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Psychiatric outcomes associated with chronic illness in adolescence: A systematic review

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ABSTRACT

Recent years have seen an increased focus on the high rates of psychiatric comorbidities in adults with chronic illness. This systematic review explored whether chronic illness in adolescents was similarly associated with poor psychiatric outcomes. The literature search identified 129 articles, only 5 of which were indicated to be at a low risk of methodological bias. Four of these articles found a strong relationship between asthma in adolescence and an increase in the prevalence of anxiety and depressive disorders, while the remaining article, which focused on diabetes mellitus, indicated similarly increased rates of psychiatric illness. Trends among the remaining studies suggested that many illnesses were not associated with poor adolescent mental health. Please note that chronic conditions with a neurological aetiology were excluded from the main review due to indications of qualitative differences in comorbidities. Findings highlight that the well-being of adolescents with chronic illness warrants a specific research focus.

Introduction

Michaud, Suris, and Viner (2007) defined the current milieu as one of epidemiological transition - a transition in which conditions which are controllable, albeit with prolonged medical intervention, are overtaking acute and infectious disease as the primary focus of public healthcare systems worldwide. Due to rapid advances in medical technology and knowledge in the twentieth century, as well as the concurrent growth in more sedentary lifestyle practices marked by high caloric diets, the prevalence of these "chronic" or "long-term" conditions has increased exponentially across all age groups (see Vos et al., 2015; Weisz, 2014). The Department of Health in England and Wales (e.g. 2012) currently estimate that about 30% of the population across the two countries have at least one long-term condition, which they define as "those conditions that cannot at present be cured, but can be controlled by medication and/or other therapies", with 12% of those aged from 10 to 19 estimated to be affected. However, this report notes, that due to the variations in registries, this may be an underestimate of the true population prevalence – for example, in the 'Health Behaviour in School Aged Children Survey 2014' in England, 23% of the over 5000 11–15 year olds surveyed self-identified as having a long-term medical illness and/or disability.

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In recent years, the Department of Health of England and Wales has become increasingly focused on the high rates of psychiatric comorbidities amongst people living with chronic illness (Mental Health Network/NHS Confederation, 2012; Naylor et al., 2012). It has been estimated that, overall, adults living with long-term physical health conditions are two to three times more likely to experience a diagnosable mental health condition (Naylor et al., 2012), with rates of comorbid depressive disorders being particularly pervasive (Academy of Medical Royal Colleges, 2009). However, the prevalence of such psychiatric comorbidities among children and adolescents remains unclear (e.g. Sawyer, Drew, Yeo, & Britto, 2007).

Despite a parallel growth in the prevalence of long-term conditions among child and adolescent groups (e.g. Berntsson & Köhler, 2001; Michaud et al., 2007), there has been a relative dearth of focus on the impact of chronic disease within these younger age groups within the wider literature (Sawyer et al., 2007; Schmidt, Petersen, & Bullinger, 2003). Recent years have seen calls for an increased focus on younger age groups (e.g. Holmbeck, 2002; Sawyer et al., 2007), and the rationale for such a specific focus is clear when it comes to the examination of psychiatric comorbidities. Juvenile-onset mental illnesses often have a unique set of predisposing risk factors and neurobiological characteristics when compared with adult onset forms of these disorders (e.g. Jaffee et al., 2002; Kaufman, Martin, King, & Charney, 2001). Moreover, the high rates of psychiatric comorbidities among adults living with long-term conditions have been partially attributed to common lifestyle risk factors (Naylor et al., 2012), and lifestyle factors play a more minor role in the onset of childhood forms of these conditions (Sawyer et al., 2007). Therefore, it cannot be assumed that similarly elevated rates of mental illness will be identifiable among this age group.

Existing meta-analyses have highlighted the need for a specific focus on younger populations in isolation from their adult counterparts. Although evidence from these reviews suggest that children and adolescents living with chronic illness are more likely to suffer from elevated rates of internalising and externalising symptomatology (Lavigne & Faier-Routman, 1992; Pinquart & Shen, 2011b), depressive symptomatology (Bennett, 1994; Pinquart & Shen, 2011c), and anxiety (Pinquart & Shen, 2011a), the overall small to medium magnitude of the effects sizes, and findings of variation in effect across conditions, would suggest the association between chronic illness in the formative years and poorer mental health outcomes is not as strong as that found in older populations. However, methodological artefacts among the studies included could have limited the insight of these meta-analyses. Barlow and Ellard (2006) argue that sampling issues are endemic in this field, with use of small, selective convenience samples widespread. Indeed, the dependence on small, clinic-based samples was noted among these reviews, with Lavigne and Faier-Routman (1992) hypothesising this as the source of the significant variability in mental health outcomes within conditions in their review. Moreover, concerns have also been raised regarding the use of psychometric ratings scales, such as the 'Child Behaviour Checklist', as prevalence measures of psychiatric illness among this population, due to the presence of a large number of items focusing on somatic symptoms (Canning & Kelleher, 1994), and significant variations in the assessment of the child's well-being between raters (Pinquart & Shen, 2011b).

One clear limitation in these reviews is the lack of specific focus on differentiating outcomes between child and adolescent populations. Such a limitation should be considered in the context of wider discussions, which theorise chronic disease as being particularly tied to poor mental health outcomes in adolescence (e.g. Sawyer et al., 2007), due to the likely disruption these conditions pose to normal developmental milestones of this period, such as increased autonomy from parents (e.g. Schmidt et al., 2003; Surís, 2003). This lack of age-specific focus may be due to the methodological approach of the studies included in these analyses. Many studies focusing on these younger age groups include a broad age range, often from early childhood into early adulthood (e.g. Dantzer, Swendsen, Maurice-Tison, & Salamon, 2003), with McClellan and Cohen (2007) noting that many studies are unable to assess the effects of age due to their small, selective samples. When including age as covariate in the larger meta-analyses, Bennett (Bennett, 1994) and Pinquart and Shen (2011a, 2011b, 2011c) indicated that age of the study child did not seem to have a significant impact on outcomes, with the only age-related effects being noted were an age-related reduction in anxiety disorders (Pinquart & Shen, 2011a) and an early childhood reduction of internalising and externalising behavioural symptoms (Pinquart & Shen, 2011b). However, Williams, Holmbeck, and Greenley (2002) argue that such methods are imprecise due to the limitations in sample power overall. Indeed, the lack of identifiable age-related variations would seem counter-intuitive when other age-related variations in chronic disease outcomes are considered – for example, it has been found that adherence to medical regimens is as its lowest in adolescence (Holmbeck, 2002; Viner & Davies, 2012, pp. 1–11).

Given the concerns surrounding the empirical support underlying previous reviews in the area of paediatric chronic illness, an extensive systematic review of the literature was conducted with a strict focus on the quality of the evidence in order to build a more solid empirical insight into the mental health outcomes associated with the presence of chronic illness in youth. It was considered important, given the limitations in the empirical base, to start with a focus on the establishment of associations, rather than looking specifically at causative relationships. Therefore, the over-arching question of this review was: "Is there evidence to suggest that living with a chronic illness in adolescence is associated with poorer mental health outcomes?"

Methods

Search strategy

Eligible studies were identified through a comprehensive literature search of the following four bibliographical databases: PsycInfo, Medline, Embase and Web of Science using the popular denoted terms for long-term conditions (e.g. "chronic

illness", "chronic disease"), substantially prevalent chronic disease conditions of childhood and adolescence (e.g. asthma, diabetes, anemia/anaemia) and terms for the psychiatric outcomes (e.g. "conduct disorder", "mental health", depress*, anxiety). The age range was filtered to children and adolescents on all databases. Search area was limited to the title and abstract, with the exception of the 'Web of Science' database, where this option was not available. Results were also limited to articles in English and those classed as journal articles. To determine the studies that were eligible, one author read the abstract and/or titles of every record retrieved for the selection criteria. The two remaining authors read titles and abstracts on articles on which there was a lack of clarity regarding suitability. Differences in opinion were resolved by consensus.

For inclusion studies had to meet the following criteria: (a) be an original research study that measures a mental health outcome in a sample of young people affected by chronic illness; (b) be inclusive of a sample aged between ten and nineteen years; (c) compare the levels of psychological adjustment or the frequency of psychiatric diagnoses between children and adolescents with chronic physical illness and their healthy peers or test norms; (iv) based on data collected in the year 2000 or later. This last criterion was used to ensure that the medical regimes of the young people in the chronic illness sample would be approximately representative of current cohorts of adolescents living with these chronic health conditions.

An initial challenge under this quality criterion was to delineate the exact boundaries of what would constitute a chronic illness. Wider discussions have highlighted the debate underlining the inconsistencies in the definition of such conditions (e.g. van der Lee, Mokkink, Grootenhuis, Heymans, & Offringa, 2007) arising from the lack of somatic comparability between such conditions (e.g. Weisz, 2014). Among studies that used a non-specific definition of chronic illness all studies were included regardless of what specific conditions the study's chosen definition would include. However, among studies which looked at the specific impact of a named chronic illness condition, a strict inclusion criterion was imposed. Given the large number of studies identified in pilot studies, this review departed from previous reviews by excluding conditions where although the primary diagnosis may be treatable, follow-on medical treatment may be required (e.g. various forms of cancer), and where psychological processes have been proposed as primary aetiological factors (e.g. Chronic Fatigue Syndrome, Chronic Pain). This decision was based on suggestions that the psychiatric sequelae of mental health outcomes in these conditions require a unique framework of analysis – for example, the consideration of the effects of cranial radiation in cancer (e.g. Stuber, 1996). It was hoped that such an exclusion would allow for a more strict focus on the similarities and contrasts between more prevalent forms of chronic illness among this age group, such as asthma (Hagell, Coleman, & Brooks, 2015).

Initial readings also indicated a clear qualitative difference in the mental health outcomes associated with conditions arising from neurological aetiologies. Although a disproportionate rate of psychiatric disorders among both children and adolescents living with such conditions was consistently indicated, evidence suggested that some aspects of these comorbidities were attributable to the typology of the condition. For example, longitudinal studies identifying precedents of epilepsy among children indicated marked differences in psychological adjustment and behaviour in the months preceding the first recognised seizure (e.g Austin et al., 2001; Jones et al., 2007). Moreover, it was indicated that internalising and externalising issues vary across time as a function of seizure frequency (Austin et al., 2002; Kobayashi et al., 2013). Similarly, it has been suggested that the psychological profile of children with tuberous sclerosis shows strong associations with the underlying neurological impact of the condition (de Vries, Hunt, & Bolton, 2007). Therefore, although it was clear that there was an elevated rate of psychiatric comorbidities in neurologically-based conditions, the findings suggested these were not so much associations, but a related symptom of the condition. Consequently, the findings of studies focusing on such conditions will not be explicity discussed within this article. Please note that chronic illness conditions such as sickle cell disease and diabetes may have a neurological impact, however, the studies pertaining to these conditions were retained as the conditions themselves do not arise from a neurological basis.

Quality assessment

In order to base conclusions on a stronger body of studies than those in previous reviews, it was deemed crucial that a quality rating was assigned to each study to assess the risk of bias. To make this rating as objective as possible, the 'Newcastle-Ottawa Quality Assessment Scale for Cohort Studies' was used. As detailed by Wells et al. (2014) the content validity and inter-rater reliability of the scale have been established. In the scale, stars are awarded for each quality item in order to aid quick visual assessment of quality. Stars are awarded based on the quality of the sample (both exposed and comparative); the validity of assessment methods; and the consistency of longitudinal measurement.

Literature search

The search yielded 5205 unique citations. Of these, 4922 did not meet the inclusion criteria based on their titles and abstracts. Of the remaining 283 articles, 154 additional papers did not meet the inclusion criteria on reading of the full text. This process resulted in 129 articles that met the inclusion criteria (a flow diagram of this search process is presented in Fig. 1). 99 of these studies examined the outcomes associated with a specific condition; 21 studies examined the non-specific effects of chronic illness without reference to the conditions being examined; and 9 studies cross-referenced the outcomes associated with different long-term conditions.

Of the 99 studies that focused on the outcomes associated with specific conditions, 69 of the studies focused on the conditions of asthma and diabetes. Therefore, there was a notable shortage of identifiable research concerning many conditions at the outset of this review.

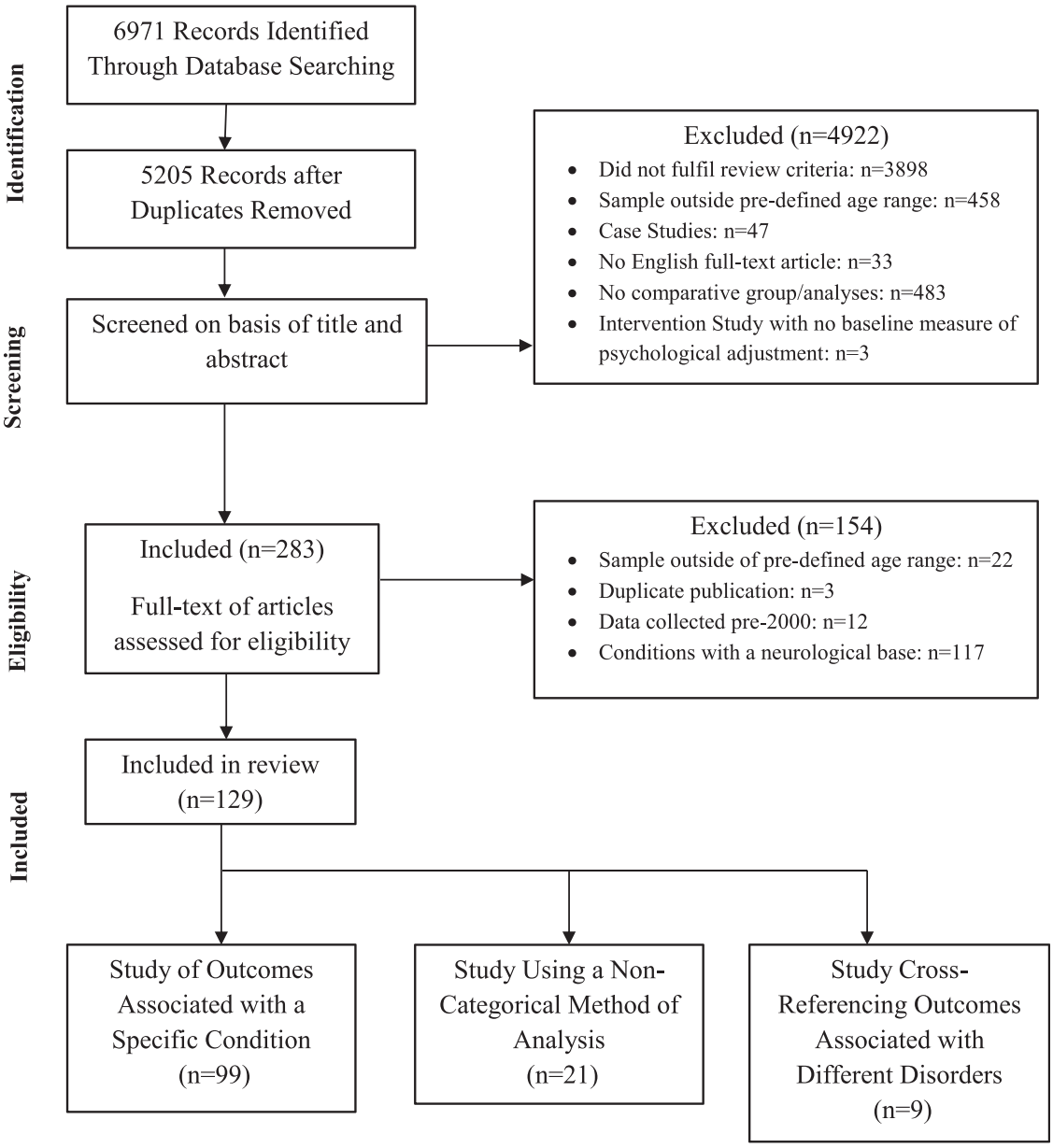

Fig. 1. Flowchart for Selection of Studies. Flowchart depicting the process by which studies were excluded from the review, or retained for further study.

Data extraction

All comparative data relating to mental health in chronic illness (including mean differences, risk ratios, odds ratios etc.) was extracted from the study, regardless of the nature of the summary measure. Magnitude of scores was also extracted when reported, alongside any sub-group analysis.

Assessment of study quality

Depending on the ratings of the quality assessment scale, the following criteria were imposed to identify studies at a low risk of introducing bias to findings: studies must have had (i) the exposed sample should somewhat represent the average young person living with that illness condition in the community; (ii) the comparative group should be comparable to the exposed cohort in terms of demographic characteristics and suffer from no major medical issues; (iii) The exposure measure should not be reliant on parent- or self-report of diagnosis; (iv) The mental health measure should be at low risk of

introducing subjective bias or inflating somatic symptoms; (v) The study should at least have adjusted for the confounding effects of demographic variables.

The 'Newcastle-Ottawa' rating scale gives a higher quality rating to studies that use a longitudinal methodology. Although longitudinal research provides a better insight into the stability of associations over time, a lack of longitudinal data in the research area was highlighted at the outset (e.g. Sawyer et al., 2007). Therefore, this quality criterion was not used as a basis to exclude studies from the main review.

Several notable methodological issues were found among many of the eligible studies after the application of the quality assessment. Amongst the studies that examined the mental health association of a specific condition, the most notable issue was the use of small, selective samples, with further reliance on comparison groups of convenience or norms. For example, the only study which examined psychiatric associations of Cystic Fibrosis was based on 43 children who received check-ups at the Danish Cystic Fibrosis Centre in a set time period and the comparison was based on scale norms. Furthermore, some studies went so far as to recruit their comparative samples from other clinical groups – for example, in studies of the associations with Systematic Lupus Erythematosis (Louthrenoo, Krairojananan, Chartapisak, & Opastirakul, 2012), Sickle Cell Disease (Amr, Amin, & Hablas, 2010) and Juvenile Arthritis (Brace, Scott Smith, McCauley, & Sherry, 2000) at least some members of the comparative groups were recruited from other medical clinics. Furthermore, there was limited adjustment for the effects of confounding variables among these studies. Therefore, there are significant concerns regarding the validity of such studies given their dependence on possibly biased groups.

It should be noted that among the 21 studies that used a non-categorical framework of analysis - which assumes that common psychosocial trajectories arise from chronic illness, regardless of the specific diagnosis - samples were generally larger and more representative. However, assessments of physical and mental health were generally of a lower quality amongst these studies, with many studies dependent on single-item outcome measures (e.g. Blackman & Conaway, 2013; Curtis & Luby, 2008). It should also be noted that there were specific variations in the definitions of chronic illness used, and indeed the conditions examined, across this set of studies.

When the pre-determined quality criteria were applied, only 5 of the 129 studies were indicated to be at a low risk of introducing bias in the review. Four of these studies examined the mental health outcomes associated with asthma, while one study examined the outcomes associated with diabetes. The findings of these five studies will be reviewed in depth. The trends in the remaining studies will be overviewed in balance with their identifiable limitations.

Results

Characteristics of studies

Characteristics of the five highlighted studies are shown in Table 1. The two studies conducted by Chen and colleagues (Chen et al., 2014b, 2014a) utilised data from the National Health Insurance Research Database of Taiwan, which is a database of the medical claims of 100,000 subjects (approximately 4.3% of the population). As of 2014, 99.9% of Taiwan's population were enrolled in this insurance programme, and it is believed that this database is representative of the general population. Delmas and colleagues (Delmas et al., 2011) used data from a national school survey conducted with students across France, while Katon and colleagues (Katon et al., 2007) identified their sample from the administrative data of a health maintenance organisation in the state of Washington in the United States. This data included a large proportion of the state's population, ensuring that it was characteristic of the population of this area. The participant's records had to have fulfilled one or more of the following criteria for youth to be deemed as having an active asthma diagnosis: (a) hospitalization with an asthma diagnosis and one or more asthma prescriptions; (b) one or more emergency room or urgent care visits with an asthma diagnosis and one or more asthma prescriptions; (c) 2 office visits with an asthma diagnosis and one or more asthma prescriptions; (d) only 1 asthma visit, but 2 asthma prescriptions filled on different days; (e) four or more prescriptions for asthma medication; (f) one or more visit with an asthma diagnosis in the past year and another in the past 18 months and one or more asthma prescription during that year. Wändell, Ljunggren, Wahlström, & Carlsson (2014) used data from an in-depth survey of health and demographic characteristics of all living persons in Stockholm County in Sweden collected on January 1st, 2011.

The included studies represented cohorts from a variety of locations internationally, namely within Asia, Europe, and North America. Moreover, all samples were somewhat representative and contained relatively large samples overall, with all the respective cohorts with a chronic condition of a substantial size to provide adequate power to the analyses. In addition, two of the five studies were longitudinal, which added extra explanatory strength to the associations identified. However, the significant variation in location between the studies means that cross-cultural factors may need to be taken into consideration. It is known that the patient's culture plays a significant role in both their experience, and perception of, their physical illness (Turner, 1996) and in the expression of mental illness (Patel, Flisher, Hetrick, & McGorry, 2007).

Associations between adolescent chronic illness and mental health outcomes

The four studies which examined the mental health outcomes associated with asthma only included adolescents. These studies predominantly measured emotional disorders. The study of Wändell et al. (2014) included a wider range of psychiatric

Table 1
Characteristics of the studies that achieved the pre-determined quality criteria.

Study	Condition Examined	Country of Origin	Study Design	Sample Size (n)	Age Range (Mean)	Asthma Measure	Psychological Outcome	Psych. Outcome Measure
Chen et al. (2014a)	Asthma	Taiwan	Cross-Sectional	7265 (1453 with asthma)	10-15 years (M = 11.69)	Recorded diagnosis of asthma by a paediatrician, pulmonologist, or rheumatologist between Jan 1, 1998, and Dec 31, 2000 in medical claims	Mood Disorders	Recorded diagnosis by psychiatrist within medical claims during the period from baseline to December 31, 2010
Chen et al. (2014b)	Asthma	Taiwan	Longitudinal	9449 (725 with asthma)	10-15 Years (M = 11.69 (SD:1.59))	Recorded diagnosis of asthma by a paediatrician, pulmonologist, or rheumatologist in the year 2003 in medical claims	Mood Disorders	Recorded diagnosis by psychiatrist within medical claims during the period from baseline to December 31, 2010
Delmas et al. (2011)	Asthma	France	Longitudinal	7000 (8.5% approx. with asthma)	9th grade students (approx. 13–16 years) (M = 15.1)	Medical examination (inclusive of anthropometric measures) by school doctor and nurse, and response patterns on the French version of the standardised International Study of Asthma and Allergies in Childhood (ISSAC) Questionnaire	Major Depressive Episodes	The Composite International Diagnostic Interview – Short Form
Katon et al. (2007)	Asthma	United States	Cross-Sectional	1379 (781 with asthma)	11-17 years (M = 14)	Fulfilling no. of criteria relating to prescriptions and healthcare use	Anxiety and Depressive Diagnoses	The Diagnostic Interview Schedule for Children NIMH DISC 4.0
Wändell et al. (2014)	Type 1 Diabetes Mellitus	Sweden	Cross-Sectional	471 685	0-18 Years	Diagnosis Recorded in Linked Medical Records	Mental Health Diagnoses	Diagnoses recorded in linked Medical Records

Table 2
Comparative risk indicated in studies that achieved the pre-determined quality criteria.

Study	Condition Examined	Mental Health Outcome	Comparative Risk	Moderator of Association
Chen et al. (2014a)	Asthma	Major Depression	*Prevalence:* 2.8% versus 1.1% *Adjusted Hazard Ratios*[a]: 1.81 (95% CI: 1.14–2.89)	None examined
		Any Depressive Disorder	*Prevalence:* 6.1% versus 2.6% *aHR*[a]: 1.74 (95% CI: 1.27–2.37)	
		Bipolar Disorder	*Prevalence:* 1% versus 0.3% *aHR*[a]: 2.27 (95% CI: 1.01–5.07)	
Chen et al. (2014b)	Asthma without Comorbid Diagnosis of ADD/ADHD	Major Depression	No longer significant association	Comorbid Diagnosis of ADD/ADHD
		Any Depressive Disorder	No longer significant association	
		Bipolar Disorder	No longer significant association	
Delmas et al. (2011)	Asthma	Major Depressive Episodes	*Prevalence*: 14.2% versus 9.2% *aOR*[b]: 1.7 (95% CI: 1.2–2.3)	Current Patterns of Symptomatology The incidence in children with past asthma symptomatology was not statistically significant (aOR: 1.2; 95% CI: 0.7–2.0)
Katon et al. (2007)	Asthma	Anxiety and Depressive Disorders (Overall)	*Prevalence:* 16.3% versus 8.3% *aOR*[c]: 1.83 (95% CI: 1.28–2.62)	Being female (aOR: 1.96; 1.27–3.03), Living with a currently unmarried parent (aOR: 1.96; 1.26–3.07)
		Major Depression	*Prevalence:* 4% versus 7.2% *aOR*[c]: 1.65 (95% CI: 0.99–2.76)	
		Dysthymia	*Prevalence:* 0% versus 0.1% *aOR*[c]: -	A more recent diagnosis of asthma (aOR: 0.94; 0.89–0.98)
		Panic Disorder	*Prevalence:* 1.2% versus 2.5% *aOR*[c]: 1.93 (95% CI: 0.78–4.77)	
		Generalised Anxiety Disorder	*Prevalence:* 2.2% versus 1.2% *aOR*[c]: 1.8 (95% CI: 0.71–4.56)	Higher externalizing scores on the CBCL (aOR 1.03; 1.01–1.05)
		Social Phobia	*Prevalence:* 3.3% versus 1.4% *aOR*[c]: 2.28 (95% CI: 0.99–5.26)	
		Separation Anxiety	*Prevalence:* 3.4% versus 1.9% *aOR*[c]: 1.69 (95% CI: 0.82–3.48)	A lower physical health score on the asthma-specific functional impairment scale (aOR: 0.95; 0.94–0.96)
		Agoraphobia	*Prevalence:* 7.5% versus 3.4% *aOR*[c]: 1.92 (95% CI: 1.13–3.28)	
Wändell et al. (2014)	Type 1 Diabetes Mellitus	Any Psychiatric Diagnosis	*Prevalence:* 25.31% versus 14.18% Female 27.47% versus 18.46% Male *Age-Adjusted Lifetime Odds Ratio:* 1.296 (95% CI: 1.267–1.326) Female 1.3999 (95% CI: 1.368–1.432) Male	Increasing odds of 5–6% of any psychiatric diagnosis for each added life-year

Table 2 (*continued*)

Study	Condition Examined	Mental Health Outcome	Comparative Risk	Moderator of Association
		Schizophrenia	*Prevalence:* 0.01% versus 0% Female 0.09% versus 0.01% Male *Age-Adjusted Lifetime Odds Ratio:* 3.439 (95% CI: 3.057–3.868) Female 2.787 (95% CI: 2.514–3.089) Male	
		Bipolar Disorders	*Prevalence:* 0.33% versus 0.12% Female 0% versus 0.06% Male *Age-Adjusted Lifetime Odds Ratio:* 1.714 (95% CI: 1.54–1.905) Female 1.6 (95% CI: 1.429–1.792) Male	
		Depression	*Prevalence:* 5.24% versus 2.1% Female 2.93% versus 1.06% Male *Age-Adjusted Lifetime Odds Ratio:* 1.412 (95% CI: 1.365–1.46) Female 1.531 (95% CI: 1.474–1.591) Male	
		Anxiety	*Prevalence:* 4.68% versus 2.94% Female 3.21% versus 1.51% Male *Age-Adjusted Lifetime Odds Ratio:* 1.276 (95% CI: 1.227–1.327) Female 1.35 (95% CI: 1.289–1.414) Male	

[a] Adjusted by gender, age at enrolment, level of urbanisation, and comorbid allergic diseases.
[b] Adjusted for current asthma, gender, age, family structure, and the father's employment status.
[c] Adjusted for ethnicity, education, marital status, Medicaid and Pediatric CDS.

diagnoses, however the younger age group subsumed all young people aged from 0 to 18 years. The main findings of these studies can be seen in Table 2.

The four studies focusing on asthma unanimously indicated a strong association between this condition in adolescents and emotional disorder diagnoses, inclusive of depressive and anxiety disorders. Adjusted odds ratios between the studies indicated a substantially increased risk for both anxiety and depression, which was at least 50% higher than that of the comparative samples. The study of Katon et al. (2007) highlighted a particularly high prevalence of social phobia (adjusted OR: 2.28 (95% CI: 0.99–5.26)), and agoraphobia (adjusted OR: 1.92 (95% CI: 1.13–3.28)), among American adolescents living with asthma, but the wide confidence intervals for the adjusted odds ratios indicate that the samples may have not been large enough to examine the exact prevalence of specific psychiatric disorders with precision. Therefore, based on these four studies, it does appear that asthma in adolescence is associated with poorer mental health outcomes.

These four studies suggested that the association between anxiety and depressive disorders and asthma may be particularly acute in some population sub-groups. Chen et al. (2014b) found that the presence of asthma, in the absence of comorbid conduct disorders at baseline, was not associated with a statistically significant increase of emotional disorders among their sample, suggesting that comorbid behavioural symptomatology was a key factor in the associated psychiatric outcomes. However, it should be noted that this study was based on a Taiwanese population and that this finding was not replicated in the remaining three samples, meaning that this may be a culturally-specific finding. However, Katon et al. (2007) did find that externalising behaviour scores were predictive of the prevalence of anxiety and depressive disorders in their sample of French adolescents, suggesting that the role of comorbid behavioural problems warrants further research.

The findings of Delmas et al. (2011) indicated that those who had been diagnosed with asthma, but were not currently experiencing symptoms of their condition, did not have a higher prevalence of major depressive episodes, meaning that the strong association indicated (approximately 70% increased prevalence) was applicable to only the adolescents currently experiencing symptoms of their condition. Moreover, the findings of Katon et al. (2007) highlight important contextual factors in the prediction of the associated mental health outcomes among the American adolescents living with asthma in their sample, such as living with an unmarried parent and functional impairments. However, the cross-sectional nature of the study means that it was not possible to elucidate whether these factors played a cumulative or a moderating role in this association.

Wändell et al. (2014) indicated that there was a higher prevalence of psychiatric diagnoses among both females and males in the diabetes cohort in comparison to their healthy peers. The prevalence rate of any psychiatric diagnosis was 10% higher among these children and adolescents. As in the asthma studies, this increased prevalence extended in particular towards mood disorders, inclusive of anxiety, depression and bipolar disorder (approximately 50% higher prevalence across both genders), with the exception that males aged 0–18 years with Type 1 diabetes had a lower prevalence of bipolar disorders. This study only considered the impact of age by including it as a covariate in the regression models focusing on the prevalence of psychiatric disorders across the lifespan. This makes it difficult to distinguish unique variations in mental illness associations between children and adolescents. However, the covariate analyses indicated increasing odds of 5–6% for each added life-year in the population of Stockholm County, suggesting that adolescents living with Type 1 Diabetes may be experiencing a higher prevalence of mental health disorders than children of a younger age. Yet, this age effect should be considered in context. In spite of the overall low prevalence rates of schizophrenia in youth with diabetes, the age-adjusted odds ratios show a substantially increased prevalence of schizophrenia in the diabetic sample, with the age-adjusted odds ratios calculated as 3.439 (95% CI: 3.057–3.868) for women and 2.787 (2.514–3.089) for men. The authors isolated the association identified between schizophrenia and diabetes in the cohort, from that found between diabetes and other psychiatric disorders, due to the weight gain caused by antipsychotics – which increases the risk of developing diabetes – and the common genetic links identified for the two disorders. Therefore, the association between Diabetes Type 1 disease in adolescence specifically and poorer mental health outcomes requires further elucidation.

Finally, it should be noted that the increased prevalence of anxiety and depressive disorders among females noted consistently amongst the samples studied is consistent with the general female preponderance associated with the juvenile-onset of such disorders (e.g. Thapar, Collishaw, Pine, & Thapar, 2012).

Trends in remaining studies

The trends among the studies that did not achieve the quality criteria can be seen in Table 3 (Appendix A lists the related studies). Surprisingly, given the methodological issues noted regarding many of the studies focusing on the impact of named conditions – that of the dependence on small, clinic-based samples and possibly biased measures – the only consistent associations identified were between the conditions of asthma, diabetes mellitus and thalassemia, and depressive and emotional symptomatology. In the remaining conditions, small to moderate associations were identified which often varied based on the rater used – for example, when considering the associations of inflammatory bowel disease to emotional symptomatology, significant associations were identifiable based on parental ratings only. This contrasts strongly with the strong associations identified between chronic illness and psychiatric outcomes in adult samples.

Yet, the studies which examined the impact of chronic illness non-categorically uniformly indicated an increased prevalence of both emotional disorders and conduct disorders. Such a contrast raises questions of whether it is only a small number of conditions that is driving these findings of association – indeed, inter-disease variability in prevalence were noted amongst many of the studies, and neurological conditions were often named as having the strongest association with mental health outcomes – or whether the widespread dependence on small samples is obscuring identifiable associations between chronic illness in adolescence and poor mental health outcomes. It should be noted that no identifiable differences were suggested between adolescents and children living with chronic illness in terms of associated mental health outcomes, with the exception that adolescents with asthma were consistently found to be more maladjusted than their younger counterparts. However, most of these studies were small samples which included age as a covariate in statistical models, meaning that the studies may not have been adequately powered to fully assess the differential association of chronic illness in adolescence to mental well-being, as opposed to childhood.

Discussion

The major question of this review was: “Is there evidence to suggest that living with a chronic illness in adolescence is associated with poorer mental health outcomes?” Significantly, this review suggests that currently the research base is not one on which this question can be reliably answered with any degree of confidence. The studies which achieved the quality criteria unanimously demonstrated a strong positive association between chronic disease conditions and a disproportionate rate of psychiatric comorbidities in adolescents, and in particular anxiety and depressive disorders. However, only five studies achieved these quality criteria, and four were focused on one condition – asthma. It should also be noted that amongst these four studies the criteria that defined a diagnosis of asthma was fairly rigorous, with the study of Katon et al. (2007) and Delmas et al. (2011) suggesting that it was only children who were experiencing on-going asthmatic symptomatology that

Table 3
Trends among the remaining studies that did not achieve the pre-determined quality criteria.

Condition	Number of Studies	Emotional Outcomes	Behavioural Outcomes	Possible Moderator of Association
Asthma	42	Increased prevalence of depression and anxiety (Approximately 50%–70% higher prevalence)	Findings were mixed but, overall, it was suggested that there was approximately a 20% increase in the prevalence of conduct disorders	Functional Impairment (Cross-Sectional – not possible to assess directionality) High risk of juvenile-onset psychopathology (Asthma no longer an exacerbating factor risk)
Diabetes (Type I Sub-Type Only)	26	Likely increase in prevalence of emotionally-predominated disorders	Likely increase in prevalence of conduct disorders	Age (Adolescents showing higher levels of maladjustment) Glycaemic control (Findings mixed) Functional Impairment Family Climate
Sickle Cell Disease	6	Mixed Evidence (Parent ratings support but this is contradicted by self-report and teacher ratings) Slight increase in anxiety disorders only based on psychiatric interview (However, poor quality comparative group)	Mixed evidence (Parent and teachers reports support, but not self-report or ratings of secondary caregivers)	Gender (Females at higher risk) Low Family Income Experience of Frequent Painful Crises More severe sub-types of the condition (Associate with mothers ratings only)
Thalassemia	3	Increase in emotional symptoms above clinical threshold	Increase in prevalence of conduct disorders	More severe symptoms of thalassemia
Juvenile Arthritis	3	No association	No association	Active status of arthritis symptoms
Inflammatory Bowel Disease	3	Increase in Emotional Symptoms above Clinical Threshold (Parents Ratings Only)	No association	More severe sub-types of the condition Time of onset of condition (Adolescent-Onset having stronger association with somatisation)
Haemophilia	2	Increase in depressive symptoms, but below clinical thresholds	No association	Severe sub-types of the condition (However, means still below a level of clinical significance)
Chronic Kidney Disease	3	No association	No association	Reliance on Dialysis
Non-Alcoholic Fatty Liver Disease	2	Increase in emotional symptoms (Clinical Significance not examined)	No association	BMI (Only supported by one of the two eligible studies; other found no association)
Cystic Fibrosis	1	Increase in anxiety symptoms in boys aged 7–10 years	No association	Socio-economic factors
Epidermolysis Bullosa	1	Increase in emotional symptoms (Means not in clinical range)	No association	Severity (However, this was not a statistically significant association)
Oesophageal Atresia	1	No association	No association	None identified
Familial Mediterranean Fever	1	Increase in depressive symptoms of clinical significance No relationship with anxiety	No association	Condition severity (but not condition duration or genotype)
Systematic Lupus Erythematosus	1	No association	No association	None identified
Primary Ciliary Dyskinesia	1	Increase in emotional symptoms in borderline clinical range	No association	None identified
Eosinophil-Associated Gastrointestinal Disorders	1	Increase in emotional symptoms	Increase in behavioural difficulties	None identified
Non-Categorical Examination of Chronic Illness	26	Increased prevalence of emotional symptomatology	Increased prevalence of conduct problems	Diagnosis (Higher risk associated with neurological conditions) Functional Impairments Child's Perception of Severity Socio-Economic Deprivation Social Development
Cross-Reference of Mental Health Outcomes Between Disorders	9	n/a (due to significantly high risks of methodological bias)	n/a (due to significantly high risks of methodological bias)	–

were at risk of this associated rate of psychiatric comorbidities. The final study suggested there were similarly elevated levels of psychiatric conditions amongst young people living with diabetes mellitus, however the specific prevalence of such conditions among adolescents was not examined. Significantly, trends among the remaining studies suggested that the psychiatric comorbidities of young people may differ notably from adults living with such conditions, with limited evidence of associated poor psychiatric outcomes for many illnesses. However, it cannot be discounted that methodological biases, such as reliance on convenience samples, may account for these trends. Moreover, the use of broadly inclusive age ranges may mean that acute age-related risks are being obscured. This is specifically a limitation within the wider context of theoretical discussions of the risks posed by such conditions to normal developmental trajectories in adolescence (e.g.Michaud et al., 2007; Sawyer et al., 2007). It reflects a wider issue in the health field, where the data of adolescents is often subsumed with other age groups (Hagell et al., 2015), regardless of the unique health profiles of this group (e.g. Holmbeck, 2002).

The findings of this systematic review contrast with the findings of previous meta-analyses in this area. These reviews indicated small to moderate effect sizes of chronic illness on mental health outcomes, with no true demarcation between children and adolescents. Similar conclusions would be made in this review if findings were assessed overall, without the support of the quality rating scheme. Yet, the findings of the studies indicated to be at a low risk of bias in this review indicated strong and positive associations between asthma and diabetes in adolescence and the prevalence of psychiatric disorders, and in particular anxiety and depressive disorders. Given that studies that failed to reach the quality criteria also indicated positive associations for these conditions, it might suggest that these conditions, unique from other chronic illness conditions, are associated with poorer mental health outcomes. However, it may also suggest that methodological limitations in this field are obscuring true associations and risks for adolescents living with chronic illness. Such a question can only be resolved by further research in this area.

Among the five studies which reached the quality criteria, two very different methodologies were identifiable – the studies of Chen et al. (2014a, 2014b) and Wändell et al. (2014) focused on retrospective analyses of administrative data; while the studies of Delmas et al. (2011) and Katon et al. (2007) used more extensive interview schedules and medical testing in their study cohorts. Although these types of evidence differ qualitatively, the review supports a view of both as strong sources of evidence, especially given how relatively little knowledge exists regarding the psychiatric comorbidities of adolescent chronic illness. However, both methodologies present advantages and challenges as avenues of future research. Medical and psychiatric diagnoses listed in administrative data are likely reflective of stringent testing, and high quality, representative comparative groups are easily identifiable. However, it may be that a number of children living with a chronic illness who may have a comorbid psychiatric disorder may be overlooked, due to a lack of referral for psychiatric assessment. This limitation is overcome in cohort studies which are reliant on high quality interviews, and this is one of the distinct advantages of this methodology over the use of administrative data. However, this approach is resource heavy, with a significant amount of administrative burden.

Clearly, the major indication of this review is that the mental health of adolescents warrants further attention. Although the studies of the highest quality among this body suggest elevated levels of psychiatric comorbidities, as has been found in adult-forms of such conditions, trends amongst remaining studies suggested that the elevated rates of comorbidities may not be identifiable across conditions. Such a finding would indicate that a more condition-specific framework of analysis is needed amongst this age group. This study in particular highlights current sampling methods as a particular methodological limitation, and emphasises that future research needs to be more reliant on larger samples that are more representative of young people living with the condition, and that comparative samples must be reflective of the general population. Studies should be designed with later identification of age-specific risks in mind, and longitudinal data is needed in order to further investigate the role of moderating and mediating variables.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.adolescence.2017.05.014.

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