

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mental Disorder in Children with Physical Conditions: A Pilot Study
AUTHORS	Butler, Alexandra; Van Lieshout, Ryan; Lipman, Ellen; MacMillan, Harriet; Gonzalez, Andrea; Gorter, Jan Willem; Georgiades, Kathy; Speechley, Kathy; Boyle, Michael; Ferro, Mark

VERSION 1 – REVIEW

REVIEWER	Sophie Bennett UCL Great Ormond Street Institute of Child Health
REVIEW RETURNED	30-Aug-2017

GENERAL COMMENTS	<p>Overall, this appears to be a well-conducted and interesting study on an understudied topic. There have been few longitudinal studies to date investigating mental health problems in the context of chronic physical illness in children and young people. However, the description of the study in the paper as presented is unclear, due to the combination of both feasibility and pilot aims. Although I am aware that definitions of feasibility and pilot studies vary, the study as presented appears underpowered for the analyses presented, but there is limited information regarding feasibility (for example using NIHR definitions - https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/research-programmes/RfPB/FAQs/Feasibility_and_pilot_studies.pdf). If the primary aim of the study is to investigate feasibility of the process, then the authors may prefer to focus on this and remove, or shorten, aspects of the statistical analysis (or vice versa if it is primarily pilot).</p> <p>Specific recommendations:</p> <p>Throughout I am not clear on the aims of the study, how it fits into the current literature, or how it fits in to the larger study.</p> <p>Abstract It is not clear from the abstract what the study entails. Further detail should be provided in addition to 'pilot study'. For example, one of the aims is to methodologically assess the feasibility of 'studying mental disorder among children newly-diagnosed with chronic physical illness' – this is broad and unclear whether any intervention was offered.</p> <p>Strengths and limitations 'this is the first study to examine child physical-mental multimorbidity across a number of different conditions'.</p>
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This may be related to the wide-scope of the language used, but I am not sure that this is the first such study; several studies investigate the relationship between mental health and chronic physical illness in children across a range of conditions (e.g. recently - Jones, L. C., Mrug, S., Elliott, M. N., Toomey, S. L., Tortolero, S., & Schuster, M. A. (2017). Chronic Physical Health Conditions and Emotional Problems From Early Adolescence Through Midadolescence. *Academic Pediatrics*). The authors should be clear about what is unique to this study or delete this.
'this study was likely underpowered to detect differences between children with and without multimorbidity...' – it is probably also underpowered to detect differences within those with multi-morbidity (i.e. all of the statistics are likely to be underpowered, which as a feasibility/pilot may be appropriate, but the authors should be clearer about this from the outset).

Introduction

Para 1 – 'many of these children will be adversely affected by their disorders or their treatment, subsequently developing additional conditions, including mental disorders'. This sentence implies causation and that the increased prevalence of mental health disorders is always seen after onset of physical symptoms of the chronic illness, which may not be the case. In some cases (e.g. epilepsy), rates of mental health disorders are elevated prior to physical illness onset. This has relevance to the aims of investigating effects over time for different chronic illnesses.

Para 4 – 'the extent to which multimorbidity influences other aspects of parental health... is unknown' – needs clarification, as studies have investigated this (e.g. Piquart, M. (2017). Parenting stress in caregivers of children with chronic physical condition—A meta-analysis. *Stress and Health*.)

Para 5 - 'the burden and correlates of multimorbidity... is not well known' – as above, needs clarification as there are many published prevalence studies.

Para 6 – hypothesis regarding socioeconomic disadvantage is not discussed within the background literature.

Methods

The methods and measures are well reported.

I am not clear whether this reports on the full 'REACH' study or a part of the dataset.

Sample - Why were these particular chronic illnesses chosen? Were children with intellectual disability and/or ASD included? Were these assessed/recorded?

Ethics – the full ethical approval details (e.g. board and number) are not provided.

Measures – MINI-KID why were the particular mental health disorders chosen? Has the VAs been validated across groups of different chronic illnesses (rather than within one chronic illness)?

Results

I am not sure how helpful it is to statistically report differences in the prevalence of specific disorders in specific chronic illnesses given the very small numbers in each group (e.g. elevated ADHD and ODD in children with food allergy).

Discussion

Overall, the discussion points are interesting and valid, but could be more speculative given the small sample size.

	<p>'the majority of families... (data not shown)' - this suggests that this is a small subset of data from a larger study – see comment in methods about needing further information regarding this.</p> <p>The strong retention rate/lack of missing data may, but do not necessarily indicate minimal burden. As discussed, families may be more willing to give up their time.</p> <p>'A number of children were ineligible... illness duration was greater than 6 months'. This data , or reference to it , is not included within the results – a section on feasibility of this in the results may be helpful (if presented as a feasibility study).</p> <p>Discussion of association between chronic illness and anxiety again assumes causation – there is no data within this study to confirm whether anxiety was present prior to illness diagnosis.</p>
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REVIEWER	Hiran Thabrew University of Auckland, New Zealand
REVIEW RETURNED	11-Sep-2017

GENERAL COMMENTS	<p>This manuscript outlines the results of a pilot study to investigate the occurrence of multiple co-morbidity in children with long-term physical conditions at the time of diagnosis and six months later.</p> <p>Strengths of the study include its comprehensive design and clear reporting framework. In addition, the authors address the main research questions with interesting and useful commentary within the discussion section.</p> <p>Areas for improvement of the manuscript relate to the following:</p> <ol style="list-style-type: none"> 1. The study data originated from the REACH study, which has not been fully described/referenced. Some of the reasoning behind the methodology, ethics processes (not described) and assumptions made/deviations from protocol (if there was one, I couldn't find one online) are unclear. 2. Although MINI KIDS data was collected from older children and parents, only parent data is presented in this paper. Was the child data well-correlated with parent report as suggested by previous studies of the instrument? If not, why not? 3. What methods were used to deal with the limited amount of missing data? 4. Given the wealthiness of participants, generalisability to a wider audience should be more guarded. 5. Given the study was conducted in Canada, no mention is made regarding ethnicity, which I find disappointing and surprising. Something should be stated, even if it's that the study was not powered to detect differences between subgroups.
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REVIEWER	Melissa Bright University of Florida United States
REVIEW RETURNED	15-Sep-2017

GENERAL COMMENTS	<p>This study pursues 2 separate goals: first to determine feasibility of recruiting child/adolescent patients in a study of physical and mental disorders and second to examine comorbidity of physical and mental disorders. Overall the study is well organized but I'm not convinced that the study is original, particularly the initial aim of determining feasibility of recruiting and retaining child participants from a hospital. The authors do not offer any unique aspects of their study or explanation as to why recruiting these patients would more difficult than any other study that recruits children and families from clinical settings.</p> <p>Other minor notes include: The authors do not justify their inclusion criteria or desired sample and do not give any exclusion criteria. The authors do not give explanation for their hypotheses, particularly the specific expectations of 50% with positive screens and a decrease in depression 6 months later.</p> <p>The authors do not give explanation for the limited mental disorders they chose. Are the 62 families that were approached all that were eligible across 12 months and 2 hospitals? That seems incredibly low. Second paragraph, first line: "mental disorders are common" – this needs some clarification and perhaps edit. The sentence reads "in children" but the citation is about adolescents (13-17 years). Additionally, the citation gives quite a few %s. the authors should clarify what number they are calling "common."</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I am not clear on the aims of the study, how it fits into the current literature, or how it fits in to the larger study.

RESPONSE: In the context of the broader literature, the novelty of this pilot study is the recruitment and study of children newly-diagnosed with a variety of (the most common) chronic physical conditions. As such, we explicitly state our objectives on page 8, paragraph 2: "Anticipating substantial hardships and stress associated with receiving a diagnosis of a physical condition in childhood within families, as well as the uncertainty surrounding prognosis, we conducted a pilot study to assess the feasibility of recruiting of eligible participants, estimating respondent burden related to data collection, and the extent of missing data and attrition. Substantively, the aims of the pilot study were to: 1—examine the initial prevalence of multimorbidity in a clinical sample of children newly-diagnosed with a physical condition, as well as rates six months later; 2—identify correlates of multimorbidity in children and parents; and, 3—explore the influence of multimorbidity on changes in child quality of life and parental psychosocial outcomes over six-months of follow-up." As reviewed in the Introduction, only one study recruited incidence cases, but was limited to diabetes.

We also note on page 8, paragraph 1 that, “While other studies have examined prevalence of multimorbidity, those studies were based on population, not clinical samples of prevalent cases and did not measure DSM-aligned diagnoses; are out-dated; or, focus on a single physical condition.” Because participants (youth and their parents) had just received a new diagnosis of a chronic physical condition and, in some cases recruited into the study on the day the physician disclosed the diagnosis to the family, we thought it prudent to conduct a pilot study prior to implementing a larger, more expensive cohort study. In this pilot study we have been able to estimate recruitment rates, verify data quality (i.e., low missing data and attrition), and confirm that burden of multimorbidity is high in this group of children. These findings are presented in detail in the Discussion (specifically page 16-18).

Abstract

- It is not clear from the abstract what the study entails. Further detail should be provided in addition to ‘pilot study’. For example, one of the aims is to methodologically assess the feasibility of ‘studying mental disorder among children newly-diagnosed with chronic physical illness’ – this is broad and unclear whether any intervention was offered.

RESPONSE: Regarding the Design heading in the Abstract, we have added that the design is a “prospective pilot study” to indicate that repeated measures were administered to participants (page 3, paragraph 2). Design-related details are also provided in the Setting, Participants, and Outcome Measures sections. Because we are following the guidelines of BMJ Open which indicate a brief note on study design, we are unable to add more detail to the Abstract. As our manuscript presents on a pilot study, our objectives fall under the umbrellas of methodological aims that assess feasibility of recruiting and measuring mental health among children newly-diagnosed with physical conditions and substantive aims that examine burden and correlates of multimorbidity. We have included (within the constraints of the Abstract word count) our methodologic and substantive aims as follows: “Methodologically, to assess the feasibility of participant recruitment and retention, as well as missing data in studying mental disorder among children newly-diagnosed with chronic physical conditions (i.e., multimorbidity). Substantively, to examine the prevalence of multimorbidity, identify sociodemographic correlates, and model the influence of multimorbidity on changes in child quality of life and parental psychosocial outcomes over a six-month follow-up.” Given the word count limit in the Abstract, we also further expand on our objectives to provide clarification on page 8, paragraph 2 which state, “...we conducted a pilot study to assess the feasibility of recruiting of eligible participants, estimating respondent burden related to data collection, and the extent of missing data and attrition. Substantively, the aims of the pilot study were to: 1—examine the initial prevalence of multimorbidity in a clinical sample of children newly-diagnosed with a physical condition, as well as rates six months later; 2—identify correlates of multimorbidity in children and parents; and, 3—explore the influence of multimorbidity on changes in child quality of life and parental psychosocial outcomes over six-months of follow-up.”

Strengths and limitations

- ‘this is the first study to examine child physical-mental multimorbidity across a number of different conditions’. This may be related to the wide-scope of the language used, but I am not sure that this is the first such study; several studies investigate the relationship between mental health and chronic physical illness in children across a range of conditions (e.g. recently - Jones, L. C., Mrug, S., Elliott, M. N., Toomey, S. L., Tortolero, S., & Schuster, M. A. (2017). Chronic Physical Health Conditions and Emotional Problems From Early Adolescence Through Midadolescence. *Academic Pediatrics*). The authors should be clear about what is unique to this study or delete this.

RESPONSE: We thank the Reviewer for bringing this study to our attention and have since added those findings to the Introduction (page 7, paragraph 1). The novelty of our study is that we focus on the mental health of child who are newly-diagnosed with a variety of different chronic physical conditions. We have clarified our language in the Strengths and Limitations section (page 5) to make this more explicit, “This is the first study to examine mental disorder in children newly-diagnosed with a number of different conditions.”

- ‘this study was likely underpowered to detect differences between children with and without multimorbidity...’ – it is probably also underpowered to detect differences within those with multimorbidity (i.e. all of the statistics are likely to be underpowered, which as a feasibility/pilot may be appropriate, but the authors should be clearer about this from the outset).

RESPONSE: Thank you for this feedback. In order to highlight these issues, within the Strengths and Limitations section, we have revised our statement to include the Reviewer’s point that, “This study was likely underpowered to detect differences within and between children with and without multimorbidity and the small sample size limits generalizability.”

Regarding statistical power, we did not compute post hoc statistical power given the strong arguments that have been put forward criticizing this approach (see Goodman & Berlin. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994;121:200-206 and Hoenig & Heisey. The abuse of power: the pervasive fallacy of power calculations for data analysis. *Am Statist* 2001;55:1-6). We agree with the Reviewer’s comment that statistical power is often less of a concern in pilot study and as we note on page 10, paragraph 1 and page 20, paragraph 2, our sample size was based on guidelines for the conduct of pilot studies.

Introduction

- Para 1 – ‘many of these children will be adversely affected by their disorders or their treatment, subsequently developing additional conditions, including mental disorders’. This sentence implies causation and that the increased prevalence of mental health disorders is always seen after onset of physical symptoms of the chronic illness, which may not be the case. In some cases (e.g. epilepsy), rates of mental health disorders are elevated prior to physical illness onset. This has relevance to the aims of investigating effects over time for different chronic illnesses.

RESPONSE: We have revised the sentence, softening the language, by stating “These children may be adversely affected...” (page 6, paragraph 1). We note to the Reviewer that our language was deliberately causal, as there is evidence that chronic physical conditions, treatments, and associated adverse events can result in the development of mental health problems. We used the term, “many” and not “all” children to support the Reviewer’s assertion that with some conditions, such as epilepsy, behavioural problems may manifest prior to the diagnosis of their physical condition.

- Para 4 – ‘the extent to which multimorbidity influences other aspects of parental health... is unknown’ – needs clarification, as studies have investigated this (e.g. Pinquart, M. (2017). Parenting stress in caregivers of children with chronic physical condition—A meta-analysis. *Stress and Health*.)
- Para 5 - ‘the burden and correlates of multimorbidity... is not well known’ – as above, needs clarification as there are many published prevalence studies.

RESPONSE: We thank the Reviewer for bringing this study to our attention and have now cited that paper earlier in the paragraph (page 7, paragraph 2). The work by Pinquart (2017) focuses on children with chronic physical conditions, not children with physical-mental multimorbidity. We have revised our language to state that impact of multimorbidity “not well known” (page 7, paragraph 2).

In regards to the Reviewer's second point, we have added following, clarifying that the burden/correlates of youth multimorbidity is not well known: "While other studies have examined prevalence of multimorbidity, those studies were based on population, not clinical samples of prevalent cases and did not measure DSM-aligned diagnoses; are out-dated; or, focus on a single physical condition."

- Para 6 – hypothesis regarding socioeconomic disadvantage is not discussed within the background literature.

RESPONSE: Because this was not the focus of our analyses, we have removed this from the manuscript (page 9, paragraph 1).

Methods

- The methods and measures are well reported.
- I am not clear whether this reports on the full 'REACH' study or a part of the dataset.

RESPONSE: This is a very helpful point. While this manuscript reports on the primary objective of the full REACH study, since the term 'REACH' was used informally among investigators to refer to this study, we have removed it from the manuscript to reduce potential confusion among readers (page 9, paragraph 2).

- Sample - Why were these particular chronic illnesses chosen? Were children with intellectual disability and/or ASD included? Were these assessed/recorded?

RESPONSE: This is an excellent question. Asthma, diabetes, epilepsy, food allergy or juvenile idiopathic arthritis were chosen for study as they represent some of the most common physical conditions among children. Child IQ was not tested and children were not excluded if their parents indicated intellectual disability or ASD. We have added these statements to the Methods on page 9, paragraph 2.

- Ethics – the full ethical approval details (e.g. board and number) are not provided.

RESPONSE: Thank you for pointing out this oversight. We now include this information on page 10, paragraph 2.

- Measures – MINI-KID why were the particular mental health disorders chosen? Has the VAs been validated across groups of different chronic illnesses (rather than within one chronic illness)?

RESPONSE: Major depressive episode, separation anxiety disorder, social phobia, specific phobia, generalized anxiety disorder, attention deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder were chosen for study as these are the most common mental disorders in children. We have included this statement and appropriate citation on page 11, paragraph 1. It is unclear to us what is meant by "VAs" in the second question and have not addressed this in the manuscript.

Results

- I am not sure how helpful it is to statistically report differences in the prevalence of specific disorders in specific chronic illnesses given the very small numbers in each group (e.g. elevated ADHD and ODD in children with food allergy).

RESPONSE: While this is an important issue, we chose to present statistical tests for the prevalence of specific mental disorders so as to provide a complete picture of our findings to readers.

Discussion

- Overall, the discussion points are interesting and valid, but could be more speculative given the small sample size.

- RESPONSE: We agree that substantive findings from this paper are mostly speculative and thus throughout the Discussion we have now provide statements that better highlight this: “Whether markers of inflammation, such as pro-inflammatory cytokines mediate the relationship between physical and mental disorder is unknown.” and “Given the small number of children with food allergy in our sample, these interpretations are by no means definitive, but instead are offered as hypotheses to be tested rigorously in larger samples.” We have also attempted to be as explicit as possible in the manuscript about the pilot nature of the study and its relatively small sample size. Thus, we believe that readers will recognize that the substantive findings are preliminary, explanations for these findings are speculative, and that further research is needed.

- ‘the majority of families... (data not shown)’ - this suggests that this is a small subset of data from a larger study – see comment in methods about needing further information regarding this.

RESPONSE: As we clarify above, the findings from this manuscript reflect the full sample of participants. The final question of the survey asked parents to rank according to preference the following methods of data collection: online, mail, or in-home interview. Most parents selected paper questionnaires as their top preference. We thought this useful to present in the Discussion, but because we did not include these data in the paper, we noted, “data not shown.”

- The strong retention rate/lack of missing data may, but do not necessarily indicate minimal burden. As discussed, families may be more willing to give up their time.

RESPONSE: Thank you. We agree with the Reviewer and have removed this statement from the manuscript (page 17, paragraph 1).

- ‘A number of children were ineligible... illness duration was greater than 6 months’. This data , or reference to it , is not included within the results – a section on feasibility of this in the results may be helpful (if presented as a feasibility study).

RESPONSE: Unfortunately, we did not tally the number of ineligible children and thus, these data are not available. This observation was based on anecdotal feedback provided by the research and clinical staff to study investigators.

- Discussion of association between chronic illness and anxiety again assumes causation – there is no data within this study to confirm whether anxiety was present prior to illness diagnosis.

RESPONSE: We agree with the Reviewer and have revised this section to state, “While this study did not measure mental disorder prior to the diagnosis of a physical conditions, elevated rates of anxiety disorder at the time of diagnosis may be attributable to the uncertainty that children may experience (either before or after diagnosis)...” (page 18, paragraph 2). The remaining discussion surrounding anxiety points to evidence in the literature (and not these data) that may explain the development of anxiety after a diagnosis of a chronic physical condition.

Reviewer: 2

- Strengths of the study include its comprehensive design and clear reporting framework. In addition, the authors address the main research questions with interesting and useful commentary within the discussion section.

Areas for improvement of the manuscript relate to the following:

- The study data originated from the REACH study, which has not been fully described/referenced. Some of the reasoning behind the methodology, ethics processes (not described) and assumptions made/deviations from protocol (if there was one, I couldn't find one online) are unclear.

RESPONSE: In response to a comment from another reviewer, this manuscript reports on the primary objective of the REACH (pilot) study (i.e., no prior publications). Given that 'REACH' was used informally among investigators to refer to this study, we have removed it from the manuscript to avoid confusion among readers (page 9, paragraph 2). We have now added justification for each inclusion criterion and now include exclusion criteria (page 9, paragraph 2) and have provided information regarding ethical approval (page 10, paragraph 2).

In the original protocol, we proposed the use of in-home computer-assisted interviews for data collection. However, due to a budget cut of approximately 5% by the funding agency, this approach could not be implemented and we used mail surveys instead. Interestingly, as we note in the Discussion, families rated mail surveys as their preferred choice for data collection. We can confirm that no deviations in the protocol/methodology were made after the initiation of the study.

- Although MINI KIDS data was collected from older children and parents, only parent data is presented in this paper. Was the child data well-correlated with parent report as suggested by previous studies of the instrument? If not, why not?

RESPONSE: Only 32 children in our sample met the age criteria to self-report on the MINI-KID. Agreement among these 32 child-parent dyads was relatively low, with kappa ranging from 0.05 to 0.39. Direct comparison with the agreement findings presented by Sheehan (2000) is difficult. In that study, kappa ranged from 0.52 to 0.81, suggesting moderate to strong agreement. However, in the study by Sheehan (2000), parents were present during the administration of the MINI-KID to children, which may have contributed to the high agreement.

In our study, the MINI-KID was administered to children privately, without parental presence or influence. In addition, 80% of the sample studied by Sheehan (2000) was children who were outpatients for psychiatric services which also may have contributed to the high levels of agreement. Sheehan (2000) did not report the agreement among the 36 control children and their parents (i.e., controls were from the community). As child-parent agreement was not a primary objective in the study we do not include it in the manuscript. However, we are investigating agreement and the factors that may influence agreement in our sample in a more rigorous manner.

- What methods were used to deal with the limited amount of missing data?

RESPONSE: As the Reviewer correctly notes, there were limited amount of missing data. In light of this finding, as well as the pilot nature of the study, we used a complete case analysis. We note this in the manuscript on page 14, paragraph 2.

- Given the wealthiness of participants, generalisability to a wider audience should be more guarded.

RESPONSE: We agree with the Reviewer and now highlight that relatively high socioeconomic status of families limits the generalizability of the findings (page 19, paragraph 2).

- Given the study was conducted in Canada, no mention is made regarding ethnicity, which I find disappointing and surprising. Something should be stated, even if it's that the study was not powered to detect differences between subgroups.

- RESPONSE: In response to this concern, we now note in the Results on page 15, paragraph 1 that 94% of parents were Caucasian. We also include in Table 1 that 20% of parents in the study were actually immigrants.

Reviewer: 3

- This study pursues 2 separate goals: first to determine feasibility of recruiting child/adolescent patients in a study of physical and mental disorders and second to examine comorbidity of physical and mental disorders. Overall the study is well organized but I'm not convinced that the study is original, particularly the initial aim of determining feasibility of recruiting and retaining child participants from a hospital. The authors do not offer any unique aspects of their study or explanation as to why recruiting these patients would be more difficult than any other study that recruits children and families from clinical settings.

RESPONSE: We thank the reviewer for making these points and providing an opportunity for us to more clearly highlight the more original aspects of this work. In the context of the broader literature, the novelty of this pilot study is the recruitment and study of children newly-diagnosed with a variety (the most common) chronic physical conditions. As reviewed in the Introduction, only one study recruited incidence cases, but this was limited to diabetes. As a result, we have limited knowledge about mental disorder in relation to the onset of chronic physical conditions in children (page 6, paragraph 3; page 8, paragraph 1). Because participants (youth and their parents) had just received a new diagnosis of a chronic physical condition and, in some cases recruited into the study on the day the physician disclosed the diagnosis to the family, we thought it prudent to conduct a pilot study prior to implementing a larger, more expensive cohort study. The hardships and stress associated with receiving a diagnosis in childhood, as well as the uncertainty surrounding a child's prognosis was a critical factor in conducting this pilot study. We have added this point to the manuscript on page 8, paragraph 2. In this pilot study we have been able to estimate recruitment rates, verify data quality (i.e., low missing data and attrition), and that burden of multimorbidity is high in this group of children.

Other minor notes include:

- The authors do not justify their inclusion criteria or desired sample and do not give any exclusion criteria.

RESPONSE: Thank you for pointing this out. We have now added justification for each inclusion criterion and now include exclusion criteria (page 9, paragraph 2). We also cite the paper by Hertzog (2008) that guided our target sample size.

- The authors do not give explanation for their hypotheses, particularly the specific expectations of 50% with positive screens and a decrease in depression 6 months later.

RESPONSE: This is an excellent point. We have now added that our hypothesis of 50% prevalence and then a subsequent decrease is based on limited previous research (page 9, paragraph 1). We have removed our disorder-specific hypotheses.

- The authors do not give explanation for the limited mental disorders they chose.

RESPONSE: We have now made this more explicit by indicating that the eight mental disorders studied represent the most common mental disorders in childhood (page 11, paragraph 1).

- Are the 62 families that were approached all that were eligible across 12 months and 2 hospitals? That seems incredibly low.

RESPONSE: Thank you for raising this issue. We have now clarified that newly-diagnosed children and their families were recruited from four outpatient clinics from two pediatric hospitals (two clinics/hospital) and noted that these centres represent specialized tertiary care (page 9, paragraph 2). Thus, our sample represents children with more severe/complex physical conditions. As we noted in our Discussion, anecdotal reports from our research staff suggested many children had an illness duration of more than six months and were thus not eligible for the study. These children—those who are diagnosed by another physician, but received follow-up care at a pediatric centre—are the largest group of patients.

- Second paragraph, first line: “mental disorders are common” – this needs some clarification and perhaps edit. The sentence reads “in children” but the citation is about adolescents (13-17 years). Additionally, the citation gives quite a few %s. the authors should clarify what number they are calling “common.”

RESPONSE: This is an important point and we thank the reviewer for making it. We have now revised this statement as follows, “Mental disorders of any type are common in children and adolescents and disproportionately affect young people with chronic physical conditions (herein physical conditions)” on page 6, paragraph 2.

VERSION 2 – REVIEW

REVIEWER	Sophie Bennett UCL Great Ormond Street Institute of Child Health, UK
REVIEW RETURNED	26-Oct-2017

GENERAL COMMENTS	The authors have responded to all comments and this is an interesting study and paper.
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REVIEWER	Hiran Thabrew University of Auckland, New Zealand
REVIEW RETURNED	02-Nov-2017

GENERAL COMMENTS	Thanks for addressing most of my previous comments. The updated manuscript looks much clearer. I would appreciate a brief statement in the text (+/- tables) regarding the exclusion of child-report MINI-KID(c) data from the results section as this is not adequately explained.
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REVIEWER	Melissa Bright University of Florida USA
REVIEW RETURNED	15-Oct-2017

GENERAL COMMENTS	<p>Unfortunately I am still not convinced that this study is original. A quick search of mental health and chronic conditions in children yields a number of studies:</p> <p>Cadman, D., Boyle, M., Szatmari, P., & Offord, D. R. (1987). Chronic illness, disability, and mental and social well-being: findings of the Ontario Child Health Study. <i>Pediatrics</i>, 79(5), 805-813.</p> <p>Stein, R. E., & Jessop, D. J. (1984). Relationship between health status and psychological adjustment among children with chronic conditions. <i>Pediatrics</i>, 73(2), 169-174.</p> <p>Bennett, D. S. (1994). Depression among children with chronic medical problems: a meta-analysis. <i>Journal of Pediatric Psychology</i>, 19(2), 149-169.</p> <p>The authors state in their reply that their emphasis is on "newly diagnosed" children but don't offer sufficient evidence about why this aspect is particularly important or more important than recently diagnosed, or previously diagnosed. I also find it highly problematic that all child outcomes were parent reported, particularly for the adolescents.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sophie Bennett

Institution and Country: UCL Great Ormond Street Institute of Child Health, UK

Please state any competing interests or state 'None declared': None declared

The authors have responded to all comments and this is an interesting study and paper.

RESPONSE: Thank you.

Reviewer: 2

Reviewer Name: Hiran Thabrew

Institution and Country: University of Auckland, New Zealand

Please state any competing interests or state 'None declared': None declared

Thanks for addressing most of my previous comments. The updated manuscript looks much clearer. I would appreciate a brief statement in the text (+/- tables) regarding the exclusion of child-report MINI-KID(c) data from the results section as this is not adequately explained.

RESPONSE: We are pleased that our initial revision addressed your previous concerns. In addressing a similar comment from another reviewer, we have now included results from the subset of children who were age-eligible (n=33) to provide self-reports (page 16-19; Table 3). Generally, while agreement between parents and children was relatively low (but consistent with previous studies), estimates of association between child multimorbidity and quality of life were similar between parent and child reports on the MINI-KID and KIDSCREEN-27.

Reviewer: 3

Reviewer Name: Melissa Bright

Institution and Country: University of Florida, USA

Please state any competing interests or state 'None declared': None declared

Comment: Unfortunately I am still not convinced that this study is original. A quick search of mental health and chronic conditions in children yields a number of studies:

Cadman, D., Boyle, M., Szatmari, P., & Offord, D. R. (1987). Chronic illness, disability, and mental and social well-being: findings of the Ontario Child Health Study. *Pediatrics*, 79(5), 805-813.

Stein, R. E., & Jessop, D. J. (1984). Relationship between health status and psychological adjustment among children with chronic conditions. *Pediatrics*, 73(2), 169-174.

Bennett, D. S. (1994). Depression among children with chronic medical problems: a meta-analysis. *Journal of Pediatric Psychology*, 19(2), 149-169.

The authors state in their reply that their emphasis is on "newly diagnosed" children but don't offer sufficient evidence about why this aspect is particularly important or more important than recently diagnosed, or previously diagnosed. I also find it highly problematic that all child outcomes were parent reported, particularly for the adolescents.

RESPONSE: While research in the intersection of physical and mental health in children continues to grow, salient gaps in the literature remain. Relevant knowledge gaps are presented in the Introduction (page 9, paragraph 1). The articles identified by the reviewer do not address these gaps. Each is rather dated (in two cases, 30+ years since publication) and none is longitudinal in design which prevents the examination of changes over time. The study by Cadman et al. (1987) is based on a population sample and did not include physician diagnoses of physical conditions or DSM-aligned assessments of mental disorder. Stein & Jessop (1984) limited their study to younger children aged 5-10 years, a noteworthy methodological feature given that evidence suggests mental disorder is more prevalent in older children/adolescents and agreement between child and parent reports of mental disorder are influenced by child age (see reference #58 in manuscript). The meta-analysis by Bennett (1994) focused on depression only and since then, Piquart & Shen (2011) have published an updated analysis. We refer to the Piquart & Shen (2011) paper, as well as other meta-analysis they have conducted in the Introduction. None of the articles (Cadman, Stein, or Bennett) focused on newly-diagnosed children, though evidence (from Piquart & Shen) show that effect sizes for mental disorder are larger for children with shorter illness duration (i.e., closer to diagnosis). This suggests that the time at or soon after diagnosis with a physical condition is a unique period of potential vulnerability. We make this point in the Introduction (page 9, paragraph 2) and have added a number of references that speak to this unique context. Specifically, there is evidence that symptoms of mental disorder are highest in individuals with shorter illness duration, suicide attempts are highest soon after diagnosis, parents experience the greatest psychological distress early in the course of the illness, and quality of life of children is typically lowest during the first six months post-diagnosis.

Regarding child-reported outcomes, we have now included results from the subset of children who were age-eligible (n=33) to provide self-reports (page 16-19; Table 3). Generally, while agreement between parents and children was relatively low (but consistent with previous studies), estimates of association between child multimorbidity and quality of life were similar between parent and child reports on the MINI-KID and KIDSCREEN-27.