Title: Impact of cystic fibrosis on unaffected siblings: a systematic review

Short Title: Impact of cystic fibrosis on siblings

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Abbreviations:

CF (Cystic Fibrosis), NBS (newborn bloodspot screening), CFTR (cystic fibrosis trans-membrane conductance regulator)

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 CFTR 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 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 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).

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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 cystic fibrosis 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; 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.

The contents pages of the Journal of Cystic Fibrosis from June 2002 to April 2017 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 Version 2) 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 two reviewers using the relevant 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, nine PhD theses and one MSc thesis were retrieved and reviewed. Of these, 13 peer reviewed papers, four PhD theses and one MSc thesis met the inclusion criteria and were included in the review. Reasons for exclusion can be seen in the adapted PRISMA flowchart (Figure 1 online only).

Study Characteristics

Study characteristics are presented in Table 1 (online only). Of the 13 studies included in the review; ten focused solely on CF[9-18], three focused on CF and other condition(s)[6, 19, 20]. Six

were conducted in America[9, 10, 13, 16, 19, 20], three in the UK[11, 12, 15], two in Belgium[6, 14] and two in Sweden[17, 18]. Four studies included parents[9, 15, 16, 20], three included siblings[6, 10, 14], three included parents and siblings[11, 13, 19], two included affected children and their siblings[17, 18] and one included parents, siblings and the affected child[12]. Eight studies used questionnaires[6, 9, 11, 13, 14, 17, 18, 20], one used interviews[15], three used interviews and questionnaires[10, 12, 19] and one used interviews, phone ratings and diaries[16]. Of the 4 PhDs included, one was conducted in the UK[21] and three were conducted in America[22-24] as was the MSc thesis[25]. All collected data from unaffected siblings, four focused solely on CF[21, 23-25] one compared the impact of three chronic conditions[22].

Thematic Analysis

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

Family functioning

Views of Parents and siblings: Foster *et al.*[12] used semi-structured interviews to explore impact of CF with eight patients with CF, eight unaffected siblings (aged 9-21 years), eight mothers and one father. 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 pre-school children half of whom had a younger child with CF and an older unaffected sibling and half had two 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. Half of the children had a younger sibling with CF and 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 CF and non-CF siblings 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 (aged 2-16 years) with CF and 39 mothers of children (aged 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 to 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 (aged 8 to 17years) 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 five unaffected siblings of children with CF aged 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 aged 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.*[14] used the Child Health Questionnaire (CHQ) and the Sibling Perception Questionnaire (SPQ) to assess the impact of illness on 39 unaffected siblings of children with CF. 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.*[17] assessed sibling self-esteem in 55 families with a child with CF and an unaffected sibling aged 6–14years from four CF centers using the "I think I am"

self-evaluation questionnaire (SEQ). 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". Females with CF scored significantly lower than females in the reference group for the "relations to parents and family" subscale. Similarly, in one study, 40% of unaffected siblings in the CF group reported themselves as the most disturbed or most unhappy family member.[19]

Foster *et al* [11] identified correlates of maternal well-being in mothers with children and adolescents with CF. Fifty mothers completed the Short Form 36 and the CF Problem Checklist while 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 Laroque's study[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.*[13] used a convenience sample of 40 parents and 31 unaffected siblings (aged 8-18 years) of children with CF.. A demographic questionnaire and previously validated tools were used for data collection. Younger children exhibited more internalizing behaviors than older adolescents while 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*[18] followed the same group of children aged 18-26 to explore self-esteem, life satisfaction and attitudes towards the CF sibling relationship and was one of only two studies that focused on adult siblings. 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 aged 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 towards 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 towards 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’ towards 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 one study[10], 54 adult siblings and their partners (n=30) were unable to correctly recall their carrier status. Almost half the unaffected siblings overestimated while half underestimated carrier frequency and30% 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 Larocque’s study[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[22] 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. There were no significant differences between condition groups. Conversely, Derouin and Jessee's study[19] indicated differences between unaffected siblings of children with CF and unaffected siblings of children with asthma; 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'[20] 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). In the CF group 68% of responses alluded to negative manifestations while 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 commonest 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 Havermans study[6], unaffected siblings (n=131) aged 10-18 completed the Child Health Questionnaire (CHQ) and the Sibling Perception Questionnaire (SPQ) to determine impact of type 1 diabetes, cancer, congenital heart disease (CHD) and CF. Responses were compared to 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. Additionally, 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 CFTR 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, ,15]. 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 gender and age: Studies indicated gender[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 gender specific.

Only two 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 one 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 in order 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 focussed solely on CF while three 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 focussed on parents perceptions which may not accurately represent unaffected siblings views and experiences. Of the 13 included studies, eight 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, questionning the gerneralisability 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 specifially to support unaffected siblings of children with CF throughout their life taking into account age and gender.. 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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