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Health Outcomes of Parents of Children with Chronic Illness: A Systematic Review and Meta-Analysis

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Objective To assess health outcomes of parents caring for children with chronic illnesses compared with parents of healthy children.

Study design We searched OvidSP MEDLINE, EBM Reviews–Cochrane Central Register of Controlled Trials, EMBASE, and EBSCOHost CINAHL through September 2019. Included were English-language studies reporting health conditions or mortality of parents of affected children compared with healthy controls.

Results Of 12 181 screened publications, 26 met inclusion criteria. Eight studies reported on anxiety, 23 on depression, 1 on mortality, and 1 on cardiovascular disease. Parents of chronically ill children had greater anxiety (standardized mean difference 0.42; 95% CI 0.24-0.60; $P < .001$) and depression scores (standardized mean difference 0.35; 95% CI 0.26-0.45; $P < .001$) than parents of healthy children. Thirty-five percent of parents of affected children met cut-offs for clinical depression, compared with 19% in the control (relative risk 1.75; 95% CI 1.55-1.97). Fifty-seven percent of such parents met cut-offs for anxiety, compared with 38% in the control (relative risk 1.40; 95% CI 1.18-1.67). One study of mothers of children with congenital anomalies reported a greater mortality risk than a comparison (adjusted hazard ratio 1.22; 95% CI 1.15-1.29), and another reported that these mothers experience an increased risk of cardiovascular disease (adjusted hazard ratio 1.15; 95% CI 1.07-1.23).

Conclusions Parents of chronically ill children experience poorer mental health (more anxiety and depression), and mothers of those with congenital anomalies may have greater risk of cardiovascular disease and mortality than parents of unaffected children. Our findings suggest a need for targeted interventions to attenuate adverse parental caregiver health outcomes. *(J Pediatr 2019;■:1-12)*.

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Medical, surgical, and technological advances have led to an increase in the number of chronically ill children who are dependent on parents as primary caregivers.[1] These parents often endure a multitude of challenges associated with caregiving. For some, parenting a chronically ill child may be accompanied by a sense of purpose, leading to positive effects on health and well-being, whereas for many, the parental responsibilities of caring for a chronically ill child, coupled with instinctive worry and financial burdens, may be stressful.[2,3]

Chronic stress has been reported as more prevalent among parents caring for chronically ill children than parents of healthy children.[4] Mothers of disabled children are 2-3 times more likely to experience distress than mothers of healthy children.[5] Exposure to stress alone can be linked to many chronic illnesses due to its influence on biological and psychological pathways.[4] Stress can dramatically shorten telomeres, the noncoding, protective ends of chromosomes, which has been associated with premature cell death, and the development of age-related diseases such as cancer, cardiometabolic dysfunction, and diabetes.[6,7] Chronic stress also can cause hyperactivation of the hypothalamic–pituitary–adrenal axis, leading to excessive secretion of glucocorticoids,[6] which has been linked to psychological, metabolic, and immune system dysfunction.[8,9]

Previous research on pediatric caregivers has reported that parents of chronically ill children experience greater levels of stress,[3,4] poorer health-related quality of life,[10-13] and worse sleep[14-20] when compared with parents of healthy children. Chronic parental psychological stress may negatively affect the emotional health and development of children, also raising concern on the impact of parental stress on children's health outcomes.[21,22]

Given the conflicting experiences described in the literature reflecting both positive and negative impacts of caregiving, it is important to understand whether parental caregiving is associated with adverse health outcomes and not just mediators of such outcomes, such as chronic stress. In particular, little is known about the long-term physical and psychological health outcomes of caregivers themselves. The aim of this systematic review is to compare the health

SMD	Standard mean difference

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outcomes of parental caregivers of chronically ill children with those of healthy children. We hypothesized that poorer health outcomes would be reported in parental caregivers of chronically ill children compared with parents of healthy children.

Methods

A systematic review of the published literature was facilitated by an experienced librarian. We conducted a literature search of OvidSP MEDLINE (1950 to September week 1 2019), EBM Reviews–Cochrane Central Register of Controlled Trials, EMBASE (1980 to September week 1 2019), and EBSCOHost CINAHL (1982 to September week 1 2019). The OVID-MEDLINE search strategy used in the study is summarized in **Table I** (available at www.jpeds.com). The literature search was performed according to the standards of PRISMA[23] and reported using both the PRISMA 2009 Checklist[24] and Meta-analysis of Observational Studies in Epidemiology[25] guidelines (**PRISMA and MOOSE checklists**; available at www.jpeds.com). Publications were selected in a 2-step process independently by 2 reviewers. In the first phase, each reviewer assessed the titles and relevant abstracts. The second phase consisted of a full-text review of the relevant articles based on the inclusion criteria. The raters met regularly to review the classification and evaluation of the studies and data. Disagreements between the reviewers were resolved through discussion and adjudication by a third reviewer. References of selected articles were hand-searched for additional relevant articles. All steps of the literature review were facilitated using Covidence software (Cochrane, Melbourne, Australia).[26]

Eligibility

Studies were included in the systematic review if they evaluated health outcomes of parents who were primary caregivers of children (0-18 years old) with chronic illnesses, defined as those suffering from a physical, developmental, behavioral, or emotional condition lasting at least 3 months,[27] reported a clinically diagnosable physical or mental health outcome for the parental caregiver, and included a comparison group of parents of healthy children (including experimental [eg, randomized controlled trials], cohort, case–control, and cross-sectional designs). Studies were excluded if they focused on caregivers of adults, evaluated nonparental caregivers (eg, siblings), lacked a comparison group (eg, case series or uncontrolled before-after studies), presented solely qualitative data, or reported outcomes that were traits or symptoms that could be mediators of health outcomes (eg, stress), but not specific clinical diagnoses. For instance, articles that reported on mood symptoms were only included if they reported outcomes using a scale that could be operationalized to screen or diagnose clinical depression. Articles not written in English or not available in full text were excluded. Efforts were made to contact authors of studies that presented inadequate data for extraction. The studies of those authors who failed to respond to 2 e-mail queries were subsequently excluded from the review.

Data Extraction

Subsequent to the selection of studies, a single reviewer extracted the data from each paper, followed by an additional reviewer who independently verified the collected data. Single publications that presented findings stratified by different types of child chronic conditions and/or by parental gender were classified as separate cohorts. All data were tabulated based on study design, country, parental gender, child chronic conditions, measurement tools, and reported health outcomes.

Risk of Bias

The risk of bias was assessed independently by 2 study investigators for all included studies using the Newcastle–Ottawa Scale[28] for nonrandomized trials and a modified form of the scale for cross-sectional studies.[29] Any disagreement was resolved by discussion between the 2 investigators. The scale (range 0-9) consists of 3 distinct criteria including, Selection, Comparability, and Outcome; scores of 0-3 were considered as low quality and high risk of bias, 4-6 as moderate quality and risk of bias, and 7-9 as high quality and low risk of bias.[28]

Statistical Analyses

Effect sizes were calculated for rating scales with continuous data as standard mean difference (SMD) with 95% CIs. Extracted data from each study were descriptively presented in a tabular form and the findings for each health outcome were visualized through forest plots. For each health outcome, the SMD across the identified studies was summarized through a meta-analysis, using a random effects model for continuous data. A positive SMD indicates greater scores in the exposed group (parents of chronically ill children) and a negative score indicates greater scores in the unexposed group (parents of healthy children). The percentage of variability attributed to heterogeneity between the studies was assessed using the I^2 statistic. Using the Cochrane Handbook guidelines for systematic reviews, an I^2 of 0%-40% represented possibly unimportant heterogeneity, 30%-60% moderate heterogeneity, 50%-90% substantial heterogeneity, and 75%-100% considerable heterogeneity.[30] Statistical significance was set at a conventional P value of $<.05$. Stratified analyses were performed when possible by parental gender (fathers vs mothers). Review Manager (RevMan), version 5.3 (London, United Kingdom)[31] was used to conduct all of the presented analyses.

Given the potential challenges in interpreting mean differences on varied scales clinically,[32] a supplementary analysis was conducted comparing the percentages of parents scoring above or below clinical cutoff scores established by scales for depression and anxiety. Data were collected from the most frequently used scales among the selected studies, including the Hospital Anxiety and Depression Scale[33] for both anxiety and depression, Center for Epidemiologic Studies Depression Scale[34] for depression, and the Beck Depression Inventory[35] for depression, presenting cutoff scores of 7, 16, and

10, respectively.[36] Due to the continuous nature of the measures for depression and anxiety, the scores were initially standardized via the z statistic, using mean and SD, followed by the percentage and relative risk calculation. Total percentage values for each population in the relevant outcomes were calculated through a random effects meta-analysis of the individual arms. The standardization method was not applied to studies already reporting on percentage values of the desired categorical outcomes.[37,38]

Results

Identification of Relevant Studies

Of 12 181 potential titles and abstracts identified in initial screening, 115 were assessed for full-text eligibility and 26 met study inclusion criteria. The PRISMA flowchart is presented in **Figure 1** (available at www.jpeds.com).

Study Characteristics

Table II summarizes the study characteristics of the 26 relevant studies. The included studies reported on the following health outcomes: anxiety,[39] depression,[5,37,38,40-52] both anxiety and depression,[53-59] mortality,[60] and cardiovascular disease.[61] Data gathered on health outcomes were available from 9 countries: Australia,[56] Canada,[40] Denmark,[60,61] Ireland,[62] the Netherlands,[57] Portugal,[58] Saudi Arabia,[53,54] Turkey,[39,41,55,59] and the US.[5,37,38,42-51] Of the 26 studies, 22 used a cross-sectional design,[5,37-42,44-49,52-59,62] 3 were prospective cohort studies,[43,60,61] and 1 was a case–control study.[50] Child chronic conditions included sickle cell anemia,[42] human immunodeficiency virus infection,[42] asthma,[40,59] cystic fibrosis,[46,59] cerebral palsy,[5,40,41,55] spina bifida,[50,52] type 1 diabetes mellitus,[46,58] epilepsy,[39,40] autism,[48] Down syndrome,[38,48] congenital anomalies,[60,61] and unspecified mental/intellectual,[37,40,44,46,53,54,56] physical,[53,54] or sensory disabilities/chronic illnesses.[43,53,54,57] Fifteen studies examined only mothers,[5,37,39,41-46,52-54,59-61] 10 examined both mothers and fathers in either separate or unified cohorts,[38,40,47-50,55,57,58,62] and only 1 study exclusively assessed fathers.[56]

Reported Outcomes/Meta-Analysis

Two individual meta-analyses were performed on studies reporting outcomes of anxiety and depression, respectively. Of the 8 studies that reported anxiety as a health outcome, parents of a chronically ill child had increased anxiety scores compared with parents of healthy children (SMD 0.42; 95% CI 0.24-0.60; $P < .001$) with high statistical heterogeneity ($I^2 = 78\%$; $P \leq .001$; **Figure 2**). Among the 23 studies reporting on depression, parents of a chronically ill child had increased depression scores compared with parents of healthy children (SMD 0.35; 95% CI 0.26-0.35; $P < .001$) with high statistical heterogeneity ($I^2 = 69\%$; $P \leq .001$; **Figure 3**). A single study of mothers of children with congenital anomalies reported a greater mortality risk compared with mothers of unaffected children (adjusted hazard ratio 1.22; 95% CI 1.15-1.29).[60] An additional study evaluating a similar cohort of mothers of children with congenital anomalies also reported a greater risk of cardiovascular disease in exposed mothers (adjusted hazard ratio 1.15; 95% CI 1.07-1.23).[61] Stratified analyses by parent gender were not feasible due to a lack of gender-specific data, primarily on fathers. The results of the percentage analysis comparing parents above and below the cut-off scores for depression and anxiety are found in **Table III**. Thirty-five percent (95% CI 0.28-0.44) of parents of affected children met cut-offs for clinical depression, compared with 19% (95% CI 0.15-0.24) of parents of unaffected children (relative risk 1.75; 95% CI, 1.55-1.97; $P \leq .001$). With respect to anxiety, 57% (95% CI 0.45-0.69) of parents of chronically ill children met cut-off criteria, compared with 38% (95% CI 0.27-0.50) of parents of healthy children (relative risk 1.40; 95% CI 1.18-1.67; $P \leq .001$). Quality assessment scores of included studies rated 1 study as low quality,[59] 16 studies as moderate quality,[5,37-39,41-44,47,48,50,52-55,57] and 9 studies as high quality[40,45,49,56,58,60-63] (**Table II**).

Discussion

Our findings suggest that parental caregiving for a chronically ill child is associated with worse overall mental health compared with parental caregiving of healthy children, particularly anxiety and depression. There was only 1 study focusing on physical health outcomes that met our inclusion criteria,[61] in addition to 1 study reporting on mortality.[60] We could not formally compare findings in mothers and fathers, as there were relatively few fathers included in the reports.

These findings support the need for developing and evaluating interventions targeting the health and well-being of parents of chronically ill children. Our findings also support the need for screening specifically for mood and anxiety disorders in parents of children with chronic illness, an activity reimbursed by Medicaid in the US in some, but not all, states.[64] A Cochrane review on psychological interventions for parents of children with chronic illness, that included 47 randomized control trials, reported that there is little evidence available supporting the efficacy of psychological therapies for parents of children with a number of common chronic illnesses. However, the study reported that some psychological therapies, such as problem-solving therapy, were efficacious in improving parental mental health and behavior.[65]

Our review also found a paucity of data on fathers, suggesting a need for additional research acknowledging paternal caregiving roles and understanding its effects on fathers. The reasons for a lack of data on fathers may be attributed to the reality that mothers more commonly assume the role of primary caregiver as well as the difficulty in recruiting fathers for studies.[66] Nevertheless, fathers are presumably still

Table II. Description of included studies presented by outcome including study quality of assessment

Authors	Year	Country	Study design	Pediatric population	Caregiver population (exposed)	Caregiver population (unexposed)	Measure	Outcome	Quality assessment scores (out of 9)	SMD (95% CI)*
Anxiety										
Al-Eithan et al[54]	2012	Saudi Arabia	Cross-sectional	Severe or chronic medical conditions	N = 86 Mothers	N = 32	HADS	Anxiety	5	0.40 (−0.00 to 0.81)
Al-Eithan et al[53]	2010	Saudi Arabia	Cross-sectional	Physical, sensory, or mental disability	N = 75 Mothers	N = 35	HADS	Anxiety	6	1.36 (0.92 to 1.80)
Basaran et al[55]	2013	Turkey	Cross-sectional	Cerebral palsy	N = 143 Mothers (135), fathers (3), and other (5)	N = 60	BAI	Anxiety	6	0.52 (0.21 to 0.82)
Giallo et al[56]	2015	Australia	Cross-sectional	Aged 3-15 y with intellectual disability	N = 315 Fathers	N = 497	DASS	Anxiety	7	0.02 (−0.12 to 0.16)
Moreira et al[58]	2013	Portugal	Cross-sectional	Aged 8-12 y diagnosed with type I diabetes	N = 49 Mothers and fathers	N = 77	HADS	Anxiety	7	0.57 (0.20 to 0.93)
Moreira et al[58]	2013	Portugal	Cross-sectional	Aged 13-18 y diagnosed with type I diabetes	N = 55 Mothers and fathers	N = 65	HADS	Anxiety	7	0.27 (−0.09 to 0.63)
Serin et al[39]	2015	Turkey	Cross-sectional	Epilepsy	N = 100 Mothers	N = 100	BAI	Anxiety	6	0.48 (0.20 to 0.76)
van Oers et al[57]	2014	The Netherlands	Cross-sectional	"Chronically ill" under treatment in a children's hospital	N = 566 Mothers	N = 386	HADS	Anxiety	6	0.37 (0.24 to 0.51)
van Oers et al[57]	2014	The Netherlands	Cross-sectional	"Chronically ill" under treatment in a children's hospital	N = 123 Fathers	N = 368	HADS	Anxiety	6	0.18 (−0.02 to 0.38)
Yilmaz et al[59]	2008	Turkey	Cross-sectional	Asthma	N = 62 Mothers	N = 35	HADS	Anxiety	3	0.45 (0.03 to 0.87)
Yilmaz et al[59]	2008	Turkey	Cross-sectional	Cystic fibrosis	N = 21 Mothers	N = 35	HADS	Anxiety	3	0.40 (−0.15 to 0.94)
Depression										
Al-Eithan et al[54]	2012	Saudi Arabia	Cross-sectional	Physical, mental, or sensory disabilities that need hospital rehabilitation	N = 86 Mothers	N = 32	HADS	Depression	5	0.24 (−0.17 to 0.65)
Al-Eithan et al[53]	2010	Saudi Arabia	Cross-sectional	Physical, sensory, or mental disability	N = 75 Mothers	N = 35	HADS	Depression	6	0.74 (0.33 to 1.16)
Basaran et al[55]	2013	Turkey	Cross-sectional	Cerebral palsy	N = 143 Mothers (135), fathers (3), and other (5)	N = 60	BDI	Depression	6	0.38 (0.08 to 0.69)
Blacher et al[37]	1997	US	Cross-sectional	Intellectual disability	N = 148 Mothers	N = 101	CES-D	Depression	6	0.35 (0.09 to 0.60)
Brehaut et al[40]	2009	Canada	Cross-sectional	Asthma, allergies, bronchitis, cerebral palsy, epilepsy, heart condition or disease, kidney condition or disease, mental handicap, or "other"	N = 2495 Mothers (2201), fathers (214), and other (80)	N = 3633	CES-D	Depression	7	0.17 (0.12 to 0.22)
Breslau and Davis[45]	1986	US	Cross-sectional	Cystic fibrosis, cerebral palsy, myelodysplasia, or multiple handicaps	N = 310 Mothers	N = 357	CES-D	Depression	8	0.39 (0.23 to 0.54)

(*continued*)

Table II. Continued

Authors	Year	Country	Study design	Pediatric population	Caregiver population (exposed)	Caregiver population (unexposed)	Measure	Outcome	Quality assessment scores (out of 9)	SMD (95% CI)*
Bristol et al[49]	1988	US	Cross-sectional	Autistic or severe communication-impaired	N = 31 Mothers	N = 25	CES-D	Depression	7	0.55 (0.01 to 1.08)
Bristol et al[49]	1988	US	Cross-sectional	Autistic or severe communication-impaired	N = 31 Fathers	N = 25	CES-D	Depression	7	0.19 (−0.34 to 0.77)
Cappelli et al[50]	1990	US	Case-control	Spina bifida	N = 23 Mothers	N = 23	CES-D	Depression	6	0.19 (−0.39 to 0.72)
Cappelli et al[50]	1990	US	Case-control	Spina bifida	N = 23 Fathers	N = 23	CES-D	Depression	6	−0.17 (−0.75 to 0.41)
Civilibal et al[52]	2014	Turkey	Cross-sectional	Spina bifida	N = 30 Mothers	N = 30	BDI	Depression	4	2.61 (1.91 to 3.31)
Gallagher et al[62]	2014	Ireland	Cross-sectional	Developmental/ learning disabilities (ie, dyslexia, speech and language difficulty, slow progress, dyspraxia, ADHD, autism/ Asperger's, other)	N = 627 Mothers (624) and fathers (3)	N = 7941	CES-D	Depression	7	1.01 (1.43 to 2.35)
Giallo et al[56]	2015	Australia	Cross-sectional	Aged 3–15 y with Intellectual Disability	N = 315 Fathers	N = 497	DASS	Depression	7	0.26 (0.12 to 0.40)
Gowen et al[43]	1989	USA	Cohort	Down syndrome, cerebral palsy, developmental delay due to meningitis, trisomy 18, spina bifida, and other developmental delays	N = 21 Mothers	N = 20	CES-D	Depression	5	0.27 (−0.35 to 0.89)
Harris and McHale[44]	1989	USA	Cross-sectional	Intellectual disability	N = 30 Mothers	N = 30	BDI	Depression	5	0.41 (−0.11 to 0.92)
Miller et al[5]	1992	USA	Cross-sectional	Cerebral palsy, paraplegia/ hemiparesis, developmental delay, orthopedic, quadriplegia, spina bifida, or brain damage (other than cerebral palsy)	N = 69 Mothers	N = 63	BSI	Depression	5	0.37 (0.02 to 0.71)
Moreira et al[58]	2013	Portugal	Cross-sectional	Aged 8-12 y diagnosed with type I diabetes	N = 49 Mothers and fathers	N = 77	HADS	Depression	7	0.42 (0.06 to 0.78)
Moreira et al[58]	2013	Portugal	Cross-sectional	Aged 13-18 y diagnosed with type I diabetes	N = 55 Mothers and fathers	N = 65	HADS	Depression	7	0.03 (−0.33 to 0.39)
Moskowitz et al[42]	2007	US	Cross-sectional	Sickle cell disease	N = 14 Mothers	N = 36	CES-D	Depression	5	0.90 (0.25 to 1.54)
Moskowitz et al[42]	2007	US	Cross-sectional	HIV	N = 44 Mothers	N = 36	CES-D	Depression	5	0.48 (0.04 to 0.93)

(*continued*)

Table II. Continued

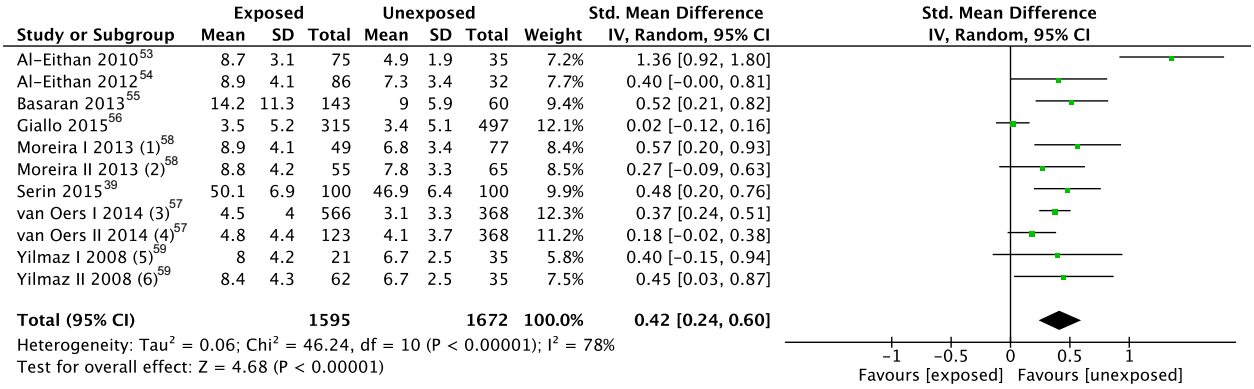
Authors	Year	Country	Study design	Pediatric population	Caregiver population (exposed)	Caregiver population (unexposed)	Measure	Outcome	Quality assessment scores (out of 9)	SMD (95% CI)*
Scott et al[38]	1997	US	Cross-sectional	Down syndrome	N = 54 Mothers	N = 54	BDI	Depression	5	0.36 (0.05 to 0.77)
Scott et al[38]	1997	US	Cross-sectional	Down syndrome	N = 54 Fathers	N = 54	BDI	Depression	5	Not applicable
Seltzer et al[47]	2001	US	Cross-sectional	Intellectual disability, developmental disability, cerebral palsy, brain damage, schizophrenia, major depression, or other mental health problems	N = 92 Mothers	N = 126	CES-D	Depression	5	0.13 (−0.14 to 0.40)
Seltzer et al[47]	2001	US	Cross-sectional	Intellectual disability, developmental disability, cerebral palsy, brain damage, schizophrenia, major depression, or other mental health problems	N = 73 Mothers	N = 92	CES-D	Depression	5	0.10 (−0.21 to 0.40)
Seltzer et al[47]	2001	US	Cross-sectional	Intellectual disability, developmental disability, cerebral palsy, brain damage, schizophrenia, major depression, or other mental health problems	N = 34 Mothers	N = 126	CES-D	Depression	5	0.54 (0.15 to 0.92)
Seltzer et al[47]	2001	US	Cross-sectional	Intellectual disability, developmental disability, cerebral palsy, brain damage, schizophrenia, major depression, or other mental health problems	N = 19 Mothers	N = 92	CES-D	Depression	5	0.14 (−0.35 to 0.63)
Terzi et al[41]	2016	Turkey	Cross-sectional	Cerebral palsy	N = 85 Mothers	N = 42	BDI	Depression	5	0.96 (0.57 to 1.35)
van Oers et al[57]	2014	The Netherlands	Cross-sectional	"Chronically ill" under treatment in a children's hospital	N = 566 Mothers	N = 368	HADS	Depression	6	0.37 (0.24 to 0.51)

(*continued*)

Table II. Continued

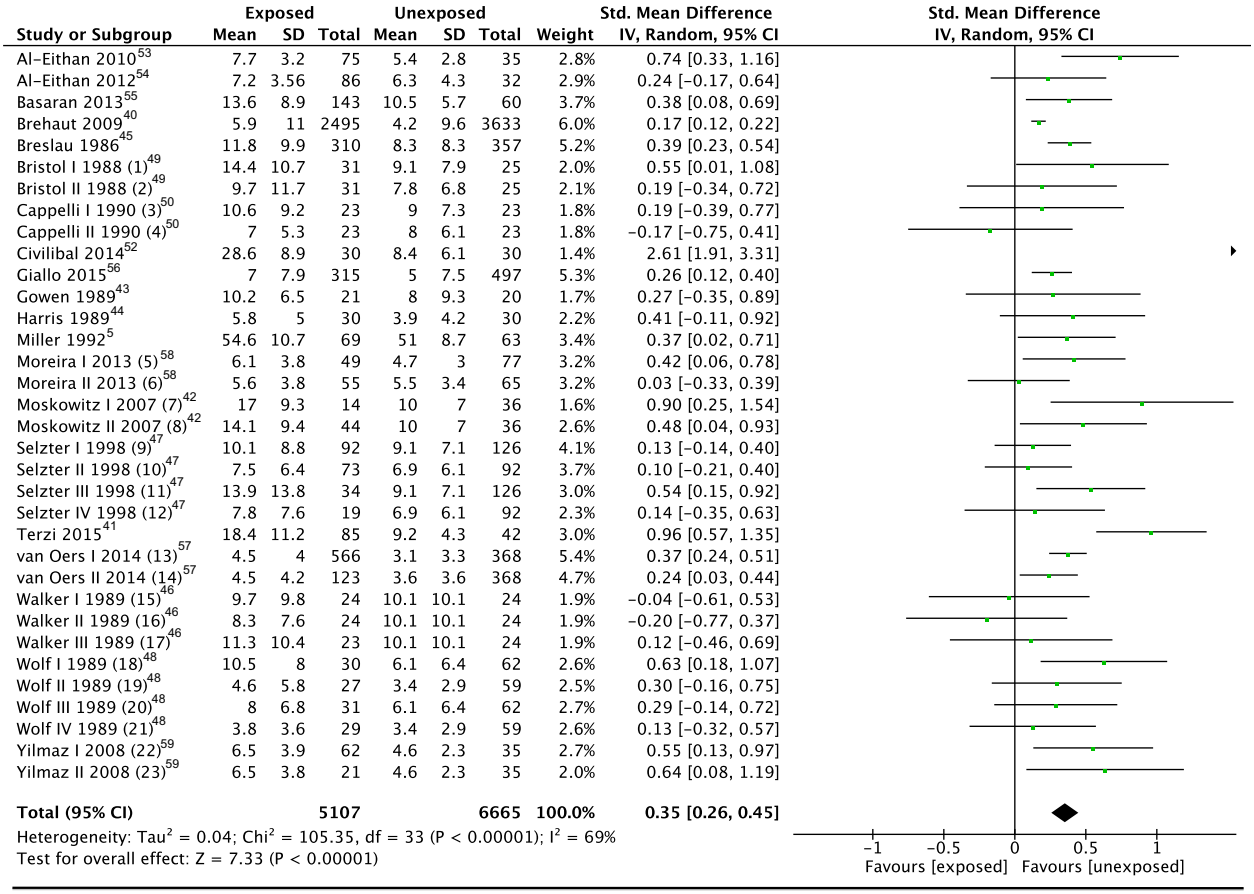
Authors	Year	Country	Study design	Pediatric population	Caregiver population (exposed)	Caregiver population (unexposed)	Measure	Outcome	Quality assessment scores (out of 9)	SMD (95% CI)*
van Oers et al[57]	2014	The Netherlands	Cross-sectional	"Chronically ill" under treatment in a children's hospital	N = 123 Fathers	N = 368	HADS	Depression	6	0.24 (0.03 to 0.44)
Walker et al[46]	1989	US	Cross-sectional	Intellectual disability	N = 24 Mothers	N = 24	CES-D	Depression	4	−0.04 (−0.61 to 0.52)
Walker et al[46]	1989	US	Cross-sectional	Diabetes mellitus	N = 24 Mothers	N = 24	CES-D	Depression	4	−0.20 (−0.77 to 0.37)
Walker et al[46]	1989	US	Cross-sectional	Cystic fibrosis	N = 23 Mothers	N = 24	CES-D	Depression	4	0.12 (−0.46 to 0.68)
Wolf et al[47]	1989	US	Cross-sectional	Autism	N = 30 Mothers	N = 62	BDI	Depression	6	0.63 (0.18 to 1.07)
Wolf et al[48]	1989	US	Cross-sectional	Autism	N = 27 Fathers	N = 59	BDI	Depression	6	0.30 (−0.16 to 0.75)
Wolf et al[48]	1989	US	Cross-sectional	Down syndrome	N = 31 Mothers	N = 62	BDI	Depression	6	0.29 (−0.14 to 0.72)
Wolf et al[48]	1989	US	Cross-sectional	Down syndrome	N = 29 Fathers	N = 59	BDI	Depression	6	0.13 (−0.32 to 0.57)
Yilmaz et al[59]	2008	Turkey	Cross-sectional	Asthma	N = 62 Mothers	N = 35	HADS	Depression	3	0.55 (0.13 to 0.97)
Yilmaz et al[59]	2008	Turkey	Cross-sectional	Cystic fibrosis	N = 21 Mothers	N = 35	HADS	Depression	3	0.64 (0.08 to 1.19)
Mortality										
Cohen et al[60]	2016	Denmark	Cohort	Major congenital anomalies	N = 41 508 Mothers	N = 413 742	N/A	Mortality	9	Not applicable†
Physical Health										
Cohen et al[61]	2018	Denmark	Cohort	Major congenital anomalies	N = 42 943 Mothers	N = 428 401	N/A	Cardiovascular disease	9	Not applicable‡

BAI, Beck Anxiety Inventory; *BDI*, Beck Depression Inventory; *BSI*, Brief Symptom Inventory; *CES-D*, Centre for Epidemiological Studies in Depression Scale; *DASS*, Depression Anxiety Stress Scale; *HADS*, Hospital Anxiety and Depression Scale; *N/A*, not available.
*A positive SMD indicates more anxiety in the exposed (parents of chronically ill children) compared with the unexposed (parents of healthy children).
†Reported as an increased adjusted hazard ratio of 1.22 (95% CI 1.15-1.29) among mothers of children with major congenital anomalies vs a comparison cohort.
‡Reported as an increased adjusted hazard ratio of 1.15 (95% CI 1.07-1.23) among mothers of children with major congenital anomalies vs a comparison cohort.



(1) Children with Type I Diabetes aged 8-12, (2) Children with Type I Diabetes aged 13-18, (3) Mothers, (4) Fathers, (5) Children with Asthma, (6) Children with Cystic Fibrosis

Figure 2. Forest plot of anxiety scores of parents of chronically ill children (exposed) compared with parents of healthy children (unexposed). IV, Inverse Variance



(1) Mothers, (2) Fathers, (3) Mothers, (4) Fathers, (5) Children with Type I Diabetes aged 8-12, (6) Children with Type I Diabetes aged 13-18, (7) Children with Sickle Cell Disease, (8) Children with HIV, (9) Mothers of children with developmental disabilities, (10) Fathers of children with developmental disabilities, (11) Mothers of children with severe mental health problems, (12) Fathers of children with severe mental health problems, (13) Mothers, (14) Fathers, (15) Children with Mental Retardation, (16) Children with Diabetes, (17) Children with Cystic Fibrosis, (18) Mothers of autistic children, (19) Fathers of autistic children, (20) Mothers of children with Down Syndrome, (21) Fathers of children with Down Syndrome, (22) Children with Asthma, (23) Children with Cystic Fibrosis

Figure 3. Forest plot of depression scores of parents of chronically ill children (exposed) compared with parents of healthy children (unexposed).

Table III. Parents with and without chronically children scoring above clinical cut-off scores for anxiety and depression

Authors	Year	Mean (SD)		Cut-off %		Relative risk (CI)
Anxiety-HADS		Affected	Unaffected	Affected	Unaffected	
Al-Eithan et al[54]	2012	8.9 (4.1)	7.3 (3.4)	68%	54%	4.95 (2.17-11.28)
Al-Eithan et al[53]	2010	8.7 (3.1)	4.9 (1.9)	71%	13%	1.27 (0.89-1.81)
Moreira et al[58]	2013	8.9 (4.1)	6.8 (3.4)	68%	48%	1.40 (1.03-1.90)
Moreira et al[58]	2013	8.8 (4.2)	7.8 (3.3)	66%	60%	1.09 (0.83-1.44)
van Oers et al[57]	2014	5.9 (4.1)	4.8 (3.5)	39%	26%	1.49 (1.23-1.82)
van Oers et al[57]	2014	4.8 (4.4)	4.1 (3.7)	31%	22%	1.42 (1.02-1.97)
Yilmaz et al[59]	2008	8.0 (4.2)	6.7 (2.5)	59%	45%	1.25 (0.75-2.10)
Yilmaz et al[59]	2008	8.4 (4.3)	6.7 (2.5)	63%	45%	1.38 (0.91-2.07)
Depression-HADS						
Al-Eithan et al[54]	2012	7.2 (3.6)	6.3 (4.3)	52%	43%	1.20 (0.77-1.86)
Al-Eithan et al[53]	2010	7.7 (3.2)	5.4 (2.8)	59%	59%	2.05 (1.18-3.58)
Moreira et al[58]	2013	6.1 (3.8)	4.7 (3.0)	41%	22%	1.85 (1.08-3.17)
Moreira et al[58]	2013	5.6 (3.8)	5.5 (3.4)	36%	33%	1.13 (0.69-1.85)
van Oers et al[57]	2014	4.5 (4.0)	3.1 (3.3)	27%	12%	2.23 (1.64-3.04)
Van Oers et al[57]	2014	4.5 (4.2)	3.6 (3.6)	28%	17%	1.61 (1.12-2.32)
Yilmaz et al[59]	2008	6.5 (3.9)	4.6 (2.3)	45%	15%	3.16 (1.34-7.45)
Yilmaz et al[59]	2008	6.5 (3.8)	4.6 (2.3)	45%	15%	3.00 (1.16-7.76)
Depression-BDI						
Basaran et al[55]	2013	13.6 (8.9)	10.5 (5.6)	66%	54%	1.23 (0.95-1.61)
Civilibal et al[52]	2014	28.6 (8.9)	8.4 (6.1)	98%	40%	2.42 (1.55-3.76)
Harris and McHale[44]	1989	5.8 (5.0)	3.9 (4.2)	20%	7%	3.00 (0.66-13.69)
Scott et al[38,*]	1997	–	–	20%	13%	1.57 (0.85-2.91)
Terzi and Tan[41]	2016	18.4 (11.2)	9.2 (4.3)	77%	43%	1.81 (1.25-2.62)
Wolf et al[48]	1989	10.5 (7.8)	5.0 (3.8)	52%	9%	5.51 (2.40-12.65)
Wolf et al[48]	1989	4.6 (5.8)	3.8 (5.5)	18%	13%	1.37 (0.49-3.79)
Wolf et al[48]	1989	8.0 (6.8)	5.0 (3.8)	39%	9%	4.00 (1.66-9.64)
Wolf et al[48]	1989	3.8 (3.6)	3.8 (5.5)	4%	13%	0.25 (0.03-1.94)
Depression-CES-D						
Blacher et al[37]	1997	–	–	50%	33%	1.53 (1.11-2.11)
Brehaut et al[40]	2009	5.9 (11.0)	4.2 (9.6)	18%	11%	1.61 (1.42-1.82)
Breslau and Davis[45]	1986	11.8 (9.9)	8.3 (8.3)	33%	18%	1.88 (1.43-2.48)
Bristol et al[49]	1988	14.4 (10.7)	9.1 (7.9)	44%	19%	2.26 (0.94-5.42)
Bristol et al[49]	1988	9.7 (11.7)	7.8 (6.8)	29%	11%	2.42 (0.73-8.00)
Cappelli[50]	1990	10.6 (9.2)	9.0 (7.3)	28%	17%	1.50 (0.49-4.62)
Cappelli[50]	1990	7.0 (5.3)	8.0 (6.1)	4%	9%	0.50 (0.05-5.14)
Gowen et al[43]	1989	10.2 (8.0)	9.26 (6.5)	26%	11%	2.38 (0.52-10.90)
Moskowitz et al[42]	2007	17.0 (9.26)	10.0 (7.0)	54%	20%	2.94 (1.31-6.57)
Moskowitz et al[42]	2007	14.1 (9.36)	10.0 (7.0)	42%	20%	2.10 (0.99-4.47)
Seltzer et al[47]	2001	10.1 (8.8)	9.1 (7.1)	25%	17%	1.50 (0.89-2.54)
Seltzer et al[47]	2001	7.5 (6.4)	6.9 (6.1)	9%	7%	1.47 (0.52-4.19)
Seltzer et al[47]	2001	13.9 (13.8)	9.1 (7.1)	44%	17%	2.65 (1.54-4.56)
Seltzer et al[47]	2001	7.8 (7.6)	6.9 (6.1)	14%	7%	2.42 (0.66-8.84)
Walker et al[46]	1989	9.7 (9.8)	10.1 (10.1)	26%	28%	0.86 (0.34-2.18)
Walker et al[46]	1989	8.3 (7.6)	10.1 (10.1)	16%	28%	0.57 (0.19-1.70)
Walker et al[46]	1989	11.3 (10.4)	10.1 (10.1)	32%	28%	1.04 (0.43-2.51)

BDI, Beck Depression Inventory; *CES-D*, Centre for Epidemiological Studies in Depression Scale; *HADS*, Hospital Anxiety and Depression Scale.
*Pooled percentages from combining data on mothers and fathers.

influenced by the illness of their child and may face stress when parenting a chronically ill child.[56]

The scarcity of published studies focused on physical health outcomes and mortality may be explained by the feasibility issues, as studies need large sample sizes and prolonged observation periods to detect events that may be uncommon, such as premature mortality. However, the observed results pertaining to mental health may very well be associated with chronic stress, which has been found to be associated with poorer physical health outcomes, including cardiovascular, gastrointestinal, immune, and neurologic health issues.[2]

Previous studies of health outcomes of caregivers have focused largely on elderly patients. One systematic review reported conflicting findings across studies.[67] Some studies in that review described greater mortality and adverse physical and psychological outcomes among informal caregivers compared with noncaregivers, and others reported positive health outcomes and lower mortality rates among caregivers. The potential protective effects of caregiving for elderly patients reported in some studies may be attributed to the "healthy caregiver" hypothesis, suggesting that healthier individuals tend to take on a caregiving role and thereby acquire health benefits. In contrast, almost all of the studies reported in our review reported negative health impacts on caregivers, suggesting that caregiving of children might be distinguishably different from caregiving of adults. Parents caring for children with a chronic illness may face a different

reality than caregivers of adults, influenced by factors such as age of the caregiver, nature of the care provided, and/or the degree of choice present when assuming the caregiving role.

Data comparing clinically diagnosable health outcomes of parents of chronically ill children with parents of healthy children are more limited. Many studies have focused on self-reported quality of life or on important mediators of health outcomes such as stress or sleep. Studies evaluating domains of quality of life, including psychological, physical, sleep quality, and general health, have reported that parents of chronically ill children experience poorer quality of life compared with parents of healthy children.[10-12,59,66,68] These findings have been attributed to a number of explanations, including financial and emotional burdens, social isolation, and the stress that may accompany caring for a child with a chronic illness.[12,68] A meta-analysis of 18 studies published in 2006 reported a similar effect size to our report for depressive symptoms among mothers of children with developmental disabilities compared with mothers of non-disabled children.[36] However, the review did not report on fathers, was limited to North American data, focused narrowly on symptoms associated with depression as opposed to more comprehensive health outcomes, and incorporated less than one-half the number of studies included in our review. Moreover, of these 18 studies included in the previous published meta-analysis, 10 reported directly on depression and were included in our review, and the remainder did not fit our inclusion criteria, as they focused on factors that may be mediators of depression, such as stress. Another meta-analysis of 19 studies reported greater levels of parental stress among parents of children with disabilities and chronic health conditions but did not measure clinically diagnosable outcomes and also did not report on fathers.[2]

Limitations of our study include the lack of clinically confirmed diagnoses, as all included studies relied on self-reports based on various tools screening for the presence of depression and/or anxiety, and health administrative data for mortality and cardiovascular disease. Study quality varied. Almost all included studies used a cross-sectional design or were short in duration of follow-up, making it difficult to assess the incidence of adverse health outcomes over an extended period of time and preventing the assessment of whether the observed parental health outcomes may have predated the onset of chronic illness in the child, which may be attributed to shared genetics underlying poor health. Among those studies whose outcomes relied on self-reports, different assessment tools were used across studies, which may partially explain the relatively high level of heterogeneity in both depression and anxiety. Another potential source of heterogeneity was that studies were from varying countries and across different years, such that treatment and support available for families of chronically ill children may have varied over time and place. The considerable range in pediatric chronic conditions evaluated among the studies may also contribute to greater heterogeneity, because the nature of the child's condition may influence the amount and type of impact on parental health. Due to the diversity of chronic illnesses reported across the studies, stratified analysis based on the nature of the pediatric conditions was not possible. Similarly, comparing outcomes across parental genders was unachievable because of the paucity of data on fathers compared with mothers. Our analysis was restricted to studies written in English, thereby potentially excluding relevant studies published in other languages, particularly from families with different cultural backgrounds. Many studies had small sample sizes and hence relatively imprecise risk estimates.

These findings indicate that these parents may be at risk of suboptimal health outcomes and are a potential target for screening and interventions aimed at improving their health and well-being. Future research should incorporate comprehensive health outcomes to better understand the short and long-term health outcomes of parental caregiving. ■

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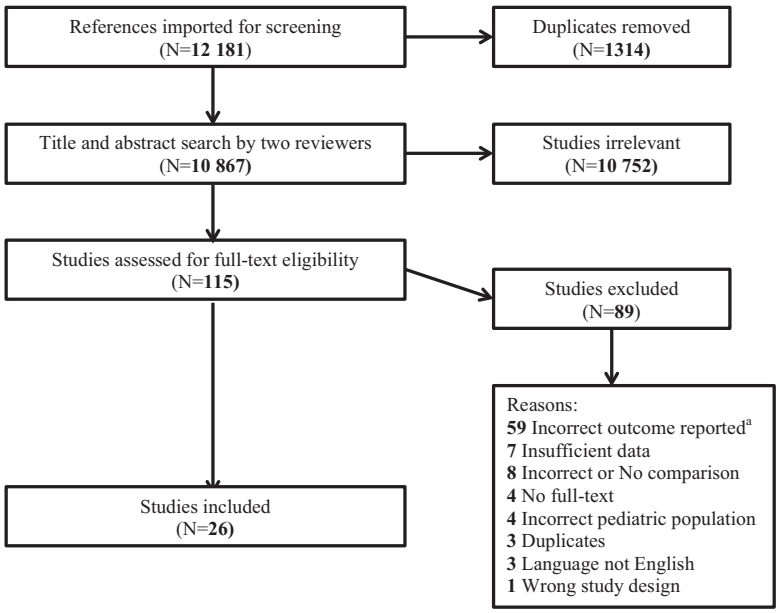

Figure 1. Flow diagram of study review and inclusion. [a]Such outcomes are those that are not considered a clinically diagnosable physical or mental health outcomes (eg, quality of life, stress, fear, life satisfaction).

Table I. Search strategy

Database: Ovid MEDLINE(R) epub ahead of print, in-process & other non-indexed citations, ovid MEDLINE(R) daily and ovid MEDLINE(R) <1946 to Present>

1 exp Chronic Disease/ (248330)
2 Disabled Children/ (5416)
3 (special adj2 need*).tw,kf. (7735)
4 (complex* adj2 (medical* or care* or healthcare* or need*)).tw,kf. (10443)
5 (technolog* adj2 depend*).tw,kf. (690)
6 (medical* adj2 fragil*).tw,kf. (220)
7 1 or 2 or 3 or 4 or 5 or 6 (271031)
8 exp Parents/ (93635)
9 exp maternal behavior/ or maternal deprivation/ or exp parent-child relations/ or parenting/ or paternal behavior/ or paternal deprivation/ (70144)
10 Caregivers/ (28978)
11 (parent or parents or parenting or mother* or father* or caregiver* or care-giver*).tw,kf. (455588)
12 8 or 9 or 10 or 11 (514716)
13 7 and 12 (8915)
14 "Quality of Life"/ (156035)
15 Mortality/ (38821)
16 exp Cardiovascular Diseases/ (2185370)
17 health status/ or health status disparities/ (83126)
18 health/ or cardiorespiratory fitness/ or family health/ or men's health/ or mental health/ or physical fitness/ or exp women's health/ (127449)
19 exp Mental Disorders/ (1113719)
20 (qualit* adj2 life*).tw,kf. (222449)
21 mortalit*.tw,kf. (628648)
22 (cardio* adj2 (health* or disease*)).tw,kf. (156686)
23 (health* adj2 (level* or status*)).tw,kf. (68346)
24 ((mental* or psyc*) adj2 (health* or disease* or illness* or status*)).tw,kf. (181866)
25 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (4200620)
26 13 and 25 (4005)
27 (infan* or newborn* or new-born* or neonat* or neo-nat* or child* or adolescen* or juvenile* or teen* or girl* or boy* or youth* or toddler* or paediatric* or pediatric*).mp. [***Age group Textword search terms***] (3961935)
28 26 and 27 (3078)