

Childhood chronic physical illness and adult emotional health: a systematic review and meta-analysis

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Abstract

Background: Childhood chronic physical illness is associated with a greater vulnerability for emotional problems (i.e., depression and anxiety) in childhood. However, little is known about life-long effects of childhood chronic physical illness on mental health. The present study aims to systematically review evidence for associations between eight chronic physical illnesses with childhood onset (arthritis, asthma, cancer, chronic renal failure, congenital heart disease, cystic fibrosis, type 1 diabetes, and epilepsy) and adult emotional problems.

Methods: A database search of MEDLINE, PsycARTICLES, PsycINFO, and ScienceDirect was undertaken, and random effects meta-analyses were used to synthesize evidence from eligible studies.

Results: In total, 37 studies were eligible for the systematic review ($n = 45,733$) and of these, 34 studies were included into the meta-analyses ($n = 45,358$). There were overall associations between childhood chronic physical illness and adult depression (OR = 1.31; 95% CI [1.12, 1.54]) and anxiety (OR = 1.47; 95% CI [1.13, 1.92]). Separate meta-analyses for childhood asthma, type 1 diabetes and cancer were also conducted, with cancer being significantly associated with adult depression (OR = 1.19; 95% CI [1.00, 1.42]).

Conclusions: The effects of childhood chronic physical illness on the risk of emotional problems persist beyond childhood and adolescence. Mental health prevention and intervention strategies targeting children with chronic physical illnesses can have long-term benefits.

Childhood chronic physical illness is defined as a health problem lasting three months or more, affecting the child's normal activities, resulting in functional limitations, dependencies or the need for hospitalization or health care (Stein, Bauman, Westbrook, Coupey, & Ireys, 1993). This refers to a wide range of disorders, including highly prevalent conditions with serious disabling consequences, such as arthritis, asthma, cancer, chronic renal failure, congenital heart disease, cystic fibrosis, type 1 diabetes, and epilepsy. In the past four decades, with advances of medical therapies, nearly 20% of children and adolescents with chronic physical illnesses live for a long time (Perrin, Bloom, & Gortmaker, 2007; van der Lee, Mokkink, Grootenhuis, Heymans, & Offringa, 2007). This highlights the increasing need for investigations into effects of these conditions on life-long mental health and wellbeing.

Recent meta-analyses indicate that children with chronic physical illnesses have greater vulnerability to psychosocial problems in childhood and adolescence (Pinquart & Shen, 2011b, 2011c). These children face significant challenges due to their physical conditions which might disrupt their psychological well-being (Ferro, Boyle, & Avison, 2015). Psychological problems in childhood are known to be precursors to poor mental health in adulthood, and previous research has suggested that, as children with chronic physical illnesses grow older, their psychosocial problems may either decrease, or persist and become more severe with time (Huurre & Aro, 2002; Pless, Power, & Peckham, 1993). However, there is limited evidence for the link between different childhood chronic physical illnesses and common mental health problems in adulthood. To our knowledge, the only one, non-systematic, review on this subject was conducted more than 15 years ago (Gledhill, Rangel, & Garralda, 2000). This review showed mixed evidence for the risk of adult mental health problems across different types of childhood chronic physical illness. A comprehensive systematic review of associations between childhood chronic physical illness and adult emotional problems is an important step for developing more targeted and effective preventive intervention strategies. The present paper aims to systematically review and analyze the evidence from studies investigating the effects of different types of childhood chronic physical illness that are

highly prevalent (such as arthritis, asthma, cancer, congenital heart disease, cystic fibrosis, type-1 diabetes, and epilepsy) and/or understudied (such as arthritis and chronic renal failure), on adult emotional problems (i.e., depression, anxiety).

Method

Search Strategy

This review was conducted in accordance with the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000). A systematic database search including titles and abstracts from January 1980 to July 2016 was performed using PsycINFO, PsycARTICLES, MEDLINE (National Library of Medicine), and ScienceDirect (Elsevier) databases. The following search terms were used: (*“chronic illness”* OR *“chronic disease”* OR *“chronic disability”* OR *“chronic physical illness”* OR *“arthritis”* OR *“asthma”* OR *“cancer”* OR *“cystic fibrosis”* OR *“diabetes”* OR *“epilepsy”* OR *“rheumatism”* OR *“congenital heart disease”* OR *“chronic renal failure”*) combined with age related search terms (i.e., *“child*”* OR *“adolesc*”* OR *“pediatr*”* OR *“youth”*) and psychosocial outcome related search terms (i.e., *“depress*”* OR *“anxi*”* OR *“fear”* OR *“panic”* OR *“mental health”* OR *“psychological health”*) combined with (*“adult*”* OR *“adolesc*”*) using the Boolean operator “AND”. Pilot searches were conducted in order to test the sensitivity and specificity of the search terms. Reference lists and citations of eligible articles were examined for identification of any eligible study not previously located through the database search.

Inclusion and Exclusion Criteria

Original studies published in English in peer-reviewed journals were included. Review papers, book chapters, conference proceedings and dissertations were excluded. Studies were included if they used longitudinal prospective, cross-sectional, or case-control designs. Case reports and studies without valid control groups were excluded. From studies with overlapping samples, the most relevant and/or recent study was selected.

Measures of childhood chronic physical included self-reports, parental reports and medical reports; with first illness diagnosis or measurement before the age of 16. Eight chronic physical illnesses with childhood onset were included: arthritis (i.e., rheumatism or rheumatoid arthritis), asthma, cancer, chronic renal failure, congenital heart disease, cystic fibrosis, type 1 diabetes, and epilepsy. Intellectual disability and neurodevelopmental disorders were excluded from the list of childhood chronic physical illnesses, because our primary aim was to explore the effects of chronic physical conditions. If intellectual disability/neurodevelopmental disorder was reported in addition to chronic physical illness, this study would have been included, however no such studies were identified. Studies with participants who were symptomatic, asymptomatic, in remission, or cured of childhood chronic physical illness at the time of study were considered eligible.

Both diagnostic as well as dimensional measures of depression, anxiety, and unspecified emotional problems, reported after the age of 16 were considered eligible. The age 16 was used as a threshold for the onset of the childhood chronic physical illness; and in order to be as inclusive as possible we set up the age above 16 as a threshold for inclusion of later mental health problems. Diagnostic outcomes included: unipolar depressive episode, major depression, generalized anxiety disorder, panic disorder, phobias, social anxiety disorder, post-traumatic stress disorder, obsessive-compulsive disorder, or health anxiety based on Diagnostic and Statistical Manual of Mental Disorders, Research Diagnostic Criteria, International Classification of Diseases, or other psychiatric or psychological evaluations. Dimensional outcomes of depression, anxiety or unspecified emotional symptoms on standardized scales were also eligible. Participants were excluded if they had other mental health problems (e.g., schizophrenia, bipolar disorder, learning disability, substance abuse) in addition to depression and/or anxiety.

Eligibility criteria were applied during two phases: 1) title and abstract screening, and 2) full text screening. A second independent evaluator screened 10% of the title and abstracts, and 10% of full texts. Any discrepancies were resolved during consensus meetings.

Data Extraction

A coding form was created to record each study's key information. Effect sizes for depression, anxiety and unspecified emotional symptoms were coded individually. The quality of each study was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Elm et al., 2007).

Data Synthesis and Statistical Analyses

Analyses were conducted using the *metafor* package for R (v.3.2). Odds ratios (ORs) were estimated from available descriptive statistics using standard computational techniques for dichotomous and continuous data (Borenstein, Hedges, Higgins, & Rothstein, 2009; Field & Gillett, 2010) when not reported in the original studies. Log ORs were computed for the meta-analyses. Random-effects meta-analyses were performed separately for each outcome (i.e., depression, anxiety, and unspecified emotional symptoms). First, associations with specific chronic physical illnesses were tested. Then, the overall association with any type of childhood chronic physical illness was investigated. Heterogeneity of effect sizes was tested using the Cochrane Q and I^2 statistics to examine and quantify the amount of observed variance accounted for by true heterogeneity rather than sampling error (Higgins, Thompson, Deeks, & Altman, 2003). Summary statistics of log ORs and their 95% confidence intervals (CIs) were exponentiated to allow ease of interpretation.

Effects of possible moderators, such as age at diagnosis of childhood chronic physical illness, duration of illness, time elapsed between the onset of the childhood illness and adult mental health, type of measure of childhood chronic physical illness (medical record versus self-report), type of sample (community versus clinical), and age and sex of participants were also investigated with meta-regression analyses.

To determine if publication bias was present, Begg's funnel plot, Egger's test of asymmetry, and trim-and-fill adjustment methods were used.

Results

The search identified 3,170 sources. After exclusion of duplicates, book chapters and dissertations, 2,495 titles and abstracts were extracted for screening. At phase one, 2,495 papers were screened and 161 papers were selected for full-text screening. There was 95% inter-rater agreement ($k = .73$, 95% CI [0.66, 0.80], $p < .001$). At phase two, additional 18 articles were identified from the reference lists, resulting in 179 full texts for screening. There was 89% inter-rater agreement ($k = .68$, 95% CI [0.48, 0.88], $p = .002$). The disagreements were resolved during a number of consensus meetings.

Figure 1 here

A total of 37 studies were identified as eligible for the systematic review (Table 1): asthma ($k = 6$), cancer ($k = 18$), congenital heart disease ($k = 3$), cystic fibrosis ($k = 2$), diabetes ($k = 8$), epilepsy ($k = 4$), and rheumatoid arthritis ($k = 1$). No eligible studies of chronic renal failure were found.

Table 1 here

Of the 37 studies identified, three had insufficient information to calculate effect sizes (Baca, Vickrey, Vassar, & Berg, 2015; Eddington, Mullins, Fedele, Ryan, & Junghans, 2010; Tluczek et al., 2014). Therefore, 34 studies ($n = 45,358$) were used for the meta-analyses. In several studies, effect sizes were reported individually for each sex, age group, chronic illness, mental health outcome, resulting in 48 effect sizes in total, including 33 effect sizes for depression (Figure 2), 25 - for anxiety (Figure 3), and 26 - for unspecified emotional problems (Figure 4).

Of the 16 studies that reported the associations between childhood chronic physical illness and anxiety, ten studies used a general (unspecified) measure of anxiety (Alwash, Hussein, &

Matloub, 2000; Baldin et al., 2015; Ferro, Boyle & Avison, 2015; Gianinazzi et al., 2013; Kremer et al., 2016; Ly et al., 2011; Michel et al., 2010; Muller, Hess, & Hager, 2013; Servitzoglu et al., 2008; Zeltzer et al., 2008), and three studies focused on Post-Traumatic Stress Disorder (PTSD) (Brown, Madan-Swain, & Lambert, 2003; Kamibeppu et al., 2010; Schwartz & Drotar, 2006). Two studies reported the associations between childhood chronic illness and PTSD as well as general anxiety (Kazak et al., 2010; Seitz et al., 2010). One study explored the association between childhood chronic illness and Obsessive Compulsive Disorder (OCD) as well as general anxiety (Sivertsen et al., 2014).

Associations with specific types of childhood chronic physical illnesses

Asthma

A total of 2,975 participants with childhood asthma ($M_{age} = 19.9$) and 9,655 physically healthy controls ($M_{age} = 20.1$) took part in six studies. A meta-analysis of the four studies that measured depression (Chaney et al., 1999; Chen et al., 2014; Ferro et al., 2016; Kokkonen, 2001) showed that adults with childhood asthma did not have a higher risk of depression as compared to controls (OR = 1.64; 95% CI [0.82, 3.28]). Two studies measured emotional symptoms using the mental component of a health related quality of life scale and reported lower risk of emotional symptoms for individuals without asthma (Eddington et al., 2010; Fedele et al., 2009). Only one study measured anxiety and reported no differences between participants with childhood asthma and controls (Ferro et al., 2016).

Cancer

A total of 13,094 participants with childhood cancer and 7,079 healthy controls were included across 18 studies (Brown, Madan-Swain, & Lambert, 2003; Gianinazzi et al., 2013; Gunn et al., 2013; Harila, Niinivirta, Winqvist, & Harila-Saari, 2011; Kamibeppu et al., 2010; Kazak et al., 2010; Kremer, Schieber, Metzler, Schuster, & Erim, 2016; Mackie, Hill, Kondryn, & McNally, 2000; Maunsell, Pogany, Barrera, Shaw, & Speechley, 2006; Michel, Rebholz, von der Weid, Bergstraesser, & Kuehni, 2010; Schwartz & Drotar, 2006; Seitz et al., 2010; Servitzoglou,

Papadatou, Tsiantis, & Vasilatou-Kosmidis, 2008; Stam, Grootenhuis, Caron, & Last, 2006; Sundberg et al., 2010; Teta et al., 1986; Zeltzer et al., 1997; Zeltzer et al., 2008). On average, cancer survivors were 28.8 years old, and controls were 26.3 years old, as reported in 17 studies. Cancer survivors' mean age at illness diagnosis was 8.5 years (computed from 15 studies). The mean time since illness diagnosis was reported in eleven studies, with an average of 22.0 years.

A meta-analysis of the 18 effect sizes showed that a history of childhood cancer was significantly associated with adult depression (OR = 1.19; 95% CI [1.00, 1.42]). A meta-analysis of 17 effect sizes indicated that a history of childhood cancer was not significantly associated with adult anxiety (OR = 1.35; 95% CI [0.97, 1.89]). A meta-analysis of 18 effect sizes indicated that a history of childhood cancer was not significantly associated with adult unspecified emotional symptoms (OR = 1.06; 95% CI [0.95, 1.19]).

Type 1 Diabetes

A total of 548 participants with diabetes and 10,379 healthy controls took part across eight studies (Blanz, Rensch-Riemann, Fritz-Sigmund, & Schmidt, 1993; Kokkonen, 2001; Kremer et al., 2016; Ly, Anderson, McNamara, Davis, & Jones, 2011; Northam, Lin, Finch, Werther, & Cameron, 2010; Palladino et al., 2013; Sivertsen, Petrie, Wilhelmsen-Langeland, & Hysing, 2014; Tebbi, Bromberg, Sills, Cukierman, & Piedmonte, 1990). On average, participants with diabetes were 20.4 years old and controls were 19.7 years old. The prospective studies followed the participants up to 12 years ($k = 3$). Three studies reported the age at diabetes diagnosis, with the mean of 7.6 years. Four studies reported mean time since the illness diagnosis, with an average of 9.0 years.

A meta-analysis did not find a significant association between childhood-onset diabetes and depression (OR = 1.36; 95% CI [0.80, 2.31]). Only three studies investigated anxiety, with two showing non-significant differences between individuals with childhood-onset diabetes and controls (Ly et al., 2011; Sivertsen et al., 2014), and only one indicating a higher level of anxiety for participants with childhood-onset diabetes (Kremer et al., 2016). Of the three studies that investigated unspecified symptoms, two showed that people with diabetes had higher symptom

levels compared to controls (Blanz et al., 1993; Tebbi et al., 1990), and one study found non-significant differences (Northam et al., 2010). Meta-analyses for these studies were not conducted.

Other childhood chronic physical illnesses

We were not able to perform separate meta-analyses for any other specific childhood illnesses because of insufficient number of studies ($k < 4$). For congenital heart disease, there were three samples, of which two were from the same study – therefore a separate-meta-analysis was not conducted. Below we present the narrative analyses for the studies included in the systematic literature review.

Congenital Heart Disease: A total of 999 participants with congenital heart disease ($M_{age} = 27.7$) and 229 healthy controls ($M_{age} = 25.4$) took part in three studies. One study focused on individuals who had undergone a Fontan corrective procedure, and reported that individuals with congenital heart disease had higher level of depression than healthy controls (Pike et al., 2012). However, other studies did not find significant association between congenital heart disease and depressive (Kokkonen, 2001), anxiety, or unspecified emotional symptoms (Muller, Hess, & Hager, 2013).

Cystic Fibrosis: A total of 141 participants (68 with cystic fibrosis and 73 healthy controls) took part in two studies (Blair, Cull, & Freeman, 1994; Tluczek et al., 2014). On average, participants with cystic fibrosis were 18.6 years old, and the healthy controls were 18.0 years old. Both studies investigated unspecified emotional symptoms and found non-significant association.

Epilepsy: A total of 528 participants with childhood-onset epilepsy and 440 physically healthy controls took part in four studies (Alwash, Hussein, & Matloub; Baca et al., 2015; Baldin, Hesdorffer, Caplan, & Berg, 2015; Kokkonen, 2001). Three studies reported the mean age of participants, as 22.36 for individuals with epilepsy and 22.5 for healthy controls. Two studies reported mean age at illness diagnosis as 7.6 years. One study reported that individuals with epilepsy had a significantly higher prevalence of depression and anxiety compared to controls (Alwash et al., 2000). Other studies found non-significant differences between individuals with and

without childhood epilepsy for depression (Kokkonen, 2001), anxiety (Baldin et al., 2015) and unspecified symptoms (Baca et al., 2015).

Rheumatoid Arthritis: One study of 35 participants with rheumatoid arthritis and 123 healthy controls found no association between rheumatoid arthritis and adult depression (Kokkonen, 2001).

Overall association with childhood chronic physical illness

A meta-analysis showed that, compared to those without a history of childhood chronic physical illness, adults with childhood chronic physical illness were more likely to have depression (Figure 2; OR = 1.31; 95% CI [1.12, 1.54]).

Figure 2 here

A significant overall association was also found for anxiety (Figure 3; OR = 1.47; 95% CI [1.13, 1.92]). Individual meta-analyses were performed to examine whether the type of anxiety affected the association with childhood chronic physical illness. A meta-analysis of the thirteen studies measuring general anxiety found a significant overall association (OR = 1.55; 95% CI [1.25, 1.92]), which was similar to the meta-analyses for any anxiety. A meta-analysis of the five studies measuring PTSD showed a similar trend for association with childhood chronic illness (OR=1.65; 95%CI [0.69, 3.96]), although the results did not reach the significance level. Yet, this finding should be interpreted with caution as the number of studies reporting PTSD is low.

Figure 3 here

For unspecified emotional problems, the association did not reach statistical significance (Figure 4; OR = 1.10; 95% CI [0.98, 1.24]).

Figure 4 here

Sensitivity Analyses

Significant heterogeneity was observed across the studies of depression ($Q = 84.7$, $df = 32$, $p < .001$, $I^2 = 65.3\%$); anxiety ($Q = 138.2$, $df = 24$, $p < .001$, $I^2 = 86.0\%$), and unspecified emotional symptoms ($Q = 41.5$, $df = 25$, $p = .020$, $I^2 = 40.7\%$). Meta-regression analyses showed that differences in mean age at the time of illness diagnosis did not explain the between-study variability for depression ($p = .50$), anxiety ($p = .32$), or unspecified emotional symptoms ($p = .44$). This was also the case for duration of illness ($p = .10$, $.44$, and $.17$, respectively); time elapsed between the onset of the childhood illness and adult mental health ($p = .91$, $.64$, and $.89$, respectively); type of sample ($p = .29$, $.69$, and $.08$, respectively); age of participants ($p = .66$, $.56$, and $.38$, respectively), and sex of participants ($p = .70$, $.24$, and $.29$, respectively).

Meta-regression analyses showed that differences in type of the source information about childhood chronic physical illness (medical records or self-report) had a significant effect on the between-study variability in depression ($b = -.55$, $SE = .28$, $p = .048$); studies using medical reports had lower effect sizes than studies using self-reports of childhood chronic illness. Sensitivity analyses were performed to examine whether the overall association between childhood chronic illness and depression remained significant when only studies using medical record were included. The results were similar to the original meta-analysis ($OR=1.25$; 95% CI [1.06, 1.46]). Differences in the type of the source information did not explain the between-study variability for anxiety ($p = .93$), or unspecified emotional problems ($p = .15$).

Meta-regression analyses including year of data collection as a moderator showed a significant effect on the between-study variability in anxiety ($b = -.07$, $SE = .01$, $p = .027$), such that more recent studies had significantly lower effect sizes than earlier studies. However, differences in

year of data collection did not explain the between-study variability for depression ($p = .80$), or unspecified emotional problems ($p = .23$).

Furthermore, sensitivity analyses were performed to examine whether the overall association between childhood chronic illness and adult emotional problems remained significant when cancer studies were excluded from the analysis. More than half of the studies (18 out of 34) included in the meta-analyses were cancer studies. By excluding these within the sensitivity analyses, we checked whether the results were not unduly affected by these studies. The results of the analyses without cancer studies were similar to the initial meta-analyses for depression (OR=1.48; 95%CI [1.09, 2.02]), anxiety (OR=1.75; 95%CI [1.13, 2.71]), and unspecified emotional problems (OR=1.31; 95%CI [0.93, 1.84]).

Finally, we have performed a sensitivity analysis for the quality of studies. Of the 37 studies reviewed to be included in the systematic review and meta-analysis, all achieved at least 60% on the STROBE checklist (with the maximum score of 82%, and the median score of 73%). Meta-regression analyses using the median score as a threshold for low/high quality studies did not explain the between-study variability for depression ($p = .78$), anxiety ($p = .07$), or unspecified emotional problems ($p = .91$).

Table 2 here

Publication bias

Potential publication bias was unlikely as Begg's rank correlation tests and Egger's regression tests were non-significant for all the meta-analyses (eFigure 1).

Discussion

The present systematic review and meta-analysis focused on long-term effects of eight childhood chronic physical illness on emotional problems. In line with a previous non-systematic review (Gledhill et al., 2000), our findings suggest that adults with childhood-onset chronic physical illnesses are more likely to experience emotional problems than those without. Although the identified effects are small, the considered illnesses have relatively high population prevalence; therefore, they have a high public health importance.

A possible explanation for our findings is that children with chronic physical illnesses have increased vulnerability for emotional problems during their childhood (Pinquart & Shen, 2011c) which may persist over time, and research suggests that emotional problems in childhood and adolescence precede and predict adulthood problems (Zahn-Waxler, Klimes-Dougan, & Slattery, 2000). For example, the psychological distress of going through an illness or treatment, such as feelings of loss of control over the body (Pinquart & Shen, 2011a), and maladaptive illness cognitions (Verhoof, Maurice-Stam, Heymans, Evers, & Grootenhuis, 2014), may contribute to the development of emotional problems in adulthood. Another possible explanation is that the illness symptoms or treatment methods these children endure may alter the brain development that can have long-term effects on their mental health. For example, it is known that alterations of the HPA-axis related to chronic physical illnesses (Purdy, 2013) may affect emotional health across the life course (Lupien, McEwen, Gunnar, & Heim, 2009).

Our findings indicated that factors related to childhood chronic illness, such as age at diagnosis and illness duration, and participant related factors, such as age and sex, did not moderate the associations between childhood chronic physical illness and adult emotional problems. However, these findings should be treated with caution since not all the studies provided sufficient information for all the moderation analyses. We did reveal that the cohort effect was of importance, so that more recent studies, of anxiety, in particular, reported lower effects than earlier ones. This could be related to more effective treatments and therapies available for children with chronic

physical illness in recent years. Another explanation could be the improved precision of measures of anxiety in more recent studies. However, meta-analyses for the specific types of anxiety disorders were limited to PTSD (five studies in total), and the results of this analysis were inconclusive.

With regards to specific childhood chronic physical illnesses, separate meta-analyses did not confirm that childhood-onset type 1 diabetes or asthma were significantly associated with emotional problems in later life. However, in line with previous research, our results indicated that childhood cancer contributed to an increased risk of adult depression. Possible explanations for the increased risk for depression could be that childhood cancer survivors can experience worsening physical health over time, as well as worsening pain and ending analgesic use. Their negative effects on psychological health have previously been reported in childhood cancer survivors (Brinkman et al., 2013). Taking into account the heterogeneity of cancer, it is possible that only some types of cancer or some treatments of cancer have significant long-term effects on emotional problems. For example, brain tumours, blood cancers, or radiation treatments can affect brain function in a way that influences emotionality. However due to insufficient information, we were unable to analyse the effects of different types of cancers and treatment methods.

Strengths and Limitations

To the best of our knowledge, this is the first study to systematically evaluate the associations between childhood chronic physical illness and adulthood emotional problems. The search that focused on eight chronic physical illnesses provided data from more than 40,000 participants from multiple regions across the world.

The results of the present review should be evaluated in the context of several limitations. First, there is a lack of studies evaluating the long-term psychological consequences of chronic physical illness. Indeed, most of the existing evidence is based on cross-sectional or case-control studies with retrospective measures, whereas population-based prospective longitudinal studies are still rare in this field. Only four of the studies included in our meta-analysis used prospective

longitudinal designs. Prospective longitudinal designs are preferred because they allow researchers to assess mental health prospectively, and to limit forgetting and recall bias.

Given the retrospective nature of designs of most of the studies, they did not allow us to control for childhood mental health diagnosis and/or treatment. It is possible that the associations between childhood chronic illness and mental health emerge in childhood and track to adulthood. Indeed, the majority of mental health problems have onset in early life, with 50% of individuals presenting symptoms by the age of 14 years (Kessler et al., 2007). However, many individuals with early onset affective symptoms do not develop recurrent problems, whereas others have repeated affective symptoms across the life course (Musliner, Munk-Olsen, Eaton, & Zandi, 2016).

Second, a few studies were available for separate analyses of various types of childhood chronic physical illness, such that individual meta-analyses were conducted only for asthma, cancer, and type 1 diabetes. Further, no studies of emotional problems among individuals with chronic renal failure were found. One possible reason for the limited information on this disease might be the historical absence of a common definition and classification of the illness.

Due to differences across illnesses and limited information provided by the studies, the analysis for illness severity was not conducted. The analyses conducted for other illness-related factors, such as the type of report of childhood illness, type of sample, and the time span between the onset of childhood chronic physical illness and adult mental health, did not reveal significant effects on the reported associations. However, not all the studies provided sufficient information; therefore, we might not have enough power to reveal significant effects.

Third, even though a quality assessment for each study and additional meta-regression analyses to control for the possible effect of study quality on the reported overall associations were conducted, unknown aspects of study quality might have influenced the results.

Fourth, the results might be constrained by the studies published in prior reports (i.e., the file drawer problem). Due to the time constraints, unpublished reports were excluded from analysis and since the studies that fail to report significant differences are less likely to be published in peer

reviewed journals, it is possible that the analysis overestimated the differences between people with childhood chronic physical illness and their healthy peers. Furthermore, some published studies were excluded as they either did not report sufficient details for analysis, did not have control conditions, or used test norms as controls. However, we found no evidence of publication bias in this review.

Implications and Directions for Future Research

Our findings have important implications for clinical care. They suggest that information about a history of childhood chronic physical illness might be used to identify individuals who are at risk of developing emotional problems. It will be important to explore individual disorders for further such risk assessments. Interventions aimed at improving psychological well-being and resilience in early life for children with chronic physical illnesses could help prevent the burden linked to emotional problems in adulthood.

In future, larger, well-controlled studies using samples of adults with a history of specific childhood chronic physical illnesses are needed. Prospective studies with control conditions are imperative since following children with and without chronic illnesses as they grow up may provide much needed causal information on the associations between emotional problems and childhood chronic illness. Existing studies have generally focused on young adults and the effects of chronic illness in older age groups remain unknown. Additional research to understand effects of various specific conditions (e.g., chronic renal failure, arthritis) is necessary. Finally, taking into account the heterogeneity in the course of affective disorders, it is important to identify mental health trajectories based on the age of onset and recurrence across the lifespan, as opposed to using cross-sectional diagnoses at a single time point. This can be a critically important step in our understanding of how childhood chronic physical illness effect mental health across the life course.

In conclusion, the present review provided evidence that childhood chronic physical illness is associated with an increased risk for adult emotional problems. Combined with previous findings on the impact of childhood chronic illnesses on mental health, the findings of the present study

highlight the need for preventative measures for long-term mental health problems associated with childhood chronic physical illness.

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Table 1.
Description of Studies Included in the Systematic Review (N=37) and Meta-Analysis (N=34)

Chronic illness	Author, Year, Country	Study Design	Follow-Up Period	Project /Cohort Name	Chronic illness report	Total sample size (% females)	No. of cases (% females)	No. of controls (% females)	Age (SD)	Cases Age (SD)	Controls Age (SD)	Outcome Variable	Outcome Instrument (Interview or Self-report)	STROBE %
<u>Asthma</u>														
	Chaney et al., 1999 (USA)	Case-Control			Self-report	133 (66.9%)	39 (56.4%)	94 (71.3%)		19.50 (1.47)	19.50 (1.40)	Depression	IDD (SR)	72.7
	Chen et al. 2014 (Taiwan)	Prospective	12 years	Taiwan National Insurance Research Database	Medical Report	7265 (41.8%)	1453 (41.8%)	5812 (41.8%)	19.50 (1.40)			Depression	Psychiatric diagnosis (I)	76.5
	*Eddington et al., 2010 (USA)	Case-Control			Self-report	104 (73.1%)	52 (73.1%)	52 (73.1%)		20.13 (2.23)	20.23 (2.72)	Unspecified Emotional Problems	SF-36 (mental component) (SR)	66.7
	Fedele et al., 2009 (USA)	Case-Control			Self-report	130 (69.2%)	65 (69.2%)	65 (69.2%)		20.22 (2.22)	20.05 (1.91)	Unspecified Emotional Problems	SF-36 (mental component) (SR)	66.7
	Ferro et al., 2016 (Australia)	Prospective	21 years		Medical Report	4767 (51.2%)	1258 (54.4%)	3509 (50.0%)	20.60 (0.90)			Depression, Anxiety (General)	Young-Adult Self-Report (SR)	82.4
	Kokkonen et al., 2001 (Finland)	Case-Control			Medical Report	457	334 [A:108]	123 (51.2%)		23.10	23.10	Depression	PSE (I)	63.6
<u>Cancer</u>														
	Brown et al., 2003 (USA)	Case-Control			Medical Report	94 (56.4%)	52 (55.8%)	42 (57.1%)		17.00 (3.44)	16.67 (3.44)	Anxiety (PTSD)	PTSD-RI (SR)	72.7
	Gianinazzi et al., 2013 (Switzerland)	Case-Control		Swiss Childhood Cancer Survivor Study	Medical Report	509 (46.8%)	407 (45.5%)	102 (52.0%)		17.90 (1.50)	18.30 (1.50)	Depression, Anxiety (General), Unspecified Emotional Problems	BSI (SR)	79.8
	Gunn et al., 2013 (Finland)	Case-Control			Medical Report	108 (0.0%)	52 (0.0%)	56 (0.0%)		29.00	30.00	Depression, Unspecified Emotional Problems	BDI (SR), SF-36 (emotional well-being) (SR), GHQ (SR)	72.7
	Harila et al., 2011 (Finland)	Case-Control			Medical Report	220 (65.0%)	74 (64.9%)	146 (65.1%)		24.00	25.00	Depression, Unspecified Emotional Problems	BDI (SR), GHQ (SR)	66.7
	Kazak et al., 2010 (USA)	Case-Control			Medical Report	337 (51.9%)	167 (52.7%)	170 (51.2%)		20.20 (3.20)	21.80 (3.20)	Depression, Anxiety (General & PTSD), Unspecified Emotional Problems	BSI (SR), PCL-C (SR), SF-12 (psychosocial component) (SR)	69.7

Table 1.
Continued

Chronic illness	Author, Year, Country	Study Design	Follow-Up Period	Project /Cohort Name	Chronic illness report	Total sample size (% females)	No. of cases (% females)	No. of controls (% females)	Age (SD)	Cases Age (SD)	Controls Age (SD)	Outcome Variable	Outcome Instrument (Interview or Self-report)	STROBE %
	Kamibepu et al., 2010 (Japan)	Case-Control		Childhood Cancer Survivor Study	Medical Report	1185 (58.4%)	185 (58.4%)	1000 (58.4%)		F:23.20 (4.90) M:23.10 (5.10)	F:23.90 (5.40) M:23.80 (5.80)	Depression, Anxiety (PTSD)	K10-J (SR), IES-R (SR)	75.8
	Kremer et al., 2016 (Germany)	Case-Control			Self-Report	68 (52.9%)	33 (45.5%)	35 (60.0%)		23.80 (3.80)	23.50 (3.30)	Depression, Anxiety (General)	HADS (SR)	78.9
	Mackie et al., 2000 (UK)	Case-Control		Manchester Children's Tumor Registry	Medical Report	204 (44.1%)	102 (44.1%)	102 (44.1%)		25.60 (ALL); 26.10 (WT)	25.80	Depression	SADS-L (I)	69.7
	Maunsell et al., 2006 (Canada)	Case-Control		Canadian Childhood Cancer Surveillance & Control Program	Medical Report	2811 (53.4%)	1334 (51.9%)	1477 (54.8%)		23.00 (5.20)	23.60 (5.40)	Unspecified Emotional Problems	SF-36 (mental component) (SR)	69.7
	Michel et al., 2010 (Switzerland)	Case-Control		Swiss Childhood Cancer Survivor Study	Medical Report	1541 (48.9%)	987 (45.8%)	554 (54.5%)		27.90 (6.00)	32.50 (8.20)	Depression, Anxiety (General)	BSI (SR)	75.8
	Schwartz et al., 2006 (USA)	Case-Control			Medical Report	140 (58.6%)	57 (52.6%)	83 (62.7%)		21.70 (2.65)	22.17 (3.02)	Depression, Anxiety (PTSD), Unspecified Emotional Problems	CES-D (SR), PCL-C (SR), SF-36 (psychological health) (SR)	69.7
	Seitz et al., 2010 (Germany)	Case-Control		German Childhood Cancer Registry	Medical Report	1847 (63.2%)	820 (51.0%)	1027 (72.9%)		30.44 (6.05)	31.52 (7.00)	Depression, Anxiety (General & PTSD)	HADS (SR), Expert system for Diagnosing Mental Disorders DIA-X/M-CIDI (I), PDS (SR)	75.8
	Servitzoglou et al., 2008 (Greece)	Case-Control			Medical Report	238 (59.2%)	103 (57.3%)	135 (60.7%)		19.80	19.30	Anxiety (General), Unspecified Emotional Problems	STAI (SR), SF-36 (mental component) (SR)	69.7
	Stam et al., 2006 (Netherlands)	Case-Control			Medical Report	836 (52.4%)	334 (52.1%)	502 (52.6%)		24.30 (4.00)	24.20 (3.80)	Unspecified Emotional Problems	SF-36 (mental component) (SR)	75.8
	Sundberg et al., 2010 (Sweden)	Case-Control			Medical Report	481	217	264		24.00	25.00	Unspecified Emotional Problems	SF-36 (mental component) (SR)	72.7
	Teta et al., 1986 (USA)	Case-Control		Connecticut Tumor Registry	Medical Report	1037 (52.7%)	450 (52.2%)	587 (53.0%)				Depression	Interview to Diagnose Definite Major Depression Syndrome (I)	72.7

Zeltzer et al., 1997 (USA)	Case-Control	Children's Cancer Group	Medical Report	982 (51.4%)	573 (49.5%)	409 (52.7%)	22.60 (3.20)	25.20 (4.80)	Depression, Unspecified Emotional Problems	Profile of Mood States (SR)	75.7
Zeltzer et al., 2008 (USA & Canada)	Case-Control	Childhood Cancer Survivor Study	Medical Report	7535 (51.3%)	7147 (51.3%)	388 (52.1%)	32.00**	33.00**	Depression, Anxiety (General), Unspecified Emotional Problems	BSI (SR), SF-36 (mental component) (SR)	72.3

Table 1.
Continued

Chronic illness	Author, Year, Country	Study Design	Follow-Up Period	Project /Cohort Name	Chronic illness report	Total sample size (% females)	No. of cases (% females)	No. of controls (% females)	Age (SD)	Cases Age (SD)	Controls Age (SD)	Outcome Variable	Outcome Instrument (Interview or Self-report)	STROBE %
<u>Congenital Heart Disease</u>														
	Kokkonen et al., 2001 (Finland)	Case-Control			Medical Report	457	334 [CHD:66]	123 (51.2%)	23.10	23.10		Depression	PSE (I)	63.6
	Müller et al., 2013 (Germany)	Case-Control			Medical Report	919 (46.7%)	879 (46.1%)	40 (60.0%)	F:29.13 (10.20) M:27.29 (9.38)	F:35.49 (15.56) M:31.91 (12.15)		Depression, Anxiety (General), Unspecified Emotional Problems	CES-D (SR), STAI (SR), SF-36 (mental health) (SR)	66.7
	Pike et al., 2012 (USA)	Case-Control			Medical Report	120 (56.7%)	54 (51.9%)	66 (60.6%)	25.60 (9.00)	24.50 (9.20)		Depression, Unspecified Emotional Problems	PHQ-9 (SR), SF-36 (mental component) (SR)	66.7
<u>Cystic Fibrosis</u>														
	Blair et al., 1994 (Scotland)	Case-Control			Self-report	60 (53.3%)	29 (31.0%)	31 (74.2%)	19.30 (2.70)	18.20 (2.60)		Depression, Unspecified Emotional Problems	DSM-III-R Diagnostic interview (I), GHQ (SR)	72.7
	*Tluczek et al., 2014 (USA)	Case-Control		Wisconsin NBC Project	Medical Report	81 (50.6%)	39 (51.3%)	42 (50.0%)	18.22 (1.80)	17.90 (1.70)		Depression, Unspecified Emotional Problems	Emotional Symptoms Index (SR), Internalising Problems Measure (SR)	75.8
<u>Diabetes</u>														
	Blanz et al., 1993 (Germany)	Case-Control			Medical report	186 (41.9%)	93 (41.9%)	93 (41.9%)	18.10	18.60		Unspecified Emotional Problems	DSM-III-R Diagnostic interview (I)	60.6
	Kokkonen et al., 2001 (Finland)	Case-Control			Medical Report	457	334 [K:63]	123 (51.2%)	23.10	23.10		Depression	PSE (I)	63.6

Kremer et al., 2016 (Germany)	Case-Control			Self-Report	74 (66.2%)	39 (71.8%)	35 (60.0%)		23.60 (4.10)	23.50 (3.30)	Depression, Anxiety (General)	HADS (SR)	78.9
Ly et al. 2001 (Australia)	Prospective	10 years		Medical Report	67	33 (45.56)	34		19.30 (0.50)	19.50 (0.50)	Depression, Anxiety (General)	BDI (SR), STAI (SR)	79.4
Northam et al., 2010 (Australia)	Prospective	12 years		Medical report	179 (51.4%)	105 (50.5%)	74 (52.7%)		20.70 (4.30)	20.80 (4.00)	Unspecified Emotional Problems	Youth Self-report & Young Adult Self-report Questionnaire (SR)	64.7
Palladino et al., 2013 (USA)	Prospective	1 year		Medical report	239 (52.3%)	117 (50.4%)	122 (54.1%)		18.15 (0.41)	18.02 (0.49)	Depression	CES-D (SR)	79.4

Table 1.
Continued

Chronic illness	Author, Year, Country	Study Design	Follow-Up Period	Project /Cohort Name	Chronic illness report	Total sample size (% females)	No. of cases (% females)	No. of controls (% females)	Age (SD)	Cases Age (SD)	Controls Age (SD)	Outcome Variable	Outcome Instrument (Interview or Self-report)	STROBE %
	Sivertsen et al., 2014 (Norway)	Cross-Sectional		The Youth@Hordaland Study	Self-report	9883 (53.3%)			19.90 (0.48)			Depression, Anxiety (General & OCD)	SMFQ (SR); SCARED (SR); Compulsive Behaviour Inventory (SR)	75.0
	Tebbi et al., 1990 (USA)	Case-Control			Medical Report	113 (62.8%)	58 (62.1%)	55 (63.6%)		24.30 (5.50)	25.10 (4.30)	Unspecified Emotional Problems	GWB (SR)	66.7
Epilepsy														
	Alwash et al., 2000 (Jordan)	Case-Control			Medical Report	202 (47.0%)	101 (46.5%)	101 (47.5%)				Depression, Anxiety (General)	Psychiatric assessment (I)	66.7
	*Baca et al., 2014 (USA)	Prospective	9 years	Connecticut Study of Epilepsy	Medical Report	190 (58.4%)	108 (56.5%)	82 (61.0%)		21.60 (3.80)	20.70 (2.10)	Unspecified Emotional Problems	SF-36 (mental component) (SR)	76.5
	Baldin et al., 2015 (USA)	Prospective	15 years		Medical Report	391 (52.4%)	257 (49.0%)	134 (59.0%)		22.50 (3.50)	23.60 (5.00)	Anxiety (General)	Diagnostic Interview Survey-IV (I)	79.4
	Kokkonen et al., 2001 (Finland)	Case-Control			Medical Report	457	334 [E:62]	123 (51.2%)		23.10	23.10	Depression	PSE (I)	63.6
Rheumatoid Arthritis														
	Kokkonen et al., 2001 (Finland)	Case-Control			Medical Report	457	334 [RA:35]	123 (51.2%)		23.10	23.10	Depression	PSE (I)	63.6

Note. A: Asthma participants; ALL: Acute Lymphoblastic Leukaemia survivors; BDI: Beck Depression Inventory; BSI: Brief Symptom Inventory; CES-D: Center for Epidemiological Studies Depression Scale; CHD: Congenital heart disease participants; D: Diabetes participants; E: Epilepsy participants; F: Females; GHQ: General Health Questionnaire; GWB: General Well-Being Measure; HADS: Hospital Anxiety and Depression Scale; IDD: Inventory to Diagnose Depression; I: Interview; IES-R: The Impact of Event Scale Revised; K-10-J: Kessler Psychological Distress Scale Japanese version; M: Males; No. of: Number of; OCD: Obsessive-Compulsive Disorder; PCL-C: Post Traumatic Stress Disorder Checklist Civilian Version; PDS: Post Traumatic Stress Diagnostic Scale; PHQ: The Patient Health Questionnaire- Depression Module; PSE: Present State Examination; PTSD: Post-Traumatic Stress Disorder; PTSD-RI: Post Traumatic Stress Disorder Reaction Index; RA: Rheumatoid arthritis participants; SADS-L: Schedule for Affective Disorder and Schizophrenia Lifetime; SCARED Inventory: The Screen for Child Anxiety Related Disorders Inventory; SD: Standard deviation; SF-12: 12-Item Short Form Health Survey; SF-36: 36-Item Short Form Health Survey; SMFQ: The Short Version of Mood and Feelings Questionnaire; SR: self-report; STAI: The State – Trait Anxiety Inventory; STROBE: Quality assessment percentage based on Strengthening the reporting of observational studies in epidemiology (STROBE) checklist; WT: Wilm’s Tumour; *Studies with insufficient information for the meta-analysis **median

Accepted version

Table 2.
Results of moderation analyses using meta-regressions

Moderator	Effect Size for	<i>k</i>	Estimate	<i>se</i>	<i>z</i>	95 % CI		<i>Q_E</i>
						<i>LL</i>	<i>UL</i>	
Mean Age	Depression	22	-.010	.021	-.447	-.052	.032	78.62*** (<i>df</i> = 28)
	Anxiety	14	.027	.029	.587	-.040	.074	102.24*** (<i>df</i> = 22)
	Unspecified Emotional Problems	18	-.025	.017	-.879	-.047	.018	40.50* (<i>df</i> = 24)
Sex	Depression	6	.089	.229	.390	-.360	.538	15.31 (<i>df</i> = 9)
	Anxiety	6	.430	.364	1.180	-.284	1.144	45.69*** (<i>df</i> = 12)
	Unspecified Emotional Problems	7	.113	.106	1.059	-.096	.321	14.70 (<i>df</i> = 13)
Mean Age at Illness Diagnosis	Depression	16	.022	.033	.671	-.043	.087	45.93*** (<i>df</i> = 17)
	Anxiety	12	.050	.050	1.002	-.048	.149	120.99*** (<i>df</i> = 18)
	Unspecified Emotional Problems	15	-.042	.054	-.772	-.147	.064	18.36 (<i>df</i> = 15)
Duration of Illness	Depression	9	-.046	.028	1.649	-.101	.009	37.62*** (<i>df</i> = 11)
	Anxiety	8	-.021	.028	-.768	-.076	.033	53.03*** (<i>df</i> = 12)
	Unspecified Emotional Problems	11	-.028	.020	-1.385	-.067	.012	20.89 (<i>df</i> = 12)
Time Since Illness Diagnosis	Depression	13	-.002	.021	.910	-.043	.039	50.33*** (<i>df</i> = 18)
	Anxiety	13	.012	.025	.467	-.037	.060	109.04*** (<i>df</i> = 20)
	Unspecified Emotional Problems	15	-.002	.012	-.136	-.026	.022	20.98 (<i>df</i> = 18)
Sample (Clinical vs Community)	Depression	23	.222	.209	1.061	-.188	.631	84.15*** (<i>df</i> = 31)
	Anxiety	16	-.188	.465	-.404	-1.080	.723	134.20*** (<i>df</i> = 23)
	Unspecified Emotional Problems	18	.637	.358	1.780	-.064	1.338	37.34* (<i>df</i> = 24)
Illness Record (Medical vs Self-Report)	Depression	23	-.546	.276	-1.975*	-1.087	-.004	79.66*** (<i>df</i> = 31)
	Anxiety	16	.037	.431	.086	-.809	.882	138.13*** (<i>df</i> = 23)
	Unspecified Emotional Problems	18	-.455	.320	-1.423	-1.082	.172	38.58* (<i>df</i> = 24)
Year of Data Collection	Depression	23	.003	.010	.250	-.018	.023	84.05*** (<i>df</i> = 31)
	Anxiety	16	-.066	.030	-2.216*	-.125	-.008	93.19*** (<i>df</i> = 23)
	Unspecified Emotional Problems	18	-.013	.011	-1.202	-.034	.008	38.14* (<i>df</i> = 24)
Study Quality	Depression	23	-.051	.186	-.274	-.415	.313	83.86*** (<i>df</i> = 31)
	Anxiety	16	-.510	.280	-1.821	-1.059	.039	134.99*** (<i>df</i> = 23)
	Unspecified Emotional Problems	18	.013	.122	.110	-.226	.253	40.45* (<i>df</i> = 24)

* $p < .05$

Note. Sample variable is dummy coded as 0 = Clinical sample, 1 = Community sample. Sex variable is dummy coded as 0 = male, 1 = female. Illness Record variable is dummy coded as 0 = medical report, 1 = self-report.

CI = confidence interval, Estimate = estimate for ρ when transformed to Fisher's z is used as the dependent variable, k = number of studies, LL = lower limit, Q_E = test for heterogeneity, se = Standard error, UL = upper limit, z = z-value

Accepted version

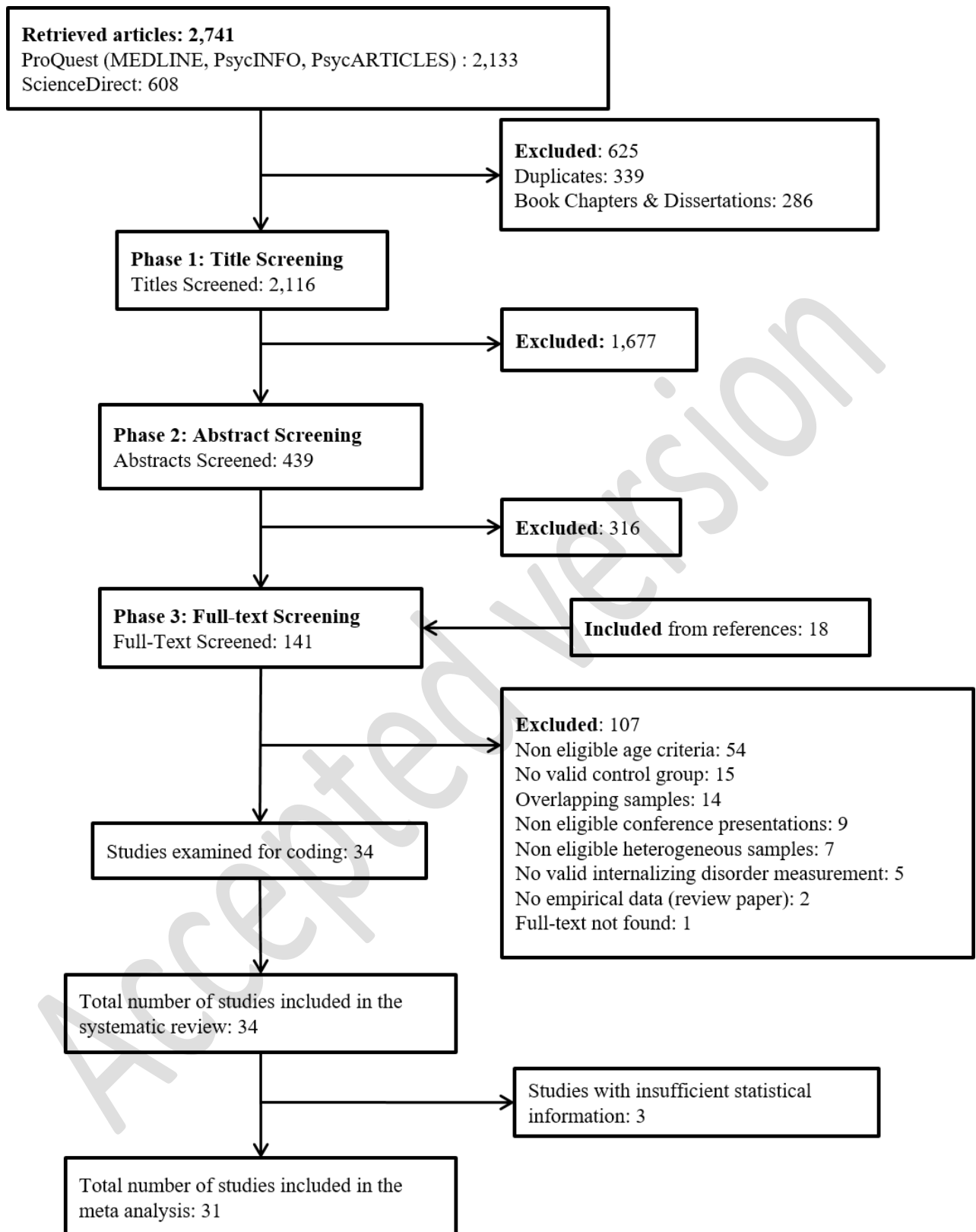


Figure 1. Study selection procedure for the systematic review and meta-analysis of the association between childhood chronic physical illness and emotional problems

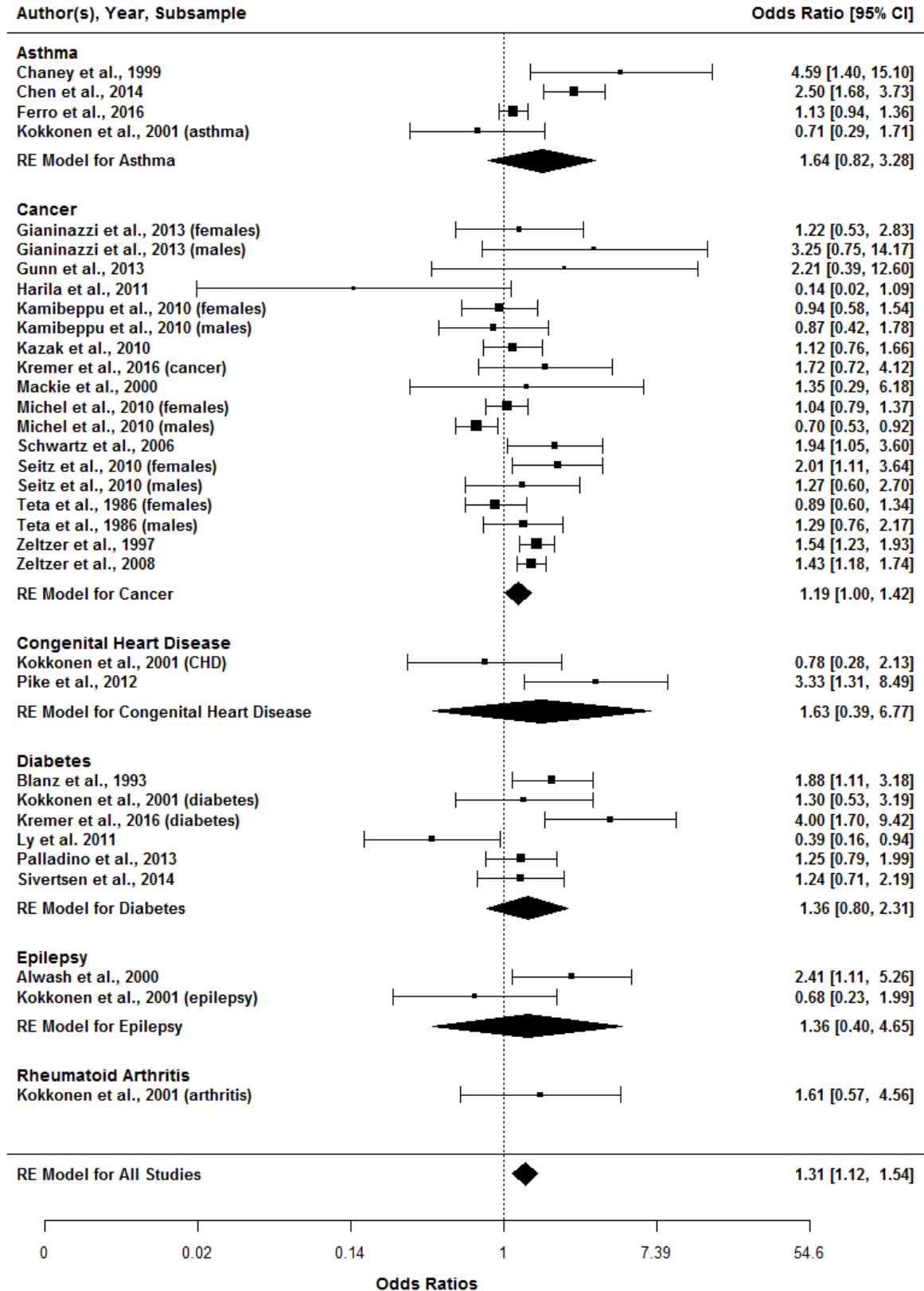


Figure 2. Meta-analysis of studies investigating the associations between childhood chronic physical illness and depression

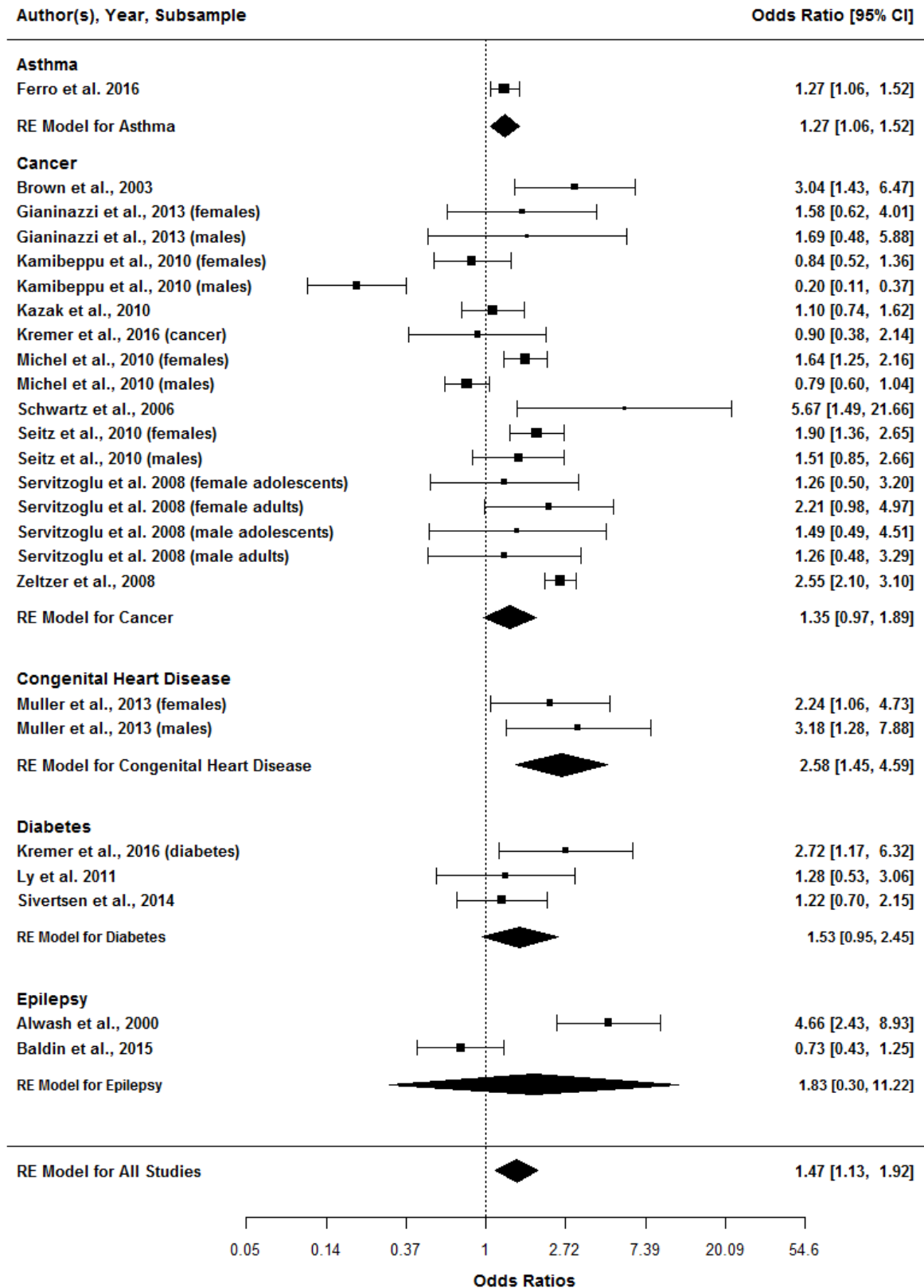


Figure 3. Meta-analysis of studies investigating the associations between childhood chronic physical illness and anxiety

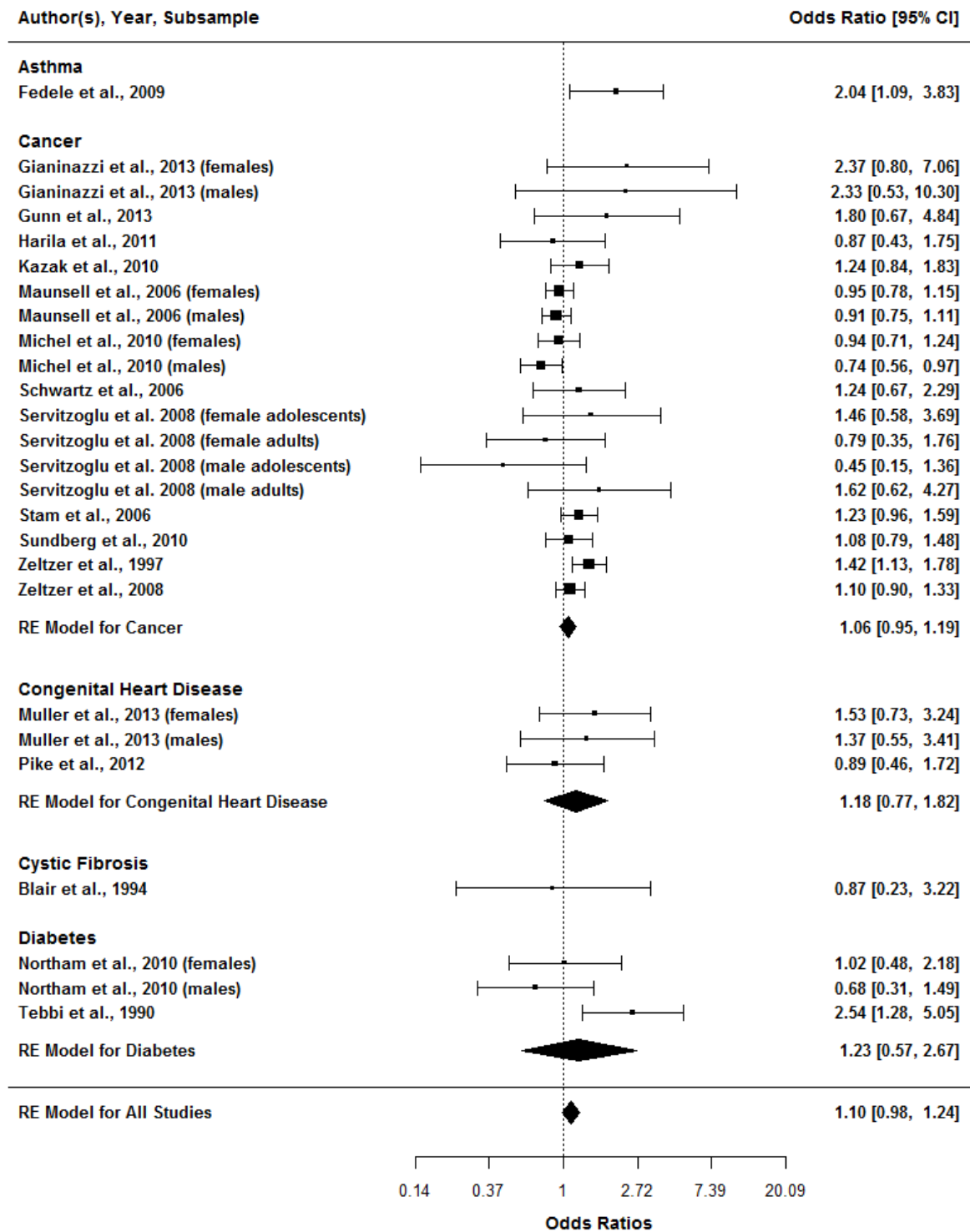


Figure 4. Meta-analysis of studies investigating the associations between childhood chronic physical illness and unspecified emotional problems