REVIEW

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Systematic Review: Anxiety in Children and Adolescents With Chronic Medical Conditions

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Objective: Youth with chronic medical conditions (CMCs) have been reported to be at increased risk for developing anxiety disorders. Importantly, suffering from anxiety may also have an impact on their disease-related outcomes. This study set out to systematically review the literature on anxiety and seven CMCs (asthma, congenital heart disease, diabetes, epilepsy, inflammatory bowel disease, juvenile idiopathic arthritis, and sickle cell disease) among youth.

Method: A systematic review was performed according to the PRISMA statement. Searches were conducted across PubMed, PsycNET, Embase, and reference lists of the included studies (1990–2018). Three independent reviewers screened titles and abstracts and conducted full-text assessment. Studies were included if they reported the prevalence of anxiety or the association of anxiety on disease-related outcomes in children and/or adolescents with the focal CMCs.

Results: A total of 53 studies met the predetermined inclusion criteria. Across the CMCs, the prevalence of anxiety disorder was increased in youths with CMCs compared to the general population. Evidence for a relationship between anxiety and adverse disease-related outcomes was limited. For asthma, inflammatory bowel disease, and sickle cell disease, there was some evidence indicating that anxiety was associated with adverse outcomes; supported by two longitudinal studies, one in asthma and one in inflammatory bowel disease. For diabetes, results were inconsistent; with some studies indicating that anxiety was associated with worse and others with better treatment adherence.

Conclusion: The prevalence of anxiety disorders in youth with CMCs is higher than that in the general population. Anxiety may also be associated with adverse disease-related outcomes for youths, but it is not possible to draw definitive conclusions. Longitudinal studies making use of parent/youth composite anxiety measures and a combination of parent/youth reported and objective measures of disease-related outcomes are needed. Given the burden of disease of anxiety disorders, regardless of the impact on the disease outcomes, screening for and treatment of anxiety is recommended in youths with CMCs.

Key words: anxiety, medical, physical, illness

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Physical conditions and mental disorders often systematically co-occur both in adults and in children,[1-4] with a recently published study of 6,482 adolescents finding that over 35% of adolescents in the United States demonstrated "mental–physical comorbidity," that is, meeting criteria for at least one mental disorder and one physical disease.[4] The *Lancet* series on Global Mental Health therefore concluded that mental health must be incorporated into all aspects of health.[1]

Tegethoff *et al.*[4] found that the combination of physical diseases and anxiety disorders was most common, occurring in 21% of the population. Moreover, for many physical diseases, the risk of anxiety was higher than the risk of other mental disorders. The experience of anxiety is highly significant in its own right, and is associated with poor prognosis if untreated,[5] the development of other mental health problems,[6] and significant psychosocial implications such as compromised academic achievement and peer relationships.[7] It has also been suggested that, in combination with a CMC, anxiety may be associated with worse physical disease outcomes, for example due to poorer treatment adherence.[8]

We present a systematic review focusing specifically on anxiety in youth with CMCs. CMCs were defined as conditions that (1) have a duration of at least 6 months; (2) have a relapsing or deteriorating pattern; and (3) produce consequences that have an impact on quality of life. Life-limiting diseases (such as cancer or cystic fibrosis) and those causing intellectual or physical disabilities (such as cerebral palsy) have not been included, as these conditions present qualitatively different challenges to youths and their families. Physical conditions without a known medical

cause, such as irritable bowel syndrome, and chronic pain conditions, such as functional abdominal pain or migraine, have also been excluded. The criteria noted above led to the inclusion of the following: asthma, type 1 diabetes (referred to as "diabetes"), epilepsy, congenital heart disease (CHD), inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), and sickle cell disease (SCD). All seven CMCs are associated with significant functional morbidity and health care use.

This systematic review aimed to address two research questions (1) What is the prevalence of anxiety disorder across each of the CMCs?, and (2) What is the impact of anxiety on physical disease−related outcomes for the different CMCs? It was hypothesized that anxiety disorders would be more prevalent in all CMCs compared to the general population, and that elevated anxiety in youths with CMCs would be associated with worse disease-related outcomes.

METHOD

A systematic review of the literature on anxiety in children or adolescents with chronic physical illnesses was performed according to the PRISMA guidelines.[9] The review protocol was developed in advance and registered with the Prospective Register of Systematic Reviews (PROPERO)[10] (CRD42019119346) (Table S1, available online).

Searches across three electronic psychological and medical databases (PubMed, PsycNET, and Embase) were conducted to identify studies published between 1990 and December 2018 using variants of keywords that fit with three clusters of search strings combined with "AND" functions (1) age group (child, adolescents, or pediatric), (2) anxiety, and (3) chronic medical conditions. These included asthma, type 1 diabetes mellitus, epilepsy, congenital heart disease, rheumatoid or juvenile arthritis, inflammatory bowel disease, and sickle cell anaemia (see full search terms in Table S1, available online). References lists of included articles and review articles identified in the database searches were also manually searched.

Study eligibility was assessed by three independent unblinded reviewers (AH, HK, and HT) by systematically screening the titles and abstracts. Relevant full texts were reviewed in detail. Published peer-reviewed journal articles were included if they were published in English and measured anxiety (either self- or parent/caregiver-report) in children or adolescents with any of the aforementioned CMCs. Studies included were cross-sectional, longitudinal, and/or case-control designs. Studies measured anxiety in various ways, such as using diagnostic interviews (ie, the Schedule for Affective Disorders and Schizophrenia for Children), validated psychometric measures (ie, State Trait Anxiety Inventory for Children), and medical or public databases. Prevalence data were extracted only for studies that used diagnostic interviews with an established cut-off criterion. Studies were excluded if (1) the sample were of a mean age older than 18 years; (2) anxiety symptoms were not reported or could not be distinguished from related but distinct constructs such as illness-specific anxiety (ie, fear of hypoglycemia) or internalizing problems (ie, anxiety and depressive symptoms measured as a single construct); or (3) chronic physical illness could not be discerned from other conditions or disorders.

The prevalence of "any anxiety disorder" was used. Studies reviewed spanned various versions of both the *DSM* (*DSM-III-R*, *DSM-IV*, *DSM-IV-TR,* and *DSM-5*) and the *International Classification of Diseases* (*ICD*) (*ICD-9* and *ICD-10*). If a diagnosis was regarded as an anxiety diagnosis at the time that the study was conducted, using the diagnostic taxonomy that was used, it was treated as an anxiety diagnosis in this review. In most studies, "any anxiety disorder" was the reported outcome. Where individual anxiety diagnoses were reported, prevalence for "any anxiety disorder" was manually calculated. Studies that lacked control groups were benchmarked against the diagnostic prevelance rate for "any anxiety diagnosis" of 6.5% from the meta-analysis of international community samples examining prevalence rates of diagnosable (*ICD* or *DSM* criteria) mental disorders published by Polanczyk *et al.*[11]

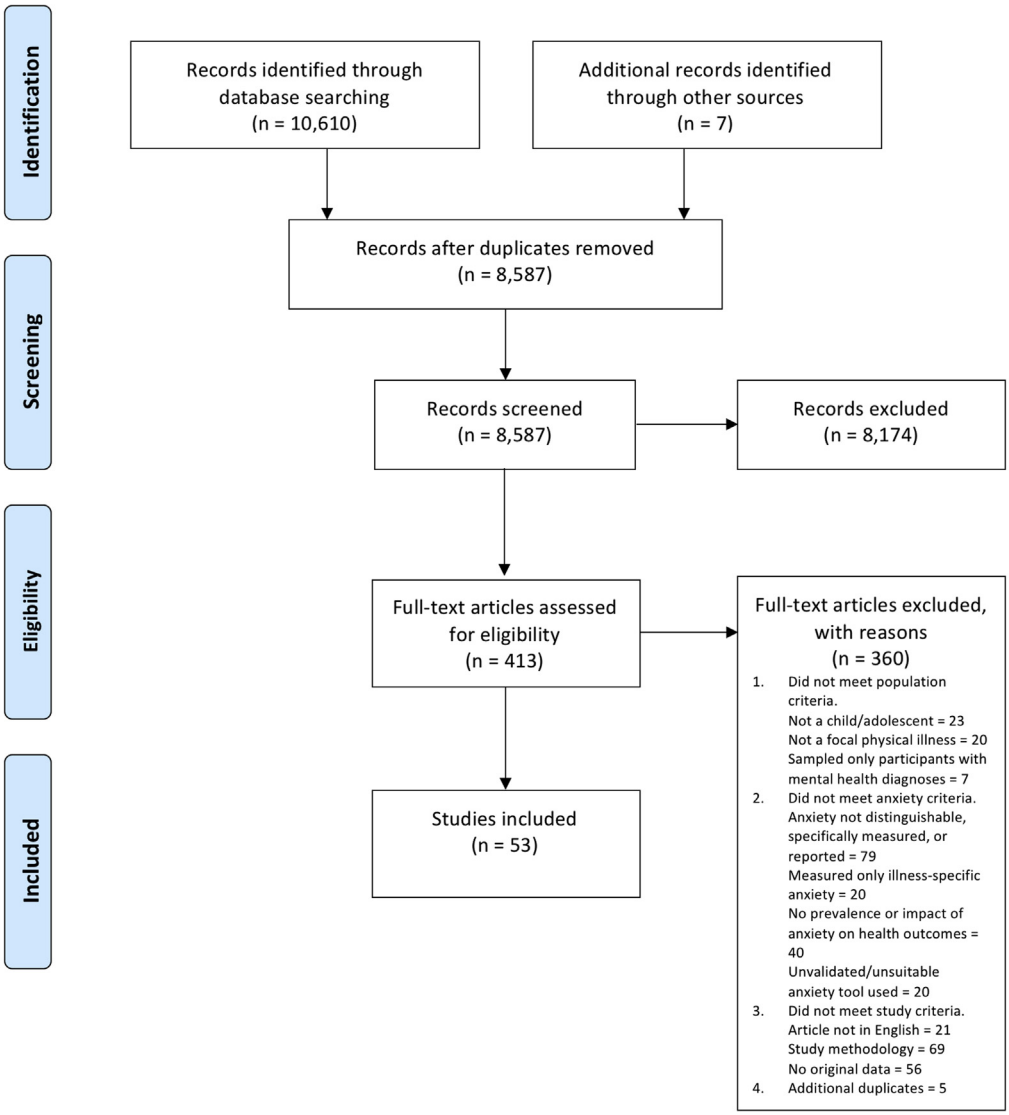
RESULTS

A total of 53 studies were identified for final inclusion, of which 29 reported anxiety disorder prevalence and 24 reported impacts of anxiety on disease-related outcomes. A flow diagram detailing the steps of the study review process is provided in Figure 1. Findings from the 53 studies on prevalence and impacts of anxiety on disease-related outcomes are summarized in Table 1[12-40] and Table 2.[41-64] The methodological strengths and limitations of each study reviewed are outlined in Tables S2 and S3, available online.

Prevalence of Any Anxiety Disorder in Children With CMCs

Key characteristics of the studies reviewed are important in understanding the results of the review. Less than half of the studies (12 of 29) reported prevalence of any anxiety disorder based on what is regarded as the diagnostic gold standard in this field—namely, a combination of youth and parent interviews. Although 18 of the 29 studies had a control group, in 3 studies, no prevalence data were reported for the control group, preventing prevalence rate comparisons. In addition, in a number of instances, the

FIGURE 1 PRISMA Flow Diagram



control group did not represent the general population of youths. Finally, samples of youths with CMCs were recruited in a variety of ways, including through treatment sites, enrollment in an insurance plan, and involvement in community surveys. Studies providing prevalence data for anxiety disorders were identified for all of the CMCs except CHD.

Asthma

Eleven cross-sectional (six case-control with five reporting prevalence rates in the control group) studies were identified. The prevalence rates for any anxiety disorder in children with asthma varied widely, ranging from 5.1%[13] to 49.2%.[14] It is noteworthy that in the five studies with a control group, the prevalence rates in the control groups showed the same wide range, from 3.1% to 37.7%, suggesting that these differences are explained partly by differences in the anxiety assessment across studies. Of the five case-control studies,[12-16] four reported higher rates of any anxiety disorder in the group of youths with asthma. Moreover, all studies without a control group (with 3 of the 6 studies using the same sample)[17-22] reported higher prevalence rates than the global prevalence rate of 6.5% as reported by Polanczyk *et al.*[11]

Given the wide range in prevalence rates, we considered the increase in risk for an anxiety disorder between case participants and control participants. The risk seems to be most increased compared to the control group participants

TABLE 1 Characteristics and Findings Regarding the Prevalence of Anxiety Disorders in Children and Adolescents With Chronic Medical Conditions

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Asthma				
Bussing *et al.* 1996[12] (USA; cross-sectional case-control study)	N = 68 youths (37 participants with asthma; 31 healthy control participants). Youths with asthma recruited from pediatric university clinic and private practices; controls recruited through the public school system.	Participants with asthma (mean = 11 y): 12 female participants, 25 male participants. Control participants (mean = 11.7 y): 12 female participants, 19 male participants.	K-SADS based on *DSM-III-R* criteria; diagnoses based on combined parent and youth interviews.	Significantly higher prevalence of any anxiety disorder in the asthma patient group (43.2%) compared to the healthy controls (19.4%) in the past 12 mo.
Calam *et al.* 2005[13] (UK; cross-sectional)	N = 9,834 youths recruited into a nationwide youth mental health survey. 1,505 of these youths had asthma according to parent report.	5–15 y. 4,929 female participants, 4,905 male participants.	The Development and Well-Being Assessment was given to parents, youths and teachers. Youth and adolescent psychiatrists reviewed the verbatim accounts and identified *International Classification of Diseases (ICD)–10* diagnoses.	5.1% of youths with asthma met criteria for any anxiety diagnosis compared with 3.1% of youths who did not have asthma. This was a significant difference.
Katon *et al.* 2007[14] (USA; cross-sectional case-control)	N = 1,379 youths. 769 youths with at least one type of asthma-related pharmacy and/or health care use in past 12 months (eg, ≥4 prescriptions for asthma medication). 582 age-matched control participants with no asthma-related pharmacy or health care use. Both groups recruited via their enrollment in an insurance plan for ≥6 mo.	11–17 y. Participants with asthma (mean = 14 y): 358 female participants, 411 male participants. Control participants (mean = 14.1 y): 294 female participants, 288 male participants.	C-DISC-IV, based on *DSM-IV* criteria; diagnoses based on youth interviews.	18.72% of youths with asthma met criteria for any anxiety disorder in the past 12 mo compared to 9.1% of controls. This was a significant difference.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Ortega *et al.* 2002[15] (USA and Puerto Rico; cross-sectional case-control)	N = 1,295 youths recruited from the community (199 with a history of asthma; 37 with other chronic illness; remainder were healthy control participants).	9–17 y. 609 female participants, 686 male participants. Participants with asthma: 81 female participants, 118 male participants. Participants with chronic medical conditions: 14 female participants, 23 male participants Healthy control participants: 514 female participants, 545 male participants.	DISC (v.2.3—compatible with *DSM-III-R*); diagnoses based on combined parent and youth interviews.	49.2% of youths with a history of asthma met criteria for an anxiety disorder in the past 6 mo, compared to 37.7% of youths without a history of asthma. This was a significant difference.
Ortega *et al.* 2004[16] (Puerto Rico; cross-sectional case-control)	N = 1,891 youths recruited from the community (612 had a parent-reported asthma diagnosis; 416 had a parent-reported lifetime history of asthma attack; the remaining youths had no history of an asthma attack).	4–17 y. Sex split of the participants not reported.	C-DISC-IV, based on *DSM-IV* criteria; diagnoses based on combined parent and youth interviews.	Youths with an asthma diagnosis were not more likely than youths with no asthma diagnosis to meet criteria for an anxiety disorder (percentages not reported). Youths with a lifetime history of an asthma attack were significantly more likely (11.2%) than those without this history (5.6%) to meet criteria for any anxiety disorder.
Katon *et al.* 2006[17] (USA; cross-sectional)	N = 769 youths with at least one type of asthma-related pharmacy and/or health care use in past 12 mo (eg, ≥4 prescriptions for asthma medication). Recruited via their enrollment in an insurance plan for ≥6 mo.	11–17 y. Sex split of participants not specified.	Phone version of anxiety and depression modules of the C-DISC-IV, based on *DSM-IV* criteria; diagnoses based on youth interviews.	9% of youths met criteria for any anxiety disorder in the past 12 mo.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
McCauley *et al.* 2007[18] (USA; cross-sectional)	N = 767 youths (where youths were receiving active asthma treatment). Recruited from the clinics of a health maintenance organization.	11–17 y (mean = 13.9 y). 356 female participants, 411 male participants.	Telephone version of the anxiety and depression modules of the C-DISC-IV, based on *DSM-IV* criteria; diagnoses based on youth interviews.	8.9% of youths met criteria for an anxiety disorder in the past 12 mo.
Richardson *et al.* 2006[19] (USA; cross-sectional)	N = 767 youths with at least one type of asthma-related pharmacy and/or health care use in past 12 months (eg, ≥4 prescriptions for asthma medication). Recruited via their enrollment in an insurance plan for ≥6 mo.	11–17 y. 356 female participants, 411 male participants.	Telephone version of the anxiety and depression modules of the C-DISC-IV, based on *DSM-IV* criteria; diagnoses based on youth interviews.	8.9% of youths met criteria for any anxiety disorder in the past 12 mo.
Ross *et al.* 2007[20] (Canada; cross-sectional)	N = 53 youths. Youths demonstrated objective evidence of asthma and received treatment for asthma at an emergency department within past 12 mo.	12–18 y (mean = 14.6 y). 26 female participants, 27 male participants	ADIS-IV-P/C; final diagnoses based on composite diagnostic profile.	40% of youths met criteria for any anxiety diagnosis.
Vila *et al.* 1999[21] (France; cross-sectional case-control)	N = 186 (93 youths with asthma who attended a children's hospital; 93 youths with insulin-dependent diabetes mellitus (IDDM) who attended a children's hospital).	8–17 y. Participants with asthma (mean = 11.8 y): 29 female participants, 64 male participants. Demographic characteristics of the participants with IDDM were not provided.	K-SADS, modified to assess *DSM-IV* criteria.	42.6% of youths with asthma met criteria for any anxiety diagnosis.
Vila *et al.* 2000[22] (France; cross-sectional case-control)	N = 164 (82 youths with moderate-to-severe persistent asthma who attended a children's hospital; 82 matched healthy control participants recruited from a school in the same community.	8–15 y. Participants with asthma (mean = 11.3 y): 27 female participants, 55 male participants. Healthy control participants (mean = 11 y): 26 female participants, 56 male participants.	K-SADS, modified to assess *DSM-IV* criteria, administered only to children with asthma.	35% of youths with asthma met criteria for any anxiety diagnosis.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Diabetes (T1DM)				
Bakare *et al*. 2008[23] (Nigeria; cross-sectional case-control)	N = 135. A total of 45 youths with type 1 diabetes mellitus (T1DM), 45 youths with sickle cell disease (SCD), 45 healthy control participants). Youths with T1DM and SCD were recruited through an outpatient clinic and had been diagnosed for ≥1 y. Healthy control participants were recruited from nearby public schools.	9–17 y. Participants with SCD: 19 female participants, 26 male participants. Participants with T1DM: 23 female participants, 22 male participants. Control participants: 23 female participants, 22 male participants.	Youth version of the C-DISC-IV, based on *DSM-IV* criteria.	17.8% of youths with T1DM met criteria for any anxiety disorder compared to 0% in each of the SCD and healthy control groups.
Khandelwal *et al*. 2016[24] (India; cross-sectional case-control)	N = 184 (84 youths with T1DM, 100 matched healthy control participants). Youths were recruited from a pediatric hospital with a diagnosis of T1DM; healthy control participants were recruited from the pediatric hospital either having presented with acute minor illness or accompanying other patients enrolled in the study.	6–14 y. Participants with T1DM (mean = 11.1 y): 29 female participants, 55 male participants. Control participants (mean = 10.7 y): 32 female participants, 68 male participants.	*DSM-5* Parent/Guardian rated Level 1 Cross-Cutting Symptom Measure, child age 6–17 y (2-stage interview developed by the American Psychiatric Association).	32.1% of youths with T1DM compared with 8% of healthy control participants were reported to demonstrate anxiety symptoms. This was a significant difference.
Butwicka *et al*. 2016[25] (Poland; cross-sectional)	N = 207 youths with T1DM (duration of ≥1 y) attending a pediatric hospital clinic	8–18 y (mean = 13.5 y). 87 female participants, 120 male participants.	K-SADS-PL diagnoses based on *DSM-IV-TR* criteria; combined parent and youth interviews.	15.5% met criteria for a current anxiety diagnosis; 19.3% met criteria for any lifetime anxiety disorder.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Epilepsy				
Adewuya *et al.* 2005[26] (Nigeria; cross-sectional case-control)	N = 336 (166 youths with epilepsy; 170 matched healthy control participants). Youths with epilepsy diagnosed ≥1 y prior and recruited from hospital outpatient clinic. Healthy control participants recruited from youth outpatient hospital records.	12–18 y. Participants with epilepsy (mean = 14.9 y): 65 female participants, 101 male participants. Control participants (mean = 14.8 y): 67 female participants, 103 male participants.	DISC-IV; diagnoses based on *DSM-IV* criteria; combined parent and youth interviews.	33.1% of youths with epilepsy met criteria for any anxiety disorder compared to 12.4% of healthy controls. This was a significant difference.
Caplan *et al.* 1997[27] (USA; cross-sectional case-control)	N = 115 youths (30 with complex partial seizures; 24 with primary generalized epilepsy with absences; and 61 healthy control participants). Epilepsy samples recruited from neurology outpatient clinics and private practices. Healthy control participants recruited through schools.	Participants with primary generalized epilepsy with absences (mean = 10.1 y): 15 female participants, 9 male participants Participants with complex partial seizures (mean = 10.8 y): 10 female participants, 20 male participants Control participants (mean = 9.5 y): 16 female participants, 45 male participants.	Primary generalized epilepsy: K-SADS-E diagnoses based on *DSM-IV* criteria; combined parent and youth interviews. Diagnostic Interview for Children and Adolescents—youth interview generating *DSM-III* diagnoses. Used for the group with complex partial seizures.	41.6% of youths with primary generalized epilepsy with absences met criteria for any anxiety diagnosis, compared to 3.3% of youths with complex partial seizures. This was not tested for significance.
Caplan *et al.* 2005[28] (USA; cross-sectional case-control)	N = 264 youths (100 with complex partial seizures; 71 with childhood absence epilepsy; 93 healthy control participants). Youths with epilepsy recruited from neurology clinics and required to have had one or more seizures in past year. Healthy control participants were recruited from schools in the community.	5–16 y. Participants with complex partial seizures (mean = 10.7 y): 51 female participants, 49 male participants. Participants with childhood absence epilepsy (mean = 9.8 y): 40 female participants, 31 male participants. Control participants (mean = 10.6 y): 48 female participants, 45 male participants.	K-SADS-E, diagnoses based on *DSM-IV* criteria; combined parent and youth interviews.	35% of youths with epilepsy met criteria for any current anxiety disorder. 27% in the group with complex partial seizures compared to 50% in the childhood absence epilepsy group met criteria for any current anxiety disorder. The difference between the childhood absence epilepsy group and the group with complex partial seizures was significant.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Jones *et al.* 2007[29] (USA; cross-sectional case-control).	N = 103. A total of 53 youths with recent onset (<1 y) epilepsy recruited from pediatric neurology clinics; 50 healthy control participants who were first-degree cousins of the participants with epilepsy.	8–18 y. Participants with epilepsy (mean = 12.7 y): 22 female participants, 31 male participants. Control participants (mean = 12.7 y): 27 female participants, 23 male participants.	K-SADS-PL, diagnoses based on *DSM-IV* criteria; combined parent and youth interviews.	35.8% of youths with epilepsy compared with 22.0% of healthy controls met lifetime criteria for any anxiety disorder. This was a significant difference.
Adewuya *et al.* 2005[30] (Nigeria; cross-sectional)	N = 102 youths with epilepsy (diagnosed ≥1 y prior); recruited from hospital outpatient clinic.	12–18 y (mean = 14.5 y). 37 female participants, 65 male participants.	DISC-IV, diagnoses based on *DSM-IV* criteria; combined parent and youth interviews.	31.4% of youths met criteria for any anxiety disorder in the past 12 mo.
Alfstad *et al.* 2016[31] (Norway; cross-sectional)	N = 101 youths with epilepsy (52 with focal epilepsy; 49 with genetic generalized epilepsy) recruited following hospital admissions for epilepsy.	10–19 y (mean = 14.1 y). 52 female participants, 49 male participants.	K-SADS-PL, diagnoses based on *DSM-IV* criteria; combined parent and youth interviews.	23.8% of youths with epilepsy diagnosed with any current anxiety disorder.
Gatta *et al.* 2018[32] (Italy; longitudinal)	N = 49 youths with recent-onset epilepsy referred to health service.	4–18 y (mean = 9.6). 22 female participants, 27 male participants.	K-SADS-PL, diagnoses based on *DSM-IV* criteria.	45% of youths with recent-onset epilepsy met criteria for a clinical anxiety disorder at baseline. At the 18-mo follow-up, the frequency and duration of seizures had improved for 90% of youths, and the prevalence rate for any anxiety diagnosis had reduced to 26% of youths.
Jones *et al.* 2015[33] (USA; cross-sectional case-control)	N = 137. A total of 88 youths with recent onset (<1 y) epilepsy, 49 healthy control participants. Healthy control participants were first-degree cousins of the participants with epilepsy.	8–18 y. Participants with epilepsy (mean = 12.52 y): 45 female participants, 43 male participants. Control participants (mean = 13.22 y): 27 female participants, 22 male participants.	K-SADS-PL, diagnoses based on combined parent and youth interviews.	28.4% of youths with epilepsy met criteria for any anxiety disorder. Prevalence rates of anxiety disorders were not reported for control groups.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Inflammatory Bowel Disease (IBD)				
Engstrom *et al*. 1991[34] (Sweden; cross-sectional case-control)	N = 40 (20 youths with IBD recruited through department of gastroenterology; 20 matched healthy control participants).	9–18 y. 11 female participants, 9 male participants in each group. Participants with IBD (mean = 16.5 y); control participants (mean = 16.4 y).	CAS, *DSM-III-R* diagnostic interview conducted with youths.	25% of youths with IBD met criteria for any anxiety disorder compared with 10% of healthy controls. No test for significance.
Engstrom *et al*. 1992[35] (Sweden; cross-sectional case-control)	N = 80 (20 youths with IBD recruited through department of gastroenterology; 20 youths with headache recruited through schools; 20 youths with diabetes recruited through department of pediatrics; 20 healthy control participants recruited from a school).	9–18 y. 11 female participants, 9 male participants in each group. Participants with IBD (mean = 16.5 y), participants with headache (mean = 16.6 y), participants with diabetes (mean = 16.4 y), control participants (mean = 16.4 y).	CAS, *DSM-III-R* diagnostic interview conducted with youths.	20% of youths with IBD met criteria for any anxiety disorder compared with 0% of youths with headache, 10% of youths with diabetes, and 5% of healthy controls. No significance test.
Juvenile Idiopathic Arthritis (JIA)				
Vandvik *et al*. 1990[36] (Norway; cross-sectional)	N = 106 youths hospitalized for the first time in a pediatric rheumatology ward.	1–17 y, 64 female participants, 42 male participants.	CAS—structured *DSM-III-R* diagnostic interview conducted with youths.	16.6% of school-aged youths (n = 72) who were interviewed met criteria for any anxiety disorder.
Sickle Cell Disease (SCD)				
Amr *et al*. 2010[37] (Saudi Arabia; cross-sectional case control)	N = 312. A total of 110 youths with SCD; 202 control). Youths with SCD recruited from pediatric hematology unit. Control participants recruited from outpatient clinic for mild illnesses.	13–18 y, Participants with SCD (mean = 16.8 y): 20 female participants, 90 male participants. Control participants (mean = 16.9 y): 30 female participants, 172 male participants.	Clinical interview (SCICA) (most likely, only with youths), using *DSM-IV-TR* diagnostic criteria.	17.3% of youths with SCD met criteria for any anxiety disorder compared to 7.9% of controls. This was a significant difference.

(*continued*)

TABLE 1 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings and Interpretation
Cepeda *et al.* 1997[38] (USA; cross-sectional case-control)	N = 65 (39 youths with SCD recruited from a sickle cell outpatient clinic; 26 control participants recruited from an acute care clinic)	6–19 y. Participants with SCD (mean = 11.2 y): 16 female participants, 23 male participants. Control participants (11.5 y): 13 female participants, 13 male participants.	Clinical interview of youths, using *DSM-III-R* diagnostic criteria.	10% of youths with SCD met criteria for a current anxiety disorder compared to 15% of controls. This was not significantly different.
Thompson *et al.* 1998[39] (USA; cross-sectional case-control)	N = 80 (40 youths with SCD; 40 youths with cystic fibrosis). Youths recruited through medical centers.	7–12 y. Participants with SCD: 22 female participants, 27 male participants. Participants with cystic fibrosis: 14 female participants, 29 male participants.	CAS, diagnoses based on *DSM-III* criteria.	27.5% of youths with SCD met criteria for any anxiety disorder, compared with 35% of youths with cystic fibrosis.
Benton *et al.* 2011[40] (USA; cross-sectional)	N = 40 youths with diagnosed SCD recruited from pediatric hospital.	12–19 y. 20 female participants, 20 male participants.	Children's Interview for Psychiatric Syndromes, diagnoses based on *DSM-IV* criteria combined parent and youth interviews.	15% of youths with SCD met criteria for a current anxiety disorder.

Note: *ADIS-IV-P/C = Anxiety Disorders Interview Schedule for Children for* DSM-IV: *Parent and Child versions; CAS = Child Assessment Schedule; CMC = chronic medical condition; DISC = Diagnostic Interview Schedule for Children; IBD = inflammatory bowel disease; ICD = International Classification of Diseases; IDDM = insulin-dependant diabetes mellitus; JIA = juvenile idiopathic arthritis; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; SCD = sickle cell disease; SCIA = Semistructured Clinical Interview for Children and Adolescents; T1DM = type 1 diabetes mellitus.*

[a]*Studies are ordered according to chronic medical conditions (CMCs), with studies including a control group first and then (below the boldface line) studies with cases only.*

TABLE 2 Characteristics and Findings Regarding the Association of Anxiety With Disease-Related Outcomes in Children and Adolescents with Chronic Medical Conditions

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Asthma					
Bender *et al.* 2000[41] (USA; cross-sectional data obtained prior to randomisation of participants into a clinical trial)	N = 1,041 youths with mild-to-moderate asthma, recruited from clinical centers	5–12 y. 420 female participants, 621 male participants.	Revised Children's Manifest Anxiety Scale and Social Anxiety Scale for Children–Revised, self-report questionnaires.	Anxiety scores in youths with asthma were not correlated with measures of pulmonary function and airway reactivity or days of oral steroid use in the past 6 mo.	
Bruzzese *et al.* 2016[42] (USA; cross-sectional)	N = 386 youths with persistent asthma. Recruited through schools after parents endorsed that youths had an asthma diagnosis, had persistent asthma, and had taken prescribed asthma medication in the past 12 mo.	11–14 y (mean = 12.8 y). 174 female participants, 212 male participants.	Social and Separation Anxiety subscales of the Screen for Child Anxiety and Emotional Disorders self-report questionnaire.	Social anxiety was not associated with asthma care. Separation anxiety was negatively (only slightly) associated with asthma responsibility: at a certain level of asthma-related anxiety and social anxiety, higher separation anxiety was associated with lower self-responsibility. Specific asthma-related anxiety played an independent role in asthma care, where social and separation anxiety had a weak to no relationship with asthma care.	
Bush *et al.* 2007[43] (USA; cross-sectional)	N = 769 youths with asthma. Population-based sample identified on basis of pharmacy and/or health care use.	11–17 y (mean = 14 y). 358 female participants; 411 male participants.	Telephone youth version of the Computerized Diagnostic Interview Schedule for Children (C-DISC-IV).	Meeting criteria for any anxiety disorder was significantly associated with being a current smoker vs. a nonsmoker; and with being a susceptible vs. nonsusceptible nonsmoker.	
Goodwin *et al.* 2005[44] (USA; cross-sectional)	N = 74 youths diagnosed with moderate-to-severe persistent asthma and recruited through an asthma clinic.	5–11 y (mean = 8.08 y). 33 female participants, 41 male participants.	DISC Predictive Scales–a screening measure derived from the DISC-IV. Youths aged 5–8 y were interviewed with parent present; youths aged 9–11 y were interviewed individually.	Probable diagnoses of anxiety disorders were not significantly associated with higher levels of health care service use.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Kean *et al.* 2006[45] (USA; cross-sectional case-control)	N = 200 (Participants with history of life-threatening asthma event, n = 49; asthma control participants, n = 71; healthy control participants, n = 80). Participants who had been through a life-threatening event were recruited through hospitals and referrals; asthma control participants and healthy control participants were recruited through research databases, referrals, and advertising.	12–18 y (mean = 14.7 y). Participants in life-threatening asthma group: 41 female participants, 59 male participants. Participants in asthma control group: 46 female participants, 54 male participants. Healthy control participants: 52 female participants, 48 male participants.	Multidimensional Anxiety Scale for Children, youth self-report questionnaire. University of Carolina Los Angeles Post-Traumatic Stress Disorder Reaction Index—youth self-report questionnaire. Impact of Events Scale—Revised, parent-report of posttraumatic stress symptoms.	Adolescent posttraumatic stress and anxiety symptoms were each significantly correlated with asthma functional morbidity (rated by parents). Multiple hierarchical regression indicated that asthma-related posttraumatic stress symptoms and disease severity were the only significant predictors of functional morbidity.	
Letitre *et al.* 2014[46] (Netherlands; cross-sectional case-control)	N = 140 (participants with asthma, n = 70; healthy control participants, n = 70). Particpants with asthma were recruited from pediatric asthma clinics; healthy control participants were recruited via word-of-mouth through the participants with asthma.	8–15 y (mean = 11.3 y). Participants with asthma: 27 female participants, 43 male participants. Control participants: 31 female participants, 39 male participants.	State-Trait Anxiety Inventory for Children, self-report questionnaire. Revised Fear Survey for Children, self-report questionnaire.	Significant correlation between higher State-Trait Anxiety Inventory for Children trait anxiety scores and poorer asthma control. No significant correlation between asthma control and Revised Fear Survey for Children. No significant correlation between anxiety measures and predicted forced expiratory volume. Patients who had an asthma exacerbation in the past year had higher anxiety trait scores than those without an exacerbation.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
McGrady *et al.* 2010[47] (USA; cross-sectional)	N = 151 youths with current asthma diagnosis recruited through primary care clinic.	11–18 (mean = 15.8 y). 91 female participants, 60 male participants.	10-Item Multidimensional Anxiety Scale for Children (self-report questionnaire)	Higher levels of anxiety symptomatology on the Multidimensional Anxiety Scale for Children–10 were associated with higher self-reported asthma symptoms. Greater anxiety was also associated with stronger perceptions that asthma had a negative impact on one's life and emotions and was more difficult to control. These negative illness perceptions were related to greater levels of asthma symptoms.	
Shams *et al.* 2018[48] (USA; longitudinal)	N = 86 black youths with a physician diagnosis of asthma. Youths also had to demonstrate evidence of either reversible airflow limitation or airway hyperresponsiveness. Recruited through community. Sample size reduced to 67 at follow-up.	12–21 y. 39 female participants, 47 male participants.	Hospital Anxiety and Depression Scale, anxiety subscale	Anxiety symptoms were associated with poorer asthma control, poorer asthma-related quality of life, and more insomnia problems at baseline. After adjusting for demographic factors, youths with probable anxiety disorders on the Hospital Anxiety and Depression Scale—anxiety sub-scale at baseline had significantly increased odds of persistent uncontrolled asthma and emergency department use at the 1-year follow-up. There were no differences based on probable anxiety diagnosis in physician visits or systemic corticosteroid receipt. Adolescents with probable anxiety disorders reported missing significantly more school or work days in the previous 3 months.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Vuillermin *et al.* 2010[49] (Australia; cross-sectional case-control)	N = 477 youths (158 with asthma; 319 nonasthmatic). Participants were recruited based on parent survey responses to a larger study, where they indicated asthmatic symptoms in their child or children.	5–13 y (mean = 9.0 y). Sex split between groups was not reported.	Spence Children's Anxiety Scale, completed by youths and parents.	According to both the parent and youth Spence Children's Anxiety Scale versions, there was no difference in health care use for youths with asthma whose SCAS score was in the clinical range compared to those in the nonclinical range. Spence Children's Anxiety Scale—Child scores that were in the clinical range were significantly associated with increased likelihood of using an asthma-preventive medication. Spence Children's Anxiety Scale—Parent scores that were in the clinical range were significantly associated with increased school absenteeism.	
Diabetes					
Berger *et al.* 2018[50] (Austria; cross-sectional).	N = 241 youths with T1DM (duration of of ≥1 y) recruited through diabetes care centers.	10–22 y (mean = 14.3 y). 138 female participants, 103 male participants.	Children's Diagnostic Interview for Psychiatric Disorders (CDI-MD, German version) assesses *DSM-IV* and *ICD-10* criteria. Youths interviewed only.	Elevated rates of specific phobia and social anxiety disorder were found in the insulin-manipulating group ("insulin purging" only) compared to the adherent group. Regression showed that psychiatric comorbidity did not predict HbA1c. However, there was a significant relationship between insulin manipulation and HbA1c as the proxy for metabolic control.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Ceylan *et al.* 2017[51] (Turkey; cross-sectional case-control)	N = 140 youths (70 youths with T1DM; 70 control participants). Youths with T1DM recruited through endocrinology unit. Healthy control participants recruited through schools.	12–15 y (mean = 13.71 y). 62 female participants, 78 male participants. Sex split between conditions was not reported.	Social Anxiety Scale for Adolescents, youth self-report questionnaire.	Higher Social Anxiety Scale for Adolescents scores were associated with self-reported moderate (as opposed to poor or good) levels of compliance with diet and endorsement of restricted food and drink intake. No other significant Social Anxiety Scale for Adolescents differences in diabetes-related outcomes were found.	
Di Battista *et al.* 2009[52] (USA and Canada; cross-sectional)	N = 76 youths with T1DM recruited from 2 diabetes centers.	13–18 y (mean = 15.9 y). 43 female participants, 33 male participants	Social Anxiety Scale for Adolescents, youth self-report questionnaire.	Social anxiety was negatively correlated with insulin and dietary adherence in boys but not in girls. Fear of hypoglycemia was found to mediate the relationship between social anxiety and reduced insulin adherence. Social anxiety was associated with significantly lower diabetes-related quality of life in participants of both sexes.	
Herzer *et al.*, 2010[53] (USA; cross-sectional)	N = 276 youths with a T1DM diagnosis receiving care at a pediatric diabetes center.	13–18 y (mean = 15.6 y). 131 female participants, 145 male participants	State Trait Anxiety Inventory, self-report questionnaire.	Less frequent blood glucose monitoring and suboptimal glycemic control were significantly associated with higher levels of state anxiety.	
Hilliard *et al.* 2011[54] (USA; longitudinal)	N = 145 youths with a T1DM diagnosis (according to American Diabetes Association criteria); recruited through diabetes treatment centers.	13–18 y (mean = 15.5 y). 74 female participants, 71 male participants.	State Trait Anxiety Inventory for Children, self-report questionnaire.	At baseline, higher state anxiety scores were significantly correlated with: higher HbA1c, less frequent blood glucose monitoring, and lower parent-reported quality of life. At the 12-month follow-up, state anxiety was a significant predictor of HbA1c levels but not blood glucose monitoring.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Kovacs *et al.* 1990[55] (USA; longitudinal)	N = 95 youths with newly diagnosed insulin-dependent diabetes mellitus (IDDM) recruited through a hospital endocrinology inpatient unit.	8–13 y (mean = 11.1 y). 51 female participants, 44 male participants.	Revised Children's Manifest Anxiety Scale– self-report questionnaire	Over a 6-year follow-up period, there was no relationship between Revised Children's Manifest Anxiety Scale scores and GHb when initial diabetes symptoms were controlled for. Higher Revised Children's Manifest Anxiety Scale scores at any point in time were associated with increased distress about the IDDM treatment regimen.	
Kristensen *et al.* 2014[56] (Denmark; cross-sectional)	N = 786 youths in the Danish Childhood Diabetes Registry– national registry of all youths with T1DM.	4–17 y (mean = 12.3 y). 405 female participants, 381 male participants.	Beck Youth Inventory Second Edition, anxiety subscale.	Beck Youth Inventory scores were significantly correlated with HbA1c and treatment adherence (as rated by parents and youths).	
Kristensen *et al.* 2018[57] (Denmark; cross-sectional)	N = 519 youths in the Danish Registry for Childhood and Adolescent Diabetes– national registry of all youths with T1DM.	2–17 y (mean = 14.6 y).	Beck Youth Inventory Second Edition, anxiety subscale.	In the adolescent structural equation model, lower levels of youth anxiety were associated with poorer metabolic control (HbA1c), and higher levels of anxiety were associated with better treatment adherence.	
Inflammatory Bowel Disease (IBD)					
Giannakopoulos *et al.* 2016[58] (Greece; cross-sectional)	N = 85 participants with IBD recruited from a gastroenterology unit.	8–18 y (mean = 13.2 y). 50 female participants, 35 male participants.	Revised Children's Manifest Anxiety Scale, self-report questionnaire	There was a positive correlation between anxiety symptoms and disease activity.	
Reigada *et al.* 2011[59] (USA; cross-sectional)	N = 36 youths with IBD recruited from pediatric gastroenterology medical centers.	12–17 y (mean = 15.3 y). 18 female participants, 18 male participants.	Screen for Anxiety-Related Emotional Disorders, youth self-report	There was a positive correlation between anxiety symptoms and current disease activity. However, when current disease activity was accounted for, anxiety scores did not predict more negative disease-related outcomes (either in terms of impact as rated by youths [eg, school absences] or in terms of medical service use as rated by parents).	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Reigada *et al.* 2015[60] (USA; cross-sectional)	N = 93 youths with Crohn's disease. Retrospective medical chart review of youths seen at pediatric gastroenterology centers.	9–18 y (mean = 13.2 y). 42 female participants, 51 male participants.	Screen for Anxiety-Related Emotional Disorders, youth self-report	Youths whose disease was rated as moderate to severe self-reported significantly higher levels of anxiety compared to youths with inactive disease. Youths' school anxiety was significantly related to poorer well-being, more abdominal pain, and more loose stools. Separation and general anxiety were not related to any disease-activity variables.	
Reigada *et al.* 2016[61] (USA; longitudinal)	N = 86 youths with IBD recruited from pediatric gastroenterology centers.	11–18 y (mean = 14.7 y). 38 female participants, 48 male participants.	Screen for Anxiety-Related Emotional Disorders, youth and parent self-report	Youths who experienced 2 or more relapses over the subsequent 12 mo had significantly higher baseline anxiety scores than youths who experienced fewer relapses. Regardless of reporter (parent or youth), higher scores on the Screen for Anxiety-Related Emotional Disorders independently predicted higher gastrointestinal health care use and hospital-based care after controlling for disease-related factors.	
Juvenile Idiopathic Arthritis (JIA)					
Banasiak *et al.* 2010[62] (Poland; cross-sectional)	N = 30 youths diagnosed within last 2 y with JIA. Recruited from hospital outpatient clinics.	11–19 y. 19 female participants, 11 male participants.	State Trait Anxiety Inventory	High self-reported levels of experiencing arthritis-related pain were significantly positively correlated with both state and trait anxiety.	
Ding *et al.* 2008[63] (UK; cross-sectional)	N = 60 youths diagnosed with JIA for at least 6 mo. Recruited from rheumatology service.	7–18 y (mean = 12.3 y). 39 female participants, 21 male participants.	Revised Children's Manifest Anxiety Scale	Total Revised Children's Manifest Anxiety Scale score was significantly positively correlated with parent report of physical disability in youths but not with disease activity measures.	

(*continued*)

TABLE 2 Continued

Study (Authors, Year, Reference, Country, Type)[a]	Participants	Age (Mean and/or Range) and Sex	Measure	Findings	Interpretation
Sickle Cell Disease (SCD)					
Myrvik *et al.* 2012[64] (USA; cross-sectional)	N = 21,255 participants with SCD who were admitted to hospital for a vaso-occlusive crisis over a 1-y period. Data collected from health care database.	0–20 y (mean = 13 y). 39 female participants, 21 male participants.	*ICD-9-CM* discharge diagnoses.	The presence of any anxiety diagnosis was associated with significantly longer hospital length of stay after controlling for confounding variables (such as medical procedures associated with increased risk of complications). Length of stay was 23% longer for youths with an anxiety diagnosis compared to that in patients with no psychiatric diagnosis.	

Note: *ADIS = Anxiety Disorders Interview Schedule; CAS = Child Assessment Schedule; CMC = chronic medical condition; DISC = Diagnostic Interview Schedule for Children; IBD = inflammatory bowel disease; ICD = International Classification of Diseases; IDDM = insulin-dependant diabetes mellitus; JIA = juvenile idiopathic arthritis; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; SCD = sickle cell disease; T1DM = type 1 diabetes mellitus.*

[a]*Studies are ordered according to chronic medical conditions (CMCs).*

when children with asthma are identified through a clinic or health care service[12,15] instead of through community samples.[13,14]

Overall, the studies suggest that the prevalence rate of anxiety disorders is increased in children with asthma, with the more severely affected groups (ie, the ones identified through use of clinical services) having the most increased risk. However, the latter is speculative, as this was not statistically tested, but was based on inspection of the differences in risk in the five case-control studies.

Type 1 Diabetes

Three studies were identified, including 336 youths.[23-25] The prevalence rates for any anxiety disorder in children with diabetes ranged from 15.5% to 32.1% compared to 0% to 8% in the control groups.[23,24] All 3 studies suggested higher prevalence rates in the group of children with diabetes, compared either to the controls or to the global prevalence rate of 6.5% as reported by Polanczyk *et al.*[11] All studies recruited youths through diabetes treatment sites, but used different ways to assess anxiety disorders.

Epilepsy

Eight studies were identified (7 cross-sectional and one longitudinal), including 784 youths. The prevalence rates for any anxiety disorder in children with epilepsy varied from 23.8% to 50%. In healthy controls, the rates varied between 12.4% and 22.0%. In the two studies comparing patients with epilepsy to health controls, children with epilepsy had a significantly higher risk. Moreover, all studies without a control group reported higher prevalence rates than the global prevalence rate of 6.5% as reported by Polanczyk *et al.*[11] All studies recruited from treatment sites. Six of the eight studies used a parent/youth composite diagnosis.[26,28-31,33]

Two of the case-control studies compared different types of epilepsy,[27,28] with the results suggesting that experiencing complex partial seizures is associated with minimally increased risk for anxiety disorders (if at all) compared to experiencing primary generalized epilepsy, or childhood absence epilepsy.

Finally, in a longitudinal study, Gatta *et al.*[32] reported that approximately 45% of youth with recent-onset epilepsy met criteria for an anxiety disorder, with this rate reducing to 26% by 18 months later. Between baseline and 18-month follow-up, over 43% of youths had been recommended psychotherapy. However, it is unclear which youths were referred and how many actually received psychological care between assessments.

Overall, children with epilepsy seemed to be at increased risk for anxiety disorder, although this risk may differ across types of epilepsy.

Inflammatory Bowel Disease

Two studies were identified,[34,35] including 80 youths. Both made use of the same group of youths with inflammatory bowel disease (IBD; recruited through a hospital gastroenterology department) and compared them on a youth interview with a matched group of healthy controls,[34] as well as with groups of youths with diabetes, headaches, and a healthy control group.[35] In the first study, 25% of youths with IBD met criteria for a current anxiety diagnosis compared to 5% of healthy controls.[34] In the second study, 25% of youths with IBD met criteria for a current anxiety diagnosis compared to 0% of youths with headaches, 10% of youth with diabetes, and 5% of healthy controls.[35] Overall, the children with IBD seemed at increased risk for anxiety disorders.

Juvenile Idiopathic Arthritis

One cross-sectional study was identified,[36] including 106 youths. Based on an interview with youths hospitalized for the first time with juvenile idiopathic arthritis (JIA) alone, 16.6% met criteria for a current anxiety diagnosis compared to the benchmark of 6.5%.[11]

Sickle Cell Disease

Four cross-sectional studies[37-40] (3 case-controls) were identified, including 229 youths. The prevalence rates for any anxiety disorder in children with sickle cell disease (SCD) varied between 10% to 27.5%. In the 2 studies with a non-CMC control group, the prevalence rates in the control groups ranged from 7.9%[37] to 15%.[38] In one of these studies, the difference between youths with SCD and healthy controls was not significant The one study without a control group[40] reported a higher prevalence rate than the global prevalence rate of 6.5% as reported by Polanczyk *et al.*[11] One study compared the rates of anxiety disorders between youths with SCD and youths with CF and found similar rates (27% and 35% respectively[39]). It is difficult to draw any conclusions from these studies, as the two non-CMC control groups did not represent the general population of youths. One control group were youths recruited from an acute care clinic where "none were known" to have a CMC, but where this was not a stated exclusion criterion.[38]

Impact of Anxiety on Disease-Related Outcomes

In all, 24 studies examined the effect of anxiety on disease outcomes of youths with CMCs. No studies were identified for CHD or epilepsy. Of the 24 studies, 16 were cross-sectional in design, meaning that it is the association between (rather than the impact of) anxiety and disease-related outcomes that is reported. Across CMCs, the vast majority of studies relied only on youth self-report measures of anxiety. A wide range of disease-related outcomes (often measured via youth- and/or parent-report and not complemented by objective measures) were reported.

Asthma. Nine studies (8 cross-sectional and 1 longitudinal) were identified, including 2,855 youths. Most relied on youth self-report measures of anxiety. The outcomes investigated can be divided into (1) level of morbidity and health care use, (2) school absenteeism, and (3) asthma management/lifestyle behavior. Regarding level of morbidity and health care use, three studies[41,44,49] did not find an association with anxiety, but three others did.[44-47] The results of Letitre *et al.*[46] differed across anxiety measures and outcome, with one questionnaire associated with poorer asthma control, but no association found between another questionnaire and poorer asthma control. Neither of the two questionnaires were associated with forced expiratory volume. The one longitudinal study reported that, after adjusting for demographic factors, youths with probable anxiety disorders had significantly increased odds of persistent uncontrolled asthma and emergency department use at the 1-year follow-up.[48]

Anxiety was found to be associated with school absenteeism.[44,49] Finally, Bruzzese *et al.*[42] reported that social anxiety was not associated with asthma care, whereas separation anxiety had a very weak negative relationship with perceived responsibility for managing asthma. Bush *et al.*[43] reported that meeting criteria for an anxiety disorder was significantly associated with being a current smoker among an asthma sample.

In summary, overall these studies suggest a possible association between anxiety and adverse disease-related and educational outcomes.

Type 1 Diabetes. Eight studies were identified (6 cross-sectional and 2 longitudinal), including 2,208 youth. All but one study[50] relied on youth self-report questionnaire measures of anxiety. They all focused on the association between anxiety and disease management/metabolic control. Three studies reported an association between higher anxiety and poorer management,[52-54] one study did not find an association,[55] whereas Kristensen *et al.*[56,57] found a relationship between *elevation* of youth anxiety scores and both *reduced* HbA1c levels and *improved* treatment adherence (as rated by both youth and parents). Ceylan *et al.*[51] investigated the association between social anxiety and 10 diabetes-related outcomes, of which 2 were signficiant: the association between higher social anxiety and self-reported moderate (as opposed to either "poor" or "good") dietary compliance, as well as with restricted food and drink intake.

Finally, rates of specific phobia and social anxiety disorder were significantly elevated in "insulin-manipulating" youths (engaged in insulin-purging behaviors) compared to youths adherent to treatment.[50] Insulin manipulation was in turn related to HbA1c. In summary, for diabetes, there is inconsistent and contradictory evidence of an association between the presence of anxiety and metabolic control and treatment adherence.

Inflammatory Bowel Disease. Four studies (3 cross-sectional and 1 longitudinal) were identified, including 159 youth. All relied on youth self-report measures of anxiety. All studies showed an association between anxiety symptoms and disease activity.[58-61] Most notable was that, in the one longitudinal study identified, higher baseline anxiety was associated with more relapses over the 1-year follow-up, even in the group of youths with inactive disease at baseline; and both parent- and youth-report of anxiety independently predicted higher levels of gastrointestinal health care use and hospital-based care.[61] For youths with IBD, there is evidence for an association between anxiety and increased disease activity.

Juvenile Idiopathic Arthritis. Two cross-sectional studies were identified, including 90 youths. Both relied on youth-only self-report measures of anxiety.[62,63] In a sample in which the majority of youths experienced minimal disease activity and only a small number reported high levels of JIA-related pain, both trait and state anxiety scores were significantly correlated with higher levels of self-reported pain.[60] Ding *et al.*[61] reported that there was a significant positive correlation between youth-reported anxiety and parent-reported physical disability, but no relationship between anxiety and measures of disease activity.

Sickle Cell Disease. One cross-sectional study was identified,[64] including 21,255 youth. Participants were youths with SCD who had been hospitalized following a vaso-occlusive crisis. The investigators found that, for this specific group of SCD patients, after accounting for potential confounding variables, the length of hospital admission was 23% longer longer for youths with any anxiety disorder compared to those with no psychiatric diagnosis.

DISCUSSION

This systematic review includes 53 studies examining the prevalence of anxiety disorders and the association of anxiety and disease-related outcomes across 7 different CMCs in youths with an average age of 18 years or younger. A total of 29 studies examining the prevalence of anxiety disorders were identified. As hypothesized, prevalance rates of anxiety disorder were high in all included CMCs, affecting approximately 20% to 50% of children and adolescents. In case-control studies, rates were substantially higher in patients than in healthy controls. Prevalence rates in both the case patient and control groups varied widely. This was likely due to the way in which anxiety disorders were measured, with variation in informants and diagnostic interviews. In the case patients, sampling methods (treatment sites, recruitment through an insurance plan, community surveys) and the assessment of the illness (parent-report versus clinician-verified) may also have mattered. The results for children with asthma and epilepsy suggest that more severely affected children (ie, children with asthma recruited through clinics instead of community services, or children with generalized epilepsy versus partial epilepsy) experience more anxiety. The methodological strengths and limitations of each study reviewed are outlined in detail in Table S2, available online. The most significant limitation is that less than half of the studies reviewed relied on a parent/youth diagnostic composite representing the diagnostic gold standard in the field of youth anxiety. With specific reference to youth with CMCs, Canning *et al.*[65] found that, compared to healthy control parent−youth dyads, more cases were identified by parent report for all CMCs. Among youths with CMCs, reliance on only one informant (parent or child) using a structured diagnostic interview resulted in failure to identify between one-third and one-half of all psychiatric disorders.[66]

A total of 26 studies examining the impact of anxiety on disease-related outcomes were identified, with no studies found for CHD or epilepsy. For all childhood CMCs, the literature relating to this question was limited, both in quantity and in quality. The available evidence was mixed. For asthma, there was some indication that anxiety was associated with poorer symptom control, school absenteeism, and higher rates of smoking. The association with poorer symptom control was supported by a longitudinal study. For IBD, anxiety was found to be associated with increased disease activity in youths with IBD, not only cross-sectionally but also in one longitudinal study. In addition, anxiety was associated with greater pain in individuals with JIA, and longer lengths of hospitalizations for youths with SCD presenting in vaso-occular crisis, but there were only three studies. For diabetes, the evidence for an association between anxiety and disease-related outcomes was inconsistent, with some studies indicating a negative association between elevated anxiety and metabolic control and treatment adherence, and other studies finding a positive association between elevated anxiety and treatment adherence. The methodological strengths and limitations of each study reviewed are outlined in detail in Table S3, available online. The overwhelming limitations of these

studies, however, are their cross-sectional design and their reliance on only youth self-reported measures of anxiety and youth and/or parent measures of disease-related outcomes.

Overall, this literature review confirms our hypothesis that prevalence rates of anxiety disorders are increased in children with CMC. It is not possible yet to draw a definitive conclusion regarding the influence on disease-related outcomes. Future studies should include anxiety diagnoses based on both parent and youth report. In addition, factors that may influence the risk for an anxiety disorder in children with a CMC require further exploration. Clearly, to gain further insight into the association of anxiety with disease-related outcomes, longitudinal studies are necessary. It is important to note that they should aim to include measures of anxiety and disease-related outcomes at baseline and follow-up, to test causal associations when controlling for disease activity. Children who are more severely affected by their CMCs require regular reviews in clinics, with outcomes recorded on electronic medical records. Therefore, it should be feasible to set up a prospective study with reasonable follow-up rates. Finally, given the high level of psychiatric comorbidity among children and adolescents with anxiety disorders, future studies using validated instruments to assess for different psychiatric disorders are required.

Given that untreated anxiety remains a significant problem in its own right, we also recommend clinical trials as an integral future research direction. Families in which a youth has a CMC sometimes have to manage very time-consuming and burdensome treatment regimens. Therefore, 10 to 16 sessions of child-focused cognitive–behavioral therapy (CBT), long regarded as the gold-standard approach to treating anxiety disorders in youth,[67] may not be feasible for these families. More flexible alternatives in the treatment of anxiety, such as bibliotherapy, Internet-based, parent-focused, and/or brief interventions, are likely to be more appropriate. Fortunately, a number of flexible delivery options have been developed and evaluated for youth anxiety. However, the "goodness-of-fit" (and the extent to which CMC-related adaptation may be required) of these interventions for youths with a CMC and comorbid anxiety is not clear and should be investigated in randomized controlled trials performed in these prospective cohorts.

For current clinical practice, the findings of our review do indicate that health professionals working with youth with these common CMCs should routinely screen for anxiety. Although a youth/parent-structured diagnostic interview would be ideal, this is unlikely to be practical in most medical settings. Instead, a psychometrically validated anxiety questionnaire (such as the Screen for Child Anxiety and Emotional Disorders [SCARED] or the Spence Children's Anxiety Scale [SCAS]) could be given to both youths and parents as standard procedure. Youths with elevated scores on either the parent or child version of the screener would ideally receive further assessment and, where appropriate, psychological intervention. Screening should not occur immediately following diagnosis of a CMC, as it seems likely that this would result in a number of false-positive case identifications. Instead, it is important to allow youths and their families time to adjust to the diagnosis and to develop a sense of competence in managing the symptoms of the CMC to the extent possible. Indeed, Gatta *et al.*[32] noted that the prevalence of anxiety disorders was higher at diagnosis among youths with epilepsy, with some remission 18 months later. Unfortunately, it is unclear whether the diagnostic remission was due to epilepsy-related factors (specifically, reduction in frequency and duration of seizures) or to access to treatment for anxiety (with over 40% of participants being recommended to receive psychotherapy).

In conclusion, anxiety disorders are more prevalent in youths with CMCs. There is some evidence that anxiety is related to adverse disease-related outcomes for youths with CMCs, although much more longitudinal research is required. As our understanding of the longitudinal course of anxiety in relation to CMCs in youths develops, as well as our understanding of the most appropriate interventions targeted to this specific group, the assessment and treatment implications of this mental–physical comorbidity will become clearer. In the meantime, health services should provide routine assessment for anxiety disorders and appropriate interventions so as to reduce the burden of illness and potential adverse disease-related outcomes associated with comorbid mental illness in youths with CMCs.

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