Predictors of persistence of anxiety disorders across the lifespan: a systematic review

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Despite the substantial disease burden of anxiety disorders, physicians have a poor understanding of factors that predict their typical persistent course. This systematic review of predictors of persistent anxiety disorders covered 48 studies with 29 690 patients diagnosed with an anxiety disorder that were published in PubMed, PsycINFO, and Web of Science between Jan 1, 1980 (introduction of DSM-III), and Dec 1, 2019. We also compared predictors between children, adolescents, adults, and older adults (ie, ≥55 years). A persistent course was primarily predicted by clinical and psychological characteristics, including having panic attacks, co-occurring personality disorders, treatment seeking, poor clinical status after treatment, higher severity and longer duration of avoidance behaviour, low extraversion, higher anxiety sensitivity, and higher behavioural inhibition. Unlike disorder onset, sociodemographic characteristics did not predict persistence. Our results outline a profile of patients with specific clinical and psychological characteristics who are particularly vulnerable to anxiety disorder persistence. Clinically, these patients probably deserve additional or more intensive treatment to prevent development of chronicity.

Introduction

Anxiety disorders are among the most common mental health disorders and impose a substantial burden on affected individuals, their relatives,[1,2] and society.[3,4] Estimated lifetime prevalence ranges from 16% to 34%[5,6] and already reaches 20% at the end of adolescence.[7] Persistent anxiety disorders and the associated disabilities adversely affect patient's daily lives, social relationships, as well as school and work performances across the lifespan.[8]

The naturalistic multi-year course of anxiety disorders is characterised by great heterogeneity. Some patients recover quickly and pass through one episode without relapse or recurrence. However, many patients gradually develop a persistent course, which is defined as either a chronic or an intermittent trajectory with repeated remissions and relapses. Percentages of persistence vary from approximately 40% to 60%, depending on definition of chronicity, anxiety disorder diagnosis, and presence of comorbid other anxiety or depressive disorders.[9,10] In order to attenuate disease burden via care optimisation and prevention strategies, the timely identification of patients with a poor prognosis is important. For this purpose, finding the factors associated with increased risk for anxiety persistence is essential. A related question is whether predictors of anxiety disorder persistence manifest themselves differently in childhood than in adulthood (as early identification allows for prevention measures)[11] or have a more stable presentation across the lifespan.

Several factors, including female gender, vulnerable personalities, low socioeconomic status, and somatic diseases were found to be associated with the onset of anxiety disorders.[12,13] These predictors of anxiety disorder onset must be distinguished from factors that predict disorder persistence once a disorder has developed. Studies of predictors of a persistent course of anxiety disorders are scarce and typically cover only one or few variables simultaneously. Consequently, these study results are often inconclusive and difficult to compare. For instance, studies on the association between gender or age and anxiety disorder persistence yielded conflicting results.[10,12,14,15] Clinical characteristics such as comorbid other anxiety, or depressive disorders, personality disorders, symptom severity, earlier age of onset, and panic attacks seem to be important predictors, but not all studies support these associations.[10,16–20] Consequently, there is much uncertainty as to what kind of factors predict a persistent course of anxiety disorders, which impedes theories about underlying processes and prevention strategies. We therefore aimed in this Review to systematically evaluate and synthesise all predictors of anxiety disorder persistence using a system of weights that guided our interpretation of the evidence. These weights were based on key study characteristics, including sample size, participation and attrition rates, the measurement of predictors and outcomes, inclusion of covariates, and statistical analyses and reporting of results.

Methods

Study parameters

A prerequisite to review predictors of anxiety disorder persistence is a clear definition of persistence. A persistent course included both a chronic course as well as a fluctuating course with repeated remissions and relapses or recurrences.[9,21] One complication, however, is that the literature does not have clear and consistent operationalisations of remission, recovery, relapse, and recurrence, with different studies using different definitions and time frames.[9,22,23] Furthermore, course patterns have been described by means of changes in severity ratings of anxiety symptoms as well as by the presence or absence of episodes of an anxiety disorder.[22,24] In this Review, we therefore refrained from detailed distinctions between remission, recovery, relapse, and recurrence, and defined persistence as having an anxiety disorder diagnosis at both baseline and follow-up. Because our focus is on predictors of persistence, more

than on the different intermediate course trajectories that many studies do not have data for, we did not describe the intervening period in detail as this would have made it difficult to present an overall representation that does justice to this comprehensive systematic review. Consequently, a persistent course trajectory is a course without any documented remission or recovery during the entire follow-up period and a course with remission or recovery during follow-up, followed by relapse or recurrence such that the criteria for an anxiety disorder diagnosis were met again. A course in which the baseline anxiety disorder remitted or recovered but no relapse or recurrence was observed at the final measurement was considered non-persistent.

Previous studies showed low diagnostic stability of specific anxiety disorder diagnoses over time,[25,26] which reflects high aetiological and symptomatic overlap[27,28] and comorbidity between different anxiety disorders.[5,29] Therefore, we did not distinguish between specific anxiety disorders when defining course patterns. In addition, comorbidity between anxiety and depression is very common (approximately 50%), and comorbid depression is included as one of the predictors of anxiety disorder persistence.

Predictors of anxiety disorder persistence were defined as factors that increase the chance of developing a persistent course, to be contrasted against a non-persistent course. We used the term predictor in the broad sense of the word, thus predictors were either fixed (eg, gender and race); variable, which means that they can change but cannot be manipulated or if manipulated cannot change the outcome (eg, age and income level); or potentially causal, which means that these factors can be manipulated and when manipulated affect the outcome (eg, smoking, drinking; interventions were not considered).[30]

Search strategy and selection criteria

We did a systematic review by searching the databases PubMed, PsycINFO, and Web of Science from Jan 1, 1980 (ie, introduction of the DSM-III), to Dec 1, 2019, with the following search terms: ("anxiety disorders"[MeSH:NoExp] OR "agoraphobia"[MeSH] OR "anxiety, separation"[MeSH] OR "panic disorder"[MeSH] OR "phobic disorders"[MeSH] OR "anxiety disorder*" OR "agoraphobia" OR "panic disorder*" OR "phobia*" OR "selective mutism" AND ("chronic"[tiab] OR "persisten*"[tiab] OR "recurren*"[tiab] OR "relapse"[tiab] OR "unfavourable"[tiab] OR "unfavorable"[tiab] OR "maintenan"*[tiab] OR "course"[tiab] OR "stable"[tiab] OR "remit*"[tiab] OR "remission"[tiab]) AND ("prognost"*[tiab] OR "risk factor*" OR "predict*"[tiab] OR "risk factors"[MeSH]). Studies on animals were excluded, and studies were limited to English, Dutch, or German (appendix p 1). The search was restricted to original studies reporting on patients with an anxiety disorder diagnosis at baseline, defined according to the DSM[31] or the ICD.[32] Included anxiety disorders were agoraphobia, generalised anxiety disorder, panic disorder, selective mutism, separation anxiety disorder, social anxiety disorder (social phobia), and specific phobia (appendix p 2).

A previous study found that the median time to first remission of anxiety disorders is 16 months for pure anxiety disorders and 24 months for comorbid anxiety-depressive disorders,[10] thus a follow-up period of at least 2 years is a conservative threshold to cover remission. We therefore focused on studies with a follow-up of at least 2 years. Studies using the same sample population were not excluded in advance, because different samples from these populations and different study designs might have resulted in different outcomes. As our focus was on the naturalistic course of anxiety disorders, only observational studies were considered.

Two authors (JHMH-H and SM) independently selected relevant articles from the electronic databases. Discrepancies were discussed until consensus was derived. When study title and abstract potentially fulfilled our criteria, the complete article was perused. Data extraction and quality assessment of the studies were done.

The current study was done in concordance with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P).[33]

Data analysis

We extracted the following data: sample size, age, gender, recruitment setting, years of follow-up, diagnostic instruments, diagnoses at baseline, percentage of persistent anxiety disorders, and study predictors.

The quality of the selected studies was assessed with the Quality In Prognosis Studies (QUIPS) tool.[34] Each included study was screened on six domains, of which the risk of bias was assessed: study participation, study attrition, prognostic factor measurement, outcome measurement, covariate adjustment, and statistical analysis and reporting. Every domain was recorded as low, moderate, or high risk of bias. As sample size can affect the outcome and thereby is related to study quality, we added sample size as an extra bias domain. The six domains of the QUIPS tool supplemented with the sample size risk of bias were used to assess the total risk of bias of each individual study. Critical assessment of the risk of bias of the separate domains is partly a subjective process and not every domain applies to every individual study. Therefore, to assess the overall risk of bias, we omitted summarising the seven domains and used a global assessment instead (appendix p 3). By using the QUIPS tool in this way, we think that the instrument provides a good indication of the study quality, as was shown before.[34] The appendix (pp 2, 3) provides more details.

See Online for appendix

We extracted predictors of a persistent anxiety disorder course from the studies. If provided, the results of multivariate analyses were used. We counted the number of times that a predictor showed an association with

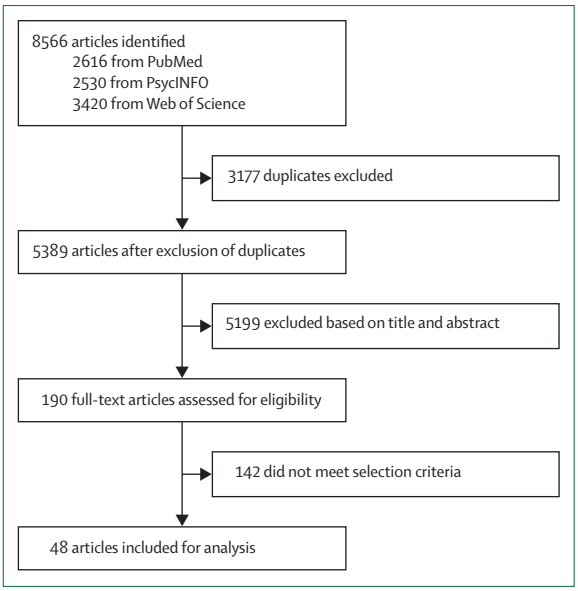

Figure: **Study selection**

disorder persistence, or yielded no association. The strength of evidence for predictors was assessed by defining four levels of evidence (ie, strong evidence, moderate evidence, limited evidence, and inconclusive evidence),[35,36] in which consistent findings refer to similar findings (positive, negative, or no association) in 75% or more of the studies analysing that predictor. Strong evidence was defined as consistent findings (≥75%) in two or more high-quality studies. Moderate evidence was defined as one high-quality study and consistent findings (≥75%) in one or more moderate-quality studies, one high-quality and one moderate-quality study and consistent findings (≥75%) in one or more low-quality studies, one high-quality study and consistent findings (≥75%) in two or more low-quality studies, consistent findings (≥75%) in two or more moderate-quality studies, or one moderate-quality study and consistent findings (≥75%) in two or more low-quality studies. Limited evidence was defined as findings of one study or consistent findings (≥75%) in one or more low-quality studies. Inconclusive evidence was inconsistent findings irrespective of study quality.

The findings in studies of children, adolescents, adults, and older adults (ie, ≥55 years) were combined to create the most complete overview of predictors. The predictors were a priori clustered into five categories: clinical characteristics included psychiatric symptoms or disorders and history of psychiatric disorders; psychological characteristics included psychological traits and cognitive functioning; biological characteristics consisted of genetic, anatomical and physiological factors, physical health and functioning, somatic disorders, and medication; sociodemographic characteristics included individual factors such as gender and age, as well as relationships, socioeconomic factors, and life-events or adversities; and the residual other category covered all factors not included in one of the previous categories.

Role of the funding source

There was no funding source for this study.

Results

The search in the three databases yielded 8566 studies. After applying the selection criteria, 48 full-text articles were selected for analysis of prognostic factors (figure). Table 1 summarises the characteristics and outcomes of the included studies. Various study populations were included: 14 studies referred to the same Netherlands Study of Depression and Anxiety (NESDA) cohort, six studies to the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) cohort, and five studies draw from the Harvard/Brown Anxiety Disorders Research Program (HARP) cohort in the USA. The NESDA studies varied in follow-up duration from 2 years to 6 years, included specific anxiety disorders or anxiety disorders in general, and sample size ranged from 235 to 1206. The NESARC studies all had follow-up periods of 3 years, studied different anxiety disorders (eg, social anxiety disorder, panic disorder, but also anxiety disorders in general), and sample size varied between 556 and 4010. Finally, the HARP studies had follow-up durations of 7, 8, and 12 years, and analysed either one anxiety disorder (panic disorder with and without agoraphobia, generalised anxiety disorder), or four anxiety disorders. Sample sizes in the HARP studies varied from 112 to 618. Because of these differences in study samples and designs, these studies of the same study populations could not be considered as duplicates and were therefore included in the full analysis.

Across the 48 included studies, the sample sizes ranged from 15 to 4010, and this systematic review covers 29 690 patients. Patients' ages ranged from 3 years to more than 85 years, or participants were only described as adults. The gender distribution was given in 41 (85%) of 48 studies. Women comprised the majority in all the studies, ranging from 58% to 78%, except for the studies of children, in which percentages of girls varied from 38% to 61%. Seven (15%) of 48 studies investigated the course of anxiety disorders in children, three (6%) in adolescents, 34 (71%) included adults, and four (8%) included older adults. 15 (31%) of 48 studies had multiple follow-up assessments (ie, three or more follow-up assessments): five (10%) studies in children, two (4%) in adolescents, eight (17%) in adults, and none in older adults. The number of assessments ranged from three to 20. Percentages of patients with persisting disorders varied extremely and ranged from 10% to 98%. Five (10%) studies did not provide percentages about persistence.

Study quality levels were categorised as low (three [6%] of 48 studies), moderate (18 [38%]), and high (27 [56%]) quality (table 1). 18 studies were qualified as moderate

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
Children													
Kates et al (2019)[37]	..	87	41 (47%)	46 (53%)	9–15	Clinical institutions	9	4	K-SADS-PL and SCID	Anxiety disorder	53%	Parent rating of child internalising symptoms; more severe family conflicts	Moderate
Bufferd et al (2018[38]	New York	89	37 (42%)	52 (58%)	3	General population around Stony Brook University	3	2	PAPA	Agoraphobia, generalised anxiety disorder, panic disorder, social anxiety disorder, selective mutism, specific phobia	34%	More behavioural inhibition; less positive emotionality; more shyness	Moderate
Ginsburg et al (2018)[39]	CAMELS	209	176 (55%)	143 (45%)	7–17	Clinical institutions	6·5	4	ADIS	Generalised anxiety disorder, separation anxiety disorder, social anxiety disorder	30% chronic course, 48% intermittent course‡	Older age; female; social anxiety disorder; less participant and family functioning; more negative life events; mental health services use; no acute treatment response	High
Ford et al (2017)[40]	BCAMHS	386	147 (38%)	239 (62%)	5–16	General population	3	2	DAWBA	Anxiety disorder	39% children expected to be at higher risk; 52% children expected to be at lower risk	Fewer peer relationships	High
Voltas et al (2017)[41]	..	242	147 (61%)	95 (39%)	9–12	General population	3	3	SCARED	Anxiety disorder	40%	Previous anxiety disorder and depressive disorder symptoms; female	Moderate
Koenen et al (2009)[42]	DMHDS	463	22 (48%)	241 (52%)	3	General population	14	4	DIS	Agoraphobia, generalised anxiety disorder, panic disorder, social anxiety disorder, specific phobia (including obsessive compulsive disorder)	48%	None	High

(Table 1 continues on next page)

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Last et al (1996)[43]	..	84	45 (54%)	39 (46%)	5–18	Clinical institutions	3–4	3–4	K-SADS-PL	Avoidant disorder, anxiety disorder not otherwise specified, overanxious disorder, panic disorder, separation anxiety disorder, social anxiety disorder, specific phobia	41%	None	Moderate
Adolescents													
Albor et al (2017)[44]	MAMHS	227	168 (74%)	59 (26%)	12–17	General population	8	2	CIDI	Specific phobia	18%	Older age of onset; parental neglect; first degree relative with specific phobia; economic adversities	High
Olino et al (2010)[18]	OADP	253	NA	NA	14–18	General population	12–16	4	K-SADS	Anxiety disorder	30%	Female; parental anxiety disorders; childhood abuse	High
Knappe et al (2009)[45]	EDSP	104	NA	NA	14–17	General population	8	4	DIA-X and M-CIDI	Social anxiety disorder	NA	Dysfunctional family functioning; parental psychopathology	Moderate
Adults													
Druiven et al (2019)[46]	NESDA	389	268 (69%)	121 (31%)	18–65	Mix	4	3	CIDI (version 2.1)	Anxiety disorder	42%	Use of benzodiazepines	High
Schotanus-Dijkstra et al (2019)[47]	NEMESIS-2	264	177 (67%)	87 (33%)	18–64	General population	3	2	CIDI (version 3.0)	Anxiety disorder	30%	Poor mental wellbeing; not living with a partner; no paid employment; more negative life-events; less health-care use	High
Hofmeijer-Sevink et al (2018)[48]	NESDA	270	181 (67%)	89 (33%)	18–65	Mix	2	2	CIDI (version 2.1)	Anxiety disorder	51% anxiety disorder, 71% comorbid anxiety-depressive disorder	Obsessive compulsive symptoms (comorbid anxiety-depressive disorder; not pure anxiety disorder); higher severity of anxiety disorder symptoms (pure anxiety disorder)	High
Spinhoven et al (2018)[49]	NESDA	235	162 (69%)	73 (31%)	18–65	Mix	3	2	CIDI (version 2.1)	Anxiety disorder	62%	More repetitive negative thinking (ie, rumination and worry); more worry	High

(Table 1 continues on next page)

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Struijs et al (2018a)[50]	NESDA	948	635 (67%)	313 (33%)	18–65	Mix	6	2§	CIDI LCI	Anxiety disorders (generalised anxiety disorder, panic disorder, social anxiety disorder)	32–43%	Higher neuroticism; less extraversion; external locus of control; more worry (general anxiety disorder); higher anxiety sensitivity (panic disorder, social anxiety disorder)	High
Struijs et al (2018b)[51]	NESDA	545	382 (70%)	163 (30%)	18–65	Mix	2	2	CIDI	Anxiety disorder	57%	Stronger trait avoidance tendency	High
De Venter et al (2017)[52]	NESDA	539	377 (70%)	162 (30%)	18–65	Mix	2	2	CIDI (version 2.1)	Panic disorder	72%	Childhood trauma; emotional neglect; psychological abuse; duration and severity of anxiety and depressive symptoms; higher neuroticism; less extraversion	Moderate
Spinhoven et al (2017)[53]	NESDA	711	491 (69%)	220 (31%)	18–65	Mix	4	2	CIDI (version 2.1)	Agoraphobia, generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder	73%	More experiential avoidance; higher anxiety sensitivity; fewer years of education; more anxiety and behavioural avoidance; latent factor, loaded on experiential avoidance, neuroticism, rumination, worry, anxiety sensitivity	High
Skodol et al (2014)[54]	NESARC	4010	2727 (68%)	1283 (32%)	≥18	General population	3	2	AUDADIS-IV	Generalised anxiety disorder, panic disorder, social anxiety disorder, specific phobia	15% generalised anxiety disorder, 13% panic disorder, 18% social anxiety disorder, 22% specific phobia	Personality disorders	Moderate
Van Mill et al (2014)[55]	NESDA	1069	716 (67%)	353 (33%)	18–65	Mix	2	2	CIDI (version 2.1)	Agoraphobia, generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder	NA	Sleep duration	High
Vergés et al (2014)[56]	NESARC	4010	NA	NA	>18	General population	3	2	AUDADIS-IV	Anxiety disorders (agoraphobia, generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder, specific phobia)	31–35%	Personality disorders	Moderate

(Table 1 continues on next page)

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Hendriks et al (2013)[57]	NESDA	834	559 (67%)	275 (33%)	18–65	Mix	2	2	CIDI (version 2.1)	Generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder, multiple anxiety	31% generalised anxiety disorder, 34% panic disorder, 47% panic disorder with agoraphobia, 45% social anxiety disorder, 60% multiple anxiety	Higher baseline duration and severity of avoidance behaviour and anxiety arousal	High
Nay et al (2013)[19]	NESARC	1939	1125 (58%)	814 (42%)	≥18	General population	3	2	AUDADIS-IV	Panic disorder, panic disorder with agoraphobia	25% panic disorder, 33% panic disorder with agoraphobia	Generalised anxiety disorder, social anxiety disorder	Low
Vreeburg et al (2013)[58]	NESDA	651	423 (65%)	228 (35%)	18–65	Mix	2	2	CIDI	Agoraphobia, generalised anxiety disorder, panic disorder, social anxiety disorder, comorbid anxiety-depressive disorder	42%	Less cortisol awakening response	High
Batelaan et al (2012)[59]	NEMESIS	136	106 (78%)	28 (22%)	≥18	General population	3	2 or 3¶	CIDI	Panic disorder, panic disorder with agoraphobia	67%	Panic attacks	High
Boschloo et al (2012)[60]	NESDA	994	656 (66%)	338 (34%)	18–65	Mix	2	2	CIDI (version 2.1) and BAI	Generalised anxiety disorder, panic disorder, social anxiety disorder	NA	Severe alcohol dependence	High
Francis et al (2012)[61]	HARP	112	72 (64%)	40 (36%)	≥18	Clinical institutions	7	10	SCALUP	Generalised anxiety disorder	24%	Stressful life events, experienced in 4 weeks before relapse	Moderate
Van Milligen et al (2012)[62]	NESDA	1206	796 (66%)	410 (34%)	18–65	Mix	2	2	CIDI (version 2.1)	Anxiety disorders (agoraphobia, generalised anxiety disorder, panic disorder, specific phobia)	47%	Lower hand grip strength	High
Wardenaar et al (2012)[63]	NESDA	810	535 (66%)	275 (34%)	18–65	Mix	2	2	CIDI (version 2.1)	Anxiety disorder, comorbid anxiety-depressive disorder	NA	Higher IDS-SR dimensions anxiety, arousal, and mood and cognition	High
Blanco et al (2011)[64]	NESARC	989	623 (63%)	366 (37%)	≥18	General population	3	2	AUDADIS-IV	Social anxiety disorder	22%	Higher symptoms severity (fear of interaction situations, number of avoided social situations, past-year treatment seeking); comorbid mood disorders	High

(Table 1 continues on next page)

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Cox et al (2011)[65]	NESARC	556	NA	NA	Adults	General population	3	2	AUDADIS-IV	Generalised social anxiety disorder, non-generalised social anxiety disorder	19% generalised social anxiety disorder, 10% non-generalised social anxiety disorder	Avoidant personality disorder	Moderate
Spinhoven et al (2011)[66]	NESDA	942	631 (67%)	311 (33%)	18–65	Mix	2	2	CIDI (version 2.1)	Anxiety disorders (agoraphobia, generalised anxiety disorder, panic disorder, social anxiety disorder)	39·4%	Higher severity and duration of symptoms; younger age of onset; less extraversion; more negative life events	High
Bringager et al (2008)[67]	Oslo	55	NA	NA	18–65	Clinical institutions (psychiatry outpatient section)	9	2	SCID	Panic disorder	26%	More severe somatic complaints	Moderate
Svanborg et al (2008)[68]	Stockholm	15	9 (60%)	6 (40%)	Adults	Clinical institutions (psychiatric care)	9	2	SCID-I and SCID-II	Panic disorder, panic disorder with agoraphobia	53%	Personality disorders; younger age of onset; longer duration of illness; childhood adversities	High
Pagano et al (2007)[69]	HARP	618	414 (67%)	204 (33%)	>18	Clinical institutions	12	20	SCALUP	Generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder	45% generalised anxiety disorder, 56% panic disorder, 58% panic disorder with agoraphobia, 39% social anxiety disorder	Personal substance use (only generalised anxiety disorder relapse); history of parental substance use (social anxiety disorder and panic disorder)	High
Rodriguez et al (2006)[20]	PCAP	113	86 (76%)	27 (24%)	Adults	Clinical institutions	2	4	SCID-IV	Generalised anxiety disorder	28% chronic course, 30% intermittent course‡	Comorbid other anxiety and depressive disorders; high psychosocial impairment; younger age of onset; female	Moderate
Bruce et al (2005)[9]	HARP	473	317 (67%)	156 (33%)	>18	Clinical institutions	12	20	SCALUP LIFE	Generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder	45% generalised anxiety disorder, 56% panic disorder, 58% panic disorder with agoraphobia, 39% social anxiety disorder	Comorbid other anxiety and depressive disorders; alcohol and other substance use disorder	High
Yonkers et al (2003)[70]	HARP	558	NA	NA	≥18	Clinical institutions	8	11	SCALUP	Generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder	40%‖ generalised anxiety disorder, 43%‖ panic disorder, 46%‖ panic disorder with agoraphobia, 31%‖ social anxiety disorder	Female	High
Kessler et al (2002)[71]**	ECA-SP/ MHS-OHS/ NEMESIS/ NCS	787	NA	NA	≥18	General population	≥3	2	CIDI and UM-CIDI	Generalised anxiety disorder	NA	Specific phobia	High

(Table 1 continues on next page)

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Weisberg et al (2002)[72]	HARP	169	113 (67%)	56 (33%)	≥18	Clinical institutions	8	11	SCALUP	Panic disorder without agoraphobia, panic disorder with agoraphobia, panic disorder panic disorder (with or without agoraphobia)	34% panic disorder without agoraphobia, 39% panic disorder with agoraphobia, 37% panic disorder (with or without agoraphobia)	Subsyndromal panic symptom; intermittent panic attacks	Moderate
Fava et al (2001)[73]	Bologna	45	28 (62%)	17 (38%)	Adults	Clinical institutions (Affective Disorders Program at University of Bologna)	2–12	2–14	SADS	Generalised social anxiety disorder	13%	Comorbid personality disorders; higher severity of symptoms; use of benzodiazepines	Moderate
Alnaes et al (1999)[74]	Oslo	131	90 (69%)	41 (31%)	18–60	Clinical institutions (psychiatry outpatient section)	6	2	SCID-I and MCMI-I	Agoraphobia, generalised anxiety disorder, panic disorder, social anxiety disorder, specific phobia	38%	Comorbid other anxiety disorders; personality disorders; personality traits	Low
O'Rourke et al (1996)[75]	..	68	47 (69%)	21 (31%)	Adults	Clinical institutions	5·3	2	ADIS-R	Panic disorder, panic disorder with agoraphobia	38%	Personality dysfunction; less Clinical institutional status after baseline measurement	Low
Rosenberg et al (1994)[76]	CNCPS (phase 2)	40	27 (68%)	13 (32%)	Adults	Clinical institutions	3	2	SCID-UP	Panic disorder	98%	Higher severity of anxiety and depressive disorders	Moderate
Older adults													
Mackenzie et al (2014)[24]	NESARC	908	527 (58%)	381 (42%)	>55	General population	3	2	AUDADIS-IV	Anxiety disorders (generalised anxiety disorder, panic disorder, panic disorder with agoraphobia, social anxiety disorder, specific phobia)	30%	Lower mental health-related quality of life; higher numbers of comorbid mental disorders; comorbid personality disorders; comorbid mood disorders	High
Almeida et al (2012)[77]	DEPS-GP	1296	855 (66%)	441 (34%)	>60	Clinical institutions	2	2	HADS-A	Anxiety disorder	32%	Age; female; being married; fewer years of education; less social support; financial strain; history of anxiety and depressive disorders; pain; poor perceived health	Moderate
Schoevers et al (2005)[23]	AMSTEL	59	37 (63%)	22 (37%)	65–84	General population	3	2	GMS-AGECAT	Generalised anxiety disorder, generalised anxiety disorder plus depressive disorder	28% generalised anxiety disorder, 47% generalised anxiety disorder plus depressive disorder	Occurrence of somatic chronic disorders between assessments; older age	Moderate

(Table 1 continues on next page)

because of their small sample sizes (eight [44%] of 18). The quality assessment of each individual study is provided in the appendix (pp 4, 5).

The weighted predictors of a persistent course, combined for all age groups, are given in table 2. An overview of all predictors of persistent anxiety and the studies reporting them is given in the appendix (pp 6–21). Factors that were associated with a persistent course were predominantly clinical and psychological characteristics. Strong clinical predictors of persistent anxiety disorders included having more panic attacks, having comorbid personality disorders, and recent treatment seeking. Poor clinical status after treatment was moderately associated with persistence. Psychological characteristics that mattered were higher severity and longer duration of avoidance behaviour, lower extraversion, and higher levels of anxiety sensitivity. Higher behavioural inhibition showed a moderately strong association with persistence. Several other clinical and psychological predictors, such as lifetime suicide attempts, more severe depressive symptoms, type of anxiety disorder, repetitive negative thinking, trait avoidance tendency, positive emotionality, shyness, and mental wellbeing showed associations with limited evidence. The same applied to a latent psychological vulnerability factor that was based on neuroticism, worry, and anxiety sensitivity. This latent factor was associated with anxiety persistence, but given that it was reported only once, this evidence was limited. Nonetheless, one of the component factors—namely, anxiety sensitivity—received strong support. Notably, sociodemographic characteristics (eg, level of education, socioeconomic status) were not consistently associated with anxiety persistence. Biological characteristics were sometimes associated with persistence, but evidence was limited and several of these characteristics showed no association. Patients with less health care use were at higher risk of a persistent course and this risk was also true of poorer health-related quality of life, although evidence for both factors was limited. For several other factors across all predictor categories, the supporting evidence remained inconclusive.

Stratification of the studies based on age consistently indicated that clinical factors were important predictors at all stages of life. The role of psychological factors in children and adolescents is less clear, because several of these factors, such as avoidance behaviour, neuroticism, extraversion, and anxiety sensitivity were not studied in these young age groups. In contrast, other factors were studied, such as positive and negative emotionality, and shyness, albeit in low numbers. As in adults, sociodemographic factors were not predictive of persistent anxiety disorders in children. In adolescents, no predictors of persistent anxiety disorders were found; the prognostic value of the factors examined was inconclusive. The low number of studies in this age group (three [6%] of 48 studies) in combination with our assessment of evidence levels makes it difficult to find

	Study or location	Sample					Follow-up (years)	Number of follow-up waves	Diagnostic instrument	Diagnosis at baseline	Persistence		Quality*
		N†	Females, n (%)	Males, n (%)	Age (years)	Recruitment setting					Percentage	Predictors	
(Continued from previous page)													
Schuurmans et al (2005)[78]	LASA	62	48 (77%)	14 (23%)	≥55	General population	6	2	DIS	Generalised anxiety disorder, panic disorder, phobic disorders including agoraphobia	23%	Higher neuroticism	Moderate

Recruitment settings that were considered mixed consisted of participants from both the general population and clinical institutions. ADIS=Anxiety Disorders Interview Schedule for DSM-IV. ADIS-R=Anxiety Disorders Interview Schedule for DSM-IV Revised. AMSTEL=Amsterdam Study of the Elderly. AUDADIS-IV=Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM IV Version. BAI=Beck Anxiety Inventory. BCAMHS=British Child and Adolescent Mental Health Surveys. CAMELS=Child/Adolescent Anxiety Multimodal Extended Long-term Study. CIDI=Composite International Diagnostic Interview. CNCPS=Cross National Collaborative Panic Study (Denmark). DAWBA=Development and Well-Being Assessment. DEPS-GP=Depression and Early Prevention of Suicide in General Practice. DIA-X/M-CIDI=computer-assisted version of the Munich-Composite International Diagnostic Interview. DIS=Diagnostic Interview Schedule. DMHDS=Dunedin Multidisciplinary Health and Development Study (New Zealand). ECA-SP=Epidemiological Catchment Area Study City (São Paulo, Brazil). EDSP=Early Developmental Stages of Psychopathology (Munich, Germany). GMS-AGECAT=Geriatric Mental State - Automated Geriatric Examination for Computer Assisted Taxonomy. HADS-A=Hospital Anxiety and Depression Scale. HARP=Harvard/Brown Anxiety Disorders Research Program. IDS-SR=Self Report Inventory of Depressive Symptomatology. K-SADS=Schedule for Affective Disorders and Schizophrenia for School-Age Children. K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version. LASA=Longitudinal Aging Study Amsterdam (Netherlands). LCI=Life Chart Interview. MAMHS=Mexican Adolescent Mental Health Survey. MCMI-I=Millon Clinical Multiaxial Inventory. MHS-OHS=Mental Health Supplement to the Ontario Health Survey (Canada). NA=not available. NCS=National Comorbidity Survey (USA). NEMESIS=Netherlands Mental Health Survey and Incidence Study. NESARC=National Epidemiologic Survey on Alcohol and Related Conditions. NESDA=Netherlands Study of Depression and Anxiety. OADP=Longitudinal study high school students Oregon (USA). PAPA=Preschool Age Psychiatric Assessment. PCAP=Primary Care Anxiety Project (USA). SADS=Schedule for Affective Disorders and Schizophrenia. SCALUP LIFE=SCID and Schedule for Affective Disorders and Schizophrenia (Lifetime). SCALUP=Structured Clinical Interview for DSM-axis I Disorders Patient Version and Schedule for Affective Disorders and Schizophrenia (Lifetime). SCARED=Screen for Childhood Anxiety Related Emotional Disorders. SCID-I=Structured Clinical Interview for DSM-axis I Disorders. SCID-II=Structured Clinical Interview for DSM-axis II Disorders. SCID-IV=Structured Clinical Interview for the DSM-IV. SCID-UP= SCID-UP = Structured Clinical Interview for DSM-III R Disorders, Upjohn Version. UM-CIDI=modified version of CIDI from University of Michigan. *Study quality based on Quality In Prognosis Studies tool, supplemented with a risk of bias domain sample size. †Number of patients with anxiety disorders. ‡Intermittent course with relapses or recurrences after remission. §Outcome based on follow-up of 2 or 6 years. ¶Outcome based on two follow-up measurements at 1 and 3 years, or based on one follow-up at either 1 year or 3 years. ||Mean of men and women. **Retrospective study.

Table 1: **Characteristics and outcome**

predictors with moderate or strong evidence. The predictors in the older adults correspond to the predictors in the adults. However, the number of studies that included older adults was low (four [8%] of 48). Therefore, as in the adolescents, the results for the older adults were less certain, despite the moderate-to-high quality of included studies.

	Age groups
Strong evidence	
Predictive	
Clinical	
More panic attacks or increased anxiety arousal	Children, adults
Comorbid personality disorder	Adults, older adults
Past 12-month treatment seeking	Children, adults
Psychological	
Higher avoidance	Adults
Lower extraversion	Adults
Higher anxiety sensitivity	Adults
Not predictive	
Clinical	
Number of episodes	Adults
Antidepressants use	Adults
Psychological treatment or therapy	Children, adults, older adults
Psychological	
Rumination	Adults
Sociodemographic	
Level of education	Adults, older adults
Race or ethnicity	Adolescents, adults, older adults
Urbanicity	Adults
Socioeconomic status (education, occupation, income)	Children, adolescents, adults, older adults
Biological	
Physical inactivity or BMI	Children, adults, older adults
Moderate evidence	
Predictive	
Clinical	
No acute treatment response or poor clinical status after treatment	Children, adults
Psychological	
Higher behavioural inhibition	Children, adults
Not predictive	
Biological	
Physical functioning or hand grip strength	Children, adults, older adults
IQ	Children
Limited evidence	
Predictive	
Clinical	
Lifetime suicide attempts	Older adults
Higher total scores and two dimensions IDS-SR	Adults
Type of anxiety disorder	Children
Psychological	
Repetitive negative thinking (rumination plus worry)	Adults
Latent factor (neuroticism, rumination, worry, anxiety sensitivity)	Adults
Trait avoidance tendency	Adults
Lower positive emotionality	Children
Higher shyness	Children
Mental wellbeing	Adults

(Table 2 continues on next page)

Discussion

This Review provides a first comprehensive overview of predictors of a persistent course of anxiety disorders across the lifespan. We focused on anxiety disorders in general, without making a distinction between specific diagnostic categories. The reviewed studies described a wide range of predictors. By weighting the predictors on the basis of reported numbers and study quality, we were able to indicate the strength of the evidence for each predictor. The methodological quality of more than 90% of included studies was moderate to high, which indicates that the results presented have a reasonable degree of reliability.

The strongest predictors for anxiety disorder persistence were clinical and psychological characteristics. Findings in the different age groups were largely comparable. The results might give the impression that psychological characteristics have an important role especially in adults and less in children, mainly because different psychological factors were tested in children (such as positive and negative emotionality and shyness) and in adults (such as avoidance, neuroticism, extraversion, rumination, and anxiety sensitivity). However, these psychological factors are developmentally related to one another; for instance, shyness and introversion are distinct but related concepts. Shyness is also related to behavioural inhibition and neuroticism.[79,80] Furthermore, positive emotionality is a temperamental seed-form of extraversion and negative emotionality is part of neuroticism.[81] All of these factors were associated with persistence of anxiety disorders, except negative emotionality and neuroticism. Future work might determine the role of negative emotionality and neuroticism in persistent anxiety disorders.

Our results for a range of clinical factors, such as anxiety symptom severity and comorbid other anxiety disorders, were inconclusive. Conflicting results were also observed for depressive symptom severity and for comorbid depressive disorders. The latter finding is particularly striking, because comorbid anxiety-depressive disorders are generally considered to have a poorer prognosis[10] and are usually associated with a higher severity of symptoms compared with pure anxiety disorders[23] and chronic depression.[82] Methodological issues, such as differences in study design and sample, might be responsible for the variability in outcomes.

Having comorbid personality disorders was strongly associated with persistent anxiety disorders. Concurrently, personality disorders, especially borderline personality disorder, and neuroticism showed strong interconnections.[83] Neuroticism has been shown to account for substantial overlap between anxiety and depression.[84] Other predictors of anxiety disorder

persistence included panic attacks, avoidance behaviour, extraversion, anxiety sensitivity, and behavioural inhibition which, similar to neuroticism, have all previously been associated with both anxiety and depressive disorders.[8,85] These results indicate that psychological vulnerabilities have a key role in the course of anxiety disorders as well as other common mental disorders.[83] This conclusion renders psychological vulnerabilities truly transdiagnostic and highly informative for our understanding of psychopathology and treatment of anxiety and depressive disorders.[28,86] Future studies on anxiety disorder persistence should account for overlapping predictors. In addition, predictors of anxiety persistence were highly heterogeneous and can be subject specific, which impedes their identification in panel studies. Anxiety disorder persistence might have diverse personal causal pathways and a highly pluralistic aetiology,[87] meaning that predictors identified in panel studies only partly reflect the causes of anxiety disorder persistence. Future studies using novel approaches including single case-control designs[88] might uncover individual differences in predictors across phenotypically comparable patients.

Psychotropic medication was not predictive of anxiety disorder persistence. However, as we included only observational studies, confounding bias cannot be excluded and the absence of an association does not imply absence of a causal relationship.[89] To elucidate the effect of medication on the persistence of anxiety disorders, randomised clinical trials are needed, but unfortunately these do not have the follow-up time needed for the current research question. In addition, the effect of potentially causal factors could not be established in these observational studies, and intervention studies that establish such causal predictors of anxiety disorders are needed to learn to prevent or change an untoward outcome of anxiety.

Salient is the absence of associations between sociodemographic characteristics and anxiety disorder persistence, such as socioeconomic status and level of education, and the inconclusive results for other socioeconomic factors as gender and age, although these characteristics were repeatedly found to be associated with onset and prevalence of anxiety disorders.[12,13] Our results support our starting point that predictors of anxiety disorder onset should be distinguished from predictors of anxiety disorder persistence.

The role of biological characteristics in predicting a persistent course of anxiety disorders was less clear. A few factors had evidently no association with persistence, but for most factors evidence of association was limited or inconclusive, mainly because these factors were studied less often. However, it cannot be excluded that publication bias has a role here, as non-significant findings are often not published.[90] It should be noted that family or parental histories of anxiety and depressive disorders and substance use disorders were placed among the biological characteristics, but are determined by a multifactorial complex consisting of genetic and environmental factors.[91–93] Placement in another predictor category is therefore also possible. Although biological

	Age groups
(Continued from previous page)	
Biological	
Chronotype	Adults
Sleep duration ≤6 h	Adults
Sleep duration ≥10 h	Adults
Lower cortisol awakening response	Adults
Sociodemographic	
Social support	Older adults
Other	
Less utilisation of health care	Adults
Health-related quality of life	Older adults
Not predictive	
Clinical	
Treatment type	Children
Psychological	
Behavioural activation	Adults
Approach avoidance tendency	Adults
Negative emotionality	Children
Hopelessness	Adults
Self-efficacy	Older adults
Mental or cognitive functioning	Older adults
Biological	
Lung function	Adults
Medical problems around birth	Children
Sociodemographic	
Insurance	Adults
Religion	Older adults
Other	
Poorer physical-health-related quality of life	Adults
Inconclusive evidence	
Clinical	
Anxiety symptom severity	Children, adults, older adults
Depressive symptom severity	Children, adults, older adults
Symptom duration or duration of episodes	Adults
History of remitted anxiety or depressive disorder, same or other than index disorder	Children, adults, older adults
Age of onset	Adolescents, adults
Comorbid other anxiety disorder or symptoms	Adolescents, adults, older adults
Comorbid depressive disorder or symptoms	Adults, older adults
Personality trait or dysfunction	Adults
Other psychiatric disorder or symptoms	Children, adults
Use of benzodiazepines	Adults
Psychosocial impairment	Adults, older adults
Psychological	
Higher neuroticism	Adults, older adults
External locus of control or mastery	Adults, older adults
Worry	Adults

(Table 2 continues on next page)

	Age groups
(Continued from previous page)	
Biological	
Somatic diseases or chronic diseases	Adults, older adults
Physical functioning or hand grip strength	Children, adults, older adults
Family history of anxiety disorder	Children, adolescents, adults
Family history of depressive or psychiatric disorder	Adolescents, adults
Parental history of substance use disorder	Adolescents, adults
Alcohol use, dependence, or disorder	Adults, older adults
Nicotine dependence or smoker	Adults, older adults
Substance use disorder or substance use	Adults
Sociodemographic	
Female gender	Children, adolescents, adults, older adults
Age	Children, adolescents, adults, older adults
Financial crisis, unemployment, or income	Adults, older adults
Nativity	Children, adults, older adults
Relationships (social class, marital status, participant or family functioning, children in household)	Children, adolescents, adults, older adults
Childhood adversity (including factors related to parenting style)	Children, adolescents, adults, older adults
Life events	Children, adults, older adults

BMI=body-mass index. IDS-SR=Inventory of Depressive Symptomatology Self Report. IQ=intelligence quotient.

Table 2: **Level of evidence**

vulnerabilities are often considered to be one of the major classes of vulnerabilities involved in the development of anxiety disorders,[94] more research is needed to elucidate their potential influence on the course of anxiety disorders, which is in line with the findings of Bosman and colleagues.[95] The role of genetic components, in combination with psychological vulnerabilities, is particularly important, but could not be addressed in depth in this Review, as genetic factors were poorly represented in the included studies.

The results of our study are not entirely consistent with those of previous studies. These discrepancies can be explained by heterogeneous study designs and outcome measures. For instance, a study[96] in the NESDA cohort with a 2-year follow-up of adults with an anxiety disorder at intake found that baseline anxiety symptom severity, partner status, and childhood trauma predicted a persistent course of anxiety. This finding was not confirmed in the current systematic review. However, in this NESDA study, a latent class growth analysis was used to identify different classes based on the presence and severity of anxiety and avoidance symptoms. Using such a data-driven method is different from the current Review, which investigated the persistence of anxiety disorders according to established diagnostic criteria. Furthermore, parental psychopathology has been related to a persistent course of social anxiety disorder in a community sample of adolescents and young adults,[16] whereas our study included several anxiety disorders and patients of all ages. Furthermore, the results of the current Review could not confirm the findings of a previous review on the natural history of anxiety disorders.[97] In the review by Angst and Vollrath,[97] it was concluded that the course is best predicted by symptom severity and duration, and comorbid depression. However, the authors investigated the course of only two anxiety disorder categories (panic disorder and generalised anxiety disorder) and the question whether personality disorders and traits were predictive of the course could not be answered, which might explain the different findings.

Individuals diagnosed with an anxiety disorder might also switch over time to a pure depressive disorder without comorbid anxiety disorders. This course type is not uncommon; it has been reported that 7–14% of individuals switch to a pure depressive disorder without comorbid anxiety disorder.[10,21] Yet, we did not find predictors of this specific course type in our systematic review. This gap in the literature needs to be addressed in future studies to get a complete understanding of the predictors of all course types of anxiety disorders. A comparison of the previously reported predictors of chronic depressive disorders[82] and those found in the current review for persistent anxiety disorders reveals that these predictors are predominantly shared. These findings underscore the increasingly favoured dimensional understanding of anxiety and depressive disorders rather than a strictly categorical interpretation of diagnostic classifications.[28] Nonetheless, a dimensional approach also leaves many questions, including why most people with high psychological vulnerabilities and trait anxiety do not develop anxiety disorders[83] or persistent course trajectories.

The results of this systematic review should be interpreted with some caution. First, studies were highly heterogeneous in methodology and type as well as the number of anxiety disorders, which prevented a proper meta-analysis. In addition, some predictors were mentioned only once or a few times, so that the importance and robustness of these predictors remain unclear. These issues were partially addressed by using a systematic evaluation of the evidence level for predictors. Second, identification of similarities and differences between the age groups was difficult because of the small number of studies in children, adolescents, and older age groups. Studies in children and adolescents were often done on symptom levels without referring to disorder diagnoses, therefore these studies fell outside the scope of this Review. Third, we included patients with a current anxiety disorder diagnosis, which was defined as present at study intake, over the past month, past 6 months, or during the past year, often using different instruments. However, all instruments used to assess diagnosis were well known and reliable. Fourth, predictors can be interconnected in their influences on disorder course trajectories, but these complexities are beyond the scope of this study. Future research might take such interactions into account to obtain a more realistic picture of the multicausal factors

contributing to the persistence of anxiety symptoms and disorders. Fifth, the follow-up duration that the included studies used ranged from 2 to 16 years. We cannot rule out the possibility that predictors found in studies with a follow-up of 2–3 years differed from predictors in studies with a longer follow-up period. To determine the effect of follow-up duration, additional studies are required. In this Review, studies with a minimum follow-up time of 2 years were selected, based on the median time to first remission (16 months for pure anxiety disorders and ≥24 months for comorbid anxiety-depression disorders). A shorter minimum follow-up time would have resulted in inclusion of more studies with potentially additional information, but based on earlier convincing research we think that our approach with a 2-year follow-up time captured the most important predictors of anxiety disorder persistence. Finally, the prevalence, aetiology, and phenomenology of anxiety disorders can be culture dependent. Differences in individualism versus collectivism, and differences in cultural values between countries with high versus middle and low national income, can influence the way anxiety disorders are expressed.[98–100] Culture might therefore also affect the association between predictors and the course of anxiety disorders, which warrants specific research frameworks and studies in different populations around the world. The current Review could not examine such cultural effects, because all included studies were done in Western countries.

This Review of predictors of persistent anxiety disorders showed clinical and psychological characteristics, such as having panic attacks, comorbid personality disorders, seeking and receiving treatment, poor clinical status after treatment, higher severity and longer duration of avoidance behaviour, lower extraversion, higher anxiety sensitivity, and higher behavioural inhibition, to be the strongest predictors of a persistent course. Sociodemographic characteristics such as socioeconomic status and level of education were not predictive of a persistent course, despite their association with the onset and prevalence of anxiety disorders. These results might help identify patients at risk of a poor prognosis, as well as to better understand anxiety disorders, improve treatment strategies, and inform future studies.

Contributors

All authors contributed to the study. JHMH-H, BFJ, HR, and RAS designed the concept of the study. JHMH-H and SM elaborated the search strategy and decided on the eligibility of studies. JHMH-H wrote the first draft of the manuscript. All authors critically contributed to data interpretation, reviewed the manuscript, and approved the publication of the manuscript.

Declaration of interests

We declare no competing interests.

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