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Mental Disorder in Children with Physical Conditions: A Pilot Study

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Authors' contributions

MAF led the study. MAF, MHB, KNS, KG, JWG, AG, HLM, ELL, and RJV conceptualized and designed the study and were responsible for acquiring funding. MHB, KNS, KG, and AG provided methodological insights. JWG, HLM, ELL, and RJV provided clinical insights. KNS and HLM helped facilitate clinic participation. AB and MAF analyzed and interpreted data and drafted the manuscript. All authors critically reviewed and revised and then approved the final manuscript as submitted.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Data will not be shared in order to protect the confidentiality of participants. This was a multisite study and we do not have approval to make the data publically available.

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Abstract

Objectives: 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.

Design: Pilot study.

Setting: Two children's tertiary hospitals.

Participants: Children aged 6-16 years diagnosed in the past six months with one of asthma, diabetes, epilepsy, food allergy, or juvenile arthritis and their parents.

Outcome measures: Response, participation, and retention rates. Child mental disorder using the Mini International Neuropsychiatric Interview at baseline and six months. Child quality of life, parental symptoms of stress, anxiety, and depression, and family functioning. All outcomes were parent reported.

Results: Response, participation, and retention rates were 90%, 83%, and 88%, respectively. Of the 50 children enrolled in the study, the prevalence of multimorbidity 58% at baseline and 42% at six months. No sociodemographic characteristics were associated with multimorbidity. Multimorbidity at baseline was associated with declines over six months in the following domains of quality of life: physical well-

being, β=-4.82 (-8.47, -1.17), psychological well-being, β=-4.10 (-7.62, -0.58), and school environment, β=-4.17 (-8.18, -0.16). There was no association with parental psychosocial outcomes over time.

Conclusions: Preliminary evidence suggests that mental disorder in children with a physical condition is very common and has a negative impact on quality of life over time. Based on the strong response rate and minimal attrition, our approach to study child multimorbidity appears feasible and suggests that multimorbidity is an important concern for families. Methodological and substantive findings from this pilot study have been used to implement a larger, more definitive study of child multimorbidity out of which should come important clinical implications.

Strengths and limitations of this study

- This pilot study includes children newly-diagnosed with chronic physical conditions.
- This is the first study to examine child physical-mental multimorbidity across a number of different conditions.
- This study was likely underpowered to detect differences between children with and without multimorbidity and the small sample size limits generalizability.
- All outcomes were parent-reported.

Introduction

The global prevalence of children with a chronic physical condition—a health problem that requires ongoing management over a period of years or decades—is common, affecting approximately 25% of children, and increasing.[1] Many of these children will be adversely affected by their disorders or their treatment, subsequently developing additional conditions, including mental disorders.[2] Compared to their peers with a physical or mental disorder only, children with multimorbidity (physical-mental comorbidity) experience greater symptom severity and impairment in both physical and mental health domains.[3] Understandably, the onset of multimorbidity remains an important concern for children, parents, health professionals, and payers.[4]

Mental disorders are common in children[5] and disproportionally affect children and young people with chronic physical conditions (herein physical conditions).[6,7] Estimates from clinical samples suggest that nearly half of children with physical conditions meet criteria for a mental disorder diagnosis.[8] In general population samples, this estimate is lower, with approximately 20-30% of children being affected.[3]

Evidence of the association between physical and mental health is robust,[9-11] but with few exceptions,[7,12] the literature base consists mostly of cross-sectional studies. This limits our understanding of mental health at the time children are diagnosed with a physical condition and how their mental health may change over time. One study found more parent-reported symptoms of problem behavior in children 6-7 years newly diagnosed with a chronic illness compared to healthy controls.[7] This effect was stable through to 10-11 years of age, highlighting the chronicity of multimorbidity in childhood. In a prospective study of children with diabetes, hazard ratios for mental disorder were highest within six-months of the diabetes diagnosis (3.0 [2.7-3.4]) compared to those with a duration of diabetes of five years or more (1.9 [1.7-2.1]), regardless of age at diagnosis,[12] suggesting that the peri-diagnostic period

may be a time of particular mental health risk. While these studies have advanced the field, opportunities exist to overcome the limitations in these studies associated with the ascertainment of physical conditions based on parent-report,[13] assessment of symptoms of problem behaviors rather than mental disorder,[14,15] and inherent weaknesses of using register-based data related to data quality and variable availability.[16]

Existing research also suggests that physical conditions and mental disorders are independently associated with poorer psychosocial outcomes including quality of life[17,18] and self-esteem,[19,20] as well as academic performance.[21,22] These adverse effects can also extend to parents and families who experience elevated stress and psychological distress, worse family functioning, and financial hardship.[23-26] Effects on child and parent psychosocial outcomes appear similar when physical and mental disorders are examined separately; however, there is little research examining whether multimorbidity exerts a compounding effect. Cross-sectional evidence suggests that children with multimorbidity experience worse quality of life compared to children with a physical or mental disorder alone.[27,28] One prospective study showed that adults who experienced multimorbidity during adolescence had lower quality of life compared to those who had a physical or mental disorder only.[29] These researchers found that among those with multimorbidity, physical conditions affected physical quality of life only; while their mental disorder negatively affected multiple domains of life quality, including physical, emotional, and social well-being. The extent to which multimorbidity influences other aspects of parental health and well-being, including parenting stress, psychopathology, and family relationships, is unknown.

Despite the progress made in understanding child multimorbidity and its effects on psychosocial outcomes, important knowledge gaps remain. First, the burden and correlates of multimorbidity,

particularly in clinical samples of children who represent the largest consumers of health services,[30] is not well known. This information is needed to inform resource allocation and the provision of services within the health system. Second, the timing of multimorbidity onset, how it changes, and its influence on psychosocial outcomes over time are not well-understood, limiting our ability to identify opportunities for intervention to prevent the development of mental disorder in children with physical conditions. This includes a lack of understanding how mental disorders may change or appear in relation to the onset of the physical condition. For example, are anxiety disorders more common at the time of diagnosis given the uncertainty surrounding prognosis? Third, effects of child multimorbidity on parental health and well-being have not been explored in much detail. Understanding these effects is key to designing, implementing, and evaluating family-centered approaches to care within the pediatric setting to promote the best possible health outcomes for children, parents, and families.[31]

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. We hypothesized that at the time of diagnosis 50% of children would screen positive for mental disorder (anxiety disorders being most common). Based on limited evidence,[12] we hypothesized that six months later, there would be a decrease in the proportion of multimorbidity (depressive disorder being most common). Finally, we hypothesized that socioeconomic disadvantage would be associated with multimorbidity; children with multimorbidity would have worse quality of life over time;

their parents, more symptoms of parenting stress, anxiety, and depression; and, their families, worse functioning compared to children with physical conditions only.

Methods

Sample

Data come from the Researching Adolescent and Child Health Study (REACH), a multisite, prospective, pilot study aimed at examining mental disorder(s) in children with physical conditions. Families were recruited from two pediatric academic hospitals in Ontario, Canada to assess mental and psychosocial outcomes in children with newly-diagnosed with physical conditions. Health professionals at the hospitals were involved at the initial point of contact and provided eligible families with an overview of the study and details regarding participation. The eligibility criteria for the study were children who: 1—were aged 6-16 years old; 2—had received a diagnosis of asthma, diabetes, epilepsy, food allergy or juvenile idiopathic arthritis within the six months prior to recruitment; and, 3—had a parent who could read English. We aimed to recruit 60 children and families (12 per condition) over a 12-month period.

Data Collection

After the medical encounter, eligible families were invited by clinic nurses to speak with research staff about the study. Research staff briefly introduced the study and provided families an information letter. Families interested in participating in the study consented for clinic nurses to send their contact information to study investigators who then followed-up with families by telephone to confirm eligibility, obtain oral consent from parents and children, and arrange for a convenient time to conduct a telephone interview to assess child mental health. Parents also completed two mailed surveys to assess psychosocial outcomes and demographic characteristics; one at baseline and one six months later, when a second telephone interview to assess mental health was conducted. Parents of all participating

children provided proxy reports and children who were ≥11 years of age self-reported on the telephone interview and to the mail survey. Parents and children also consented to have health professionals provide clinical information at the same measurement occasions. The study protocol received ethical approval from the relevant research ethics boards.

Measures

Mental disorder

Child mental disorder(s) were assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[32] The MINI-KID is a structured diagnostic interview used to assess DSM-IV disorders in children aged 6-17 years and has been validated against the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version.[32] It is composed of diagnostic modules that contain screening questions and skip patterns for each disorder. Phone interviews were administered separately: the MINI-KID(c), to children ≥11 years; and the MINI-KID(p) (proxy version) to all parents at both measurement occasions. The MINI-KID was administered by a single interviewer who underwent training that included monitored practice. The presence of eight current disorders was assessed: major depressive episode, separation anxiety disorder, social phobia, specific phobia, generalized anxiety disorder, attention deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder. The MINI-KID has demonstrated strong test-retest reliability compared to other instruments.[14] Mental disorder was classified according to parent reports on the MINI-KID.

Quality of life

Child quality of life between the two visits was measured using the KIDSCREEN-27,[33] a 27-item child and parent-reported generic measure that assesses five domains: physical well-being (five items; examines

physical activity and energy), psychological well-being (seven items; examines emotional balance and life satisfaction), autonomy and parent relations (seven items; examines family dynamics and age-appropriate freedoms), social support and peers (four items; examines nature of peer relationships) and school environment (four items; examines perception of cognition, learning, and feelings about school). Responses are scored using a five-point Likert scale and domain scores are transformed into T-values with a mean of 50 and a standard deviation of 10 (higher scores indicate better quality of life). The KIDSCREEN-27 has been found to be valid and reliable in children with and without physical conditions[33,34] and demonstrated adequate agreement between children and parents.[35] Internal consistency reliabilities for each domain from this study were good for both child (α=0.75-0.89) and parent reports (α=0.83-0.92). Because only children ≥11 years self-reported the KIDSCREEN-27 (n=28, 56%), only parent-reported KIDSCREEN-27 scores were used in these analyses.

Parental stress

The Parental Stress Scale (PSS) measures parental stress across the domains of rewards, stressors, loss of control, and satisfaction.[36] The 18 items are rated on a five-point Likert scale (eight items are reverse-coded) with higher scores (range: 18-90) indicating more parental stress. The psychometric properties of the PSS are robust: test-retest reliability (r=0.81) and convergent validity with the Parenting Stress Index (r=0.75) and Perceived Stress Scale (r=0.41).[36] Internal consistency for the PSS in this study was α=0.84.

Parental anxiety

The State Trait Anxiety Inventory (STAI) is a widely used tool for measuring anxiety. Of the 40 questions in the STAI survey, REACH considered "trait anxiety" items only which aim to measure how parents generally feel, as well as their propensity for perceived anxiety.[37] Survey responses were scored from 1-4 (seven items are reverse-coded). Scores were summed together (range: 20-80) with higher scores

indicating higher levels of anxiety. The STAI has robust psychometric properties, with trait-specific test-retest reliabilities of r=0.73-0.86 and has been shown to be valid with other questionnaires used to assess anxiety (r=0.73-0.85).[37,38] In this study, internal consistency for the STAI was α=0.89.

Parental depression

Parental symptoms of depression were measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item scale designed to assess depressive symptomatology in the general adult population over the past week.[39] The CES-D includes items that survey the domains of positive and negative affect, somatic activity, and interpersonal relations. A four-point Likert scale is used to rate the frequency of symptoms experienced. Higher scores (range: 0-60) indicate greater frequency of depressive symptoms and individuals with total scores ≥16 are typically identified as having clinically significant levels of depression.[39] Extensive research has shown the CES-D to be valid and reliable.[38,40] In this study, internal consistency for the CES-D was α=0.93.

Family functioning

The 12-item General Functioning subscale of the McMaster Family Assessment Device provided a valid and reliable measure of the health/pathology of the family (i.e., family functioning).[41,42] The scale is derived by summing items from six domains: problem solving, communication, roles, affective responsiveness, affective involvement, and behavioral control. Items are rated on a four-point Likert scale with higher scores (range: 0-36) indicating poorer overall family functioning. Internal consistency for the FAD in this study was α=0.92.

Physical Condition Disease severity

Disease severity in children was assessed and measured by a health professional using a 10 cm visual analog scale (VAS). The VAS represents a continuum of disease severity.[43] Health professionals marked the VAS at the point at which best reflected the disease severity of the child, according to their clinical judgment. The distance from the zero point of the VAS (left side) to the mark was measured and recorded as the disease severity of the child. The VAS and its scoring method has been used in a variety of populations and settings to assess well-being and pain and has the advantage of being easily comparable across study samples.[44,45]

Demographic characteristics

Sociodemographic data were collected on child and parent age, sex and immigrant status, parent marital status and educational attainment, as well as annual household income.

Analysis

Comparisons between children with and without multimorbidity were made using Mann-Whitney (continuous variables) and Fisher's Exact tests (categorical variables). Changes in the prevalence of multimorbidity from baseline to six months was using the McNemar test. Analysis of variance with post hoc Scheffé tests were conducted to compare KIDSCREEN-27 scores with available population norms.[33] Generalized linear modeling was used to examine the association between multimorbidity and children's quality of life and parent psychosocial outcomes at six-months. Outcomes were regressed on presence of multimorbidity, controlling for baseline scores for each respective outcome, as well as child age, sex, and physical condition. These covariates were included in the models to present unbiased estimates of effect. All analyses were conducted using SPSS 21 (IBM Corporation). Due to the pilot nature of this study, statistical tests were two-tailed using a significance level of α=0.10. There were no missing item-level data.

Results

Sample characteristics

Over 12 months, 62 families were approached to participate in REACH. Of these, 56 (90% response) agreed to participate. Four families were not interested in participating and two families had a child that did not meet the eligibility criteria. Fifty families (83% participation) completed the baseline assessment (telephone and mail) and forty-four (88% retention) completed the six-month follow-up (telephone and mail). Repeated attempts to contact the six families who completed the telephone interview, but did not return the complete mail survey were unsuccessful, thus the reasons for withdrawal from the study are unknown. There were no baseline differences between families lost to follow-up and those who completed the study.

Baseline characteristics are shown in Table 1. The mean age of children was 11.3 (SD 3.3) years and 52% were male. There was no difference in the number of children across physical condition subgroup, though asthma was the most common (28%) and epilepsy and food allergy, the least common (16%). Parents had a mean of age of 44.0 (5.7) years and 90% were female. Most parents were married (78%), had completed post-secondary education (78%), and had annual household incomes of ≥$90,000 Canadian dollars (58%).

Prevalence of multimorbidity

The prevalence of multimorbidity declined from 58% at baseline to 42% at six-months (p=0.09; Table 2). At baseline, 11 (22%) children had multiple mental disorders. This decreased to nine (18%) at six months. Anxiety disorder (at least one of separation anxiety, phobias, or generalized anxiety) was the most common disorder at baseline (36%) and six months (26%). Differences across physical conditions

were found for the prevalence of attention-deficit hyperactivity disorder (χ^2=6.44; p=.06) and oppositional defiant disorder (χ^2=7.53; p=0.07) at baseline and for attention-deficit hyperactivity disorder (χ^2=7.98; p=.09) at six months. In each case, the proportion of mental disorder was elevated in children with food allergy.

Correlates of multimorbidity

Results showed no differences in child and parent characteristics between children with and without multimorbidity with two exceptions (Table 1): children with multimorbidity had lower KIDSCREEN-27 psychological well-being (43.6 vs. 49.4; p=0.08) and parents reported higher STAI scores (44.2 vs. 38.2; p=0.05).

Multimorbidity and psychosocial outcomes

Comparisons of KIDSCREEN-27 scores between our sample and population norms are shown in Figure 1. Overall differences were found for the physical well-being, psychological well-being, and peer support domains. Post hoc tests showed that compared to population norms, children with multimorbidity had significantly poorer psychological well-being (t=4.21; p<0.01) and children without multimorbidity had lower peer support (t=2.66; p<0.01). Results of the unadjusted and adjusted generalized linear models of the association of multimorbidity with quality of life over time are shown in Table 3. Adjusting for child age, sex, type of physical condition, and baseline KIDSCREEN-27 score, multimorbidity was associated with lower scores in the following domains at six months: physical well-being (β=-4.82; p=0.03), psychological well-being (β=-4.10; p=0.06), and school environment (β=-4.17; p=0.09). With the exception of autonomy and parent relations, the strength of the association increased after covariate adjustment.

The same modeling strategy was used to examine the associations with parental stress, anxiety, depression, and family functioning. In both unadjusted and adjusted models, multimorbidity was not associated with any psychosocial outcomes in parents over time (Table 4). Similarly, the strength of association (though not statistically significant) increased after covariate adjustment.

Discussion

In this pilot study, over half of children screened positive for mental disorder(s) soon after being diagnosed with a physical condition and this proportion appeared to decrease six months later. Anxiety disorders were found to be the most common disorders affecting children at diagnosis and six-months later. There were no sociodemographic differences between children with and without multimorbidity. While multimorbidity did have a negative effect on child quality of life over time, our hypothesis that it would also influence parental outcomes was unsupported.

Methodologically, this pilot study has implications for the study of child multimorbidity within the clinical setting. Regarding participant recruitment, we limited the amount of contact between research staff and families during the initial contact in the clinic. This served two purposes: one, it minimized burden on the physicians and nurses whose primary focus is clinical care, as well as clinical staff managing large patient volumes. Two, it reduced the amount of information passed to families at a time when they may have felt overwhelmed with the clinical information provided by the physician about their child's diagnosis. We provided an information letter and then followed up by telephone a few days later when families were away from the clinic and had a chance to review this letter and determine if they wanted to participate. Our approach of engaging families personally in clinic, followed by telephone contact, and data collection via mail survey was found to be acceptable to families. Our strong response and retention rates contrast evidence showing reduced response rates in research

studies.[46] The majority of families in our study also noted that mail survey was the preferred method for data collection compared to online surveys and home interviews (data not shown). Overall, our methodology resulted in good coverage, with over 80% of consecutively approached eligible families participating in the study. Participation requirements had minimal burden on families as shown by the strong retention rate and lack of missing data. This suggests that the mental health of children with physical conditions is an important concern for families and that they are willing to contribute their time to such research studies. Our recruitment experience suggested that a number of children were ineligible for the study because their illness duration was greater than six months (i.e., diagnosed before six years of age). To ensure a more efficient recruitment that encompasses an even larger coverage of our target population, the larger study will include children as young as two years of age and we are expanding the number of physical conditions (e.g., bowel diseases, chronic headache, lupus).

Our estimate of the proportion of children with multimorbidity was similar to previous reports[8] and supports the chronicity of multimorbidity during the early stages of being diagnosed with a physical condition.[7] As shown in previous work in children with diabetes[12] the peri-diagnostic period represents a critical developmental period for mental health. Elevated rates of anxiety disorder may be attributable to the uncertainty that children may experience regarding the prognosis of their physical condition, including unpredictability of exacerbations, fear of death, loss of control, stigma associated with their condition, or adverse effects of medical treatment.[10] From this perspective, anxiety arises from negatively-biased thought patterns that exaggerate adverse effects of the physical condition and can undermine confidence in adapting to threatening situations.[47] Anxiety in these children may be an inherited trait or learned behavior—parents of children with multimorbidity in our sample reported more symptoms of anxiety compared to parents of children without multimorbidity. There is also emerging evidence of shared biological pathways that underlie multimorbidity. In adults, symptoms of

anxiety are associated with systemic inflammation,[48] which is elevated in individuals with physical conditions. Whether markers of inflammation, such as pro-inflammatory cytokines mediate the relationship between physical and mental disorder is unknown.

These findings also contribute to the converging evidence that risk for mental disorder is relatively consistent among children with various physical conditions.[49] One exception was that attention-deficit hyperactivity disorder was more common among children with food allergy. This increased risk is supported by some previous studies.[50,51] As in this work, attention-deficit hyperactivity disorder in our sample of children with food allergy was mainly of the inattentive subtype. Inattentiveness may co-occur with core symptoms of generalized anxiety disorder, manifesting because of hypervigilance in avoiding food allergens. From a biological perspective, there is evidence of shared immunological[52] and inflammatory[53] responses for allergic conditions and attention-deficit hyperactivity disorder which may explain this association. 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.

In general, the sample consisted of high socioeconomic two-parent families, which may have contributed to the lack of sociodemographic differences between children with and without multimorbidity. Placing the finding in the context of previous work is difficult given the absence of studies examining sociodemographic correlates of multimorbidity. Previous population-based studies conducted in Canada also showed no socioeconomic differences between children with and without physical conditions.[23,54-56] In our larger study, we will work towards a recruitment strategy that will include wider variation in the socioeconomic status to families to increase the representativeness of the sample. Contrary to expectation, no effect of multimorbidity on parental outcomes was found.

Nevertheless, information related to parental psychopathology and family environment may be important control variables used to isolate the effects of multimorbidity on child outcomes. Such family processes may also be implicated in complex pathways linking physical and mental health in children. As a result, these variables will be included in the larger study.

Multimorbidity appears to have a negative effect on children's quality of life, above and beyond the effect of having a physical condition alone.[17] This effect is pervasive, affecting multiple domains of quality of life during the first six months after a diagnosis. Of interest is the finding that the magnitude of effect seen for physical well-being, psychological well-being, and school environment was approximately half a standard deviation. This metric has been validated as the minimal clinically important difference for measures of quality of life[57] and provides evidence to support the perception that changes in child quality of life due to multimorbidity are clinically relevant. Given the early onset of multimorbidity, health professionals in the pediatric setting should consider engaging children and families in discussions about mental health soon after the diagnosis of a physical condition is made and discussion surrounding the physical condition completed. Within a holistic family-centered approach, health professionals are encouraged to apply brief screening tools to identify at-risk children and provide referrals to supportive services on a case-by-case basis. This is a critical window of opportunity given that mental disorder is strong predictor of youth suicide[58] and that risk for suicide is highest soon after an adolescent is diagnosed with a physical condition.[59] Because of the chronicity and pervasiveness of multimorbidity and its influence on child and parent psychosocial functioning, continuing monitoring during routine clinical assessments may also be warranted.

There are two noteworthy limitations. First, the study was likely underpowered to detect differences between children with and without multimorbidity and the small sample size may limit the

generalizability of findings. However, our sample size was consistent with considerations for implementing pilot studies[60] and our coverage of eligible families was good. Second, measurement of child mental health and child and parent outcomes were parent-reported. While we have found adequate agreement between parents and a small subset of children who provided self-reported quality of life,[35] significant associations may be the result of shared-method variance.

Conclusion

These preliminary findings indicate that mental disorder in children newly-diagnosed with a physical condition is common and negatively affects their quality of life over time. If these results are replicated in a subsequent larger study, health professionals should be aware of the burden of multimorbidity and prepare themselves to discuss mental health with children and their parents. Findings from this pilot study have been used to implement a large-scale study that will examine child multimorbidity in greater depth and provide more definitive clinical implications.

References

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA 2010;303:623-30.

2. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. JAMA 2007;297:2741-51.

3. Merikangas KR, Calkins ME, Burstein M, et al. Comorbidity of physical and mental disorders in the neurodevelopmental genomics cohort study. Pediatrics 2015;135:e927-38.

4. Dobbie M, Mellor D. Chronic illness and its impact: considerations for psychologists. Psychology, health & medicine 2008;13:583-90.

5. Kessler RC, Avenevoli S, Costello EJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry 2012;69:372-80.

6. Ferro MA. Major depressive disorder, suicidal behaviour, bipolar disorder, and generalised anxiety disorder among emerging adults with and without chronic health conditions. Epidemiology and psychiatric sciences 2016;25:462-74.

7. Quach J, Barnett T. Impact of chronic illness timing and persistence at school entry on child and parent outcomes: Australian longitudinal study. Academic pediatrics 2015;15:89-95.

8. Canning EH, Hanser SB, Shade KA, Boyce WT. Mental disorders in chronically ill children: parent-child discrepancy and physician identification. Pediatrics 1992;90:692-6.

9. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. J Pediatr Psychol 2011;36:1003-16.

10. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr 2011;100:1069-76.

11. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol 2011;36:375-84.

12. Butwicka A, Frisen L, Almqvist C, Zethelius B, Lichtenstein P. Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes: a population-based cohort study. Diabetes Care 2015;38:453-9.

13. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. Bmc Public Health 2013;13.

14. Boyle MH, Duncan L, Georgiades K, et al. Classifying child and adolescent psychiatric disorder by problem checklists and standardized interviews. International journal of methods in psychiatric research 2016.

15. Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY. Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International journal of methods in psychiatric research 2009;18:169-84.

16. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. European Journal of Epidemiology 2014;29:551-8.

17. Moreira H, Carona C, Silva N, Frontini R, Bullinger M, Canavarro MC. Psychological and quality of life outcomes in pediatric populations: a parent-child perspective. J Pediatr 2013;163:1471-8.

18. Bai G, Herten MH, Landgraf JM, Korfage IJ, Raat H. Childhood chronic conditions and health-related quality of life: Findings from a large population-based study. PLoS One 2017;12:e0178539.

19. Ferro MA, Boyle MH. Self-concept among children and adolescents with a chronic illness: a meta-analytic review. Health Psychol 2013;32:839-48.

20. Bolognini M, Plancherel B, Bettschart W, Halfon O. Self-esteem and mental health in early adolescence: development and gender differences. J Adolesc 1996;19:233-45.

21. Crump C, Rivera D, London R, Landau M, Erlendson B, Rodriguez E. Chronic health conditions and school performance among children and youth. Ann Epidemiol 2013;23:179-84.

22. Forrest CB, Bevans KB, Riley AW, Crespo R, Louis TA. School outcomes of children with special health care needs. Pediatrics 2011;128:303-12.

23. Ferro MA, Boyle MH. The impact of chronic physical illness, maternal depressive symptoms, family functioning, and self-esteem on symptoms of anxiety and depression in children. J Abnorm Child Psychol 2015;43:177-87.

24. Miodrag N, Burke M, Tanner-Smith E, Hodapp RM. Adverse health in parents of children with disabilities and chronic health conditions: a meta-analysis using the parenting stress index's health sub-domain. J Intellect Disabil Res 2015;59:257-71.

25. Newacheck PW, Kim SE. A national profile of health care utilization and expenditures for children with special health care needs. Arch Pediatr Adolesc Med 2005;159:10-7.

26. McCarthy MJ, Behimer G, Anderson JA, Riddle I. Caregiving for youth with co-occurring developmental disabilities and behavioral health issues when caregivers face additional health-related stressors: Analysis of risk and protective factors from a national sample. Res Dev Disabil 2016;59:399-409.

27. Lee SL, Cheung YF, Wong HS, Leung TH, Lam TH, Lau YL. Chronic health problems and health-related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ open 2013;3.

28. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev 2008;34:418-29.

29. Chen H, Cohen P, Kasen S, Johnson JG, Berenson K, Gordon K. Impact of adolescent mental disorders and physical illnesses on quality of life 17 years later. Arch Pediatr Adolesc Med 2006;160:93-9.

30. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. CMAJ 2016;188:182-8.

31. Committee On Hospital C, Institute For P, Family-Centered C. Patient- and family-centered care and the pediatrician's role. Pediatrics 2012;129:394-404.

32. Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 2010;71:313-26.

33. Ravens-Sieberer U, Auquier P, Erhart M, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Qual Life Res 2007;16:1347-56.

34. Robitail S, Ravens-Sieberer U, Simeoni MC, et al. Testing the structural and cross-cultural validity of the KIDSCREEN-27 quality of life questionnaire. Qual Life Res 2007;16:1335-45.

35. Qadeer RA, Ferro MA. Child–parent agreement on health-related quality of life in children with newly diagnosed chronic health conditions: a longitudinal study. Int J Adolesc Youth 2017.

36. Berry JO, Jones WH. The Parental Stress Scale: initial psychometric evidence. J Soc Pers Relation 1995;12:463-72.

37. Spielberger CD. State-Trait Anxiety Inventory for adults. Menlo Park: Mind Garden Inc.; 1983.

38. Okun A, Stein RE, Bauman LJ, Silver EJ. Content validity of the Psychiatric Symptom Index, CES-depression Scale, and State-Trait Anxiety Inventory from the perspective of DSM-IV. Psychol Rep 1996;79:1059-69.

39. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.

40. Ferro MA, Speechley KN. Factor structure and longitudinal invariance of the Center for Epidemiological Studies Depression Scale (CES-D) in adult women: application in a population-based sample of mothers of children with epilepsy. Arch Womens Ment Health 2013;16:159-66.

41. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Ther 1983;9:171-80.

42. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. Fam Process 1988;27:97-104.

43. Crichton N. Visual Analogue Scale (VAS). Journal of Clinical Nursing 2001;10:706-.

44. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007-19.

45. Paul-Dauphin A, Guillemin F, Virion JM, Briancon S. Bias and precision in visual analogue scales: a randomized controlled trial. Am J Epidemiol 1999;150:1117-27.

46. Couper MP. New developments in survey data collection. Annu Rev Sociol 2017;43:1-25.

47. Beck AT, Emery G, Greenberg RL. Anxiety disorders and phobias: a cognitive perspective. New York: Guildford Press; 1985.

48. Hou R, Garner M, Holmes C, et al. Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: Case-controlled study. Brain, behavior, and immunity 2017;62:212-8.

49. Stein RE, Silver EJ. Operationalizing a conceptually based noncategorical definition: a first look at US children with chronic conditions. Arch Pediatr Adolesc Med 1999;153:68-74.

50. Ferro MA, Van Lieshout RJ, Ohayon J, Scott JG. Emotional and behavioral problems in adolescents and young adults with food allergy. Allergy 2016;71:532-40.

51. Topal E, Catal F, Soylu N, et al. Psychiatric disorders and symptoms severity in pre-school children with cow's milk allergy. Allergol Immunopathol (Madr) 2016;44:445-9.

52. Besser MJ, Ganor Y, Levite M. Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNF alpha or both. Journal of neuroimmunology 2005;169:161-71.

53. Buske-Kirschbaunn A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. Psychoneuroendocrinology 2013;38:12-23.

54. Ferro MA, Boyle MH. Longitudinal invariance of measurement and structure of global self-concept: a population-based study examining trajectories among adolescents with and without chronic illness. J Pediatr Psychol 2013;38:425-37.

55. Ferro MA, Gorter JW, Boyle MH. Trajectories of depressive symptoms during the transition to young adulthood: the role of chronic illness. J Affect Disord 2015;174:594-601.

56. Gonzalez A, Boyle MH, Kyu HH, Georgiades K, Duncan L, MacMillan HL. Childhood and family influences on depression, chronic physical conditions, and their comorbidity: findings from the Ontario Child Health Study. J Psychiatr Res 2012;46:1475-82.

57. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-92.

58. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA psychiatry 2013;70:300-10.

59. Christiansen E, Stenager E. Risk for attempted suicide in children and youths after contact with somatic hospitals: a Danish register based nested case-control study. J Epidemiol Community Health 2012;66:247-53.

60. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008;31:180-91.

Table 1. Baseline sample characteristics

	Full sample	Multimorbid	Not multimorbid	P-value
N	50	29	21	
Child				
Age, years	11.3 (3.3)	11.6 (3.2)	11.0 (3.4)	0.62
Male, n (%)	26 (52)	15 (52)	11 (52)	0.96
Diagnoses, n (%)				0.98
Asthma	14 (28)	9 (31)	5 (24)	
Diabetes	9 (18)	4 (14)	5 (24)	
Epilepsy	8 (16)	4 (14)	4 (19)	
Food allergy	8 (16)	5 (17)	3 (14)	
Juvenile arthritis	11 (22)	7 (24)	4 (19)	
Disease severity, VAS	1.3 (1.2)	1.5 (1.3)	0.9 (0.9)	0.16
Quality of life, KIDSCREEN-27				
Physical well-being	48.0 (12.0)	47.4 (11.0)	48.8 (13.4)	0.77
Psychological well-being	46.1 (9.8)	43.6 (8.1)	49.4 (11.2)	0.08
Autonomy/Parent relations	48.9 (9.6)	47.5 (7.0)	50.8 (12.1)	0.72
Peer support	46.1 (11.4)	46.7 (12.1)	45.4 (10.5)	0.35
School environment	50.1 (10.8)	47.7 (8.8)	53.3 (12.4)	0.12
Parent				
Age, years	44.0 (5.7)	43.0 (4.8)	45.2 (6.3)	0.43
Female, n (%)	45 (90)	26 (90)	19 (91)	0.92
Married, n (%)	39 (78)	22 (76)	17 (81)	0.67
Post-secondary graduate, n (%)	39 (78)	22 (76)	17 (81)	0.67
Income ≥$90,000, n (%)	29 (58)	17 (59)	12 (57)	0.87
Parental stress, PSS	35.9 (7.9)	37.1 (7.3)	34.4 (8.5)	0.32
Parental anxiety, STAI	41.6 (9.8)	44.2 (9.1)	38.2 (10.0)	0.05
Parental depression CES-D	12.7 (9.9)	13.0 (9.6)	12.2 (10.5)	0.58
Family functioning, FAD	25.5 (6.3)	24.7 (6.2)	26.5 (6.6)	0.20

Results are reported as mean (standard deviation) unless otherwise noted.

Table 2. Prevalence of multimorbidity

	Full sample	Asthma	Diabetes	Epilepsy	Food allergy	Juvenile arthritis	P-value
Baseline							
Any disorder	29 (58)	9 (64)	4 (44)	4 (50)	5 (63)	7 (64)	0.88
Major depressive episode	12 (24)	4 (29)	2 (22)	1 (13)	1 (13)	4 (36)	0.74
Separation anxiety	2 (4)	0	0	1 (13)	0	1 (9)	0.43
Phobia*	15 (30)	6 (46)	1 (11)	1 (13)	3 (38)	4 (36)	0.35
Generalized anxiety	6 (12)	0	0	2 (25)	2 (25)	2 (18)	0.11
Attention-deficit hyperactivity	5 (10)	1 (7)	0	1 (13)	3 (38)	0	0.06
Oppositional defiant	9 (18)	2 (14)	1 (11)	2 (25)	4 (50)	0	0.07
Conduct	3 (6)	1 (7)	0	1 (13)	1 (13)	0	0.65
Six months							
Any disorder	21 (42)	9 (64)	1 (11)	4 (50)	2 (25)	5 (56)	0.10
Major depressive episode	2 (4)	0	0	0	0	2 (22)	0.11
Separation anxiety	3 (6)	2 (14)	0	1 (13)	0	0	0.56
Phobia*	10 (20)	5 (36)	1 (11)	1 (13)	0	3 (33)	0.25
Generalized anxiety	4 (8)	1 (7)	0	1 (13)	0	2 (22)	0.55
Attention-deficit hyperactivity	3 (6)	0	0	0	2 (25)	1 (11)	0.09
Oppositional defiant	6 (12)	2 (14)	0	2 (25)	2 (25)	0	0.31
Conduct	4 (8)	1 (7)	0	2 (25)	1 (13)	0	0.33

Results are the number (%) of children with multimorbidity. Fisher's Exact tests examined multimorbidity across the five physical conditions.

*Includes generalized, non-generalized, and specific phobias.

Table 3. Longitudinal effects of multimorbidity on child quality of life

	Unadjusted		Adjusted	
KIDSCREEN-27	**B (SE)**	**P-value**	**B (SE)**	**P-value**
Physical well-being	-3.76 (2.23)	0.09	-4.82 (2.22)	0.03
Psychological well-being	-2.06 (2.44)	0.40	-4.10 (2.14)	0.06
Autonomy/Parent relations	0.77 (2.53)	0.76	-0.67 (2.40)	0.78
Peer support	-0.59 (2.83)	0.84	-1.23 (2.66)	0.64
School environment	-3.56 (2.88)	0.22	-4.17 (2.44)	0.09

Models adjusted for child age and sex, physical condition, and baseline quality of life.

Table 4. Longitudinal effects of multimorbidity on parental outcomes

	Unadjusted		Adjusted	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Parental stress, PSS	0.28 (1.60)	0.86	-1.50 (1.51)	0.32
Parental anxiety, STAI	0.14 (2.05)	0.95	-0.24 (2.15)	0.91
Parental depression CES-D	0.30 (1.12)	0.80	0.62 (1.13)	0.58
Family functioning, FAD	1.21 (1.32)	0.36	1.47 (1.28)	0.25

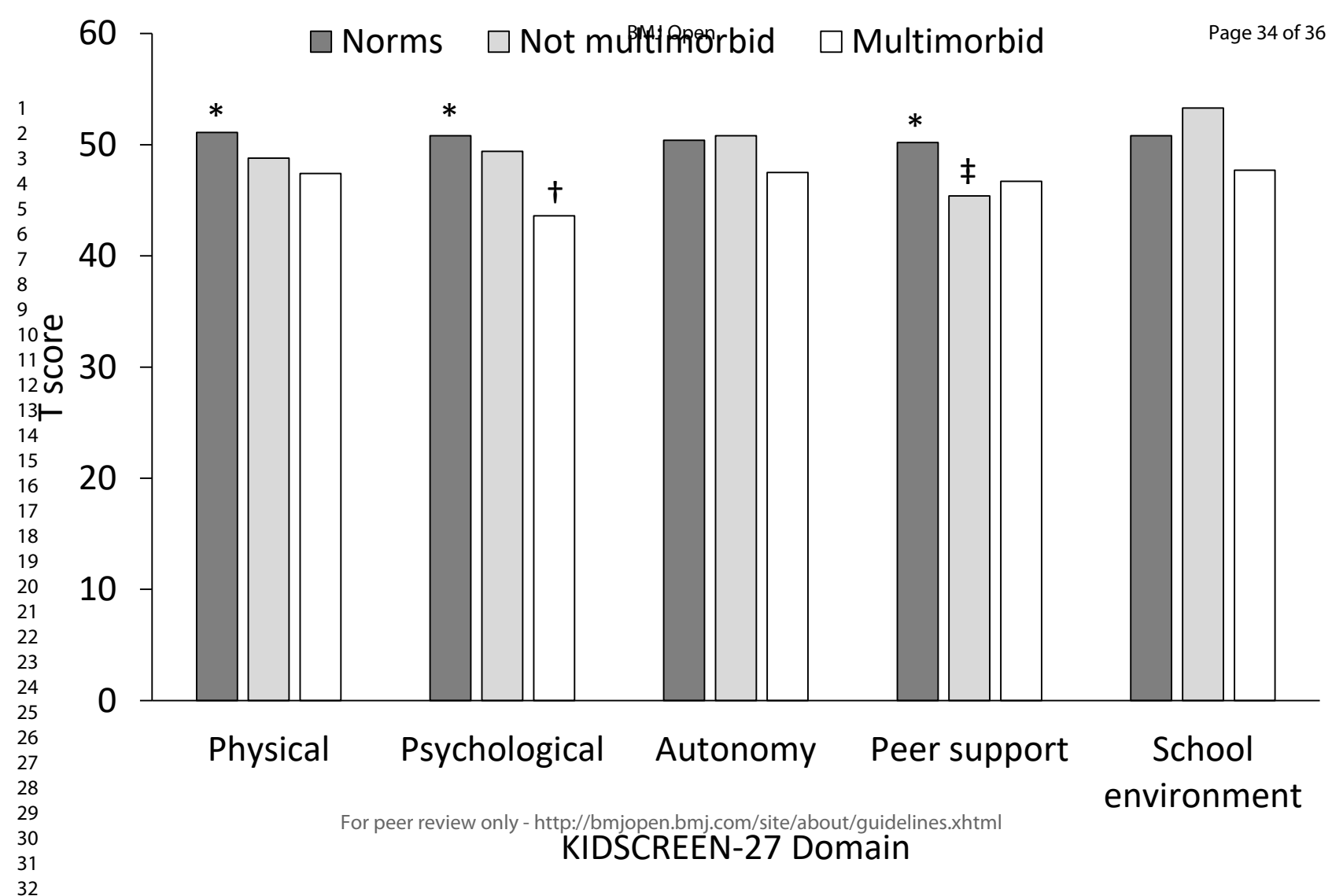
Models adjusted for child age and sex, physical condition, and baseline psychosocial outcome.

Figure 1. Comparison of KIDSCREEN-27 scores with population norms

*p<0.10 for overall F-test across the three groups.

†Multimorbid group significantly lower than normative and not multimorbid groups.

‡Not multimorbid group significantly lower than normative group.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-13
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	13
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	31-32
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18, 19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mental Disorder in Children with Physical Conditions: A Pilot Study

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Mental Disorder in Children with Physical Conditions: A Pilot Study

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Authors' contributions

MAF led the study. MAF, MHB, KNS, KG, JWG, AG, HLM, ELL, and RJV conceptualized and designed the study and were responsible for acquiring funding. MHB, KNS, KG, and AG provided methodological insights. JWG, HLM, ELL, and RJV provided clinical insights. KNS and HLM helped facilitate clinic participation. AB and MAF analyzed and interpreted data and drafted the manuscript. All authors critically reviewed and revised and then approved the final manuscript as submitted.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Data will not be shared in order to protect the confidentiality of participants. This was a multisite study and we do not have approval to make the data publically available.

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Abstract

Objectives: 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.

Design: Prospective pilot study.

Setting: Two children's tertiary-care hospitals.

Participants: Children aged 6-16 years diagnosed in the past six months with one of asthma, diabetes, epilepsy, food allergy, or juvenile arthritis and their parents.

Outcome measures: Response, participation, and retention rates. Child mental disorder using the Mini International Neuropsychiatric Interview at baseline and six months. Child quality of life, parental symptoms of stress, anxiety, and depression, and family functioning. All outcomes were parent reported.

Results: Response, participation, and retention rates were 90%, 83%, and 88%, respectively. Of the 50 children enrolled in the study, the prevalence of multimorbidity was 58% at baseline and 42% at six months. No sociodemographic characteristics were associated with multimorbidity. Multimorbidity at baseline was associated with declines over six months in the following quality of life domains: physical well-being, β=-4.82 (-8.47, -1.17), psychological well-being, β=-4.10 (-7.62, -0.58), and school

environment, β=-4.17 (-8.18, -0.16). There was no association with parental psychosocial outcomes over time.

Conclusions: Preliminary evidence suggests that mental disorder in children with a physical condition is very common and has a negative impact on quality of life over time. Based on the strong response rate and minimal attrition, our approach to study child multimorbidity appears feasible and suggests that multimorbidity is an important concern for families. Methodological and substantive findings from this pilot study have been used to implement a larger, more definitive study of child multimorbidity, which should lead to important clinical implications.

Strengths and limitations of this study

- This pilot study includes children newly-diagnosed with chronic physical conditions.
- 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 within and between children with and without multimorbidity and the small sample size limits generalizability.
- All outcomes were parent-reported.

Introduction

The global prevalence of children with a chronic physical condition—a health problem that requires ongoing management over a period of years or decades—is common, affecting approximately 25% of children, and increasing.[1] These children may be adversely affected by their disorders or their treatment, subsequently developing additional conditions, including mental disorders.[2] Compared to their peers with a physical or mental disorder only, children with multimorbidity (physical-mental comorbidity) experience greater symptom severity and impairment in both physical and mental health domains.[3] Understandably, the onset of multimorbidity remains an important concern for children, parents, health professionals, and payers.[4]

Mental disorders of any type are common in children and adolescents[5] and disproportionally affect young people with chronic physical conditions (herein physical conditions).[6,7] Estimates from clinical samples suggest that nearly half of children with physical conditions meet criteria for a mental disorder diagnosis.[8] In general population samples, this estimate is lower, with approximately 20-30% of children being affected.[3]

Evidence of the association between physical and mental health is robust,[9-11] but with few exceptions,[7,12,13] the literature base consists mostly of cross-sectional studies. This limits our understanding of mental health at the time children are diagnosed with a physical condition and how their mental health may change over time. One study found more parent-reported symptoms of problem behavior in children 6-7 years newly diagnosed with a chronic illness compared to healthy controls.[7] This effect was stable through to 10-11 years of age, highlighting the chronicity of multimorbidity in childhood. In a prospective study of children with diabetes, hazard ratios for mental disorder were highest within six-months of the diabetes diagnosis (3.0 [2.7-3.4]) compared to those with

a duration of diabetes of five years or more (1.9 [1.7-2.1]), regardless of age at diagnosis,[12] suggesting that the peri-diagnostic period may be a time of particular mental health risk. Another prospective study showed changes over time in associations of mental health with physical conditions being associated with depressive symptoms during childhood, and with anxiety symptoms during early adolescence.[13] While these studies have advanced the field, opportunities exist to overcome the limitations in these studies associated with the ascertainment of physical conditions based on parent-report,[14] assessment of symptoms of problem behaviors rather than mental disorder,[13,15,16] and inherent weaknesses of using register-based data related to data quality and variable availability.[17]

Existing research also suggests that physical conditions and mental disorders are independently associated with poorer psychosocial outcomes including quality of life[18,19] and self-esteem,[20,21] as well as academic performance.[22,23] These adverse effects can also extend to parents and families who experience elevated stress and psychological distress, worse family functioning, and financial hardship.[24-28] Effects on child and parent psychosocial outcomes appear similar when physical and mental disorders are examined separately; however, there is little research examining whether multimorbidity exerts a compounding effect. Cross-sectional evidence suggests that children with multimorbidity experience worse quality of life compared to children with a physical or mental disorder alone.[29,30] One prospective study showed that adults who experienced multimorbidity during adolescence had lower quality of life compared to those who had a physical or mental disorder only.[31] These researchers found that among those with multimorbidity, physical conditions affected physical quality of life only; while their mental disorder negatively affected multiple domains of life quality, including physical, emotional, and social well-being. The extent to which multimorbidity influences other aspects of parental health and well-being, including parenting stress, psychopathology, and family relationships, is not well known.

Despite the progress made in understanding child multimorbidity and its effects on psychosocial outcomes, important knowledge gaps remain. First, the burden and correlates of multimorbidity, particularly in clinical samples of children who represent the largest consumers of health services,[32] 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;[3,13] are out-dated;[8] or, focus on a single physical condition.[12] This information is needed to inform resource allocation and the provision of services within the health system. Second, the timing of multimorbidity onset, how it changes, and its influence on psychosocial outcomes over time are not well-understood, limiting our ability to identify opportunities for intervention to prevent the development of mental disorder in children with physical conditions. This includes a lack of understanding how mental disorders may change or appear in relation to the onset of the physical condition. For example, are anxiety disorders more common at the time of diagnosis given the uncertainty surrounding prognosis? Third, effects of child multimorbidity on parental health and well-being have not been explored in much detail. Understanding these effects is key to designing, implementing, and evaluating family-centered approaches to care within the pediatric setting to promote the best possible health outcomes for children, parents, and families.[33]

Anticipating substantial hardship 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. Based on previous clinical studies,[8] we hypothesized that at the time of diagnosis, 50% of children would screen positive for mental disorder. Based on limited evidence,[12] we hypothesized that six months later, there would be a decrease in the proportion of multimorbidity. Finally, we hypothesized that children with multimorbidity would have worse quality of life over time; their parents, more symptoms of parenting stress, anxiety, and depression; and, their families, worse functioning compared to children with physical conditions only.

Methods

Sample

Data come from a multisite, prospective, pilot study aimed at examining mental disorder(s) in children with physical conditions. Families were recruited from four outpatient clinics from two pediatric academic hospitals (specialized tertiary care centres; two clinics per hospital) in Ontario, Canada to assess mental and psychosocial outcomes in children with newly-diagnosed with physical conditions. Health professionals at the hospitals were involved at the initial point of contact and provided eligible families with an overview of the study and details regarding participation. The eligibility criteria for the study were children who: 1—were aged 6-16 years old (six is the youngest age at which our measure of mental disorder is validated; the ceiling age of 16 years ensured that during the follow-up, participants did not transfer out of the pediatric health system); 2—had received a diagnosis of asthma, diabetes, epilepsy, food allergy or juvenile idiopathic arthritis (which represent the most common physical conditions among children)[34] within the six months prior to recruitment; and, 3—had a parent who could read English (not all measures have been validated in other languages). Children were excluded if they had a degenerative neurological disorder because child and parental outcomes are well-established

in this population. Child IQ was not tested and children were not excluded if their parents indicated intellectual disability, maximizing the coverage and representativeness of our sample. Following sample size guidelines suggested for the conduct of pilot studies,[35] we aimed to recruit 60 children and families (12 per condition) over a 12-month period.

Data Collection

After the medical encounter, eligible families were invited by clinic nurses to speak with research staff about the study. Research staff briefly introduced the study and provided families an information letter. Families interested in participating in the study consented for clinic nurses to send their contact information to study investigators who then followed-up with families by telephone to confirm eligibility, obtain oral consent from parents and children, and arrange for a convenient time to conduct a telephone interview to assess child mental health. Parents also completed two mailed surveys to assess psychosocial outcomes and demographic characteristics; one at baseline and one six months later, when a second telephone interview to assess mental health was conducted. Parents of all participating children provided proxy reports and children who were ≥11 years of age self-reported on the telephone interview and to the mail survey. Parents and children also consented to have health professionals provide clinical information at the same measurement occasions. The study protocol received ethical approval from the Hamilton Integrated Research Ethics Board (14-130) and Research Ethics Board (105505).

Measures

Mental disorder

Child mental disorder(s) were assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[36] The MINI-KID is a structured diagnostic interview used to assess

DSM-IV disorders in children aged 6-17 years and has been validated against the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version.[36] It is composed of diagnostic modules that contain screening questions and skip patterns for each disorder. Phone interviews were administered separately: the MINI-KID(c), to children ≥11 years; and the MINI-KID(p) (proxy version) to all parents at both measurement occasions. The MINI-KID was administered by a single interviewer who underwent training that included monitored practice. The presence of the most common mental disorders was assessed: major depressive episode, separation anxiety disorder, social phobia, specific phobia, generalized anxiety disorder, attention deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder.[37] The MINI-KID has demonstrated strong test-retest reliability compared to other instruments.[15] Mental disorder was classified according to parent reports on the MINI-KID.

Quality of life

Child quality of life between the two visits was measured using the KIDSCREEN-27,[38] a 27-item child and parent-reported generic measure that assesses five domains: physical well-being (five items; examines physical activity and energy), psychological well-being (seven items; examines emotional balance and life satisfaction), autonomy and parent relations (seven items; examines family dynamics and age-appropriate freedoms), social support and peers (four items; examines nature of peer relationships) and school environment (four items; examines perception of cognition, learning, and feelings about school). Responses are scored using a five-point Likert scale and domain scores are transformed into T-values with a mean of 50 and a standard deviation of 10 (higher scores indicate better quality of life). The KIDSCREEN-27 has been found to be valid and reliable in children with and without physical conditions[38,39] and demonstrated adequate agreement between children and parents.[40] Internal consistency reliabilities for each domain from this study were good for both child (α=0.75-0.89) and

parent reports (α=0.83-0.92). Because only children ≥11 years self-reported the KIDSCREEN-27 (n=28, 56%), only parent-reported KIDSCREEN-27 scores were used in these analyses.

Parental stress

The Parental Stress Scale (PSS) measures parental stress across the domains of rewards, stressors, loss of control, and satisfaction.[41] The 18 items are rated on a five-point Likert scale (eight items are reverse-coded) with higher scores (range: 18-90) indicating more parental stress. The psychometric properties of the PSS are robust: test-retest reliability (r=0.81) and convergent validity with the Parenting Stress Index (r=0.75) and Perceived Stress Scale (r=0.41).[41] Internal consistency for the PSS in this study was α=0.84.

Parental anxiety

The State Trait Anxiety Inventory (STAI) is a widely used tool for measuring anxiety. Of the 40 questions in the STAI survey, REACH considered "trait anxiety" items only which aim to measure how parents generally feel, as well as their propensity for perceived anxiety.[42] Survey responses were scored from 1-4 (seven items are reverse-coded). Scores were summed together (range: 20-80) with higher scores indicating higher levels of anxiety. The STAI has robust psychometric properties, with trait-specific test-retest reliabilities of r=0.73-0.86 and has been shown to be valid with other questionnaires used to assess anxiety (r=0.73-0.85).[42,43] In this study, internal consistency for the STAI was α=0.89.

Parental depression

Parental symptoms of depression were measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item scale designed to assess depressive symptomatology in the general adult population over the past week.[44] The CES-D includes items that survey the domains of positive and negative affect, somatic activity, and interpersonal relations. A four-point Likert scale is used to rate the

frequency of symptoms experienced. Higher scores (range: 0-60) indicate greater frequency of depressive symptoms and individuals with total scores ≥16 are typically identified as having clinically significant levels of depression.[44] Extensive research has shown the CES-D to be valid and reliable.[43,45] In this study, internal consistency for the CES-D was α=0.93.

Family functioning

The 12-item General Functioning subscale of the McMaster Family Assessment Device provided a valid and reliable measure of the health/pathology of the family (i.e., family functioning).[46,47] The scale is derived by summing items from six domains: problem solving, communication, roles, affective responsiveness, affective involvement, and behavioral control. Items are rated on a four-point Likert scale with higher scores (range: 0-36) indicating poorer overall family functioning. Internal consistency for the FAD in this study was α=0.92.

Physical Condition Disease severity

Disease severity in children was assessed and measured by a health professional using a 10 cm visual analog scale (VAS). The VAS represents a continuum of disease severity.[48] Health professionals marked the VAS at the point at which best reflected the disease severity of the child, according to their clinical judgment. The distance from the zero point of the VAS (left side) to the mark was measured and recorded as the disease severity of the child. The VAS and its scoring method has been used in a variety of populations and settings to assess well-being and pain and has the advantage of being easily comparable across study samples.[49,50]

Demographic characteristics

Sociodemographic data were collected on child and parent age, sex and immigrant status, parent marital status and educational attainment, as well as annual household income.

Analysis

Comparisons between children with and without multimorbidity were made using Mann-Whitney (continuous variables) and Fisher's Exact tests (categorical variables). Changes in the prevalence of multimorbidity from baseline to six months was using the McNemar test. Analysis of variance with post hoc Scheffé tests were conducted to compare KIDSCREEN-27 scores with available population norms.[38] Generalized linear modeling was used to examine the association between multimorbidity and children's quality of life and parent psychosocial outcomes at six months. Outcomes were regressed on presence of multimorbidity, controlling for baseline scores for each respective outcome, as well as child age, sex, and physical condition. These covariates were included in the models to present unbiased estimates of effect. All analyses were conducted using SPSS 21 (IBM Corporation). Due to the pilot nature of this study, statistical tests were two-tailed using a significance level of α=0.10. As there were no missing item-level data, complete case analysis was used.

Results

Sample characteristics

Over 12 months, 62 families were approached to participate in REACH. Of these, 56 (90% response) agreed to participate. Four families were not interested in participating and two families had a child that did not meet the eligibility criteria. Fifty families (83% participation) completed the baseline assessment (telephone and mail) and forty-four (88% retention) completed the six-month follow-up (telephone and mail). Repeated attempts to contact the six families who completed the telephone interview, but did not

return the complete mail survey, were unsuccessful, thus the reasons for withdrawal from the study are unknown. There were no baseline differences between families lost to follow-up and those who completed the study.

Baseline characteristics are shown in Table 1. The mean age of children was 11.3 (SD 3.3) years and 52% were male. There was no difference in the number of children across physical condition subgroup, though asthma was the most common (28%) and epilepsy and food allergy, the least common (16%). Parents had a mean of age of 44.0 (5.7) years and 90% were female. Most parents were Caucasian (94%), married (78%), had completed post-secondary education (78%), and had annual household incomes of ≥$90,000 Canadian dollars (58%).

Prevalence of multimorbidity

The prevalence of multimorbidity declined from 58% at baseline to 42% at six-months (p=0.09; Table 2). At baseline, 11 (22%) children had multiple mental disorders. This decreased to nine (18%) at six months. Anxiety disorder (at least one of separation anxiety, phobias, or generalized anxiety) was the most common disorder at baseline (36%) and six months (26%). Differences across physical conditions were found for the prevalence of attention-deficit hyperactivity disorder (χ^2=6.44; p=.06) and oppositional defiant disorder (χ^2=7.53; p=0.07) at baseline and for attention-deficit hyperactivity disorder (χ^2=7.98; p=.09) at six months. In each case, the proportion of mental disorder was elevated in children with food allergy.

Correlates of multimorbidity

Results showed no differences in child and parent characteristics between children with and without multimorbidity with two exceptions (Table 1): children with multimorbidity had lower KIDSCREEN-27

psychological well-being (43.6 vs. 49.4; p=0.08) and parents reported higher STAI scores (44.2 vs. 38.2; p=0.05).

Multimorbidity and psychosocial outcomes

Comparisons of KIDSCREEN-27 scores between our sample and population norms are shown in Figure 1. Overall differences were found for the physical well-being, psychological well-being, and peer support domains. Post hoc tests showed that compared to population norms, children with multimorbidity had significantly poorer psychological well-being (t=4.21; p<0.01) and children without multimorbidity had lower peer support (t=2.66; p<0.01). Results of the unadjusted and adjusted generalized linear models of the association of multimorbidity with quality of life over time are shown in Table 3. Adjusting for child age, sex, type of physical condition, and baseline KIDSCREEN-27 score, multimorbidity was associated with lower scores in the following domains at six months: physical well-being (β=-4.82; p=0.03), psychological well-being (β=-4.10; p=0.06), and school environment (β=-4.17; p=0.09). With the exception of autonomy and parent relations, the strength of the association increased after covariate adjustment.

The same modeling strategy was used to examine the associations with parental stress, anxiety, depression, and family functioning. In both unadjusted and adjusted models, multimorbidity was not associated with any psychosocial outcomes in parents over time (Table 4). Similarly, the strength of association (though not statistically significant) increased after covariate adjustment.

Discussion

In this pilot study, over half of children screened positive for mental disorder(s) soon after being diagnosed with a physical condition and this proportion appeared to decrease six months later. Anxiety

disorders were found to be the most common disorders affecting children at diagnosis and six months later. There were no sociodemographic differences between children with and without multimorbidity. While multimorbidity did have a negative effect on child quality of life over time, our hypothesis that it would also influence parental outcomes was unsupported.

Methodologically, this pilot study has implications for the study of child multimorbidity within the clinical setting. Regarding participant recruitment, we limited the amount of contact between research staff and families during the initial contact in the clinic. This served two purposes: one, it minimized burden on the physicians and nurses whose primary focus is clinical care, as well as clinical staff managing large patient volumes. Two, it reduced the amount of information passed to families at a time when they may have felt overwhelmed with the clinical information provided by the physician about their child's diagnosis. We provided an information letter and then followed up by telephone a few days later when families were away from the clinic and had a chance to review this letter and determine if they wanted to participate. Our approach of engaging families personally in clinic, followed by telephone contact, and data collection via mail survey was found to be acceptable to families. Our strong response and retention rates contrast evidence showing reduced response rates in research studies.[51] The majority of families in our study also noted that mail survey was the preferred method for data collection compared to online surveys and home interviews (data not shown). Overall, our methodology resulted in good coverage, with over 80% of consecutively approached eligible families participating in the study. This suggests that the mental health of children with physical conditions is an important concern for families and that they are willing to contribute their time to such research studies. Our recruitment experience suggested that a number of children were ineligible for the study because their illness duration was greater than six months. To ensure a more efficient recruitment that encompasses an even larger coverage of our target population, the larger study will include children as

young as two years of age and we are expanding the number of physical conditions (e.g., bowel diseases, chronic headache, lupus).

Our estimate of the proportion of children with multimorbidity was similar to previous reports[8] and supports the chronicity of multimorbidity during the early stages of being diagnosed with a physical condition.[7] As shown in previous work in children with diabetes[12] the peri-diagnostic period represents a critical developmental period for mental health. While this study did not measure mental disorder prior to the diagnosis of a physical condition, 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) regarding the prognosis of their physical condition, including unpredictability of exacerbations, fear of death, loss of control, stigma associated with their condition, or adverse effects of medical treatment.[10] From this perspective, anxiety arises from negatively-biased thought patterns that exaggerate adverse effects of the physical condition and can undermine confidence in adapting to threatening situations.[52] Anxiety in these children may be an inherited trait or learned behavior—parents of children with multimorbidity in our sample reported more symptoms of anxiety compared to parents of children without multimorbidity. There is also emerging evidence of shared biological pathways that underlie multimorbidity. In adults, symptoms of anxiety are associated with systemic inflammation,[53] which is elevated in individuals with physical conditions. Whether markers of inflammation, such as pro-inflammatory cytokines mediate the relationship between physical and mental disorder is unknown.

These findings also contribute to the converging evidence that risk for mental disorder is relatively consistent among children with various physical conditions.[54] One exception was that attention-deficit hyperactivity disorder was more common among children with food allergy. This increased risk is supported by some previous studies.[55,56] As in this work, attention-deficit hyperactivity disorder in our

sample of children with food allergy was mainly of the inattentive subtype. Inattentiveness may co-occur with core symptoms of generalized anxiety disorder, manifesting because of hypervigilance in avoiding food allergens. From a biological perspective, there is evidence of shared immunological[57] and inflammatory[58] responses for allergic conditions and attention-deficit hyperactivity disorder which may explain this association. 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.

In general, the sample consisted of high socioeconomic two-parent families, which may have contributed to the lack of sociodemographic differences between children with and without multimorbidity and limits the generalizability of the findings. Placing the finding in the context of previous work is difficult given the absence of studies examining sociodemographic correlates of multimorbidity. Previous population-based studies conducted in Canada also showed no socioeconomic differences between children with and without physical conditions.[24,59-61] In our future larger study, we will work towards a recruitment strategy that will include wider variation in the socioeconomic status to families to increase the representativeness of the sample. Contrary to expectation, no effect of multimorbidity on parental outcomes was found. Nevertheless, information related to parental psychopathology and family environment may be important control variables used to isolate the effects of multimorbidity on child outcomes. Such family processes may also be implicated in complex pathways linking physical and mental health in children. As a result, these variables will be included in the larger study.

Multimorbidity appears to have a negative effect on children's quality of life, above and beyond the effect of having a physical condition alone.[18] This effect is pervasive, affecting multiple domains of

quality of life during the first six months after a diagnosis. Of interest is the finding that the magnitude of effect seen for physical well-being, psychological well-being, and school environment was approximately half a standard deviation. This metric has been validated as the minimal clinically important difference for measures of quality of life[62] and provides evidence to support the perception that changes in child quality of life due to multimorbidity are clinically relevant. Given the early onset of multimorbidity, health professionals in the pediatric setting should consider engaging children and families in discussions about mental health soon after the diagnosis of a physical condition is made and discussion surrounding the physical condition completed. Within a holistic family-centered approach, health professionals are encouraged to apply brief screening tools to identify at-risk children and provide referrals to supportive services on a case-by-case basis. This is a critical window of opportunity given that mental disorder is strong predictor of youth suicide[63] and that risk for suicide is highest soon after an adolescent is diagnosed with a physical condition.[64] Because of the chronicity and pervasiveness of multimorbidity and its influence on child and parent psychosocial functioning, continuing monitoring during routine clinical assessments may also be warranted.

There are two noteworthy limitations. First, the study was likely underpowered to detect differences between children with and without multimorbidity and the small sample size may limit the generalizability of findings. However, our sample size was consistent with considerations for implementing pilot studies[35] and our coverage of eligible families was good. Second, measurement of child mental health and child and parent outcomes were parent-reported. While we have found adequate agreement between parents and a small subset of children who provided self-reported quality of life,[40] significant associations may be the result of shared-method variance.

Conclusion

These preliminary findings indicate that mental disorder in children newly-diagnosed with a physical condition is common and negatively affects their quality of life over time. If these results are replicated in a subsequent larger study, health professionals should be aware of the burden of multimorbidity and prepare themselves to discuss mental health with children and their parents. Findings from this pilot study have been used to implement a large-scale study that will examine child multimorbidity in greater depth and provide more definitive clinical implications.

References

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA 2010;303:623-30.

2. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. JAMA 2007;297:2741-51.

3. Merikangas KR, Calkins ME, Burstein M, et al. Comorbidity of physical and mental disorders in the neurodevelopmental genomics cohort study. Pediatrics 2015;135:e927-38.

4. Dobbie M, Mellor D. Chronic illness and its impact: considerations for psychologists. Psychology, health & medicine 2008;13:583-90.

5. Kessler RC, Avenevoli S, Costello EJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry 2012;69:372-80.

6. Ferro MA. Major depressive disorder, suicidal behaviour, bipolar disorder, and generalised anxiety disorder among emerging adults with and without chronic health conditions. Epidemiology and psychiatric sciences 2016;25:462-74.

7. Quach J, Barnett T. Impact of chronic illness timing and persistence at school entry on child and parent outcomes: Australian longitudinal study. Academic pediatrics 2015;15:89-95.

8. Canning EH, Hanser SB, Shade KA, Boyce WT. Mental disorders in chronically ill children: parent-child discrepancy and physician identification. Pediatrics 1992;90:692-6.

9. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. J Pediatr Psychol 2011;36:1003-16.

10. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr 2011;100:1069-76.

11. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol 2011;36:375-84.

12. Butwicka A, Frisen L, Almqvist C, Zethelius B, Lichtenstein P. Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes: a population-based cohort study. Diabetes Care 2015;38:453-9.

13. Jones LC, Mrug S, Elliott MN, Toomey SL, Tortolero S, Schuster MA. Chronic physical health conditions and emotional problems from early adolescence through midadolescence. Academic pediatrics 2017;17:649-55.

14. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. Bmc Public Health 2013;13.

15. Boyle MH, Duncan L, Georgiades K, et al. Classifying child and adolescent psychiatric disorder by problem checklists and standardized interviews. International journal of methods in psychiatric research 2016.

16. Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY. Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International journal of methods in psychiatric research 2009;18:169-84.

17. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. European Journal of Epidemiology 2014;29:551-8.

18. Moreira H, Carona C, Silva N, Frontini R, Bullinger M, Canavarro MC. Psychological and quality of life outcomes in pediatric populations: a parent-child perspective. J Pediatr 2013;163:1471-8.

19. Bai G, Herten MH, Landgraf JM, Korfage IJ, Raat H. Childhood chronic conditions and health-related quality of life: Findings from a large population-based study. PLoS One 2017;12:e0178539.

20. Ferro MA, Boyle MH. Self-concept among children and adolescents with a chronic illness: a meta-analytic review. Health Psychol 2013;32:839-48.

21. Bolognini M, Plancherel B, Bettschart W, Halfon O. Self-esteem and mental health in early adolescence: development and gender differences. J Adolesc 1996;19:233-45.

22. Crump C, Rivera D, London R, Landau M, Erlendson B, Rodriguez E. Chronic health conditions and school performance among children and youth. Ann Epidemiol 2013;23:179-84.

23. Forrest CB, Bevans KB, Riley AW, Crespo R, Louis TA. School outcomes of children with special health care needs. Pediatrics 2011;128:303-12.

24. Ferro MA, Boyle MH. The impact of chronic physical illness, maternal depressive symptoms, family functioning, and self-esteem on symptoms of anxiety and depression in children. J Abnorm Child Psychol 2015;43:177-87.

25. Miodrag N, Burke M, Tanner-Smith E, Hodapp RM. Adverse health in parents of children with disabilities and chronic health conditions: a meta-analysis using the parenting stress index's health sub-domain. J Intellect Disabil Res 2015;59:257-71.

26. Newacheck PW, Kim SE. A national profile of health care utilization and expenditures for children with special health care needs. Arch Pediatr Adolesc Med 2005;159:10-7.

27. McCarthy MJ, Behimer G, Anderson JA, Riddle I. Caregiving for youth with co-occurring developmental disabilities and behavioral health issues when caregivers face additional health-related stressors: Analysis of risk and protective factors from a national sample. Res Dev Disabil 2016;59:399-409.

28. Pinquart M. Parenting stress in caregivers of children with chronic physical condition-A meta-analysis. Stress and health : journal of the International Society for the Investigation of Stress 2017.

29. Lee SL, Cheung YF, Wong HS, Leung TH, Lam TH, Lau YL. Chronic health problems and health-related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ open 2013;3.

30. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev 2008;34:418-29.

31. Chen H, Cohen P, Kasen S, Johnson JG, Berenson K, Gordon K. Impact of adolescent mental disorders and physical illnesses on quality of life 17 years later. Arch Pediatr Adolesc Med 2006;160:93-9.

32. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. CMAJ 2016;188:182-8.

33. Committee On Hospital C, Institute For P, Family-Centered C. Patient- and family-centered care and the pediatrician's role. Pediatrics 2012;129:394-404.

34. Miller GF, Coffield E, Leroy Z, Wallin R. Prevalence and Costs of Five Chronic Conditions in Children. J Sch Nurs 2016;32:357-64.

35. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008;31:180-91.

36. Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 2010;71:313-26.

37. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345-65.

38. Ravens-Sieberer U, Auquier P, Erhart M, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Qual Life Res 2007;16:1347-56.

39. Robitail S, Ravens-Sieberer U, Simeoni MC, et al. Testing the structural and cross-cultural validity of the KIDSCREEN-27 quality of life questionnaire. Qual Life Res 2007;16:1335-45.

40. Qadeer RA, Ferro MA. Child–parent agreement on health-related quality of life in children with newly diagnosed chronic health conditions: a longitudinal study. Int J Adolesc Youth 2017.

41. Berry JO, Jones WH. The Parental Stress Scale: initial psychometric evidence. J Soc Pers Relation 1995;12:463-72.

42. Spielberger CD. State-Trait Anxiety Inventory for adults. Menlo Park: Mind Garden Inc.; 1983.

43. Okun A, Stein RE, Bauman LJ, Silver EJ. Content validity of the Psychiatric Symptom Index, CES-depression Scale, and State-Trait Anxiety Inventory from the perspective of DSM-IV. Psychol Rep 1996;79:1059-69.

44. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.

45. Ferro MA, Speechley KN. Factor structure and longitudinal invariance of the Center for Epidemiological Studies Depression Scale (CES-D) in adult women: application in a population-based sample of mothers of children with epilepsy. Arch Womens Ment Health 2013;16:159-66.

46. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Ther 1983;9:171-80.

47. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. Fam Process 1988;27:97-104.

48. Crichton N. Visual Analogue Scale (VAS). Journal of Clinical Nursing 2001;10:706-.

49. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007-19.

50. Paul-Dauphin A, Guillemin F, Virion JM, Briancon S. Bias and precision in visual analogue scales: a randomized controlled trial. Am J Epidemiol 1999;150:1117-27.

51. Couper MP. New developments in survey data collection. Annu Rev Sociol 2017;43:1-25.

52. Beck AT, Emery G, Greenberg RL. Anxiety disorders and phobias: a cognitive perspective. New York: Guildford Press; 1985.

53. Hou R, Garner M, Holmes C, et al. Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: Case-controlled study. Brain, behavior, and immunity 2017;62:212-8.

54. Stein RE, Silver EJ. Operationalizing a conceptually based noncategorical definition: a first look at US children with chronic conditions. Arch Pediatr Adolesc Med 1999;153:68-74.

55. Ferro MA, Van Lieshout RJ, Ohayon J, Scott JG. Emotional and behavioral problems in adolescents and young adults with food allergy. Allergy 2016;71:532-40.

56. Topal E, Catal F, Soylu N, et al. Psychiatric disorders and symptoms severity in pre-school children with cow's milk allergy. Allergol Immunopathol (Madr) 2016;44:445-9.

57. Besser MJ, Ganor Y, Levite M. Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNF alpha or both. Journal of neuroimmunology 2005;169:161-71.

58. Buske-Kirschbaunn A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. Psychoneuroendocrinology 2013;38:12-23.

59. Ferro MA, Boyle MH. Longitudinal invariance of measurement and structure of global self-concept: a population-based study examining trajectories among adolescents with and without chronic illness. J Pediatr Psychol 2013;38:425-37.

60. Ferro MA, Gorter JW, Boyle MH. Trajectories of depressive symptoms during the transition to young adulthood: the role of chronic illness. J Affect Disord 2015;174:594-601.

61. Gonzalez A, Boyle MH, Kyu HH, Georgiades K, Duncan L, MacMillan HL. Childhood and family influences on depression, chronic physical conditions, and their comorbidity: findings from the Ontario Child Health Study. J Psychiatr Res 2012;46:1475-82.

62. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-92.

63. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA psychiatry 2013;70:300-10.

64. Christiansen E, Stenager E. Risk for attempted suicide in children and youths after contact with somatic hospitals: a Danish register based nested case-control study. J Epidemiol Community Health 2012;66:247-53.

Table 1. Baseline sample characteristics

	Full sample	Multimorbid	Not multimorbid	P-value
N	50	29	21	
Child				
Age, years	11.3 (3.3)	11.6 (3.2)	11.0 (3.4)	0.62
Male, n (%)	26 (52)	15 (52)	11 (52)	0.96
Diagnoses, n (%)				0.98
Asthma	14 (28)	9 (31)	5 (24)	
Diabetes	9 (18)	4 (14)	5 (24)	
Epilepsy	8 (16)	4 (14)	4 (19)	
Food allergy	8 (16)	5 (17)	3 (14)	
Juvenile arthritis	11 (22)	7 (24)	4 (19)	
Disease severity, VAS	1.3 (1.2)	1.5 (1.3)	0.9 (0.9)	0.16
Quality of life, KIDSCREEN-27				
Physical well-being	48.0 (12.0)	47.4 (11.0)	48.8 (13.4)	0.77
Psychological well-being	46.1 (9.8)	43.6 (8.1)	49.4 (11.2)	0.08
Autonomy/Parent relations	48.9 (9.6)	47.5 (7.0)	50.8 (12.1)	0.72
Peer support	46.1 (11.4)	46.7 (12.1)	45.4 (10.5)	0.35
School environment	50.1 (10.8)	47.7 (8.8)	53.3 (12.4)	0.12
Parent				
Age, years	44.0 (5.7)	43.0 (4.8)	45.2 (6.3)	0.43
Female, n (%)	45 (90)	26 (90)	19 (91)	0.92
Immigrant, n (%)	10 (20)	8 (28)	2 (10)	0.16
Married, n (%)	39 (78)	22 (76)	17 (81)	0.67
Post-secondary graduate, n (%)	39 (78)	22 (76)	17 (81)	0.67
Income ≥$90,000, n (%)	29 (58)	17 (59)	12 (57)	0.87
Parental stress, PSS	35.9 (7.9)	37.1 (7.3)	34.4 (8.5)	0.32
Parental anxiety, STAI	41.6 (9.8)	44.2 (9.1)	38.2 (10.0)	0.05
Parental depression CES-D	12.7 (9.9)	13.0 (9.6)	12.2 (10.5)	0.58
Family functioning, FAD	25.5 (6.3)	24.7 (6.2)	26.5 (6.6)	0.20

Results are reported as mean (standard deviation) unless otherwise noted.

Table 2. Prevalence of multimorbidity

	Full sample	Asthma	Diabetes	Epilepsy	Food allergy	Juvenile arthritis	P-value
Baseline							
Any disorder	29 (58)	9 (64)	4 (44)	4 (50)	5 (63)	7 (64)	0.88
Major depressive episode	12 (24)	4 (29)	2 (22)	1 (13)	1 (13)	4 (36)	0.74
Separation anxiety	2 (4)	0	0	1 (13)	0	1 (9)	0.43
Phobia*	15 (30)	6 (46)	1 (11)	1 (13)	3 (38)	4 (36)	0.35
Generalized anxiety	6 (12)	0	0	2 (25)	2 (25)	2 (18)	0.11
Attention-deficit hyperactivity	5 (10)	1 (7)	0	1 (13)	3 (38)	0	0.06
Oppositional defiant	9 (18)	2 (14)	1 (11)	2 (25)	4 (50)	0	0.07
Conduct	3 (6)	1 (7)	0	1 (13)	1 (13)	0	0.65
Six months							
Any disorder	21 (42)	9 (64)	1 (11)	4 (50)	2 (25)	5 (56)	0.10
Major depressive episode	2 (4)	0	0	0	0	2 (22)	0.11
Separation anxiety	3 (6)	2 (14)	0	1 (13)	0	0	0.56
Phobia*	10 (20)	5 (36)	1 (11)	1 (13)	0	3 (33)	0.25
Generalized anxiety	4 (8)	1 (7)	0	1 (13)	0	2 (22)	0.55
Attention-deficit hyperactivity	3 (6)	0	0	0	2 (25)	1 (11)	0.09
Oppositional defiant	6 (12)	2 (14)	0	2 (25)	2 (25)	0	0.31
Conduct	4 (8)	1 (7)	0	2 (25)	1 (13)	0	0.33

Results are the number (%) of children with multimorbidity. Fisher's Exact tests examined multimorbidity across the five physical conditions.

*Includes generalized, non-generalized, and specific phobias.

Table 3. Longitudinal effects of multimorbidity on child quality of life

	Unadjusted		Adjusted	
KIDSCREEN-27	**B (SE)**	**P-value**	**B (SE)**	**P-value**
Physical well-being	-3.76 (2.23)	0.09	-4.82 (2.22)	0.03
Psychological well-being	-2.06 (2.44)	0.40	-4.10 (2.14)	0.06
Autonomy/Parent relations	0.77 (2.53)	0.76	-0.67 (2.40)	0.78
Peer support	-0.59 (2.83)	0.84	-1.23 (2.66)	0.64
School environment	-3.56 (2.88)	0.22	-4.17 (2.44)	0.09

Models adjusted for child age and sex, physical condition, and baseline quality of life.

Table 4. Longitudinal effects of multimorbidity on parental outcomes

	Unadjusted		Adjusted	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Parental stress, PSS	0.28 (1.60)	0.86	-1.50 (1.51)	0.32
Parental anxiety, STAI	0.14 (2.05)	0.95	-0.24 (2.15)	0.91
Parental depression CES-D	0.30 (1.12)	0.80	0.62 (1.13)	0.58
Family functioning, FAD	1.21 (1.32)	0.36	1.47 (1.28)	0.25

Models adjusted for child age and sex, physical condition, and baseline psychosocial outcome.

Figure 1. Comparison of KIDSCREEN-27 scores with population norms

*p<0.10 for overall F-test across the three groups.

†Multimorbid group significantly lower than normative and not multimorbid groups.

‡Not multimorbid group significantly lower than normative group.

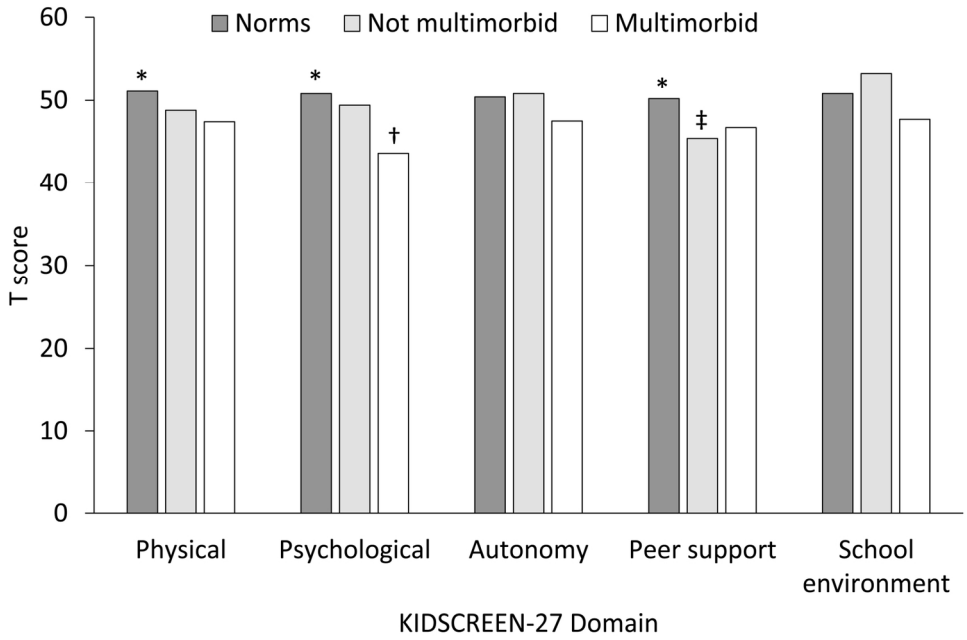

Figure 1. Comparison of KIDSCREEN-27 scores with population norms
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150x100mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-13
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	13
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	31-32
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18, 19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Mental Disorder in Children with Physical Conditions: A Pilot Study

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Mental Disorder in Children with Physical Conditions: A Pilot Study

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Authors' contributions

MAF led the study. MAF, MHB, KNS, KG, JWG, AG, HLM, ELL, and RJV conceptualized and designed the study and were responsible for acquiring funding. MHB, KNS, KG, and AG provided methodological insights. JWG, HLM, ELL, and RJV provided clinical insights. KNS and HLM helped facilitate clinic participation. AB and MAF analyzed and interpreted data and drafted the manuscript. All authors critically reviewed, revised, and then approved the final manuscript as submitted.

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Competing interests

The authors declare that they have no competing interests.

Data sharing statement

Data will not be shared in order to protect the confidentiality of participants. This was a multisite study and we do not have approval to make the data publically available.

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Michelle Diebold, Patti Guertjens, Simon Levin, Narayan Prasad (Children's Hospital London Health Sciences).

Abstract

Objectives: 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.

Design: Prospective pilot study.

Setting: Two children's tertiary-care hospitals.

Participants: Children aged 6-16 years diagnosed in the past six months with one of asthma, diabetes, epilepsy, food allergy, or juvenile arthritis and their parents.

Outcome measures: Response, participation, and retention rates. Child mental disorder using the Mini International Neuropsychiatric Interview at baseline and six months. Child quality of life, parental symptoms of stress, anxiety, and depression, and family functioning. All outcomes were parent reported.

Results: Response, participation, and retention rates were 90%, 83%, and 88%, respectively. Of the 50 children enrolled in the study, the prevalence of multimorbidity was 58% at baseline and 42% at six months. No sociodemographic characteristics were associated with multimorbidity. Multimorbidity at baseline was associated with declines over six months in the following quality of life domains: physical well-being, β=-4.82 (-8.47, -1.17), psychological well-being, β=-4.10 (-7.62, -0.58), and school

environment, β=-4.17 (-8.18, -0.16). There was no association with parental psychosocial outcomes over time.

Conclusions: Preliminary evidence suggests that mental disorder in children with a physical condition is very common and has a negative impact on quality of life over time. Based on the strong response rate and minimal attrition, our approach to study child multimorbidity appears feasible and suggests that multimorbidity is an important concern for families. Methodological and substantive findings from this pilot study have been used to implement a larger, more definitive study of child multimorbidity, which should lead to important clinical implications.

Strengths and limitations of this study

- This pilot study includes children newly-diagnosed with chronic physical conditions.
- 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 within and between children with and without multimorbidity and the small sample size limits generalizability.
- All outcomes were parent-reported.

Introduction

The global prevalence of children with a chronic physical condition—a health problem that requires ongoing management over a period of years or decades—is common, affecting approximately 25% of children, and increasing.[1] These children may be adversely affected by their disorders or their treatment, subsequently developing additional conditions, including mental disorders.[2] Compared to their peers with a physical or mental disorder only, children with multimorbidity (physical-mental comorbidity) experience greater symptom severity and impairment in both physical and mental health domains.[3] Understandably, the onset of multimorbidity remains an important concern for children, parents, health professionals, and payers.[4]

Mental disorders of any type are common in children and adolescents[5] and disproportionally affect young people with chronic physical conditions (herein physical conditions).[6,7] Estimates from clinical samples suggest that nearly half of children with physical conditions meet criteria for a mental disorder diagnosis.[8] In general population samples, this estimate is lower, with approximately 20-30% of children being affected.[3]

Evidence of the association between physical and mental health is robust,[9-11] but with few exceptions,[7,12,13] the literature base consists mostly of cross-sectional studies. This limits our understanding of mental health at the time children are diagnosed with a physical condition and how their mental health may change over time. One study found more parent-reported symptoms of problem behavior in children 6-7 years newly diagnosed with a chronic illness compared to healthy controls.[7] This effect was stable through to 10-11 years of age, highlighting the chronicity of multimorbidity in childhood. In a prospective study of children with diabetes, hazard ratios for mental disorder were highest within six-months of the diabetes diagnosis (3.0 [2.7-3.4]) compared to those with

a duration of diabetes of five years or more (1.9 [1.7-2.1]), regardless of age at diagnosis,[12] suggesting that the peri-diagnostic period may be a time of particular mental health risk. Another prospective study showed changes over time in associations of mental health with physical conditions being associated with depressive symptoms during childhood, and with anxiety symptoms during early adolescence.[13] While these studies have advanced the field, opportunities exist to overcome the limitations in these studies associated with the ascertainment of physical conditions based on parent-report,[14] assessment of symptoms of problem behaviors rather than mental disorder,[13,15,16] and inherent weaknesses of using register-based data related to data quality and variable availability.[17]

Existing research also suggests that physical conditions and mental disorders are independently associated with poorer psychosocial outcomes including quality of life[18,19] and self-esteem,[20,21] as well as academic performance.[22,23] These adverse effects can also extend to parents and families who experience elevated stress and psychological distress, worse family functioning, and financial hardship.[24-28] Effects on child and parent psychosocial outcomes appear similar when physical and mental disorders are examined separately; however, there is little research examining whether multimorbidity exerts a compounding effect. Cross-sectional evidence suggests that children with multimorbidity experience worse quality of life compared to children with a physical or mental disorder alone.[29,30] One prospective study showed that adults who experienced multimorbidity during adolescence had lower quality of life compared to those who had a physical or mental disorder only.[31] These researchers found that among those with multimorbidity, physical conditions affected physical quality of life only; while their mental disorder negatively affected multiple domains of life quality, including physical, emotional, and social well-being. The extent to which multimorbidity influences other aspects of parental health and well-being, including parenting stress, psychopathology, and family relationships, is not well known.

Despite the progress made in understanding child multimorbidity and its effects on psychosocial outcomes, important knowledge gaps remain. First, the burden and correlates of multimorbidity, particularly in clinical samples of children who represent the largest consumers of health services,[32] 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;[3,13] are out-dated;[8] or, focus on a single physical condition.[12] This information is needed to inform resource allocation and the provision of services within the health system. Second, the timing of multimorbidity onset, how it changes, and its influence on psychosocial outcomes over time are not well-understood, limiting our ability to identify opportunities for intervention to prevent the development of mental disorder in children with physical conditions. This includes a lack of understanding how mental disorders may change or appear in relation to the onset of the physical condition. For example, are anxiety disorders more common at the time of diagnosis given the uncertainty surrounding prognosis? Third, effects of child multimorbidity on parental health and well-being have not been explored in much detail. Understanding these effects is key to designing, implementing, and evaluating family-centered approaches to care within the pediatric setting to promote the best possible health outcomes for children, parents, and families.[33]

Anticipating substantial hardship, stress, and psychological distress associated with receiving a diagnosis of a physical condition in childhood within families, as well as prognostic uncertainty,[12,34-38] 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. Based on previous clinical studies,[8] we hypothesized that at the time of diagnosis, 50% of children would screen positive for mental disorder. Based on limited evidence,[12] we hypothesized that six months later, there would be a decrease in the proportion of multimorbidity. Finally, we hypothesized that children with multimorbidity would have worse quality of life over time; their parents, more symptoms of parenting stress, anxiety, and depression; and, their families, worse functioning compared to children with physical conditions only.

Methods

Sample

Data come from a multisite, prospective, pilot study aimed at examining mental disorder(s) in children with physical conditions. Families were recruited from four outpatient clinics from two pediatric academic hospitals (specialized tertiary care centres; two clinics per hospital) in Ontario, Canada to assess mental and psychosocial outcomes in children with newly-diagnosed with physical conditions. Health professionals at the hospitals were involved at the initial point of contact and provided eligible families with an overview of the study and details regarding participation. The eligibility criteria for the study were children who: 1—were aged 6-16 years old (six is the youngest age at which our measure of mental disorder is validated; the ceiling age of 16 years ensured that during the follow-up, participants did not transfer out of the pediatric health system); 2—had received a diagnosis of asthma, diabetes, epilepsy, food allergy or juvenile idiopathic arthritis (which represent the most common physical conditions among children)[39] within the six months prior to recruitment; and, 3—had a parent who could read English (not all measures have been validated in other languages). Children were excluded if they had a degenerative neurological disorder because child and parental outcomes are well-established

in this population. Child IQ was not tested and children were not excluded if their parents indicated intellectual disability, maximizing the coverage and representativeness of our sample. Following sample size guidelines suggested for the conduct of pilot studies,[40] we aimed to recruit 60 children and families (12 per condition) over a 12-month period.

Data Collection

After the medical encounter, eligible families were invited by clinic nurses to speak with research staff about the study. Research staff briefly introduced the study and provided families an information letter. Families interested in participating in the study consented for clinic nurses to send their contact information to study investigators who then followed-up with families by telephone to confirm eligibility, obtain oral consent from parents and children, and arrange for a convenient time to conduct a telephone interview to assess child mental health. Parents also completed two mailed surveys to assess psychosocial outcomes and demographic characteristics; one at baseline and one six months later, when a second telephone interview to assess mental health was conducted. Parents of all participating children provided proxy reports and children who were ≥11 years of age (n=33) self-reported on the telephone interview and to the mail survey. Parents and children also consented to have health professionals provide clinical information at the same measurement occasions. The study protocol received ethical approval from the Hamilton Integrated Research Ethics Board (14-130) and Research Ethics Board (105505).

Measures

Mental disorder

Child mental disorder(s) were assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID).[41] The MINI-KID is a structured diagnostic interview used to assess

DSM-IV disorders in children aged 6-17 years and has been validated against the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version.[41] It is composed of diagnostic modules that contain screening questions and skip patterns for each disorder. Phone interviews were administered separately: the MINI-KID(c), to children ≥11 years; and the MINI-KID(p) (proxy version) to all parents at both measurement occasions. The MINI-KID was administered by a single interviewer who underwent training that included monitored practice. The presence of the most common mental disorders was assessed: major depressive episode, separation anxiety disorder, social phobia, specific phobia, generalized anxiety disorder, attention deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder.[42] The MINI-KID has demonstrated strong test-retest reliability compared to other instruments.[15] Mental disorder was classified according to parent reports on the MINI-KID.

Quality of life

Child quality of life between the two visits was measured using the KIDSCREEN-27,[43] a 27-item child and parent-reported generic measure that assesses five domains: physical well-being (five items; examines physical activity and energy), psychological well-being (seven items; examines emotional balance and life satisfaction), autonomy and parent relations (seven items; examines family dynamics and age-appropriate freedoms), social support and peers (four items; examines nature of peer relationships) and school environment (four items; examines perception of cognition, learning, and feelings about school). Responses are scored using a five-point Likert scale and domain scores are transformed into T-values with a mean of 50 and a standard deviation of 10 (higher scores indicate better quality of life). The KIDSCREEN-27 has been found to be valid and reliable in children with and without physical conditions[43,44] and demonstrated adequate agreement between children and parents.[45] Internal

consistency reliabilities for each domain from this study were good for both child (α=0.75-0.89) and parent reports (α=0.83-0.92).

Parental stress

The Parental Stress Scale (PSS) measures parental stress across the domains of rewards, stressors, loss of control, and satisfaction.[46] The 18 items are rated on a five-point Likert scale (eight items are reverse-coded) with higher scores (range: 18-90) indicating more parental stress. The psychometric properties of the PSS are robust: test-retest reliability (r=0.81) and convergent validity with the Parenting Stress Index (r=0.75) and Perceived Stress Scale (r=0.41).[46] Internal consistency for the PSS in this study was α=0.84.

Parental anxiety

The State Trait Anxiety Inventory (STAI) is a widely used tool for measuring anxiety. Of the 40 questions in the STAI survey, REACH considered "trait anxiety" items only which aim to measure how parents generally feel, as well as their propensity for perceived anxiety.[47] Survey responses were scored from 1-4 (seven items are reverse-coded). Scores were summed together (range: 20-80) with higher scores indicating higher levels of anxiety. The STAI has robust psychometric properties, with trait-specific test-retest reliabilities of r=0.73-0.86 and has been shown to be valid with other questionnaires used to assess anxiety (r=0.73-0.85).[47,48] In this study, internal consistency for the STAI was α=0.89.

Parental depression

Parental symptoms of depression were measured with the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item scale designed to assess depressive symptomatology in the general adult population over the past week.[49] The CES-D includes items that survey the domains of positive and negative affect, somatic activity, and interpersonal relations. A four-point Likert scale is used to rate the

frequency of symptoms experienced. Higher scores (range: 0-60) indicate greater frequency of depressive symptoms and individuals with total scores ≥16 are typically identified as having clinically significant levels of depression.[49] Extensive research has shown the CES-D to be valid and reliable.[48,50] In this study, internal consistency for the CES-D was α=0.93.

Family functioning

The 12-item General Functioning subscale of the McMaster Family Assessment Device provided a valid and reliable measure of the health/pathology of the family (i.e., family functioning).[51,52] The scale is derived by summing items from six domains: problem solving, communication, roles, affective responsiveness, affective involvement, and behavioral control. Items are rated on a four-point Likert scale with higher scores (range: 0-36) indicating poorer overall family functioning. Internal consistency for the FAD in this study was α=0.92.

Physical Condition Disease severity

Disease severity in children was assessed and measured by a health professional using a 10 cm visual analog scale (VAS). The VAS represents a continuum of disease severity.[53] Health professionals marked the VAS at the point at which best reflected the disease severity of the child, according to their clinical judgment. The distance from the zero point of the VAS (left side) to the mark was measured and recorded as the disease severity of the child. The VAS and its scoring method has been used in a variety of populations and settings to assess well-being and pain and has the advantage of being easily comparable across study samples.[54,55]

Demographic characteristics

Sociodemographic data were collected on child and parent age, sex and immigrant status, parent marital status and educational attainment, as well as annual household income.

Analysis

Comparisons between children with and without multimorbidity were made using Mann-Whitney (continuous variables) and Fisher's Exact tests (categorical variables). Changes in the prevalence of multimorbidity from baseline to six months was using the McNemar test. Analysis of variance with post hoc Scheffé tests were conducted to compare KIDSCREEN-27 scores with available population norms.[43] Generalized linear modeling was used to examine the association between multimorbidity and children's quality of life and parent psychosocial outcomes at six months. Outcomes were regressed on presence of multimorbidity, controlling for baseline scores for each respective outcome, as well as child age, sex, and physical condition. These covariates were included in the models to present unbiased estimates of effect. All analyses were conducted using SPSS 21 (IBM Corporation). Due to the pilot nature of this study, statistical tests were two-tailed using a significance level of α=0.10. As there were no missing item-level data, complete case analysis was used.

Results

Sample characteristics

Over 12 months, 62 families were approached to participate in REACH. Of these, 56 (90% response) agreed to participate. Four families were not interested in participating and two families had a child that did not meet the eligibility criteria. Fifty families (83% participation) completed the baseline assessment (telephone and mail) and forty-four (88% retention) completed the six-month follow-up (telephone and mail). Repeated attempts to contact the six families who completed the telephone interview, but did not

return the complete mail survey, were unsuccessful, thus the reasons for withdrawal from the study are unknown. There were no baseline differences between families lost to follow-up and those who completed the study.

Baseline characteristics are shown in Table 1. The mean age of children was 11.3 (SD 3.3) years and 52% were male. There was no difference in the number of children across physical condition subgroup, though asthma was the most common (28%) and epilepsy and food allergy, the least common (16%). Parents had a mean of age of 44.0 (5.7) years and 90% were female. Most parents were Caucasian (94%), married (78%), had completed post-secondary education (78%), and had annual household incomes of ≥$90,000 Canadian dollars (58%).

Prevalence of multimorbidity

The prevalence of parent-reported multimorbidity declined from 58% at baseline to 42% at six months (p=0.09; Table 2). At baseline, 11 (22%) children had multiple mental disorders. This decreased to nine (18%) at six months. Anxiety disorder (at least one of separation anxiety, phobias, or generalized anxiety) was the most common disorder at baseline (36%) and six months (26%). Differences across physical conditions were found for the prevalence of attention-deficit hyperactivity disorder (χ^2=6.44; p=.06) and oppositional defiant disorder (χ^2=7.53; p=0.07) at baseline and for attention-deficit hyperactivity disorder (χ^2=7.98; p=0.09) at six months. In each case, the proportion of mental disorder was elevated in children with food allergy.

The prevalence of child-reported multimorbidity was substantially lower than that reported by parents—18% at baseline and 15% at six months. Given the low number of child age-eligible to provide

self-reports, differences in mental disorder across physical conditions were not examined. Parent-child agreement on the MINI-KID for any mental disorder was κ=0.15.

Correlates of multimorbidity

Results showed no differences in child and parent characteristics between children with and without parent-reported multimorbidity with two exceptions (Table 1): children with multimorbidity had lower KIDSCREEN-27 psychological well-being (43.6 vs. 49.4; p=0.08) and parents reported higher STAI scores (44.2 vs. 38.2; p=0.05). Among children who provide self-reports, those with multimorbidity reported lower KIDSCREEN-27 scores in the following domains: psychological well-being (38.1 vs. 49.1; p<0.01), peer support (41.6 vs. 50.7; p<0.01), and school environment (41.8 vs. 51.5; p=0.01).

Multimorbidity and psychosocial outcomes

Comparisons of parent-reported KIDSCREEN-27 scores between our sample and population norms are shown in Figure 1. Overall differences were found for the physical well-being, psychological well-being, and peer support domains. Post hoc tests showed that compared to population norms, children with multimorbidity had significantly poorer psychological well-being (t=4.21; p<0.01) and children without multimorbidity had lower peer support (t=2.66; p<0.01). Results of the unadjusted and adjusted generalized linear models of the association of parent-reported multimorbidity with quality of life over time are shown in Table 3. Adjusting for child age, sex, type of physical condition, and baseline KIDSCREEN-27 score, multimorbidity was associated with lower scores in the following domains at six months: physical well-being (B=-4.82; p=0.03), psychological well-being (B=-4.10; p=0.06), and school environment (B=-4.17; p=0.09). With the exception of autonomy and parent relations, the strength of the association increased after covariate adjustment. Though similar estimates of association were

found for child reports (multimorbidity and KIDSCREEN-27), only the association between multimorbidity and psychological well-being was statistically significant (B=-10.66; p=0.03).

The same modeling strategy was used to examine the associations with parental stress, anxiety, depression, and family functioning. In both unadjusted and adjusted models, multimorbidity was not associated with any psychosocial outcomes in parents over time (Table 4). Similarly, the strength of association (though not statistically significant) increased after covariate adjustment.

Discussion

In this pilot study, over half of children screened positive, based on parent-report, for mental disorder(s) soon after being diagnosed with a physical condition and this proportion appeared to decrease six months later. This contrasted self-reported mental disorder, in which approximately one in five children screened positive and which remained relatively stable over time. Anxiety disorders were found to be the most common disorders affecting children at diagnosis and six months later. There were no sociodemographic differences between children with and without multimorbidity. While multimorbidity did have a negative effect on child quality of life over time, our hypothesis that it would also influence parental outcomes was unsupported.

Methodologically, this pilot work has implications for the study of child multimorbidity within the clinical setting. Regarding participant recruitment, we limited the amount of contact between research staff and families during the initial contact in the clinic. This served two purposes: one, it minimized burden on the physicians and nurses whose primary focus is clinical care, as well as clinical staff managing large patient volumes. Two, it reduced the amount of information passed to families at a time when they may have felt overwhelmed with the clinical information provided by the physician about their child's

diagnosis. We provided an information letter and then followed up by telephone a few days later when families were away from the clinic and had a chance to review this letter and determine if they wanted to participate. Our approach of engaging families personally in clinic, followed by telephone contact, and data collection via mail survey was found to be acceptable to families. Our strong response and retention rates contrast evidence showing reduced response rates in research studies.[56] The majority of families in our study also noted that mail survey was the preferred method for data collection compared to online surveys and home interviews (data not shown). Overall, our methodology resulted in good coverage, with over 80% of consecutively approached eligible families participating in the study. This suggests that the mental health of children with physical conditions is an important concern for families and that they are willing to contribute their time to such research studies. Our recruitment experience suggested that a number of children were ineligible for the study because their illness duration was greater than six months. To ensure a more efficient recruitment that encompasses an even larger coverage of our target population, the larger study will include children as young as two years of age and we are expanding the number of physical conditions (e.g., bowel diseases, chronic headache, lupus).

Our study reaffirms the need to consider the perspective of multiple informants when assessing the presence of child mental disorder.[57,58] Parent-child agreement was nearly identical to previous research,[58] suggesting that the presence of a physical condition in children does not appear to influence the level of agreement between child and parent reports of mental disorder. The extent to which the excess proportion of multimorbidity identified by parents is clinically relevant requires additional study that include assessments by mental health professionals to verify clinical diagnoses of mental disorder.

Our estimate of the proportion of children with multimorbidity was similar to previous reports[8] and supports the chronicity of multimorbidity during the early stages of being diagnosed with a physical

condition.[7] As shown in previous work in children with diabetes[12] the peri-diagnostic period represents a critical developmental period for mental health. While this study did not measure mental disorder prior to the diagnosis of a physical condition, 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) regarding the prognosis of their physical condition, including unpredictability of exacerbations, fear of death, loss of control, stigma associated with their condition, or adverse effects of medical treatment.[10] From this perspective, anxiety arises from negatively-biased thought patterns that exaggerate adverse effects of the physical condition and can undermine confidence in adapting to threatening situations.[59] Anxiety in these children may be an inherited trait or learned behavior—parents of children with multimorbidity in our sample reported more symptoms of anxiety compared to parents of children without multimorbidity. There is also emerging evidence of shared biological pathways that underlie multimorbidity. In adults, symptoms of anxiety are associated with systemic inflammation,[60] which is elevated in individuals with physical conditions. Whether markers of inflammation, such as pro-inflammatory cytokines mediate the relationship between physical and mental disorder is unknown.

These findings also contribute to the converging evidence that risk for mental disorder is relatively consistent among children with various physical conditions.[61] One exception was that attention-deficit hyperactivity disorder was more common among children with food allergy. This increased risk is supported by some previous studies.[37,62] As in this work, attention-deficit hyperactivity disorder in our sample of children with food allergy was mainly of the inattentive subtype. Inattentiveness may co-occur with core symptoms of generalized anxiety disorder, manifesting because of hypervigilance in avoiding food allergens. From a biological perspective, there is evidence of shared immunological[63] and inflammatory[64] responses for allergic conditions and attention-deficit hyperactivity disorder which may explain this association. 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.

In general, the sample consisted of high socioeconomic two-parent families, which may have contributed to the lack of sociodemographic differences between children with and without multimorbidity and limits the generalizability of the findings. Placing the finding in the context of previous work is difficult given the absence of studies examining sociodemographic correlates of multimorbidity. Previous population-based studies conducted in Canada also showed no socioeconomic differences between children with and without physical conditions.[24,65-67] In our future larger study, we will work towards a recruitment strategy that will include wider variation in the socioeconomic status to families to increase the representativeness of the sample. Contrary to expectation, no effect of multimorbidity on parental outcomes was found. Nevertheless, information related to parental psychopathology and family environment may be important control variables used to isolate the effects of multimorbidity on child outcomes. Such family processes may also be implicated in complex pathways linking physical and mental health in children. As a result, these variables will be included in the larger study.

Multimorbidity appears to have a negative effect on children's quality of life, above and beyond the effect of having a physical condition alone.[18] This effect is pervasive, affecting multiple domains of quality of life during the first six months after a diagnosis. Of interest is the finding that the magnitude of effect seen for physical well-being, psychological well-being, and school environment was approximately half a standard deviation. This metric has been validated as the minimal clinically important difference for measures of quality of life[68] and provides evidence to support the perception that changes in child quality of life due to multimorbidity are clinically relevant. Given the early onset of

multimorbidity, health professionals in the pediatric setting should consider engaging children and families in discussions about mental health soon after the diagnosis of a physical condition is made and discussion surrounding the physical condition completed. Within a holistic family-centered approach, health professionals are encouraged to apply brief screening tools to identify at-risk children and provide referrals to supportive services on a case-by-case basis. This is a critical window of opportunity given that mental disorder is strong predictor of youth suicide[69] and that risk for suicide is highest soon after an adolescent is diagnosed with a physical condition.[34] Because of the chronicity and pervasiveness of multimorbidity and its influence on child and parent psychosocial functioning, continuing monitoring during routine clinical assessments may also be warranted.

There is one noteworthy limitation: the study was likely underpowered to detect differences between children with and without multimorbidity and the small sample size may limit the generalizability of findings. However, our sample size was consistent with considerations for implementing pilot studies[40] and our coverage of eligible families was good.

Conclusion

These preliminary findings indicate that mental disorder in children newly-diagnosed with a physical condition is common and negatively affects their quality of life over time. If these results are replicated in a subsequent larger study, health professionals should be aware of the burden of multimorbidity and prepare themselves to discuss mental health with children and their parents. Findings from this pilot study have been used to implement a large-scale study that will examine child multimorbidity in greater depth and provide more definitive clinical implications.

References

1. Van Cleave J, Gortmaker SL, Perrin JM. Dynamics of obesity and chronic health conditions among children and youth. JAMA 2010;303:623-30.

2. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. JAMA 2007;297:2741-51.

3. Merikangas KR, Calkins ME, Burstein M, et al. Comorbidity of physical and mental disorders in the neurodevelopmental genomics cohort study. Pediatrics 2015;135:e927-38.

4. Dobbie M, Mellor D. Chronic illness and its impact: considerations for psychologists. Psychology, health & medicine 2008;13:583-90.

5. Kessler RC, Avenevoli S, Costello EJ, et al. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. Arch Gen Psychiatry 2012;69:372-80.

6. Ferro MA. Major depressive disorder, suicidal behaviour, bipolar disorder, and generalised anxiety disorder among emerging adults with and without chronic health conditions. Epidemiology and psychiatric sciences 2016;25:462-74.

7. Quach J, Barnett T. Impact of chronic illness timing and persistence at school entry on child and parent outcomes: Australian longitudinal study. Academic pediatrics 2015;15:89-95.

8. Canning EH, Hanser SB, Shade KA, Boyce WT. Mental disorders in chronically ill children: parent-child discrepancy and physician identification. Pediatrics 1992;90:692-6.

9. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. J Pediatr Psychol 2011;36:1003-16.

10. Pinquart M, Shen Y. Anxiety in children and adolescents with chronic physical illnesses: a meta-analysis. Acta Paediatr 2011;100:1069-76.

11. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol 2011;36:375-84.

12. Butwicka A, Frisen L, Almqvist C, Zethelius B, Lichtenstein P. Risks of psychiatric disorders and suicide attempts in children and adolescents with type 1 diabetes: a population-based cohort study. Diabetes Care 2015;38:453-9.

13. Jones LC, Mrug S, Elliott MN, Toomey SL, Tortolero S, Schuster MA. Chronic physical health conditions and emotional problems from early adolescence through midadolescence. Academic pediatrics 2017;17:649-55.

14. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. Bmc Public Health 2013;13.

15. Boyle MH, Duncan L, Georgiades K, et al. Classifying child and adolescent psychiatric disorder by problem checklists and standardized interviews. International journal of methods in psychiatric research 2016.

16. Rettew DC, Lynch AD, Achenbach TM, Dumenci L, Ivanova MY. Meta-analyses of agreement between diagnoses made from clinical evaluations and standardized diagnostic interviews. International journal of methods in psychiatric research 2009;18:169-84.

17. Thygesen LC, Ersboll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. European Journal of Epidemiology 2014;29:551-8.

18. Moreira H, Carona C, Silva N, Frontini R, Bullinger M, Canavarro MC. Psychological and quality of life outcomes in pediatric populations: a parent-child perspective. J Pediatr 2013;163:1471-8.

19. Bai G, Herten MH, Landgraf JM, Korfage IJ, Raat H. Childhood chronic conditions and health-related quality of life: Findings from a large population-based study. PLoS One 2017;12:e0178539.

20. Ferro MA, Boyle MH. Self-concept among children and adolescents with a chronic illness: a meta-analytic review. Health Psychol 2013;32:839-48.

21. Bolognini M, Plancherel B, Bettschart W, Halfon O. Self-esteem and mental health in early adolescence: development and gender differences. J Adolesc 1996;19:233-45.

22. Crump C, Rivera D, London R, Landau M, Erlendson B, Rodriguez E. Chronic health conditions and school performance among children and youth. Ann Epidemiol 2013;23:179-84.

23. Forrest CB, Bevans KB, Riley AW, Crespo R, Louis TA. School outcomes of children with special health care needs. Pediatrics 2011;128:303-12.

24. Ferro MA, Boyle MH. The impact of chronic physical illness, maternal depressive symptoms, family functioning, and self-esteem on symptoms of anxiety and depression in children. J Abnorm Child Psychol 2015;43:177-87.

25. Miodrag N, Burke M, Tanner-Smith E, Hodapp RM. Adverse health in parents of children with disabilities and chronic health conditions: a meta-analysis using the parenting stress index's health sub-domain. J Intellect Disabil Res 2015;59:257-71.

26. Newacheck PW, Kim SE. A national profile of health care utilization and expenditures for children with special health care needs. Arch Pediatr Adolesc Med 2005;159:10-7.

27. McCarthy MJ, Behimer G, Anderson JA, Riddle I. Caregiving for youth with co-occurring developmental disabilities and behavioral health issues when caregivers face additional health-related stressors: Analysis of risk and protective factors from a national sample. Res Dev Disabil 2016;59:399-409.

28. Pinquart M. Parenting stress in caregivers of children with chronic physical condition-A meta-analysis. Stress and health : journal of the International Society for the Investigation of Stress 2017.

29. Lee SL, Cheung YF, Wong HS, Leung TH, Lam TH, Lau YL. Chronic health problems and health-related quality of life in Chinese children and adolescents: a population-based study in Hong Kong. BMJ open 2013;3.

30. Waters E, Davis E, Nicolas C, Wake M, Lo SK. The impact of childhood conditions and concurrent morbidities on child health and well-being. Child Care Health Dev 2008;34:418-29.

31. Chen H, Cohen P, Kasen S, Johnson JG, Berenson K, Gordon K. Impact of adolescent mental disorders and physical illnesses on quality of life 17 years later. Arch Pediatr Adolesc Med 2006;160:93-9.

32. Wodchis WP, Austin PC, Henry DA. A 3-year study of high-cost users of health care. CMAJ 2016;188:182-8.

33. Committee On Hospital C, Institute For P, Family-Centered C. Patient- and family-centered care and the pediatrician's role. Pediatrics 2012;129:394-404.

34. Christiansen E, Stenager E. Risk for attempted suicide in children and youths after contact with somatic hospitals: a Danish register based nested case-control study. J Epidemiol Community Health 2012;66:247-53.

35. Speechley KN, Ferro MA, Camfield CS, et al. Quality of life in children with new-onset epilepsy: a 2-year prospective cohort study. Neurology 2012;79:1548-55.

36. Ferro MA, Speechley KN. Examining clinically relevant levels of depressive symptoms in mothers following a diagnosis of epilepsy in their children: a prospective analysis. Soc Psychiatry Psychiatr Epidemiol 2012;47:1419-28.

37. Ferro MA, Van Lieshout RJ, Ohayon J, Scott JG. Emotional and behavioral problems in adolescents and young adults with food allergy. Allergy 2016;71:532-40.

38. Ferro MA, Van Lieshout RJ, Scott JG, Alati R, Mamun AA, Dingle K. Condition-specific associations of symptoms of depression and anxiety in adolescents and young adults with asthma and food allergy. J Asthma 2015:1-26.

39. Miller GF, Coffield E, Leroy Z, Wallin R. Prevalence and Costs of Five Chronic Conditions in Children. J Sch Nurs 2016;32:357-64.

40. Hertzog MA. Considerations in determining sample size for pilot studies. Res Nurs Health 2008;31:180-91.

41. Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry 2010;71:313-26.

42. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry 2015;56:345-65.

43. Ravens-Sieberer U, Auquier P, Erhart M, et al. The KIDSCREEN-27 quality of life measure for children and adolescents: psychometric results from a cross-cultural survey in 13 European countries. Qual Life Res 2007;16:1347-56.

44. Robitail S, Ravens-Sieberer U, Simeoni MC, et al. Testing the structural and cross-cultural validity of the KIDSCREEN-27 quality of life questionnaire. Qual Life Res 2007;16:1335-45.

45. Qadeer RA, Ferro MA. Child–parent agreement on health-related quality of life in children with newly diagnosed chronic health conditions: a longitudinal study. Int J Adolesc Youth 2017.

46. Berry JO, Jones WH. The Parental Stress Scale: initial psychometric evidence. J Soc Pers Relation 1995;12:463-72.

47. Spielberger CD. State-Trait Anxiety Inventory for adults. Menlo Park: Mind Garden Inc.; 1983.

48. Okun A, Stein RE, Bauman LJ, Silver EJ. Content validity of the Psychiatric Symptom Index, CES-depression Scale, and State-Trait Anxiety Inventory from the perspective of DSM-IV. Psychol Rep 1996;79:1059-69.

49. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.

50. Ferro MA, Speechley KN. Factor structure and longitudinal invariance of the Center for Epidemiological Studies Depression Scale (CES-D) in adult women: application in a population-based sample of mothers of children with epilepsy. Arch Womens Ment Health 2013;16:159-66.

51. Epstein NB, Baldwin LM, Bishop DS. The McMaster Family Assessment Device. J Marital Fam Ther 1983;9:171-80.

52. Byles J, Byrne C, Boyle MH, Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. Fam Process 1988;27:97-104.

53. Crichton N. Visual Analogue Scale (VAS). Journal of Clinical Nursing 2001;10:706-.

54. McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychol Med 1988;18:1007-19.

55. Paul-Dauphin A, Guillemin F, Virion JM, Briancon S. Bias and precision in visual analogue scales: a randomized controlled trial. Am J Epidemiol 1999;150:1117-27.

56. Couper MP. New developments in survey data collection. Annu Rev Sociol 2017;43:1-25.

57. De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. Psychol Bull 2005;131:483-509.

58. Jensen PS, Rubio-Stipec M, Canino G, et al. Parent and child contributions to diagnosis of mental disorder: are both informants always necessary? J Am Acad Child Adolesc Psychiatry 1999;38:1569-79.

59. Beck AT, Emery G, Greenberg RL. Anxiety disorders and phobias: a cognitive perspective. New York: Guildford Press; 1985.

60. Hou R, Garner M, Holmes C, et al. Peripheral inflammatory cytokines and immune balance in Generalised Anxiety Disorder: Case-controlled study. Brain, behavior, and immunity 2017;62:212-8.

61. Stein RE, Silver EJ. Operationalizing a conceptually based noncategorical definition: a first look at US children with chronic conditions. Arch Pediatr Adolesc Med 1999;153:68-74.

62. Topal E, Catal F, Soylu N, et al. Psychiatric disorders and symptoms severity in pre-school children with cow's milk allergy. Allergol Immunopathol (Madr) 2016;44:445-9.

63. Besser MJ, Ganor Y, Levite M. Dopamine by itself activates either D2, D3 or D1/D5 dopaminergic receptors in normal human T-cells and triggers the selective secretion of either IL-10, TNF alpha or both. Journal of neuroimmunology 2005;169:161-71.

64. Buske-Kirschbaunn A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. Psychoneuroendocrinology 2013;38:12-23.

65. Ferro MA, Boyle MH. Longitudinal invariance of measurement and structure of global self-concept: a population-based study examining trajectories among adolescents with and without chronic illness. J Pediatr Psychol 2013;38:425-37.

66. Ferro MA, Gorter JW, Boyle MH. Trajectories of depressive symptoms during the transition to young adulthood: the role of chronic illness. J Affect Disord 2015;174:594-601.

67. Gonzalez A, Boyle MH, Kyu HH, Georgiades K, Duncan L, MacMillan HL. Childhood and family influences on depression, chronic physical conditions, and their comorbidity: findings from the Ontario Child Health Study. J Psychiatr Res 2012;46:1475-82.

68. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582-92.

69. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA psychiatry 2013;70:300-10.

Table 1. Baseline sample characteristics

	Full sample	Multimorbid	Not multimorbid	P-value
N	50	29	21	
Child				
Age, years	11.3 (3.3)	11.6 (3.2)	11.0 (3.4)	0.62
Male, n (%)	26 (52)	15 (52)	11 (52)	0.96
Diagnoses, n (%)				0.98
Asthma	14 (28)	9 (31)	5 (24)	
Diabetes	9 (18)	4 (14)	5 (24)	
Epilepsy	8 (16)	4 (14)	4 (19)	
Food allergy	8 (16)	5 (17)	3 (14)	
Juvenile arthritis	11 (22)	7 (24)	4 (19)	
Disease severity, VAS	1.3 (1.2)	1.5 (1.3)	0.9 (0.9)	0.16
Quality of life, KIDSCREEN-27				
Physical well-being	48.0 (12.0)	47.4 (11.0)	48.8 (13.4)	0.77
Psychological well-being	46.1 (9.8)	43.6 (8.1)	49.4 (11.2)	0.08
Autonomy/Parent relations	48.9 (9.6)	47.5 (7.0)	50.8 (12.1)	0.72
Peer support	46.1 (11.4)	46.7 (12.1)	45.4 (10.5)	0.35
School environment	50.1 (10.8)	47.7 (8.8)	53.3 (12.4)	0.12
Parent				
Age, years	44.0 (5.7)	43.0 (4.8)	45.2 (6.3)	0.43
Female, n (%)	45 (90)	26 (90)	19 (91)	0.92
Immigrant, n (%)	10 (20)	8 (28)	2 (10)	0.16
Married, n (%)	39 (78)	22 (76)	17 (81)	0.67
Post-secondary graduate, n (%)	39 (78)	22 (76)	17 (81)	0.67
Income ≥$90,000, n (%)	29 (58)	17 (59)	12 (57)	0.87
Parental stress, PSS	35.9 (7.9)	37.1 (7.3)	34.4 (8.5)	0.32
Parental anxiety, STAI	41.6 (9.8)	44.2 (9.1)	38.2 (10.0)	0.05
Parental depression CES-D	12.7 (9.9)	13.0 (9.6)	12.2 (10.5)	0.58
Family functioning, FAD	25.5 (6.3)	24.7 (6.2)	26.5 (6.6)	0.20

Results are reported as mean (standard deviation) unless otherwise noted.

Table 2. Prevalence of multimorbidity

	Full sample	Asthma	Diabetes	Epilepsy	Food allergy	Juvenile arthritis	P-value
Baseline							
Any disorder	29 (58)	9 (64)	4 (44)	4 (50)	5 (63)	7 (64)	0.88
Major depressive episode	12 (24)	4 (29)	2 (22)	1 (13)	1 (13)	4 (36)	0.74
Separation anxiety	2 (4)	0	0	1 (13)	0	1 (9)	0.43
Phobia*	15 (30)	6 (46)	1 (11)	1 (13)	3 (38)	4 (36)	0.35
Generalized anxiety	6 (12)	0	0	2 (25)	2 (25)	2 (18)	0.11
Attention-deficit hyperactivity	5 (10)	1 (7)	0	1 (13)	3 (38)	0	0.06
Oppositional defiant	9 (18)	2 (14)	1 (11)	2 (25)	4 (50)	0	0.07
Conduct	3 (6)	1 (7)	0	1 (13)	1 (13)	0	0.65
Six months							
Any disorder	21 (42)	9 (64)	1 (11)	4 (50)	2 (25)	5 (56)	0.10
Major depressive episode	2 (4)	0	0	0	0	2 (22)	0.11
Separation anxiety	3 (6)	2 (14)	0	1 (13)	0	0	0.56
Phobia*	10 (20)	5 (36)	1 (11)	1 (13)	0	3 (33)	0.25
Generalized anxiety	4 (8)	1 (7)	0	1 (13)	0	2 (22)	0.55
Attention-deficit hyperactivity	3 (6)	0	0	0	2 (25)	1 (11)	0.09
Oppositional defiant	6 (12)	2 (14)	0	2 (25)	2 (25)	0	0.31
Conduct	4 (8)	1 (7)	0	2 (25)	1 (13)	0	0.33

Results are the number (%) of children with multimorbidity. Fisher's Exact tests examined multimorbidity across the five physical conditions.

*Includes generalized, non-generalized, and specific phobias.

Table 3. Longitudinal effects of multimorbidity on child quality of life

	Unadjusted		Adjusted	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Parent Report				
Physical well-being	-3.76 (2.23)	0.09	-4.82 (2.22)	0.03
Psychological well-being	-2.06 (2.44)	0.40	-4.10 (2.14)	0.06
Autonomy/Parent relations	0.77 (2.53)	0.76	-0.67 (2.40)	0.78
Peer support	-0.59 (2.83)	0.84	-1.23 (2.66)	0.64
School environment	-3.56 (2.88)	0.22	-4.17 (2.44)	0.09
Child Report				
Physical well-being	-7.76 (4.23)	0.07	-5.43 (4.36)	0.21
Psychological well-being	-8.58 (5.52)	0.12	-10.66 (4.78)	0.03
Autonomy/Parent relations	1.20 (4.07)	0.77	-0.26 (4.16)	0.95
Peer support	-3.19 (5.75)	0.58	-1.48 (5.52)	0.79
School environment	0.09 (5.12)	0.99	-2.02 (4.72)	0.67

Parent models include parent-reported MINI-KID and KIDSCREEN-27, whereas child models included child-reported MINI-KID and KIDSCREEN-27. Models adjusted for child age and sex, physical condition, and baseline quality of life.

Table 4. Longitudinal effects of multimorbidity on parental outcomes

	Unadjusted		Adjusted	
	B (SE)	**P-value**	**B (SE)**	**P-value**
Parental stress, PSS	0.28 (1.60)	0.86	-1.50 (1.51)	0.32
Parental anxiety, STAI	0.14 (2.05)	0.95	-0.24 (2.15)	0.91
Parental depression CES-D	0.30 (1.12)	0.80	0.62 (1.13)	0.58
Family functioning, FAD	1.21 (1.32)	0.36	1.47 (1.28)	0.25

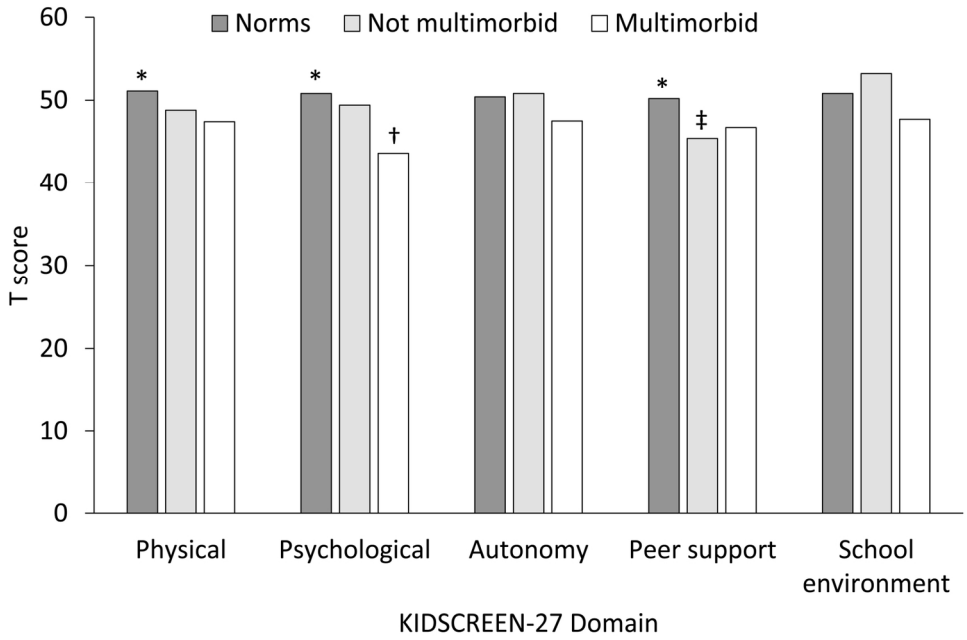
Models adjusted for child age and sex, physical condition, and baseline psychosocial outcome.

Figure 1. Comparison of KIDSCREEN-27 scores with population norms

*p<0.10 for overall F-test across the three groups.

†Multimorbid group significantly lower than normative and not multimorbid groups.

‡Not multimorbid group significantly lower than normative group.



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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-13
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	13
		(*c*) Explain how missing data were addressed	13
		(*d*) If applicable, explain how loss to follow-up was addressed	13
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	14
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	14
		(c) Summarise follow-up time (eg, average and total amount)	14
Outcome data	15*	Report numbers of outcome events or summary measures over time	14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	31-32
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18, 19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.