mz F; 56 I Dz F; 230 I Mz M; 275 I Dz M; 462 I Dz O	–	Diagnostic interviews based on DSM = III-R criteria	Structural Equation Models	Heritability estimates	18 (82%)
Hudson *et al.*, 2003[28]	Austria/Outpatient services	64 MDD 58 HC 152 relatives	Cases: 39.5 (15) Relatives (cases): 39.6 (13.7) Controls: 40.9 (14.1). Relatives (controls): 37.4 (13.1)	SCID	OR Case X Relative	OR without depression = 4.6 (1.2-18); OR with comorbid depression = 2.7 (0.59-12)	17 (77%)
Isomura *et al.*, 2015[29]	Sweden/Population records with mental disorder diagnoses	18399 SAD 2673 APD 210.720 HC 2.959.278 Relatives	–	Previous diagnoses in medical records	OR Case X Relative Correlations between siblings and half-siblings	OR First-degree = 4.74 (4.28-5.25). OR Second-degree = 2.3 (2.01-2.63). OR Third-degree = 1.72 (1.52-1.94). OR Non-biological parents = 4.01 (3.26-4.95). Correlation for siblings = 0.27; half-siblings (mother's side) = 0.13. Heritability estimated by the correlation = 0.56	17 (77%)
Kendler *et al.*, 2001[30]	USA/Twins (medical record services)	707 P Mz M; 290 P Dz M; 254 I Mz M; 290 I Dz M	36.8 (9.1)	Diagnostic Interview Scale (DIS). Version III-A	OR Case X Sibling Structural Equation Models	Differences in OR. MZ = 2.3 (0.92-5.77); DZ = 1.73 (0.50-6.07)	14 (64%)
Kendler *et al.*, 2008[31]	Sweden/Twins (medical record services)	242 P Mz F; 182 P Dz F; 240 P Mz M; 168 P Dz M; 390 P Dz O	T0: 13-14 T1: 16-17 T2 19-20	Items dealing with fear of specific situations and objects	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	17 (77%)
Knappe *et al.*, 2009[32]	Germany/Cohort population for the study of psychopathology	T0: 1395 I T1: 1228 I T2: 1169 I T3 1,022 I	T0: 14-17 T1: 16-19 T2: 18-21 T3: 24-27	CIDI	OR Case X Relative	Symptomatic: OR = 1.3 (0.76-2.23); Subthreshold: OR = 1.44 (0.75-2.78); Diagnosis: OR = 3.21 (1.21-8.49)	18 (82%)
Lahey *et al.*, 2011[33]	USA/Twins (medical record services)	1571 PMz/Dz	6-17	Child and Adolescent Psychopathology Scale	Structural Equation Models	Heritability estimates	17 (77%)
Li *et al.*, 2011[18]	Sweden/Population records with mental disorder diagnoses	42602 AD; 2093 relatives		Previous diagnoses in medical records	Standardized incidence ratios	Men: 4.49 (1.88-10.07); Women: 2.51 (0.7-7.35); Total: 3.68 (1.68-7.69)	17 (77%)
López-Solà *et al.*, 2014[34]	Australia/Twins (medical record services)	204 P Mz M; 299 P Mz F; 111 P Dz M; 194 P Dz F; 125 I Mz M; 150 I Mz F; 132 I Dz M; 192 I Dz F;	MZ: 34.5 (7.8) DZ: 33.9 (8)	SPIN	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Low *et al.*, 2008[35]	USA/Patients recruited from outpatient services and the community. Relatives contacted.	26 I SAD + PD 40 I PD 46 I SAD 32 I AD 81 I HC. 1053 relatives	SAD + PD: 39 (5.9) PD: 39.5 (5.2) SP: 40.8 (6.3) AD: 40.4 (6.2) Controls: 41 (6.3)	Schedule for Affective Disorders and Schizophrenia. Family History-Research Diagnostic Criteria	OR Case X Relatives	OR SP-SP = 1.8 (1.1-2.9)	17 (77%)
Low *et al.*, 2008[36]	USA/Patients recruited from outpatient services and the community. Relatives contacted.	76 I SAD 60 I HC 620 relatives	Cases: 39.9 (5.3) Controls: 40.9 (6.28)	SCID for cases and controls. Best estimate Diagnoses for relatives	OR Case X Relatives	Clinical OR = 2.74 (1.1-6.84); Community OR = 2.38 (0.91-6.22)	16 (73%)
Michelini *et al.*, 2015[37]	UK/Twins (medical record services)	88 P Mz M; 134 P Mz F; 64 P Dz M; 130 P Dz F; 214 P Dz O; 30 P S M; 51 P S F; 71 P S O	17 (1.66)	Spence Children's Anxiety Scale	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	21 (95%)
Middedorp *et al.*, 2005[38]	The Netherlands and Australia/ Twins (medical record services)	1334 I M; 2088 I F	Men: 35.15 Women: 35.15	CIDI	Correlations between Mz and Dz	Correlation differences Brothers: 0.20 (0.09-0.31) Sisters: 0.20 (0.09-0.31) Different gender: 0.20 (0.09-0.31)	20 (91%)
Mosing *et al.*, 2009[39]	Australia/Twins (medical record services)	1337 P Mz 1384 P Dz	Mz: 44.07 (12.4); Dz: 29.9 (2.5)	Computer algorithms based on responses in the Semi-Structured Assessment for the Genetics of Alcoholism (SSA-GA)	OR Case X Sibling Structural Equation Models	Differences in OR. MZ = 11.9 (3.7-38.8); DZ = 1.5 (0.2-11.0). Heritability estimates	17 (77%)
Nelson *et al.*, 2000[40]	USA/Twins (medical record services)	672 P F Mz/Dz	18.2	Telephone interview with questions adapted from the Diagnostic Interview for Children and Adolescents	Correlations between Mz and Dz	Heritability estimates	18 (82%)
Ogliari *et al.*, 2006[41]	Italy/Twins (medical record services)	70 P Mz M; 65 P Mz F; 50 P Dz M; 78 P Dz F; 115 P Dz O	13.03 (2.6)	SCARED	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Ogliari *et al.*, 2010[42]	Italy/Twins (medical record services)	70 P Mz M; 65 P Mz F; 50 P Dz M; 78 P Dz F; 115 P Dz O	8-17	SCARED	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Reichborn-Kjennerud *et al.*, 2007[43]	Norway/Twins (medical record services)	898 P Mz F; 529 P Dz F	–	CIDI	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)
Skre *et al.*, 2000[44]	Norway/Twins (medical record services)	17 P Mz F; 6 I Mz M; 21 I Dz F; 17I Dz M	41 (9)	Items dealing with fear of specific situations and objects	Correlations between Mz and Dz Structural Equation Models	Correlation differences Heritability estimates	20 (91%)

Reference	Country/Population	Participants	Age (Mean ± SD)	Instruments	Data analysis	Outcome	STROBE items fulfilled n (%)
Stein *et al.*, 2001[17]	Canada/Patients recruited from outpatient services and the community. Relatives contacted	31 I SAD 24 I HC 65 relatives	Cases: 42.5 (16.8) Controls: 40.7 (15.6)	SCID (cases); Fear of Negative Evaluation Scale; Social Phobia Scale; Social Interactional Anxiety Scale (subjects) Scale, Social Interactional Anxiety Scale	Factorial analysis	Being a first-degree relative explains 84% of the variance	15 (68%)
Stein *et al.*, 2002[45]	Canada/Twins (community advertisement)	55 P Mz M; 154 P Mz F; 30 P Dz M; 115P Dz F; 35 P Dz O	MzM: 36.66 (16.86) MzF: 34.82 (14.1) DzM: 31.53 (13.37) DzF: 32.38 (13.13) DzO: 29.88 (12.82)	Brief Fear of Negative Evaluation	Correlations between Mz and Dz Structural Equation Models	Correlation between twins Heritability estimates	17 (77%)
Trzaskowski *et al.*, 2012[46]	UK/Twins (medical record services)	T0: 7834 I T1: 3644 I	T0: 7 T1: 9	Anxiety-Related Behaviors Questionnaire	Correlations between Mz and Dz Structural Equation Models Correlations between factors at ages 7 and 9	Phenotypical correlation of 0.54 (0.54-0.56) between ages 7 and 9 Correlation differences between MZ and DZ in the two ages	17 (77%)
Van Hulle *et al.*, 2012[47]	USA/Twins (medical record services)	175 P Mz; 150 P Dz; 160 P Dz O	7.7 (0.7)	Diagnostic Interview Schedule for Children	Correlations between Mz and Dz	Correlation differences	17 (77%)
Waszczuk *et al.*, 2014[20]	UK/Twins (medical record services)	T0: 100 P Mz; 82 P Dz; 117 P Dz O; T1: 83 P Mz; 69 P Dz; 98 P Dz O; T2 350 P Mz; 313 P Dz; 334 P Dz O; 330 P S; T3: 243 P Mz; 207 P Dz; 232 P Dz O; 182 S; T4: 230 P Mz; 214 P Dz; 232 P Dz O; 201 P S	T0: 8 years and 6 months T1: 10 years and 1 month T2: 15 years T3: 17 years T4: 20 years	SCARED for children; SCAS for adolescents; Revised Symptoms of Anxiety Scale for adults	Structural Equation Models	Heritability estimates	19 (86%)

P: Pairs; I: Single Individuals; Mz: monozygotic twins; Dz: dizygotic twins; S: siblings; M: Male; F: Female; O: Opposite Sex; SAD: Social Anxiety Disorder Case; GAD: Generalized Anxiety Disorder Case; PD: Panic Disorder Case; AD: Anxiety Disorder Case; MDD: Major Depression Disorder Case; APD: Avoidant Personality Disorder Case; HC: Health Control; OR: Odds ratio.

The analysis of correlational differences between monozygotic and dizygotic twins and heritability models that best explain the genetic and environmental contributions to SAD, in addition to estimates of each factor, are core elements for the assessment of heritability[19]. Therefore, we extracted the data from studies describing these variables, detailed in Table 2. Among these articles, the model that best fit the sample in most studies (66.7%) was the one that considers only additive genetic factors (A) and non-shared environmental factors (E). However, a significant share of the articles (28.6%) proposed that shared environmental factors (C) were an important component of the best explicative model. The study by Waszczuk *et al.*[20], that assessed pairs of twins as they aged, was the only one that suggested two models as most adequate because of the sample characteristics. Specifically, the authors considered the ACE model to be the most adequate for children, whereas the AE model was regarded as the most adequate for adults. There was great variability in the estimated heritability rates across studies, with heritability measured according to additive genetic factors ranging between 13% and 76%.

Table 2. Correlation between Monozygotic and Dizygotic twins, model that best fits the sample, additive genetic effects, shared environmental effects and non-shared environmental effects of each study included

Reference	RMz (CI)	RDz (CI)	Model	A (CI)	C (CI)	E (CI)
Czajkowski *et al.*, 2011[22]	0.56 (0.32-0.73)	0.14 (0.23-0.48)	AE	0.55	_	0.45
Eley *et al.*, 2003[23]	Males = 0.57 Females = 0.56	Males = 0.02 Females = 0.13	AE	Males 0.76 (0.71-0.79) Females 0.66 (0.59-0.71)	_	Males 0.24 (0.21-0.29) Females 0.34 (0.29-0.41)
Eley *et al.*, 2008[24]	0.27 (-0.04-0.54)	0.14 (–.07-0.35)	ACE	0.14 (0.00-0.45)	0.10 (0.00-0.30)	0.76 (0.52-0.93)
Hallett *et al.*, 2009[14]	Mz7 = 0.7 (0.68-0.72) Mz9 = 0.77 (0.75-0.79)	Dz7 = 0.31 (0.28-0.35) Dz9 = 0.48 (0.45-0.51)	ACE	7 years 0.61 (0.57-0.63) 9 years 0.56 (0.48-0.63)	7 Years 0.07 (0.05-0.1) 9 Years 0.2 (0.13-0.26)	7 years 0.32 (0.3-0.33) 9 years 0.25 (0.23-0.27)
Hallett *et al.*, 2012[25]	MzM = 0.7 (0.67-0.72) MzF = 0.69 (0.66-0.73)	DzM = 0.30 (0.29-0.33) DzF = 0.34 (0.32-0.36)	ACE	Males 0.6 (0.54-0.66) Females 0.59 (0.53-0.65)	Males 0.09 (0.04-0.14) Females 0.10 (0.03-0.17)	Males 0.31 (0.27-0.35) Females 0.31 (0.27-0.35)
Hettema *et al.*, 2005[10]	_	_	ACE	0.1	0.11	0.79
Hettema *et al.*, 2001[26]	_	_	ACE	0.13	0.09	0.78
Isomura *et al.*, 2015[29]	_	_	_	0.56	_	_
Kendler *et al.*, 2001[30]	_	_	AE	0.2 (0-0.41)	_	0.8 (0.59-1)
Kendler *et al.*, 2008[31]	MzF 13-14 = 0.51 MzF 16-17 = 0.52 MzF 19-20 = 0.44 MzM 13-14 = 0.45 MzM 16-17 = 0.41 MzM 19-20 = 0.17	DzF 13-14 = 0.17 DzF 16-17 = 0.14 DzF 19-20 = 0.08 DzM 13-14 = 0.31 DzM 16-17 = 0.14 DzM 19-20 = 0.49	AE	13-14 = 0.49 16-17 = 0.44 19-20 = 0.34	_	13-14 = 0.50 16-17 = 0.55 19-20 = 0.65
Lahey *et al.*, 2011[33]	_	_	AE	0.45	_	0.55
López-Solà *et al.*, 2014[34]	Mz Total = 0.46 (0.39-0.52); MzM = 0.38 (0.25-0.49); MzF = 0.49 (0.40-0.56)	Dz TOTAL 0.18 (0.09-0.27) DzM 0.07 (0.11-0.25) DzF 0.24 (0.11-0.36) DzO 0.16 (0.01-0.32	AE	Males 0.34 (0.23-0.45) Females 0.47 (0.39-0.55)	_	Males 0.66 (0.55-0.77) Females 0.53 (0.45-0.61)
Michelini *et al.*, 2015[37]	MzM = 0.43 (0.24-0.59) MzF = 0.34 (0.17-0.48)	DzM/SM = 0.37 (0.18-0.54); DzF/SF = 0.24 (0.09-0.38); DzO/SO = 0.09 (-0.04-0.21)	AE	0.35 (0.26-0.44)	_	0.65 (0.56-0.74)
Mosing *et al.*, 2009[39]	_	_	AE	0.39 (0.16-0.65)	_	_
Nelson *et al.*, 2000[40]	_	_	AE	0.28 (Common factor)	_	0.72 (Specific factor)
Ogliari *et al.*, 2006[41]	0.58 (8-11 years) 0.561 (12-17 years)	0.26 (8-11 years) 0.303 (8-11 years)	AE	0.56 (0.46-0.66)	_	0.44 (0.34-0.54)
Ogliari *et al.*, 2010[42]	0.57 (0.45-0.66)	0.31 (0.19-0.42)	AE	0.56 (0.46-0.65)	_	0.44 (0.35-0.54)
Reichborn-Kjennerud *et al.*, 2007[43]	0.57 (0.29-0.78)	0.06 (-0.41-0.50)	AE	0.39	_	0.61
Skre *et al.*, 2000[44]	0.53	-0.02	AE	0.47	_	0.53
Stein *et al.*, 2002[45]	MzM = 0.462 MzF = 0.503	DzM = 0.253 DzF = 0.124 DzO = 0.143	AE	0.42 (0.32-0.51)	_	0.58 (0.49-0.69)
Trzaskowski *et al.*, 2012[46]	7 years = 0.70 (0.68-0.72) 9 years = 0.77 (0.75-0.79)	7 years = 0.31 (0.28-0.35) 9 years = 0.48 (0.45-0.51)	ACE	7 to 9 years 0.66 (0.59-0.66)	7 to 9 years 0.55 (0.35-0.75)	7 to 9 years 0.42 (0.37-0.42)
Van Hulle *et al.*, 2012[47]	0.39	0.09	_	_	_	_

Reference	RMz (CI)	RDz (CI)	Model	A (CI)	C (CI)	E (CI)
Waszczuk *et al.*, 2014[20]	_	_	ACE (Children) AE (Adults)	8 years Common factor 0.12 (0-0.24) + Specific factor 0 (0-0.07) 10 years Common factor = 0.38 (0-0.53) + Specific factor = 0 (0-0.42) Adults All variables factor = 0.4 (0.3-0.49) Fear model factor = 0.07 (0.01-0.12)	8 years Common factor = 0.0 (0-0.08) + Specific factor = 0 (0-0.04) 10 years Common factor = 0.1 (0-0.27) + Specific factor = 0 (0-0.25)	8 years Common factor = 0.28 (0.17-0.46) + Specific factor = 0.59 (0.49-0.68) 10 years Common factor = 0.21 (0.09-0.40) + Specific factor = 0.40 (0.27-0.54) Adults Common factor = 0.26 (0.18-0.34) Specific factor = 0.27 (0.22-0.33)

MzM: monozygotic males; MzF: monozygotic females; DzM: dizygotic males; DzF: dizygotic females; DzO: dizygotic different sex; SM: sibling males; SF: sibling females; SO: siblings different sex; RMz: correlations between monozygotic twins; RDz: correlations between dizygotic twins; CI: confidence interval; A: additive genetic effects; C: shared environmental effects; E: non-shared environmental effects.

Discussion

The objective of this study was to systematically review articles assessing heritability to SAD, with no limits regarding publication date and including different methodological designs. A total of 31 articles were included in the review, most of which involved pairs of twins as their sample. The studies were conducted mainly in Europe and used mostly self-reporting instruments to assess SAD symptoms. SAD heritability was estimated through correlation differences between twins and based structural equation models. We found that additive genetic factors and non-shared environmental factors formed the most adequate model to explain SAD heritability, with genetic transmission rates estimated between 13% and 76%.

The vast majority of studies that recruited twins for their samples used birth and medical follow-up records, which allowed the enrollment of a large number of twins and provided a significant amount of information on the heritability of SAD. Conversely, only one study involving twins recruited participants by means of community advertisement. This study included fewer participants than the mean in twin studies, probably as a result of the difficulty of recruiting participants through this method.

Generally speaking, genetic studies for heritability estimates require large samples[48,49] in order to ensure the statistical power of their analyses. It is thus important to encourage the creation and maintenance of records about twins, especially in low- and middle-income countries. This fact becomes evident in the present review, as no articles from developing countries were included due to not using methodological designs compatible with the investigation of SAD heritability.

Clinical interviews are regarded as the gold standard for the diagnosis of SAD and are widely used both as validation parameters for instruments that assess SAD symptoms (*e.g.*: [50,51]) and as a criterion for the selection of participants in clinical trials (*e.g.*: [52,53]) and genetic investigations (*e.g.*: [21,28]). Nevertheless, in order to be effective as diagnostic instruments, clinical interviews must be performed within a short interval from enrollment in studies because of the longitudinal instability of psychiatric diagnoses. Some of the articles reviewed here (*e.g.*: [29]) mentioned the limitation of using previous medical records without later diagnostic confirmation, which affects the reliability of the data presented.

An important feature of clinical interviews is that their outcome is a dichotomous variable, that is, a positive or negative diagnosis. On the other hand, a number of initiatives have been made for the adoption of dimensional criteria in the assessment of mental disorders ([54,55]), aiming at greater adequacy of the diagnostic process. These measures tend to bring the clinical setting closer to basic research, providing a more global comprehension of psychopathology, especially in the case of SAD, since social inhibition is an innate aspect of humans and thus of little accuracy for the establishment of psychiatric diagnosis. Particularly in genetic research, such initiatives may allow a closer association between the factors that influence a disorder and the symptoms of this disorder[56]. In this direction, the use of instruments that assess symptoms within a disorder continuum and that offer dimensional criteria for disorder assessment is of great importance[57].

Most of the studies included in this review used this type of instrument, enabling the assessment of different possibilities of symptom manifestations. However, in order to provide reliable data, the instruments must present minimally adequate psychometric qualities and be compatible with the research interests. An important issue in some of the articles reviewed here was the use of instruments that were not subject to validation studies (*e.g.*: [31]) or versions derived from other instruments without the conduction of new psychometric evaluations[14].

The concept of heritability is broad and generally refers to the proportion of the variance that can be explained by genetic factors[58]. As a result of the broadness of the concept, different methods can be employed to observe its occurrence in a given condition. The diversity in the methods used by the studies reviewed may have been a consequence of this variability. A high amount of variance explained by the fact of being related to a patient diagnosed with SAD in factorial analyses, the increased risk of being diagnosed with the disorder when a relative has received the same diagnosis (and the decrease in risk as genetic distance increases), and differences in the incidence of SAD between relatives with anxiety disorders suggest that heritability is an important variable in SAD[17,18,29]. Nonetheless, although evidence points to the participation of genetic factors in SAD, it is not yet possible to determine the degree to which these conditions contribute for the effective determination of SAD diagnosis.

According to this issue, the enrollment of pairs of twins in the studies fosters relevant progress in the study of SAD heritability. Some of the studies included in this review, for instance, estimated heritability based on correlational differences between monozygotic and dizygotic twins. This method provides a clearer assessment of the contribution of genetic factors, to the extent that it allows a certain control over common external environmental variables. However, even with this outcome, it is not yet possible to determine the precise influence of genetics in the manifestation of SAD.

The use of structural equation models associated with the inclusion of samples of twins is, therefore, an advance in this direction. With this design, it is possible to develop models that explain better how genetic and environmental factors interact within a given sample to cause SAD, including also estimates of how much of the variance can be explained by each factor. However, although

the articles reviewed did use these methods, we still observed a large amplitude in the variance explained by genetic factors in this review, which hinders precise estimates of these factors. Likewise, the diversity of results does not allow for a common interpretation of gender-related differences, nor of aspects such as the variability between age ranges regarding the establishment of diagnoses. We thus suggest the performance of studies involving carefully selected samples and instruments with adequate psychometric qualities.

One limitation of our review is the exclusion of studies that may have described results related to the heritability of SAD as secondary outcomes. Another possible limitation is the large variability in the instruments, methods, and outcomes in the studies reviewed, which hinders the homogenization in the presentation of results. This same limitation, however, ends up as an important part of this study as it describes the several ways that can used to assess heritability in SAD. Likewise, the conclusions of this review might contribute for the development of further research in this specific field.

In general terms, we conclude that heritability has been investigated in SAD through different methodological approaches, providing important evidence for a better comprehension of the factors that participate in the development of the condition. Future studies involving homogeneous samples and standardized instruments that allow a better diagnostic assessment of SAD would contribute for the estimation of more accurate heritability rates and for a better comprehension of the genetic factors associated with SAD.

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