**The Prevalence and Incidence of Anxiety and Depression Among Children, Adolescents and Young Adults with Life-Limiting Conditions: A Systematic Review and Meta-Analysis**

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**Key Points**

**Question:** What is the prevalence and/or incidence of anxiety and depression in children, adolescents, and young adults with life-limiting conditions?

**Findings:** The pooled prevalence of anxiety generated from a meta-analysis of 19 studies was 19.1%, with significant differences in prevalence found according to the type of assessment tool used. The depression prevalence estimate generated from a meta-analysis of 36 studies was 14.3%, and was associated with age.

**Meaning:** The high prevalence of anxiety and depression in children, adolescents, and young adults with life-limiting conditions highlights the need for improved services in order to address their psychological needs.

**Abstract**

**Importance:** Children, adolescents, and young adults with life-limiting conditions experience various challenges which may make them more vulnerable to mental health problems, such as anxiety and depression. However, the prevalence and incidence of anxiety and depression among this population is unknown.

**Objective:** To conduct a systematic review and meta-analysis to estimate the prevalence and/or incidence of anxiety and depression in children, adolescents, and young adults with life-limiting conditions.

**Data Sources:** Searches of Medline, PsychINFO and EMBASE were conducted to identify studies published between January 2000-January 2018.

**Study Selection:** Studies were eligible for this review if they provided primary data of anxiety or depression prevalence and/or incidence, included participants aged 5-25 years with a life-limiting condition, were conducted in an Organisation for Economic Co-operation and Development country, and were available in English.

**Data Extraction and Synthesis:** 14,866 non-duplicate articles were screened, of which 37 were included in the review. Random-effects meta-analyses were generated to provide anxiety and depression prevalence estimates. Meta-regression was conducted to analyse associations between study characteristics and each prevalence estimate.

**Main Outcome(s) and Measure(s):** Prevalence of anxiety and depression.

**Results:** Of the 37 included studies, 19 reported anxiety prevalence, and 36 reported depression prevalence. The mean age of participants was 15.4 years (age range: 6-25 years). The meta-analysis of anxiety prevalence (n= 4,547 participants) generated a pooled prevalence estimate of 19.1% (95% CI: 14.1%-24.6%). Meta-regression analysis found statistically significant differences in anxiety prevalence by assessment tool; diagnostic interviews were associated with higher anxiety prevalence than self-/parent-report measures. The depression meta-analysis (n= 5,934 participants) found a pooled prevalence estimate of 14.3% (95% CI: 10.4%-18.6%). Meta-regression analysis revealed statistically significant differences in depression prevalence by the mean age of the sample.

**Conclusions and Relevance:** The prevalence of anxiety and depression among children, adolescents, and young adults with life-limiting conditions is high, highlighting the need for increased psychological assessment and monitoring. Further research is required to determine the prevalence and incidence of anxiety and depression in a larger sample of children, adolescents, and young adults with a broader range of life-limiting conditions.

**Introduction**

Mental health problems among young people are a growing public health concern, affecting 10-20% of children and adolescents worldwide.1 US national surveys have found that 3% of children and adolescents have a diagnosis of anxiety, whilst depression prevalence ranged from 2.1%-8.1%.2 Furthermore, for three-quarters of adults with long-term mental health problems, onset occurred before the age of 24 years.3

Growing research of children, adolescents, and young adults suggests a strong link between chronic physical illness and mental health problems.4–6 Some chronic conditions are life-limiting. These include conditions for which there is no cure and which cause death, either directly, (e.g. Batten disease, Duchenne muscular dystrophy) or due to secondary health difficulties associated with the condition (e.g. severe cerebral palsy), and those where curative treatment is possible but may result in failure (e.g. cancer, organ failure). 7 After diagnosis of a life-limiting condition (LLC), children, adolescents, and young adults may encounter multiple disease-related challenges which, coupled with the stressors associated with the period of adolescence, such as puberty and the desire to become independent from one’s parents, makes navigating daily life a potentially challenging endeavour.8,9 For example, regular clinic appointments and hospitalisations can result in children and young people missing school, therefore potentially disrupting both their education and peer relationships.10 These challenges can be exacerbated by physical symptoms resulting from the LLC itself or associated treatment regimens, either through side effects such as fatigue caused by medication or direct biochemical changes which have been proposed to be linked to the onset of depression in some patients.11,12 Children, adolescents, and young adults with LLCs may also have fears surrounding the unpredictability of their future, including the fear of death, often making patients unsure if they will be able to achieve future hopes and aspirations.13

The prevalence of LLCs in England rose from 25 per 10,000 in 2000/2001 to 32 per 10,000 in 2009/2010, with the largest increase in prevalence occurring in young people between the ages of 16-19 years, which likely represents an increase in survival.14 As chronic physical illness has been found to be associated with an increased risk of mental health problems, the increased prevalence of LLC among children and young people necessitates the development of services aimed at caring for their psychological needs. This has been recognised in England and Wales by the National Institute for Health and Care Excellence (NICE) 2016 guidelines regarding end of life care for infants, children and young people with life-limiting conditions, which highlight the need for research into the range, severity and context of psychological difficulties among children and young people with LLCs in order for the subsequent design of effective interventions.15 Therefore, it is crucial that research analysing the epidemiology of anxiety and depression is systematically reviewed in order to guide future research and clinical guidance. Consequently, this systematic review and meta-analysis aims to estimate the prevalence and incidence of anxiety and depression in children and young people (aged 5-25 years) with a range of LLCs.

**Methods**

The systematic review and meta-analysis was conducted according to a review protocol registered on PROSPERO prior to review initiation.16

**Search Strategy**

EMBASE, MEDLINE and PsychINFO were searched on 15th January 2018, identifying papers published from 1st January 2000. The search consisted of the following concepts: (children/adolescents/young adults) AND (anxiety/depression) AND (life-limiting conditions), including a full list of all LLC diagnoses, using both subject headings and free text (see eTable 1 in Supplement for MEDLINE search strategy).17 Reference lists of identified systematic reviews and all included articles were searched for additional eligible papers. Grey literature was reviewed using an advanced Google search, with the first 50 PDFs screened for eligibility.

Studies were included if (1) they provided primary data of anxiety or depression prevalence or incidence, measured using validated assessment tools or coded medical report data, (2) participants were between the ages of 5-25 years, (3) participants had been diagnosed with a LLC, (4) the study was published in English or subsequently translated into English, (5) the study was conducted in a country within the Organisation for Economic Co-operation and Development (OECD). The following types of study designs were excluded (1) case studies, case series, intervention studies, qualitative studies, systematic reviews, and abstracts (2) studies which included non-LLC diagnoses and did not report data separately (3) studies of participants successfully treated for cancer.

**Study Selection**

Titles and abstracts of all studies were screened by the primary reviewer (MMB), with 20% also independently screened by a second reviewer (LR). Any discrepancies were resolved through discussion. Full texts of all studies deemed potentially eligible were retrieved and reviewed for eligibility by MMB, with LR also independently reviewing 20%. For papers where key data was missing, study authors were contacted. In the case of authors not replying to this request, the paper was not included. Studies investigating the prevalence of anxiety or depression among children and young people with DiGeorge Syndrome were excluded at this stage as mental health problems are a component of this condition

**Data Extraction**

Data was extracted by MMB, using an extraction form piloted on three eligible studies. Key study characteristics including country of study, study design, recruitment and eligibility criteria, anxiety/depression assessment tool, age and sex were extracted. The number of participants identified by the study as being anxious or depressed was recorded along with the study sample size, in order for the calculation of prevalence. For the calculation of incidence, the number of new cases identified, and the person-time used was extracted.

**Risk of Bias Assessment**

In response to the fact that included studies only reported prevalence, the protocol was amended to use a tool specifically designed to assess bias in prevalence studies18. The chosen tool consists of ten questions, which are scored positively or negatively, and according to the total score each study is characterised as being at low, moderate or high risk of bias. Any studies deemed to be at high risk of bias were excluded from the meta-analysis.

**Statistical Analysis**

STATA version 15.1 (College Station, TX, USA) was used to generate meta-analyses for anxiety and depression prevalence. Random effects meta-analyses were used due to high expected heterogeneity between studies. To stabilise variances, study data was first transformed using the double arcsine transformation.19 Study-specific confidence intervals were generated using the exact method. Heterogeneity was analysed using the I2 statistic. Heterogeneity was first explored through sub-group analysis, using the following categorical study characteristics:

* LLC diagnostic group (cancer; cystic fibrosis (CF); HIV; thalassemia; neurological conditions; chronic kidney disease (CKD))
* Study location (Europe; USA)
* Assessment tool (self-/parent-report questionnaire; diagnostic interview)
* Risk of bias (low; moderate)

Univariate meta-regression models were then conducted to assess the association between study characteristics and the pooled prevalence estimate. Models were generated for each of the aforementioned categorical study characteristics, in addition to the following quantitative study characteristics:

* Sample size
* Mean age
* Percentage of female participants in the sample

Publication bias was assessed using funnel plots and Egger’s test of bias. A significance level of *p*<0.05 was used throughout.

**Results**

The electronic search identified 14,866 non-duplicate articles, as shown in the PRISMA flow diagram (Figure 1). The full texts of 709 articles were retrieved and assessed for eligibility, resulting in the inclusion of 37 studies. Of the included articles, 19 reported anxiety prevalence, and 36 reported depression prevalence. None reported the incidence of anxiety or depression.

**Study Characteristics**

The key characteristics of the 37 included studies are summarised in Table 1. A total of 6,042 participants were included. Study sample sizes ranged from 20-2,032 participants, with a median of 50 participants (Interquartile Range (IQR): 38-96). The age range of participants was reported in 30 studies, and ranged from 6-25 years. The mean participant age from the 24 studies providing this information was 15.4 years. The proportion of females in the study sample was reported in 32 studies, with a mean of 51.5%.

A total of 18 studies (48.6%) were from the USA, and 15 (40.5%) were from Europe. In addition, one study was from Canada, one study was from Mexico, and two studies (5.4%) were multi-national; one in European countries and the USA and one in European countries only.

Of the 37 included studies, six (16.2%) assessed children, adolescents, and young adults with cancer, eight (21.6%) included children, adolescents, and young adults with CF and a further nine studies (24.3%) assessed children, adolescents, and young adults with HIV. Children, adolescents, and young adults with thalassemia were included in four studies (10.8%), whilst seven (18.9%) assessed children, adolescents, and young adults with neurological conditions, and three (8.1%) included children, adolescents, and young adults with CKD.

**Risk of Bias Assessment**

No studies were deemed to be at high risk of bias, 14 studies (37.8%) were at moderate risk of bias, and 23 studies (62.2%) were at low risk of bias. Only one study scored positively to the question regarding minimising the likelihood of non-response bias (eTable 2 in Supplement).11

**Anxiety & Depression Assessment Tools**

A total of 10 different assessment tools were used to measure the prevalence of anxiety, whilst 15 different assessment tools were used to assess depression prevalence (eTable 3 in Supplement). The most common assessment tool for measuring anxiety was the anxiety sub-scale of the Hospital Anxiety and Depression Scale (HADS), which was used in 7/19 studies, whereas the Children’s Depression Inventory (CDI) was the most common depression assessment tool, having been used in 9/36 studies. Parent-report measures were used in three studies20–22.

**Prevalence of Anxiety**

The prevalence of anxiety was reported in 19 studies, with a total of 4,547 participants. Anxiety prevalence ranged from 3.6% (95% Confidence Interval (CI) 0.4%-12.5%) to 58.3% (95% CI: 36.6%-77.9%). The pooled anxiety prevalence estimate from the random-effects meta-analysis was 19.1% (95% CI:14.1%-24.6%). The level of heterogeneity in the analysis was high (I2=92.2%, *p*<0.001) (Figure 2). Although visual inspection of the funnel plot asymmetry suggests the presence of publication bias, with fewer small studies reporting high anxiety prevalence, this was not found to be significant by Egger’s test of bias (*p*=0.406) (eFigure 1 in Supplement).

Sub-group analysis revealed differences in anxiety prevalence by diagnostic group (Figure 2). Children, adolescents, and young adults with thalassemia were reported to have the highest pooled anxiety prevalence estimate (29.4%, 95% CI: 8.8%-55.3%), followed by children, adolescents, and young adults with CF (22.8% 95% CI: 17.1%-29.1%). The lowest pooled anxiety prevalence estimate was found for children, adolescents, and young adults with neurological conditions (8.7%, 95% CI: 4.4%-14.3%). Pooled anxiety prevalence was also found to differ by study location; studies conducted in the USA were found to report a higher prevalence (20.8%, 95% CI:11.3%-32.1%) than European studies (17.2%, 95% CI: 9.9%-26.0%). Differences in pooled anxiety prevalence were also found by assessment tool, with a lower prevalence reported from studies using self-/parent-report questionnaires (14.9%, 95% CI: 10.9%-19.4%) compared to studies utilising diagnostic interviews (28.5%, 95% CI: 13.2%-46.8%). Finally, prevalence varied by the risk of bias; studies at moderate risk of bias reported a higher prevalence (23.1%, 95% CI: 7.8%-43.0%), compared to studies at low risk of bias (18.2%, 95% CI: 12.8%-24.3%) (eTable 4 in Supplement). However, meta-regression analysis showed that only the differences by assessment tool were statistically significant (β=0.15, 95% CI: 0.01-0.30, *p=*0.04). Prevalence was not significantly associated with sample size, mean age or percentage of females in the sample (eTable 5 in Supplement).

**Prevalence of Depression**

The prevalence of depression was reported in 36 studies, with a total of 5,934 participants. Depression prevalence ranged from 0.0% (95% CI: 0.0%-0.7%) to 50.0% (95% CI: 34.9%-65.1%). The pooled depression prevalence estimate from the random-effects meta-analysis was 14.3% (95% CI: 10.4%-18.6%). Substantial heterogeneity was found in the analysis (I2=93.3%, *p*<0.001) (Figure 2). Although visual inspection of the funnel plot for the depression meta-analysis suggested some publication bias due to a lack of published studies with large standard errors reporting high depression prevalence, this was not found to be statistically significant by Egger’s test of bias (*p*=0.87) (eFigure 2 in Supplement).

Sub-group analysis found that the pooled prevalence of depression differed by diagnostic group. Children, adolescents, and young adults with HIV reported the highest pooled depression prevalence (24.2%, 95% CI: 15.4%-34.2%), whilst those with neurological conditions had the lowest prevalence (7.0%, 95% CI: 1.7%-15.0%). US studies reported higher depression prevalence (18.8%, 95% CI: 12.6%-25.8%) compared to European studies (9.5%, 95% CI: 5.0%-15.1%). Differences in pooled depression prevalence were also found by assessment tool; studies that used self-/parent-report measures had a higher pooled prevalence (15.4%, 95% CI: 11.0%-20.4%) than studies using diagnostic interviews (10.5%, 95% CI: 4.0%-19.3%). Variations in depression prevalence according to the risk of bias assigned to the study were very small; studies at moderate risk of bias reported a slightly higher prevalence (14.8%, 95% CI: 6.7%-25.0%) compared to studies at low risk of bias (14.2%, 95% CI: 9.7%-19.4%) (eTable 6 in Supplement). Meta-regression analysis found only sample mean age (β=0.02, 95% CI: 0.01-0.03, *p*=0.001) to be significantly associated with pooled depression prevalence (eTable 7 in Supplement).

**Discussion**

**Key Findings**

When compared to available data from the general population, this meta-analysis of 37 studies indicates a higher prevalence of anxiety and depression in children, adolescents, and young adults with LLCs compared to the general population. The pooled anxiety prevalence estimate of 19.1% observed in this analysis is over six times higher than the prevalence of anxiety among the general population of young people in the US, 3%, and more than double the anxiety prevalence of children and young people in the UK, 7.2%.2,23 The observed prevalence of depression among children, adolescents, and young adults with LLCs was 14.3%, also higher than the range of depression prevalence estimates found for young people in the US and the UK; 2.1%-8.1%.2,23

Interestingly, the prevalence of anxiety and depression was found to vary by LLC diagnostic group. The highest pooled anxiety prevalence estimate (29.4%) was found for children, adolescents, and young adults with thalassemia, whereas those with HIV reported the highest pooled prevalence of depression (24.2%). Overall, these findings support the literature describing the challenges of living with a LLC and highlight the fact that recognition of, and provision for, psychological needs should be a core aspect of the care and support offered to this population.8,24

It was also observed that anxiety and depression prevalence estimates were modified by the type of assessment tool used, with diagnostic interviews resulting in higher anxiety prevalence. Differences in anxiety prevalence by the type of assessment tool used have been shown in previous studies, for example a systematic review of anxiety prevalence in children and adolescents with autistic spectrum disorders.25 Conversely, higher depression prevalence was associated with the use of self-/parent-report questionnaires, a finding previously reported by a systematic review of the prevalence of depression among adults with CKD.26 These findings may be partially accounted for by the diagnostic groups studied. For example, over half of the studies using diagnostic interviews concerned children, adolescents, and young adults with thalassemia and the pooled anxiety prevalence for this group was very high, whereas in the case of depression, the highest pooled prevalence was found for HIV studies, most of which used self-/parent-report measures.

Finally, age was identified by the meta-regression analysis to be significantly associated with depression prevalence. This trend is consistent to that found among young people with anxiety or depression both in the US and the UK.2,23 Although sex was not found to be associated with depression prevalence and neither sex nor age were associated with anxiety prevalence, these findings should be treated with particular caution given that many studies could not be included in the meta-regression model due to lack of reporting of age and sex data.

**Strengths & Limitations**

This review has a number of strengths. Firstly, this is the first systematic review and meta-analysis of anxiety and depression prevalence among children, adolescents, and young adults with LLCs to have been conducted. Given that there are increasing numbers of children, adolescents, and young adults living with LLCs, and recent calls have been made to recognise and address the mental health needs of this population, a comprehensive picture of existing evidence of the prevalence of depression and anxiety across this population is extremely valuable. Secondly, the comprehensenive search stratgy utilised in this review resulted in the inclusion of a total of 37 studies in the meta-analyses, from more than ten countries, covering five LLC diagnostic groups. This improves the robustness of the pooled prevalence estimates, offering a more accurate description of the epidemiology of anxiety and depression in this patient group than is afforded by single studies.

However, weaknesses in the review methadology must be noted. Firstly, only studies written in English were eligible for inclusion, limiting the generalisability of the prevalence estimates. This review is also limited by the available dataset. As such, the coverage of LLCs is far from exhaustive. Importantly, of the 6,042 participants included in the review, only 342 (5.7%) had neurological conditions, yet over 8% of children and adolescents with a LLC in England have a neurological diagnosis. 14 Importantly, intellectual disability, which brings an increased risk of mental health problems, is a common co-morbidity among this group.27 However, the identification of mental health problems or emotional distress in young people with intellectual disability can be complex due to communication limitations.28 Whilst greater efforts should be made to improve accessibility and suitability of self-/parent-report measures, for some individuals, the detection of emotional distress will rely on methods such as the interpretation of non-verbal behaviours, utterances and physiological responses.28

There are also some broader limitations in terms of the characteristics of the included studies. Firstly, many studies had very small sample sizes. When combined with the relatively narrow range of LLCs represented, this limits the ability of any analysis to produce results that are representative of the population. Additionally, this makes it more difficult to compare results with general population data. Secondly, there was poor reporting of key study data, such as the age and sex of study participants. For example, only 15 (78.9%) of the included studies reporting anxiety prevalence and 24 (66.7%) of the studies reporting depression prevalence provided the mean age of the sample, This greatly reduced the number of studies that could be included in the meta-regression models. Finally, as no studies reported longitudinal data, the incidence of anxiety and depression in children, adolescents, and young adults with LLCs could not be assessed.

**Implications and future research**

Despite these limitations, the findings have a number of key implications. Importantly, they support the argument for routine screening for mental health problems as part of the development of psychosocial standards of care.29 This would both assist the systematic identification of patients at risk of mental health problems, and the instigation of preventative steps, and identify those needing support and treatment. Data from routine screening would also be valuable evidence for those making the case for increasing the resources available for mental health and psychosocial care provision within their services.

There has already been some progress on this issue. For example, annual screening for mental health problems in cystic fibrosis patients was recommended in the European consensus on standards of care.30 However, in order for this to be performed effectively, screening tools must first be validated in children, adolescents, and young adults with LLCs, as currently the majority of anxiety and depression measurement tools have only been validated in the general population.31

In addition to work on the psychometric properties of screening instruments, two further areas of research are required. First, more large-scale studies are needed, including a broader range of LLCs, in order to consolidate existing evidence and further understand differences in the prevalence of mental health problems between different LLCs. In order for the effect of age and sex to be adequately assessed in future studies, results should be reported by sex and age band. Second, longitudinal studies are required in order to develop our understanding of the temporal associations between the diagnosis of a LLC, its trajectory, and the onset of mental health problems, whilst also allowing for an exploration of factors which increase the risk of anxiety or depression onset.

**Conclusions**

Anxiety and depression are common mental health problems among children, adolescents, and young adults with LLCs, calling for the implementation of routine screening to identify both those at risk of mental health problems and those requiring treatment. However, in order to further understand the epidemiology of anxiety and depression in this patient population larger longitudinal studies must be conducted in a wider range of life-limiting conditions, including children with neurological conditions and cognitive impairment.

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**Figure 1: PRISMA Flow Diagram**

Legend: PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Figure 2: Forest plot of pooled anxiety prevalence, grouped by LLC diagnostic group**

Legend: Forest plot of 19 studies included in the meta-analysis of anxiety prevalence. The pooled anxiety prevalence from the meta-analysis was 19.1% (95% CI:14.1%-24.6%).

**Figure 3: Forest plot of pooled depression prevalence, grouped by LLC diagnostic group**

Legend: Forest plot of 36 studies included in the meta-analysis of depression prevalence. The pooled depression prevalence from the meta-analysis was 14.3% (95% CI: 10.4%-18.6%)

**Table 1: Key characteristics of the 38 included studies**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author & Publication Date** | **Location** | **Sample Size** | **Age Range, years (Mean ±SD)** | **No. of Females/Sample Size (%)** | **Year of Data Collection** | **Anxiety Prevalence** | **Depression Prevalence** | **Risk of Bias** |
| **Cancer** | | | | | | | | |
| Hedstrom et al. (2005)11 | Sweden | 56 | 13-19 | 24/56 (43) | 1999-2003 | ✓ | ✓ | Low |
| Matziou et al. (2008)32 | Greece | 80 | 6-16 (11.2) | 35/80 (44) | 2002-2005 | 🗶 | ✓ | Low |
| Kersun et al. (2009)33 | USA | 41 | 12-19 (15.22±2.19) | 18/41 (44) | NR | ✓ | ✓ | Low |
| Durualp & Altay (2012)34 | Turkey | 20 | 6-12 | 10/20 (50) | 2010-2011 | 🗶 | ✓ | Moderate |
| Bemis et al. (2015)35 | USA | 151 | 10-17 (13.5±2.4) | 77/151 (51) | NR | 🗶 | ✓ | Moderate |
| Rivas-Molina et al. (2015) 36 | Mexico | 46 | 7-15 | 14/46 (30) | 2012 | 🗶 | ✓ | Moderate |
| **Cystic Fibrosis** | | | | | | | | |
| Casier et al. (2008)37 | Belgium | 34 | (17.31±3.05) | 18/34 (53) | NR | ✓ | ✓ | Low |
| White et al. (2009)38 | USA | 53 | 9-17 (12.4±2.57) | 31/53 (58) | 1995-1996 | ✓ | ✓ | Moderate |
| Smith et al. (2010)39 | USA | 39 | 7-17 (12.0±3.1) | 20/39 (51) | NR | 🗶 | ✓ | Low |
| Casier et al. (2011)40 | Belgium | 40 | (18.40±2.87) | 17/40 (43) | NR | ✓ | ✓ | Low |
| Modi et al. (2011)41 | USA | 59 | (15.77±2.5) | 27/59 (46) | 2006-2008 | ✓ | ✓ | Low |
| Oliver et al. (2014)42 | USA | 72 | 14-25 (19.1±3.3) | 36/72 (50) | 2010-2011 | ✓ | ✓ | Low |
| Quittner et al. (2014)43 | Multi-national (Europe & USA) | 1286 | (14.84±1.69) | 669/1286 (52) | NR | ✓ | ✓ | Low |
| Askew et al. (2017)44 | UK | 45 | 17-24 (20.7) | 18/45 (40) | NR | ✓ | ✓ | Low |
| **HIV** | | | | | | | | |
| Pao et al. (2000)45 | USA | 34 | 16-21 (18.5) | 27/34 (79) | NR | 🗶 | ✓ | Moderate |
| Murphy et al. (2001)46 | USA | 213 | 12-18 | NR | 1999-2000 | 🗶 | ✓ | Low |
| Elliott-DeSorbo et al. (2009) 47 | USA | 55 | 8-17 (12.9) | 25/55 (45) | 2001-2005 | ✓ | ✓ | Low |
| Mellins et al. (2009)22 | USA | 206 | (12.3±2.2) | 105/206 (51) | NR | ✓ | ✓ | Low |
| Andrinopoulos et al. (2011)48 | USA | 166 | 15-24 | 166/166 (100) | 2003-2005 | 🗶 | ✓ | Low |
| Martinez et al. (2012) 49 | USA | 60 | 15-24 (20.6±2.0) | 60/60 (100) | 2003-2005 | 🗶 | ✓ | Low |
| Nachman et al. (2012)50 | USA | 313 | 6-17 | NR | 2007 | ✓ | ✓ | Low |
| Salama et al. (2013)51 | USA | 59 | 14-23 (18.8) | 36/59 (61) | 2002-2003 | 🗶 | ✓ | Low |
| Brown et al. (2015)52 | USA | 2032 | (20.25±2.14) | 662/2032 (33) | 2009-2012 | ✓ | ✓ | Low |
| **Thalassemia** | | | | | | | | |
| Sadowski et al (2002)53 | Multi-national (Europe) | 38 | 6-18 | NR | 1994-1996 | ✓ | ✓ | Low |
| Aydinok et al. (2005)54 | Turkey | 38 | 6-18 (12.2±3.3) | 20/38 (53) | NR | ✓ | ✓ | Moderate |
| Cakaloz et al. (2009)55 | Turkey | 20 | 7-18 (11.1±3.02) | 13/20 (65) | NR | ✓ | ✓ | Moderate |
| Adanir et al. (2017)56 | Turkey | 24 | 12-18 (13.64±2.11) | 11/24 (46) | NR | ✓ | ✓ | Moderate |
| **Author & Publication Date** | **Location** | **Sample Size** | **Age Range, years (Mean ±SD)** | **% Female** | **Year of Data Collection** | **Anxiety Prevalence** | **Depression Prevalence** | **Risk of Bias** |
| **Neurological Conditions** | | | | | | | | |
| Laufersweiler-Plass et al. (2003)20 | Germany | 96 | 6-18 (11.17) | 49/96 (51) | NR | ✓ | ✓ | Moderate |
| Backman et al. (2005)57 | Finland | 27 | 9-21 | 14/27 (52) | NR | 🗶 | ✓ | Moderate |
| Amato et al. (2008)58 | Italy | 63 | 8-17 (15.3±2.5) | 33/63 (52) | NR | 🗶 | ✓ | Low |
| Amato et al. (2010)59 | Italy | 39 | 12-20 | NR | NR | ✓ | 🗶 | Low |
| Till et al. (2012)21 | Canada | 31 | 12-19 (16.1) | 23/31 (74) | NR | 🗶 | ✓ | Moderate |
| Elsenbruch et al. (2013)60 | Germany | 50 | 8-23 (15.4±0.6) | 0/50 (0) | 2009-2011 | 🗶 | ✓ | Moderate |
| Parrish et al. (2013)61 | USA | 36 | NR | NR | NR | 🗶 | ✓ | Moderate |
| **Chronic Kidney Disease** | | | | | | | | |
| Kogon et al. (2013)62 | USA | 44 | 7-18 | 13/44 (30) | 2011-2012 | 🗶 | ✓ | Moderate |
| Kogon et al.(2016)63 | USA | 344 | 6-17 | 142/344 (41) | 2005-2008 | 🗶 | ✓ | Low |
| Kilicoglu et al. (2016)64 | Turkey | 32 | 8-18 | 19/32 (59) | 2014 | 🗶 | ✓ | Low |