Impact of Cystic Fibrosis on Unaffected Siblings: A Systematic Review

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Objective To conduct a systematic review of the evidence to determine the impact of cystic fibrosis (CF) on unaffected siblings.

Study design We searched MEDLINE (Ovid interface, from 1946); EMBASE (Ovid interface, from 1946); CINAHL (EBSCO interface); Academic Search Complete (EBSCO interface); Psych Info (EBSCO interface); ProQuest Theses' and Dissertation's (ProQuest); British Index of Nursing (ProQuest); Web of Science (ISI, Web of Knowledge portal); PubMed (PubMed NCBI); BASE (Bielefeld Academic Research Engine); Scopus; EThOS (e-theses online service); Open Grey; and Cochrane Library. Contents pages of the Journal of Cystic Fibrosis, June 2002-April 2017 were hand searched to identify further eligible studies. Reference lists of eligible articles and relevant review papers were screened. Inclusion criteria were full studies published after 1989 in English focusing on the impact of cystic fibrosis on unaffected siblings.

Results In total, 13 papers, 4 PhD theses and 1 MSc thesis were included in the review. Four themes were identified; family functioning, psychosocial impact, knowledge of CF, and condition-specific differences.

Conclusions Most studies are old and may not accurately represent the impact of CF on unaffected siblings following changes to health care provision including newborn bloodspot screening and the advent of CF transmembrane regulator modulator therapies. Further work is needed directly with siblings rather than using mothers as proxies to determine effect of age, sex, and disease trajectory on unaffected siblings' experiences. *(J Pediatr 2019;210:112-7)*.

Over the last decade, the introduction of newborn bloodspot screening (NBS) for early identification of babies with cystic fibrosis (CF) has become more widespread and CF transmembrane conductance regulator modulator therapies have become available.[1] Together, these have changed the landscape in terms of the care and outlook for children with CF.

Most literature regarding the impact of living with a child with CF has focused on parents, especially mothers. Studies have found that caregivers have significantly higher levels of anxiety and depression,[2] which has been associated with lower life satisfaction.[3] A literature review focusing on fathers perspectives found that having a child with CF had a profound emotional impact.[4] It is clear from the literature that having a child with CF impacts parents in different ways. It would, therefore, seem fair to assume that having a sibling with CF also affects unaffected siblings, and this is likely to be unique due to the special relationships of siblings.

Studies exploring experiences of siblings often include multiple chronic illnesses such as autism, cancer, and Down syndrome[5] or diabetes, cancer, and congenital heart disease.[6] These have highlighted that these conditions impact siblings differently, and, therefore, it may not be appropriate to study numerous conditions together, nor compare findings for one condition with another. This is particularly true of CF which is life-shortening, with no current cure, involving treatment at home as well as hospital admissions, genetic in origin and, since the introduction of NBS for CF, being diagnosed very shortly after birth.[1]

We undertook a systematic search of the literature to determine the impact of CF on unaffected siblings and make recommendations for future practice, education and research.

Methods

This systematic review was undertaken in line with the guidelines of the Joanna Briggs Institute[7] and adheres to the relevant criteria of the PRISMA statement.[8] To ensure originality, transparency, and reproducibility of the review, a prospective review strategy was compiled and registered with PROSPERO, an international prospective register of systematic reviews (CRD42017064483).

CF	Cystic fibrosis
CHD	Congenital heart disease
NBS	Newborn bloodspot screening

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The following methods used in the systematic review, including eligibility, identification, screening, extraction, and analysis, were agreed between the authors in advance.

Briefly, the inclusion criteria were full studies published after 1989 (when the gene responsible for causing CF was identified) in English focusing on the impact of CF on unaffected siblings. Studies published as abstracts or conference presentations were excluded.

Thirteen electronic databases were searched in April 2017: MEDLINE (Ovid interface, from 1946); EMBASE (Ovid interface, from 1946); CINAHL (EBSCO interface); Academic Search Complete (EBSCO interface); Psych Info (EBSCO interface); ProQuest Theses' and Dissertation's (ProQuest); British Index of Nursing (ProQuest); Web of Science (ISI, Web of Knowledge portal); PubMed (PubMed NCBI); BASE (Bielefeld Academic Research Engine); Scopus; EThOS (e-theses online service); Open Grey; and Cochrane Library. In October 2018, searches were re-run in MEDLINE (Ovid interface, from 1946); CINAHL (EBSCO interface); Psych Info (EBSCO interface); and PubMed (PubMed NCBI) to ensure no further papers had been published. No additional papers were identified.

From June 2002 to April 2017, the contents pages of *The Journal of Cystic Fibrosis* were hand searched to identify further eligible studies. Reference lists of eligible articles and relevant review papers were also screened. Citations were imported into a bibliographic database (RefWorks v 2, ProQuest LLC, Ann Arbor, Michigan) for assessment of eligibility. Two researchers independently reviewed titles and abstracts to assess eligibility in a blinded standardized manner. For all potentially eligible references, the full article was obtained and inclusion/exclusion criteria were applied. The quality of each article was independently assessed by 2 reviewers using the relevant Joanna Briggs Institue (JBI) critical appraisal checklist as was data extraction using the JBI data extraction tool. Disagreements between reviewers when assessing eligibility, quality, and during data extraction were resolved through discussion and consensus. Findings from included studies were analyzed thematically using an iterative process of coding, category formation, and theme development.

Results

In total, 659 citations were identified. After duplicates were removed, the titles of 464 citations were reviewed and 395 citations were excluded at this stage. The abstracts of 69 abstracts were reviewed and 33 were excluded; 26 peer reviewed papers, 9 PhD theses, and 1 MSc thesis were retrieved and reviewed. Of these, 13 peer reviewed papers, 4 PhD theses, and 1 MSc thesis met the inclusion criteria and were included in the review. Reasons for exclusion can be seen in the adapted PRISMA flowchart (**Figure**; available at www.jpeds.com).

Study Characteristics

Study characteristics are presented in the **Table** (available at www.jpeds.com). Of the 13 studies included in the review; 10 focused solely on CF[9-18] and 3 focused on CF and other condition(s).[6,19,20] Six were conducted in the US,[9,10,13,16,19,20] 3 in the United Kingdom,[11,12,15] 2 in Belgium,[6,14] and 2 in Sweden.[17,18] Four studies included parents,[9,15,16,20] 3 included siblings,[6,10,14] 3 included parents and siblings,[11,13,19] 2 included affected children and their siblings,[17,18] and 1 included parents, siblings, and the affected child.[12] Eight studies used questionnaires,[6,9,11,13,14,17,18,20] 1 used interviews,[15] 3 used interviews and questionnaires,[10,12,19] and 1 used interviews, phone ratings, and diaries.[16] Of the 4 PhD theses included, 1 was conducted in the United Kingdom[21] and 3 were conducted in the US[22-24] as was the MSc thesis.[25] All collected data from unaffected siblings, 4 focused solely on CF,[21,23-25] and 1 compared the impact of 3 chronic conditions.[22]

Thematic Analysis

Four themes were identified (thematic analyses); family functioning, psychosocial impact, knowledge of CF, and condition specific differences.

Family Functioning. ***Views of Parents and Siblings.*** Foster et al used semistructured interviews to explore impact of CF with 8 unaffected siblings (aged 9-21 years), 8 mothers, and 1 father.[12] Parents believed unaffected siblings received less attention particularly when the child with CF was symptomatic. Children with CF recognized their unaffected sibling was treated differently in terms of discipline and tolerance. Parents and children with CF felt unaffected siblings could be resentful of attention given to the child with CF. Similar findings were reported in a study,[16] which included 40 mothers with preschool children one-half of whom had a younger child with CF and an older unaffected sibling and one-half had 2 unaffected children. Data were collected using home interviews, nightly phone ratings, and daily diaries. Mothers of children with CF spent significantly more time during mealtimes and playtimes with the child with CF. Another study[23] explored the impact of having a sibling with CF with 48 children of school age to adolescence and their mothers. One-half of the children had a younger sibling with CF, and one-half had a younger unaffected sibling. Previously validated tools and child and maternal daily phone diaries were used to collect data. Children and mothers reported that the child with CF received greater attention than the unaffected sibling particularly during mealtimes. In the CF group, male siblings had lower social skills and increased behavioral problems. Similarly, Hodgkinson and Lester[15] conducted interviews with 17 mothers of children with CF. Mothers reported feeling responsible for balancing the unequal division of attention between siblings with CF and without CF and recognized this manifested at certain times such as during hospitalization of the child with CF or following changes in their treatment regimes.

These findings were refuted by Davies[9] whose study consisted of 26 mothers of children (age 2-16 years) with CF and 39 mothers of children (age 2-16 years) without a chronic illness. The Moore and Gaffney's Dependent-Care Agent Questionnaire was used for data collection. Mothers of children with CF reported performing similar self-care activities with their unaffected child when compared with families with only well children.

Views of Unaffected Siblings. Other studies focused solely on views of unaffected siblings. One study[19] used telephone interviews and distributed self-esteem questionnaires to 15 siblings of children with CF and asthma (age 8-17 years) and 15 children with siblings with no chronic illnesses. Results indicated 60% of siblings in the CF group believed their brother/sister received special treatment. Unaffected siblings reported being aware their parents worried about the child with CF dying. Seventy-six percent of unaffected siblings reported that it was their parents, usually the mother, but sometimes the father, who served as the primary caregiver(s) for the child with CF and that having a brother or sister with CF had impacted time available to spend as a family. These findings were supported by other studies.[14,24,25] One study[25] comprised 5 unaffected siblings of children with CF age 6-10 years who engaged in sand play. The findings suggested unaffected siblings felt left out and as though they were fighting a battle. It was postulated that this could be due to the child's parents frequently referring to having to "fight CF." Larocque[24] interviewed 10 siblings age 12-22 years, to explore the experience of having a sibling with CF. Unaffected siblings described their family as normal despite their sibling having CF; this was facilitated by the child with CF having no visual cues of illness. Conversely, siblings expressed that CF being an invisible illness led to lack of public awareness, which led to lack of sympathy/empathy. Unaffected siblings also felt they were different to other children who did not have a sibling with CF as they were expected to watch over their sibling with CF, participate in their care, received less parental attention, and different parental treatment. However, unaffected siblings described not knowing their sibling before they had CF meant it had not affected their sibling relationship. Havermans et al used the Child Health Questionnaire (CHQ) and the Sibling Perception Questionnaire to assess the impact of illness on 39 unaffected siblings of children with CF.[14] Siblings of children with CF who had Pseudomonas infections reported fewer family activities and lower family cohesion. Hodges[21] dramaturgical exploration with 10 unaffected siblings of children with CF proposed unaffected siblings are placed in a decentralized position in family life but demonstrate diplomacy and wisdom in their communicative interactions so as to remain protective, loyal, and maintain family equilibrium.

Psychosocial Impact. ***Childhood.*** Wennstrom et al assessed sibling self-esteem in 55 families with a child with CF and an unaffected sibling age 6-14 years from 4 CF centers using the "I think I am" self-evaluation questionnaire.[17] When compared with the reference group, male unaffected siblings scored significantly higher on the subscales "physical characteristics" and "skills and talents" and female unaffected siblings scored significantly higher on the subscale "skills and talents" and significantly lower on the subscale "relations to parents and family." Female children with CF scored significantly lower than female children in the reference group for the "relations to parents and family" subscale. Similarly, in 1 study, 40% of unaffected siblings in the CF group reported themselves as the most disturbed or most unhappy family member.[19]

Foster et al identified correlates of maternal well-being in mothers with children and adolescents with CF.[11] Fifty mothers completed the Short Form 36 and the CF Problem Checklist and 44 unaffected siblings completed the Sibling Inventory of Behavior and the Sibling Inventory of Disagreements. Unaffected siblings who reported frequent aggression, avoidance, and disagreements with their sibling with CF had mothers who reported poor well-being.

In the study by Laroque,[24] perceived invisibility of CF led unaffected siblings to worry that their sibling with CF did not take their illness seriously. Unaffected siblings reported fear regarding prognosis and death, being concerned about their parents, and worrying about their own carrier status. However, unaffected siblings reported not talking to their parents about their feelings and experiences. Having a sibling with CF was found to increase sensitivity, empathy, maturity, independence, and sibling closeness. O'Haver et al used a convenience sample of 40 parents and 31 unaffected siblings (age 8-18 years) of children with CF.[13] A demographic questionnaire and previously validated tools were used for data collection. Younger children exhibited more internalizing behaviors than older adolescents, and older adolescents were more affected by family environment than younger children. In another study,[14] unaffected siblings (n = 39) scored higher on all subscales of the CHQ than siblings of healthy children. Older unaffected siblings reported a greater impact of having a sibling with CF than siblings younger than the affected child. Also, the impact of having a sibling with CF was significantly higher for siblings whose brother/sister with CF had been hospitalized.

Adulthood. Wenstrom et al followed the same group of children age 18-26 years to explore self-esteem, life satisfaction, and attitudes toward the CF sibling relationship and was 1 of only 2 studies that focused on adult siblings.[18] Thirty-six of the original 55 sibling pairs participated, previously validated tools were used for data collection. Life satisfaction and optimism for men with CF, women with CF, and unaffected women was low. Also, more unaffected siblings remembered themselves as being worried (troubled), feeling slighted, envious, and neglected than their siblings with CF. However, fewer unaffected siblings reported feeling angry, slighted, envious, neglected, or fussy at the time of the study.

The other study of adult unaffected siblings[10] used interviews and questionnaires with 54 unaffected siblings and 30 spouses age 18-55 years who had been tested to ascertain their

carrier status. Fear of carrying the CF gene led to unaffected siblings delaying starting a family. Also, unaffected siblings who reported resentment toward their sibling with CF were found to be significantly more likely to terminate a pregnancy if it were known that the fetus had CF. Unaffected siblings expressed slight (30%) and high (21%) resentment toward their sibling with CF. Further analysis revealed a significant relationship between levels of resentment and age of survivor at sibling's death; participants who lost their sibling with CF during their childhood or adolescence had higher resentment than those whose sibling had died before they were born. Overall, 48% of siblings expressed slight "guilt" and 15% expressed "high guilt" toward their sibling with CF. Sibling resentment was found to correlate positively with guilt; the more resentment felt, the more guilt felt by the sibling. Anxiety and depression scores in this study were found to be higher for unaffected siblings than a random normative sample.

Knowledge of CF. ***Genetic Knowledge.*** In 1 study,[10] 54 adult siblings and their partners (n = 30) were unable to correctly recall their carrier status. Almost one-half of the unaffected siblings overestimated, and one-half underestimated carrier frequency, and 30% of adult unaffected siblings and 13% of their spouses believed carrier status implies health difficulties. Seventeen percent of adult unaffected siblings and 21% of spouses believed that if neither parent carried the delta F508 defect, they could not have a child with CF.

Education About CF. Unaffected siblings of children with CF had some understanding of why their sibling had to go to hospital.[19] However, further probing revealed varying depths of knowledge; where this knowledge had been gleaned from was not reported. Simourd[25] suggested that unaffected siblings lacked understanding of CF, this was expressed as "battling the unknown." Mothers of children with CF reported feeling responsible for answering difficult questions about prognosis, educating the child with CF about a realistic idea of the future, educating the unaffected sibling, and involving them in the CF routine.[15] Mothers also reported feeling a need to educate the primary care team. In the study by Larocque,[24] most unaffected siblings wanted to know more about CF, supporting the findings of Hodgkinson and Lester.[15] However, in this study, unaffected siblings reported not discussing this with their parents.

Condition Specific Differences. Perkins explored depression and anxiety, perception of family adaptability and cohesion, and perception of the sibling relationship in unaffected siblings of children with CF, diabetes, and asthma.[22] There were no significant differences between condition groups. Conversely, the study by Derouin and Jessee indicated differences between unaffected siblings of children with CF and unaffected siblings of children with asthma[19]; 60% of siblings in the CF group, compared with 89% in the asthma group, said that they had seen changes in the ill child. No siblings of children with CF reported positive differences, whereas siblings in the asthma group did. Sixty percent of siblings in the CF group, compared with 22% in the asthma group, believed their brother/sister received special treatment. Seventy-six percent of the siblings in the CF group reported both their mother and father served as the primary caregivers while 90% of siblings in the asthma group reported mothers alone were the primary caregiver.

Williams undertook secondary analysis of data gathered during a randomized controlled trial from 44 parents' who had a child with cancer (29 parents), or CF (15 parents).[20] In the CF group, 68% of responses alluded to negative manifestations and 32% were positive manifestations. Parents in both groups rated jealousy/envy; worry/fear/anxiety; upset/anger/resentment; negative behaviors; and loneliness/sadness/depression as the most common negative manifestations. These were attributed to siblings feeling physically or emotionally isolated from parents and the attention given to the affected child. Positive manifestations included, increased family closeness; increased sibling sensitivity to the affected child and caregiving; and, increased sibling personal growth and maturation.

In the study by Havermans,[6] unaffected siblings (n = 131) age 10-18 years completed the CHQ and the Sibling Perception Questionnaire to determine impact of type 1 diabetes, cancer, congenital heart disease (CHD), and CF. Responses were compared with a matched group of siblings of healthy children. Unaffected siblings of children with CF scored higher than siblings of children with cancer and CHD in the domain behavior. In addition, for the domain mental health, unaffected siblings of children with CF and diabetes scored higher than siblings of children with CHD.

Discussion

Changes in the CF Landscape

Eight of the 13 included studies were more than 10 years old. This represents a time frame during which many of the countries where these studies were conducted implemented NBS and CF transmembrane conductance regulator modulator therapies.[26] Subsequently, most children with CF are screened, identified, and started on appropriate treatment in infancy; often before they have become symptomatic.[1] In addition, unaffected siblings of children with CF may be younger at the time of diagnosis and will not have witnessed the child with CF being unwell prior to diagnosis thereby changing unaffected siblings' experiences of having a sibling with CF.

Disease Trajectory

One study[24] reported impact of disease trajectory on unaffected siblings, that is, whether the child with CF is well, hospitalized, or in the advanced stages of the disease. Other studies alluded to the impact of exacerbations on the

unaffected sibling.[12,14] The importance of this has also been recognized in the literature[27] and suggests that interventions may need to be targeted at different stages of disease progression.

Family Functioning

Findings suggest having a sibling with CF has the potential to impact unaffected siblings in different ways and throughout childhood, adolescence, and into adulthood.[12,15,16,19] Previous studies have highlighted the impact of CF on mealtimes,[28] and these data would seem to suggest that this does not only impact on the child with CF. Findings related to the accuracy of mothers' perceptions of the impact of CF on their unaffected child were variable with some studies claiming that responses were similar between mothers and unaffected siblings[23] and others reporting differences.[24]

Family systems theory states that all components of the family are regarded as interdependent; what happens to one member, will affect all other members of the family directly and indirectly,[29] and this was borne out in the findings of several studies in this review[11,19,21] and highlights the impact on the whole family of having a sibling with CF.

Impact of Sex and Age

Studies indicated sex[17,18,23] and age[13,14] may influence impact on unaffected siblings suggesting interventions to support unaffected siblings may need to be age and sex specific.

Only 2 studies included adult unaffected siblings, which suggested impact of having a sibling with CF may change over time.[10,18] Findings suggest the psychosocial impact of having a sibling with CF changes over time and, therefore, strategies to address concerns may need to adapt to changing needs.

Knowledge of CF

In 1 study,[15] mother's reported feeling responsible for educating the unaffected sibling about CF. In other studies,[10,19] it was clear that beliefs siblings held regarding CF were not always accurate but had the potential to affect important life decisions incluidng reproductive decisions.[10] Therefore, greater clarity and attention is needed regarding who should undertake education of unaffected siblings and strategies to ensure siblings are well informed.

Positive Manifestations

Most studies focused on the negative manifestations of having a sibling with CF,[19,20] but others reported positive findings.[14,20,24] The latter could be due to unaffected siblings having witnessed the burden of illness on the affected child and, therefore, appreciating their own good health. This is an area that requires further exploration in the future to balance support and build upon unaffected siblings' strengths.

Condition Specific Differences

Studies that focussed on other conditions as well as CF highlighted condition specific differences suggesting information and support for unaffected siblings of those affected by CF may need to be targeted rather than being generic. This is supported by findings of previous studies.[5,6]

Limitations of the Review

Ten of the included studies focused solely on CF, and 3 looked at other conditions as well. It should be borne in mind that CF is a condition that primarily affects individuals of Northern European descent, and, therefore, findings of studies that include conditions that affect other ethnic groups should be reported along with context regarding cultural differences in family/caregiver structure. Four of the included studies focused on parents perceptions, which may not accurately represent unaffected siblings views and experiences. Of the 13 included studies, 8 were more than 10 years old and, therefore, the findings might be outdated. However, this also reflects the paucity of data available and the need for further research into this area. In addition, the included studies used a variety of measures and techniques to gather data so it was difficult to make comparisons between findings of studies.

Three studies[19,22,25] had small sample sizes, questioning the generalizability of the findings. Participants were also recruited from one site for each condition meaning the findings may not be representative. In another of these studies,[25] sand play was used for data collection purposes, which is not an evidence-based therapeutic technique, and, therefore, the findings should be treated with caution.

Further research needs to be conducted to ascertain if changes in the CF landscape has changed the impact of CF on unaffected siblings. Further research directly with unaffected siblings rather than using parents/carers as proxies is needed to ensure findings accurately represent their views. Impact of disease trajectory on unaffected siblings also requires further exploration to determine if different interventions are needed when the child with CF is well, hospitalized, or in the advanced stages of disease.[27] Based on the findings of these studies, interventions need to be developed specifically to support unaffected siblings of children with CF throughout their life taking into account age and sex. Health professionals working with families with a child with CF and an unaffected sibling need to be educated regarding the potential impact of CF on the unaffected sibling and interventions that are successful in suporting them. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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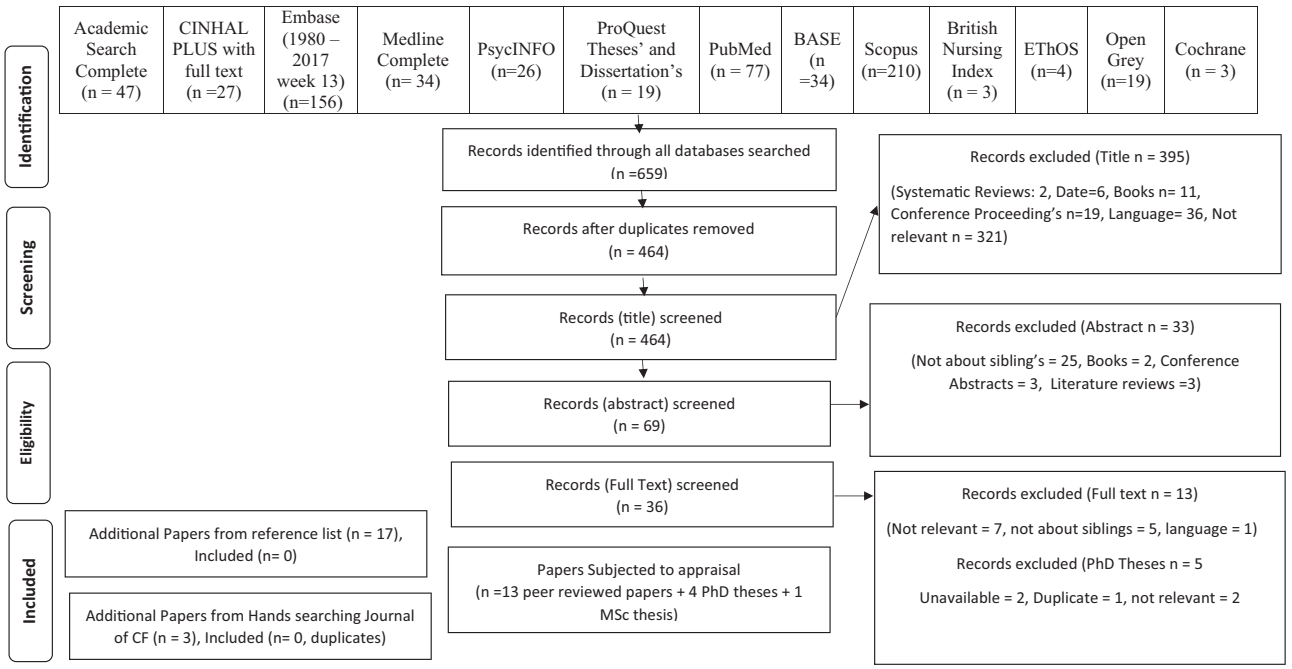

Figure. PRIMSA flowchart.

Table. Study characteristics

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Published papers							
Davies[9]	1993	US	19 mothers of children with CF and a well sibling and 19 mothers of only well children	Dependent Care Agent Instrument (Moore and Gaffney 1989)[30].	Statistical analyses including χ^2 test, Fisher exact test, and Wilcoxon rank-sum tests.	Well siblings in families with CF did not receive less care, as measured by the Dependent-Care Agent Questionnaire, when compared with a family with only well siblings.	Family functioning
Derouin and Jessee[19]	1996	US	15 children from 2 illness groups (CF and asthma) participated; 6 male and 9 female respondents age 8-17 y (CF) and 8-14 y (asthma) (Parental questionnaire data not reported)	Phone interviews and questionnaires. Quantitative data were collected using the Piers-Harris Self-concept Scale (Piers and Harris 1969)[31] and qualitative data through the use of a semistructured sibling interview protocol developed by Tritt (1983)[32] and based on Klein's Sibling Questionnaire (1976)[33]	Nonparametric descriptive analyses were used to evaluate the data from the semi-structured interviews. Responses to open-ended questions were reported in percentages.	Some illness-specific group differences were evident, which suggest that the siblings' perceptions and impressions of the impact of the illness could be diagnosis-specific. Because CF parents were perceived by the siblings as worrying about the potential early death of the ill child, the nature and focus of their parents' concerns were more stressful and anxiety-producing for the CF siblings.	Family functioning Psychosocial impact Knowledge of CF Condition specific difference
Fanos and Johnson[10]	1995	US	54 CF siblings (26 male and 28 female) and 30 spouses; age 18-55 y.	Semistructured interviews. Anxiety and depression scales derived from the Hopkins checklist (Derogatis et al 1971)[34] were used.	Simple descriptive statistics, statistical analysis including χ^2 test and qualitative analysis of interview data.	The relationship between birth order and beliefs about carrier status was significant, with last-born siblings more likely to believe they are not carriers. Higher sibling resentment was found to be significantly related to willingness to abort an affected fetus, more guilt, and assumption of carrier status. Thirty percent of siblings believed that carrier status implied health difficulties. Increased feelings of guilt were significantly related to the belief that carrier status implies health problems.	Psychosocial impact Knowledge of CF
Foster et al[11]	1998	UK	50 mothers and 44 siblings (age 8-20 y) of children and adolescents with CF	Short Form 36 (SF36, Ware and Sherbourne 1992)[35]. CF problem checklist (Sanders et al 1991)[36] Sibling Inventory of Behavior (Schaeffer and Edgerton 1981)[37]. Sibling Inventory of Disagreements (Plomin et al 1994)[38]	Descriptive statistics and statistical analyses including t-test and ANOVA and correlations.	Mothers did not rate their well-being as any different to the normal population. Siblings who reported frequent aggression, avoidance, and disagreements with their sibling with CF had mothers who reported poor well-being. Younger children had more frequent disagreements than older children.	Psychosocial impact

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Foster et al[12]	2001	UK	8 patients age 10-18 y and 8 siblings age 9 and 21 y. 8 mothers and 1 father age between 33 and 45 y.	In-depth semistructured interviews and questionnaires generated from the literature and discussions with clinicians	Analysis was based on the constant comparative method of Glaser and Strauss (1967). of the extra attention given to the patient. .	Demanding treatment and high levels of parental involvement in treatment appear to have a direct impact on siblings who were perceived to receive less parental attention than patients. Siblings were often described by parents and patients as being resentful. Parents were less tolerant of well sibling behaviors	Family functioning
Havermans et al[6]	2015	Belgium	Healthy siblings (n = 131) of children with type 1 diabetes, cancer, CHD, and CF age 10-18 for y.	QoL: CHQ-CF87 (Landgraf et al 1999)[39] Impact of illness: Sibling Perception Questionnaire (Lobato and Kao 2002)[40]	Descriptive statistics were used to examine demographic characteristics. Statistical analyses included Kruskal-Wallis, Pearson correlations, Student t tests, ANOVA, and Cohen d.	Siblings rated their QoL higher than controls (siblings of healthy children). Siblings of children with CF scored higher than siblings of children with cancer and CHD in the domain behavior. For the domain mental health, siblings of children with CF and diabetes scored higher than siblings of children with CHD.	Condition specific differences
Havermans et al[14]	2011	Belgium	39 siblings of children with CF age 10-18 y.	The Child Health Questionnaire was used to assess QoL. CHQ-CF87 (Landgraf et al. 1999)[39]. The Sibling Perception Questionnaire was used to assess impact of illness.	Simple descriptive statistics and statistical analyses including Student *t* test, Cohen d, and Pearson correlation.	Siblings of children with CF (n = 39) rated their QoL higher than siblings of healthy children on most QoL domains (eg, physical functioning, behavior, mental health). Siblings older than the child with CF reported a higher impact of CF than younger siblings. Perceived impact of illness was higher when the child with CF had been hospitalized or was intermittent or chronically infected with *Pseudomonas aeruginosa*.	Family functioning Psychosocial impact

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Hodgkinson and Lester[15]	2002	UK	17 mothers age 24-48 y of children age between 2 and 13 y.	Semistructured interviews	Themes were identified and developed by reading and re-reading transcripts. Themes were further refined and clarified using the Framework analytic approach (Bryman and Burgess 1994).	The majority of mothers felt responsible for educating their other children about CF, and for involving siblings in the CF routine as much as possible. Mothers felt responsible for balancing the unequal division of attention between CF and non-CF siblings. These problems were amplified during times of crisis, such as hospitalization or change in treatment regimes. Any family activity required careful advanced planning and there was little opportunity for spontaneity.	Family functioning Knowledge of CF
O'Haver et al[13]	2010	US	40 parents and 31 well siblings of children diagnosed with CF. Well siblings were age 8-18 y.	Demographic questionnaire designed for the purposes of the study. The Behavioral Assessment System for Children Multidimensional Scale of Perceived Social Support. The Perceived Stress Scale.	Descriptive statistics and statistical analyses including Spearman rho.	Parents reported the CF team had never discussed CF with the well sibling for 75% of the sample. Parental report of problem behavior did not demonstrate a relationship with behavior problems reported by the children. Parental report of internalizing behaviors in the adolescent siblings were related. Adolescent well siblings were more affected by the family environment than younger siblings. Parental stress and lack of social support were risk factors for the adolescent sibling's adaptation. There was a significant positive relationship between adolescent siblings' behavioral symptom index (BSI) and parental stress, and a significant negative relationship between adolescent well siblings' BSI scores and social support. Adolescents' reported behavior was highly related to their parents' reported stress and perceived social support.	Psychosocial impact

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Quittner and Opipari[16]	1994	US	40 mothers of toddlers (average age 2 y) and preschoolers (average age 41/2 y): one-half were caring for a younger child (age 1-4 y) with CF and an older healthy sibling, and one-half were caring for 2 healthy children.	Home interviews, nightly phone ratings, and daily diaries	Descriptive statistics and multivariate ANOVA.	Little evidence of parental differential treatment was found in the home or phone interview data. However, on the diary variables, both quantitative and qualitative differences in parental treatment were found in CF vs comparison families. Mothers spent more individual time with younger, chronically ill children in play and mealtime activities than with their older, healthy siblings. Further, mothers in the CF group rated time spent with older children as significantly more negative than time spent with younger children	Family functioning
Wennstrom et al[17]	2005	Sweden	55 families with 1 child with CF and 1 healthy sibling, each 6-14 y of age. The CF patient group consisted of 27 boys and 28 girls, and the healthy sibling group of 28 boys and 27 girls.	"I think I am" self-evaluation questionnaire	Descriptive statistics and statistical analyses including *t* tests, 1-way ANOVA, and Tukey test where relevant.	Gender was found to be linked to aspects of negative self-concept among both children with CF and their healthy siblings. Healthy girls as well as those with CF reported lower scores than girls in the reference group on the "mental wellbeing" and "relations to parents and family" subscales. When CF is present among siblings, girls seem to carry more of the family pain than boys.	Psychosocial impact
Wennstrom, et al[18]	2011	Sweden	Participants were 18-26 y of age. 44 individuals with CF and 38 healthy siblings returned questionnaires comprising 36 sibling pairs. The CF patient group consisted of 21 men and 23 women, and the healthy sibling group of 15 men and 23 women.	'As I see myself' self-evaluation questionnaire; the 'Ladder of life'; and the 'Sibling Mirror'	Descriptive statistics and statistical analyses including *t* tests, 1-way ANOVA, and Tukey test where relevant.	Female participants showed no signs of impaired self-esteem. Concerning life satisfaction, women in both groups and the men with CF have lower ratings than a healthy reference group. Self-esteem of women in the sibling pairs (whether with CF or healthy sisters) had improved since childhood	Psychosocial impact

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Williams et al[20]	2009	US	15 were parents of children with CF (29 were parents of children with cancer).	Secondary analysis of data from a randomized controlled trial	Content analysis was used to identify themes in parents' responses to an open-ended item about their perceptions of the effects on siblings of having a brother or sister who had either cancer or CF.	Findings predominantly reflect various manifestations of increased risk of negative outcomes. Of 53 themes tallied in the CF group, 67.9 % reflected negative manifestations of increased risk in siblings, 0% no risk; and 32.1 %, positive outcomes. Regardless of diagnosis, negative manifestations included jealousy/envy; worry/fear/anxiety; upset/anger/resentment; negative behaviors; and loneliness/sadness/depression. Other manifestations were: school problems (academic), low self-esteem, and guilt. Less than one-third of the descriptions of parents of children with CF reflected positive outcomes for well siblings: Increased family closeness; increased sibling sensitivity to the ill child and caregiving; and; increased sibling personal growth and maturation.	Condition specific differences
PhD thesis Hodges[21]	2016	UK	10 siblings age 7-11 y living with a brother or sister with CF	Narrative inquiry	Bricolage including narrative interview, visual creations/artefacts, and observations	Siblings are placed in a decentralized position in family life. Siblings demonstrate diplomacy and wisdom in their communicative interactions of being good so as to remain protective, loyal and maintain family equilibrium.	Family functioning

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Larocque[24]	2006	US	10 adolescents age 12-22 y with a sibling with CF	Interviews	Hermeneutic interpretation	Unaffected siblings described their family as normal despite their sibling having CF. Siblings felt that CF being an invisible illness led to lack of public awareness and sympathy/empathy. Unaffected siblings felt they were different to other children who did not have a sibling with CF as they were expected to watch over their sibling, participate in care, received less parental attention and different parental treatment. Unaffected siblings were fearful regarding prognosis and death, were concerned about their parents and worried about their own carrier status.	Family functioning Psychosocial impact Knowledge of CF
Opipar[23]	1996	US	48 children, one-half with a younger sibling with CF and one-half with a younger healthy sibling, and their mothers	Children completed the Childhood Depression Inventory, the Revised Children's Manifest Anxiety Scale and SSRS. Mothers were asked to complete the SSRS-Parent. Children and parents completed the Sibling Relationship Questionnaire. Children were also interviewed. Children and mothers participated in 5 phone diaries.	Multivariate ANOVA	A greater magnitude of differential treatment occurred in the CF vs the comparison group. Differential treatment was associated with sibling relationship quality and social and emotional adjustment. Mothers spent significantly more total and individual time with the younger sibling with CF than the older unaffected sibling even when time for medical treatments was excluded. Greater individual time with the younger child with CF was associated with higher rates of behavioral problems in the older unaffected child.	Family functioning

(*continued*)

Table. Continued

Authors	Year	Country	Participants	Data collection	Analysis	Main Results	Themes
Perkins[22]	1994	US	50 children age 9-18 y with a brother or sister with CF, diabetes, or asthma	Children's Depression Inventory, State-Trait Anxiety Inventory for Children, Sibling Relationship Questionnaire and family Adaptability and Cohesion Evaluation Scales II.	Multivariate ANOVA	Results indicated no differences between the 3 groups. Children with 3-4 y age spacing and male children reported the highest levels of cohesion. Increased maternal education was associated with decreased or lower levels of sibling depression. Lower income appeared to be a significant predictor of increased state and trait anxiety. Conflict in the sibling relationship was a significant predictor of depression in the well child.	Condition specific differences
MSc thesis Simourd[25]	1999	US	5 siblings of children with CF age 6-10 y	Sand play scenes and narratives of the sand worlds they created	Sand play scenes were analyzed to determine any recurring themes and metaphors.	The children lacked understanding about CF and this was expressed as "battling the unknown."	

BSI, behavioral symptom index; *QoL*, quality of life; *SSRS*, Scale and the Social Skills Rating System.

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