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REVIEW

Living with a Rare Disease: Psychosocial Impacts for Parents and Family Members – a Systematic Review

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Abstract

As rare diseases often have an onset of symptoms in childhood, the burden of the disease and associated challenges commonly fall to the individual's family members. Managing this burden, and navigating these challenges, has been found to affect the health and lifestyle of family members and lead to them experiencing negative psychosocial impacts and lower quality of life. The aim of the current study was to consolidate and summarise the published quantitative evidence on the psychosocial impacts experienced by individuals who have a family member with a rare disease. We performed a systematic literature search including quantitative studies on psychosocial impacts experienced by family members of individuals with a rare disease across three databases (PubMed, PsychINFO, and CINAHL) from inception to November 2021. Of the 2024 titles identified, 30 studies met the inclusion criteria and were included in the review. A narrative analysis revealed that family members of individuals with rare disease experience a wide range of psychosocial impacts, some of which appear to be unique to, or amplified by, the rarity of the disease. Whilst there are occasional positive outcomes of having a family member with a rare disease, overall family members have been found to experience increased psychological distress, lower quality of life, higher caregiver burden and changes to their social support. Clinical and practical implications of these findings are discussed, as well as implications and directions for future research.

Keywords Rare diseases · Psychosocial impacts · Family members · Systematic review · Burden

Highlights

- Rare diseases impact not only the individual with the disease, but also their caregivers, and other family members
- We systematically reviewed quantitative research on the psychosocial impacts experienced by caregivers and family members of individuals with rare disease
- Having a family member with a rare disease led to increased psychological distress and caregiver burden, lower quality of life, and changes to social support
- Psychosocial impacts can be unique to, or amplified by, the rarity of the disease
- Healthcare professionals should assess the psychosocial impacts experienced by family members and provide appropriate support options

Rare disease is an umbrella term used to describe diseases that have a low prevalence within the population (von der Lippe et al., 2017). Whilst there is no universally agreed-upon definition of rare disease, within Australia, rare diseases are defined as those that affect less than one in every 10,000 individuals (Zurynski et al., 2008). Although each condition is individually rare, with a total of between 6000 and 8000 distinct rare diseases (Pelentsov et al., 2016b; Putzeist et al., 2013), it is estimated that, collectively, 6–10% of the population are living with a rare disease (Elliott & Zurynski, 2015; Jaffe et al., 2010). This translates to around 450 million people worldwide (Repetto & Rebolledo-Jaramillo, 2020) and 2.2 million people, including up to 400,000 children, living with a rare disease in Australia (Anderson et al., 2013). Therefore, a significant number of people are impacted by rare disease, either by

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having a rare disease themselves, as a carer or parent of someone with rare disease.

While there is variation in the aetiology and symptoms of rare diseases (Llubes-Arrià et al., 2021), the majority of rare diseases have a genetic origin and are chronic, complex, and debilitating (Batshaw et al., 2014; Kirby, 2012). Unlike many individuals with more common diseases, individuals with rare disease often face a lack of knowledge and understanding from health and social care professionals (McMullan et al., 2021) as well as prolonged and delayed diagnosis (Beaulieu et al., 2014; Zurynski et al., 2008). On average, it takes over 5 years for an individual to receive a correct rare disease diagnosis (Vandeborne et al., 2019), with some individuals waiting decades for a diagnosis, and others never receiving one (Dong et al., 2020). From the time of symptom onset to the final diagnosis, a period called the 'diagnostic odyssey' due to its often protracted nature, many individuals with rare disease have to attend numerous medical appointments, consult with multiple different medical professionals and specialists, undergo various (at times invasive) medical investigations, and endure inappropriate treatments (Rice et al., 2020; Schieppati et al., 2008; Zurynski et al., 2017). Following this, even when diagnosed, there is commonly a lack of information available about the disease, limited treatment pathways, difficulties accessing optimal treatments, and a shortage of specialist services and support (Beaulieu et al., 2014; Zurynski et al., 2008).

Burden of Rare Disease

With the majority of rare disease having an onset of symptoms in childhood (Kirby, 2012; Zurynski et al., 2008), and being ongoing in nature, the burden of the disease and associated challenges commonly falls on the individual's family members, in particular their parents (Baumbusch et al., 2018). As well as navigating complex and confusing medical processes, parents are most likely to be the primary carer for an individual with rare disease and will often provide substantial physical, practical, and emotional aspects of care (Boettcher et al., 2021; Candy et al., 2011). The care required can often be extremely demanding, intense, and tailored to that individual's specific needs (Baumbusch et al., 2018). Although this is also frequently the case for parents of children with a more common disease, parents of children with a rare disease often face the added challenges of having little access to support services, knowledgeable professionals, or relevant advocacy groups (Boettcher et al., 2021; Rice et al., 2020). Additionally, due to the lack of available services, parents of children with a rare disease are also more likely to become the coordinator of their child's care (Baumbusch et al., 2018; Rice et al., 2020) and are left to seek needed informational and emotional support themselves, adding to their already considerable caregiving load (Boettcher et al., 2021; Rice et al., 2020).

Despite there being variation in the presentation and symptoms of different rare diseases, there appear to be similarities in the experiences of family members and the challenges they face (Baumbusch et al., 2018; Knight & Senior, 2006; Litzkendorf et al., 2016). As most parents and carers of individuals with a rare disease have to navigate additional challenges in parenthood, it is not unexpected that they are likely to experience significant caregiving burden (Wen & Chu, 2020) and impacts on their health and lifestyle (Boettcher et al., 2021). Additionally, due to impacts on both the child themselves and the parent, it is not surprising that other family members, such as siblings, are often affected by having a family member with a rare disease also (Haukeland et al., 2021; Witt et al., 2021). Whilst family caregivers report some positive aspects of supporting for an individual with a rare disease (McMullan et al., 2020), many studies have found that the challenges lead to negative psychosocial impacts, and lower quality of life, in family members of individuals with a rare disease (Anderson et al., 2013; Beaulieu et al., 2014; Boettcher et al., 2021). The effects of rare disease can be viewed through a biopsychosocial lens, and recent studies have reported that using this model can help elucidate the impacts of rare disease, and illness more generally (Wade & Halligan, 2017; Zybarth et al., 2023). Indeed, the World Health Organization's International Classification of Functioning is based on this framework (WHO, 2002), recognising the importance of taking a multi-faceted approach to wellbeing. A biopsychosocial approach recognizes rare diseases as biologically derived conditions, meaning that appropriate biomedical diagnosis and (where possible) interventions are likely to benefit both the individual and those supporting them. It also acknowledges that the specific biological characteristics of a given disorder are strongly associated with outcomes. However, biomedical factors do not fully explain the impacts of rare disease, and it has been long recognised that psychological (e.g. coping style) and social factors (e.g. access to social support) are also integral to understanding the influence and outcomes of rare disease. The aim of this review is to focus on the psychological and social (psychosocial) effects of rare disease on family members.

Psychosocial Impacts

Despite the term 'psychosocial impacts' being frequently used within the rare disease literature, and the research within this area expanding, exactly what the term

encompasses is not well defined (Fu et al., 2013; Lakhani et al., 2019; Martikainen et al., 2002). It appears to originate from the World Health Organisation's definition of psychosocial health and consist of psychological, emotional, and social aspects (Martikainen et al., 2002; McCarthy et al., 2006). However, the components of each of these aspects remain ambiguous, leading to studies investigating psychosocial impacts reporting on different outcomes and using a wide variety of measures. Whilst there is variation in the reporting of psychosocial impacts, the most commonly reported seem to include psychological distress, emotional experiences, and changes in social and family relationships, as well as education, leisure, and work activities. Additionally, whilst not entirely considered a psychosocial impact due to inclusion of physical health components (Eiroa-Orosa, 2020), and the frequent omission of occupational and leisure aspects, the terms 'quality of life' and 'caregiver burden,' appear to be used synonymously with psychosocial impacts in some literature (Fu et al., 2013; McCaffery & Barratt, 2004). Quality of life and caregiver burden measures are therefore sometimes used to capture how an individual's wellbeing may be impacted by a medical condition (Eiroa-Orosa, 2020), and the associated results may highlight some of the psychosocial impacts experienced by family members. Alternatively, quality of life is sometimes viewed as a psychosocial outcome itself (Greenwell et al., 2015) or associated with psychosocial wellbeing, where mental health and social factors can impact perceived quality of life and vice versa (Allart et al., 2013; Culbertson et al., 2020). Because to date there has been no specific definition of psychosocial impacts, we defined the psychosocial impacts as a combination of psychological, emotional, social, and educational/occupational factors that directly affect family members of individuals with a rare disease, including the quality of life. As such, in this paper psychosocial impacts are conceptualised as being broader than, but encompassing, quality of life. On the basis of existing literature, the definition was operationalised to include the psychological factors of emotion, psychological distress (including depression, anxiety, and stress), and the social factors of social isolation, social support, relationships, and participation in occupational, educational and leisure activities. Thus, whilst the term 'psychosocial impact' can at times be ambiguous, we have chosen to use this term in the interest of consistency.

Psychological and Emotional Impacts

In terms of the psychological impacts of having a family member with a rare disease, evidence suggests that caring for a child with a rare disease is associated with declines in the caregiver's psychological health (Baumbusch et al., 2018; Boettcher et al., 2020; McConkie-Rosell et al., 2018; Pelentsov et al., 2016b; Wen & Chu, 2020). In relation to emotions, Pelentsov et al. (2016a), interviewed parents of children with a range of rare diseases and reported that parents found caring for their child to be emotionally exhausting. Parents often report experiencing a wide range of emotions, including both positive emotions such as optimism (Dellve et al., 2006), and negative emotions such as guilt, fear, and frustration (Pelentsov et al., 2016a, 2016b). Likewise, Haukeland et al. (2015) found that the emotional experiences of siblings are diverse, complex, and frequently characterised by contradictory feelings.

Several studies have found that family members of individuals with rare disease often report experiencing psychological distress, including anxiety and depression (Dellve et al., 2006; Pelentsov et al., 2016b; Picci et al., 2012). Additionally, Anderson et al. (2013) reported that 43% of families who had a family member with a rare disease experienced a significant level of stress, and others have noted increased risk of post-traumatic stress disorder in parents of those with a rare disease (Roorda et al., 2022; Stewart et al. 2020). Similarly, Haukeland et al. (2021) found that siblings of individuals with a rare disease self-reported significantly poorer mental health compared to children who did not have a sibling with a rare disease.

Social Impacts and Relationships

Caring for a child with a rare disease has also been found to impact family members socially (Anderson et al., 2013; Pelentsov et al., 2016b) and can lead to strained relationships (Simpson et al., 2021). Unlike with more common diseases, many family members of individuals with a rare disease report having not met others caring for someone with the same disease (Rice et al., 2020), resulting in them feeling socially isolated and lonely (Baumbusch et al., 2018; Cardinali et al., 2019; Pelentsov et al., 2016a). A survey of 301 Australian and New Zealand parents of children with a rare disease, found that nearly three-quarters of the respondents believed that having a child with a rare disease impacted on the relationship with their partner (Pelentsov et al., 2016b) and more than half had experienced a reduction in their number of friendships since their child was born (Pelentsov et al., 2016b). Parents believed their friends and family had difficulty relating to their experience and understanding their reduced attendance at social gatherings, leading to less frequent contact (Pelentsov et al., 2016b). Similarly, Anderson et al. (2013) found that families of children with a rare disease saw their friends and relatives less often than desired due to their child's illness. Additionally, significantly poorer child-parent relationships

were found for siblings of a child with a rare disease, in comparison to controls (Haukeland et al., 2021). However, conversely, Anderson et al. (2013) also found that of the 30 families who were surveyed, 70% described becoming closer because of shared experiences when living with a child with a rare disease and 77% had positive experiences with relatives who were 'understanding and helpful'.

Educational and Occupational Impacts

Whilst there appears to be less research focussed on family member's engagement in occupational, educational and leisure activities, impacts due to the rare disease have been reported. For example, in a qualitative study, Pelentsov et al. (2016a) reported that the majority of parents had adjusted their work hours since the birth of their child. Similarly, in the quantitative study, Pelentsov et al. (2016b) found that of 301 parents, 38% reduced their working hours and 34% ceased paid employment in relation to caring for a child with a rare disease. As well, Witt et al. (2021) reported that mothers more frequently reduce their work hours, although fathers appear to be increasingly involved in their children's care.

Rationale and Aims

Boettcher et al. (2021) conducted a systematic review of the quality of life for parents of children with rare disease and found that they experienced reduced quality of life when compared to parents with healthy children. However, to our knowledge, there has been no review of the broader range of psychosocial impacts experienced by family members of an individual with a rare disease. Although knowledge of shared experiences across rare disease remains somewhat limited (von der Lippe et al., 2017), it is anticipated that integrating the quantitative literature across a range of rare diseases, will allow greater understanding of the shared psychosocial impacts that family members of people with rare disease experience. Therefore, the aims of this study were to conduct a systematic literature review to (1) consolidate and summarise the published quantitative evidence on the psychosocial impacts experienced by individuals who have a family member with a rare disease, and (2) discuss directions for future research in relation to psychosocial impacts experienced by family members of an individual with a rare disease.

Method

The authors followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

Search Strategy

Online databases Medline via PubMed (from 1966), APA PsychINFO, and CINAHL Complete (Cumulative Index to Nursing & Allied Health Literature) were systematically searched on 3rd November 2021 to identify original studies investigating the psychosocial impact on family members of living with an individual with a rare disease. The authors developed the search strategy with the support of a Learning and Research Librarian based at the University of Tasmania. In developing the search strategy, two search concepts were identified: (1) rare disease and (2) family members. As outcomes are often not well reported in the title or abstract of papers (Lefebvre et al., 2022), search terms relating to psychosocial impacts were not included.

Relevant search terms for Concept 1 included 'rare disease,' 'orphan disease' and 'rare disorder.' As there are over 6000 rare diseases (Pelentsov et al., 2016b; Putzeist et al., 2013), it was deemed infeasible to search every individual rare disease and it was anticipated that focusing on a select number of individual rare diseases would potentially restrict and bias the results. Therefore, individual rare diseases were not included within the search terms.

Search terms identified for Concept 2 included 'caregiver,' 'carer,' 'family,' 'parent,' 'relative,' and 'spouse.' Whist this review aimed to look at the impact on family members, the term 'caregivers' was included in the search as the majority of care is typically provided by family members (Baumbusch et al., 2018). Articles primarily reporting the impact on paid carers, that were not related to the individual with rare disease, were excluded. The search terms in Concept 2 were limited to the abstract and key word fields only; this decision was based on a preliminary search that identified including the terms in other fields (e.g., abstract field) led to the inclusion of many irrelevant articles and did not add any value. Similarly, search terms regarding other family members (e.g., grandparent, brother, sister etc.) were not used, as preliminary searches showed they added no value.

The final search terms are shown in Table 1. They included suitable indexing terms (i.e., MeSH terms and keywords). Prior to performing the search, the developed search string was validated by evaluating whether it could identify a set of eligible studies (Anderson et al., 2013; McMullan et al., 2021; Pelentsov et al., 2016b).

Eligibility

The suitability of citations was determined using the inclusion and exclusion criteria described in Table 2. All original, peer-reviewed articles published in English, that reported quantitative findings on the psychosocial impact of having a family member with a rare disease (included on the

Table 1 Search Strategy

Database	Search String
PubMed (Medline)	(“rare disease*“[tiab] OR “orphan disease*“[tiab] OR “rare disorder*“[tiab] OR “rare diseases”[Mesh]) AND (caregiv*[ti] OR carer*[ti] OR parent*[ti] OR famil*[ti] OR father*[ti] OR mother*[ti] OR relative*[ti] OR sibling*[ti] OR spouse*[ti] OR caregivers[Mesh] OR parents[Mesh] OR family[Mesh])
PsychINFO (Ovid)	(“rare disease*“ or “orphan disease*“ or “rare disorder*“).id,ti,ab. and ((caregiv* or carer* or parent* or famil* or father* or mother* or relative* or sibling* or spouse*).id,ti. or exp caregivers/ or exp parents/ or exp family/)
CINAHL (EBSCOhost)	((TI “rare disease*“ OR AB “rare disease*“) OR (TI “orphan disease*“ OR AB “orphan disease*“) OR (TI “rare disorder*“ OR AB “rare disorder*“) OR (MH “rare diseases”)) AND (TI caregiv* OR TI carer* OR TI parent* OR TI famil* OR TI father* OR TI mother* OR TI relative* OR TI sibling* OR TI spouse* OR (MH caregivers+) OR (MH family+))

Table 2 Eligibility Criteria for Systematic Review of the Psychosocial Impact of Having a Family Member with a Rare Disease

Eligibility Category	Inclusion Criteria	Exclusion Criteria
Study type	English language	All other languages
	Quantitative data (on psychosocial impacts)	Qualitative data
	Original, peer-reviewed	Not original, peer-reviewed (including case studies, conference proceedings and unpublished dissertations)
	Full-text available	Full-text not available
Participant type	Family members[b] of individuals with a rare disease	Not family members of an individual with a rare disease
Disease type	Included in Orphanet list of rare diseases[c]	Not included in Orphanet list of rare diseases
Outcomes/result type	Psychosocial impacts[a]	All other outcomes
	Family member results presented separately from other participant groups (if applicable)	Family member results combined with other participant groups

[a]Psychosocial impacts are defined as impacts relating to psychological, emotional, and/or social aspects of having a family member with a rare disease

[b]Majority of caregivers in study were family members

[c]Rare diseases defined as those included on the Orphanet list of rare diseases (Orphanet, 2022)

Orphanet list of rare diseases; Orphanet, 2022) were included. Papers that included data from more than one group of informants (i.e., both the person with a rare disease and family members) were only deemed eligible if the results were presented separately for the participants in the family member group. Whilst many undiagnosed diseases are rare diseases (Gahl et al., 2012), studies based primarily on data from individuals with undiagnosed diseases were excluded, however, studies were included if the majority of participants were diagnosed with a rare disease. Similarly, whilst some papers included caregivers who were not family members, the majority of caregivers in a study had to be family members to meet inclusion criteria.

Screening and Study Selection

Records returned from the database searches were merged using EndNoteX9 (The EndNote Team, 2013) and imported into the Covidence Online Software Veritas Health Innovation, Melbourne, Australia (www.covidence.org). Duplicates were removed using the Covidence ‘de-duplicate’ feature, four remaining duplicates were identified during the full-text screening and excluded.

In the first phase of screening, one reviewer (JA) independently examined the titles and abstracts of all citations identified by the search using the pre-specified eligibility criteria. Where there was any uncertainty regarding relevance, the citation was retained for further consideration in the second phase of screening. In the second phase, full-text manuscripts of citations deemed relevant during the first screening were independently screened by two reviewers (JA and CP) and papers were included or excluded in accordance with the eligibility criteria. All discrepancies between reviewers were resolved through discussion. The inclusion of all papers in the systematic review were agreed on by both reviewers.

Data Extraction and Synthesis

Reviewer (JA) extracted the relevant data from the selected articles using a pre-designed Excel spreadsheet. The data

extracted included study location, sample size, participant and family member demographics (e.g., age, gender, rare disease diagnosis, relationship), methodology (e.g., recruitment method, measure used), and results (e.g. psychosocial outcomes). Any missing information from studies was recorded in the results as 'not reported,' whilst unclear data was discussed and agreed upon by reviewers JA and CP. Given the heterogeneity of studies, and in line with previous literature reviews in this field (Boettcher et al., 2021), we conducted a narrative synthesis of the findings.

Assessment of Methodological Quality

Quality assessment of the eligible studies was performed (by reviewer JA) using the National Institutes of Health (NIH) Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (NIH, 2014). The tool comprises of 14 items, which cover design, selection bias, data collection, confounders, blinding and attrition. Several responses (*Yes*, *No*, *Not reported* and *Not applicable*) could be used, with each *Yes* responses correlating to a score of one. Based on responses, summary scores were calculated for each study, and expressed as a percentage, that could range from 0–100%, as suggested in Maass et al. (2015). The overall quality of each study was then categorised in line with the guidance for the tool which suggests that an overall score of 11–14 (72–100%) receive a rating of 'good,' those with a score of 5–10 (30–71%) receive a rating of 'fair' and a rating of 'poor' describes studies with an overall score of 0–4 (0–29%). For questions that did not apply (*NA* responses), responses were omitted, and the overall quality scoring scale was appropriately adjusted. To best capture the current state and quality of research in this field, papers were not excluded based on quality assessment, and thus all eligible articles were included.

Results

Included Studies

The database search yielded a total of 2024 articles. A total of 1727 abstracts and 170 full-text articles were reviewed. Following the full-text review, 140 articles were excluded based on the eligibility criteria, whilst 30 articles were included in the review. A flowchart of the identified and selected articles, along with the reasons for exclusion, is shown in Fig. 1.

Characteristics of Included Studies

Across the 30 eligible studies, there were 5285 participants, with sample sizes ranging from 21–1599. Of the seven studies that reported an overall mean age, the approximate mean age of participants was 41.7 years, and of the 24 studies that reported gender, around 76% of participants were women. In 17 studies, participants were primarily parents, in one study they were mostly spouses, and in the remaining six studies the relationship of the respondent to the person with a rare disease was not specified. Only two studies included spouses, one included children of the person with a rare disease and one included a grandparent and a foster mother. Of the studies that defined the parental relationships ($n = 19$), an average of 64.4% respondents were mothers, 26.1% were fathers.

A total of 12 studies were based on the impacts of a specific rare disease, while 17 studies included children with a range of rare diseases; the number of diseases was not reported in one study. The number of diseases being reported on ranged from 1 to 132. The majority of the family members, who had the rare disease, were children; with an approximate mean age of 10.4 years. In total, five studies were conducted in the each of the USA and Italy, three in Australia, Germany, and China, two in each of Spain, and the UK, and one in Sweden, South Korea, Turkey, Poland and France. Of these, three included participants from more than one country. Additionally, one study was conducted across Europe and one across both USA and Spain. Details of the study characteristics are displayed in Table 3.

Quality Assessment

Of the 30 studies evaluated using the NIH Quality Assessment tool for Observational Cohort and Cross-Sectional Studies (NIH, 2014), the majority of studies ($n = 23$; 77%) were assessed as being 'fair' quality, and seven (23%) were categorised as 'good' quality. No studies were deemed to be 'poor' quality. Sample size justification was the most commonly omitted information with none of the included studies presenting reasons for recruiting the number of participants included. Studies also frequently fell short of satisfactorily describing the participation rate of eligible persons, missed by 70% of studies, while 7% of studies did not include over 50% of eligible persons in the study. Finally, the outcome measures were not clearly defined, and presented along with their psychometric properties, in 57% of the studies. The NIH tool questions with results of studies satisfying each criterion can be found in Appendix A, Table A1, whilst the overall quality rating given to each study can be found in Table 3.

Psychosocial Outcomes/Impacts

Included studies described a diverse range of psychosocial impacts for family members of an individual with a rare disease. Therefore, psychosocial impacts were categorised

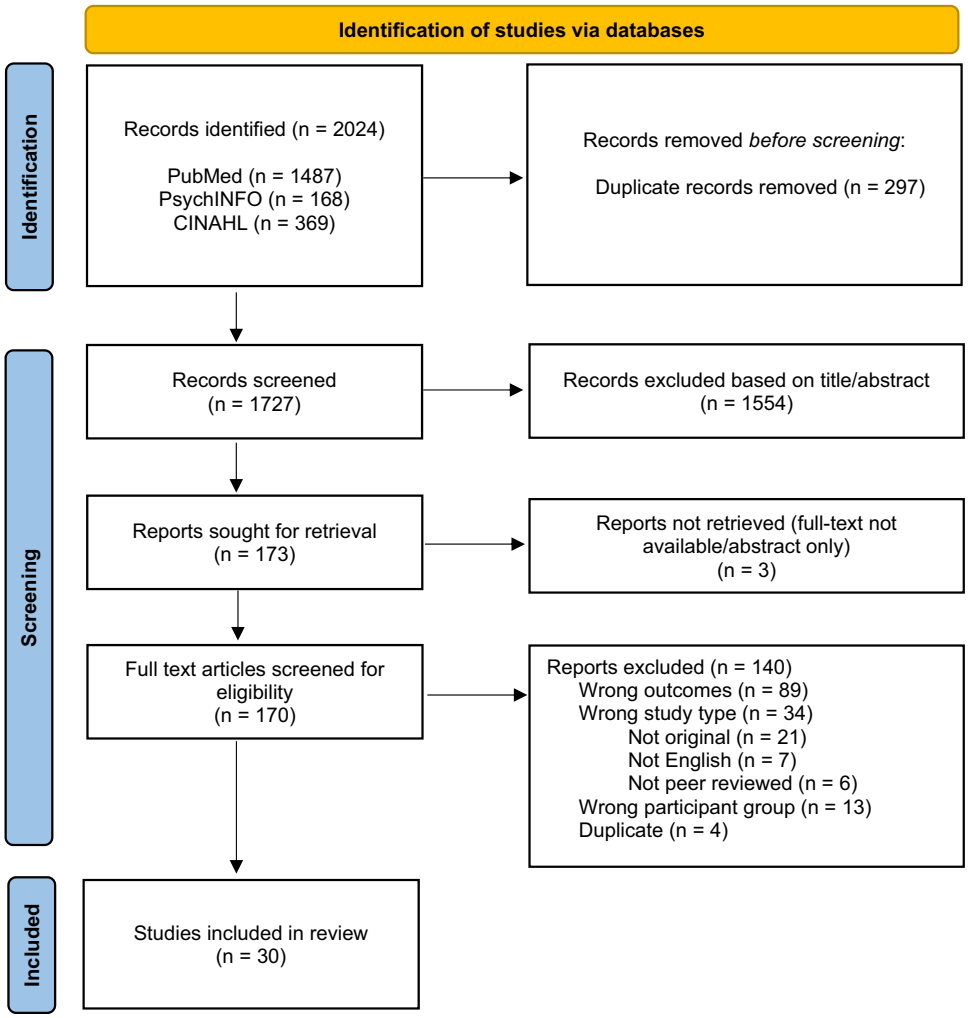

Fig. 1 PRIMSA flow diagram – selection of articles according to inclusion and exclusion criteria

into five subthemes: (1) emotional and psychological health, (2) Quality of Life (QoL) and Health-Related Quality of Life (HRQoL), (3) work and occupational, (4) caregiver burden, and (5) social and relationships. As shown in Table 4, no studies reported psychosocial impacts from all five subthemes. The results within each of the subthemes are discussed in more detail below, and a summary of the results can be found in Appendix B, Table B1.

Emotional and Psychological Health Impacts

The majority of studies ($n = 24$, 80%) reported on emotional or mental health impacts of having a family member with a rare disease. Within these studies, a total of 31 different measures (including five author-developed measures) were utilised, with six studies using more than more measure. The only measure utilised in more than one study was the Parenting Stress Index (PSI) which was used in two studies. Overall, studies generally found that having a family member with a rare disease resulted in negative impacts on participants' mental health and emotions.

Across the studies, increased levels of psychological distress (Schadewald et al., 2018; Yoo et al., 2019), including depression (Berrocoso et al., 2020; Kim et al., 2010; Li et al., 2021; Picci et al., 2015; Stewart et al., 2018; Xu et al., 2021), anxiety (Boettcher et al., 2020; Kim et al., 2010; Kolemen et al., 2021; Lagae et al., 2019; Li et al., 2021; Pelentsov et al., 2016b; Picci et al., 2015; Pohlig et al., 2017; Save et al., 2013; Silibello et al., 2016; Stewart et al., 2018; Xu et al., 2021), stress (Dellve et al., 2006; Hiremath et al., 2018; Miodrag & Peters, 2015; Moretti et al., 2021), and somatization (Li et al., 2021) were reported. Berrocoso et al. (2020) found that participants reported experiencing significantly more psychological distress than the normative healthy population, but significantly less than individuals with no diagnosis but who were suffering from significant clinical distress. Mothers were found to experience higher levels of psychological distress than fathers (Boettcher et al., 2020). Pohlig et al. (2017) reported that parents were experiencing a level of psychological distress that potentially required treatment, while Pelentsov et al. (2016b) found that many participants reported accessing treatment for a mental health problem.

Table 3 Characteristics of Included Studies ($n = 30$) and Overall Quality Assessment Results

First Author, year (location)	Sample size, *n* (% women)	Mean age, years (*SD*) or other	Relationship to person with RD (%)	Mean age of person with RD, years (*SD*) or other	Number of diseases	Quality Assessment
Anderson et al., 2013 (Australia)	30 (>80%)[h]	Not reported	Mother (80), Not specified (20)	27% 0–5 years; 37% 6–10 years; 23% 11–15 years; 13% >15 years	Multiple	Good
Berrocoso et al., 2020 (Spain)	22 (86.4%)	39.73 (7.19)	Parents (100)	6.82 (4.73)	Individual	Fair
Boettcher et al., 2020 (Germany)	110 (75 families) (65.5%)[h]	Mothers 40.1 (7.38), Fathers 43.1 (7.38)	Mother (65.5), Father (34.5)	9.5 (5.48); range 6–21 years	Multiple	Fair
De Stefano et al., 2020 (Italy)	50 (76%)	Not reported	Mother (76), Father (24)	9.7 (5.5)	Individual	Good
Dellve et al., 2006 (Sweden)	244 (138 families) (55.7%)[h]	Not reported	Mother (55.7), Father (44.3)	Median 7 years (range 1–17 years) 42% <7 years; 44% 7–12 years	Multiple	Good
Duncan et al., 2020 (USA)	21 (majority)	Not reported separately from patient sample	Caregivers – not specified (100)	8 (range 1–17)	Individual	Fair
Hiremath et al., 2018 (USA)[a]	271 (not reported)	Not reported	Parents/guardians (100)	28% 0–5 years; 33% 6–10 years; 36% 11–19 years; 1% 20–30 years; 1% 31–40 years; 2% >40 years	Multiple	Fair
Khair & Pelentsov, 2019 (UK)	231 (56.9%)[h]	1.3% 15–24 years; 8.3% 25–34 years; 55% 35–33 years; 31% 45–54 years; 4.4% 55+ years (Missing data $n = 2$)	Mother (56.9), Father (42.9)	Children up to 17 years	Multiple	Fair
Kim et al., 2010 (South Korea)	33 (100%) *and* 32 in control group[f] (100%)	37.72 (5.17); control group[f] 35.41 (4.56); overall range 29–55	Mother (100)	5.28 (2.9); control group[f] 4.38 (3.41); overall range 4 months – 16 years	Multiple	Good
Kolemen et al., 2021 (Turkey)	40 (50%)	10% 20–29 years; 50% 30–39 years; 32.5% 40–49 years; 7.5% 50–59 years	Mother (50), Father (50)	Children	Multiple	Fair
Lagae et al., 2019 (Europe)[b]	584 (≥86%)[h]	Not reported	Mother (86), Father (12), Other caregivers (2)	10.6 (not reported); median = 9 years; paediatric 83%, adult 17%	Individual	Fair

Table 3 (continued)

First Author, year (location)	Sample size, *n* (% women)	Mean age, years (*SD*) or other	Relationship to person with RD (%)	Mean age of person with RD, years (*SD*) or other	Number of diseases	Quality Assessment
Li et al., 2021 (China)	1599 (not reported separate to patients)	34.4 (6.7)	Family members – not specified (100)	Not reported	Multiple	Fair
Magliano, 2014 (Italy)	502 (85%)	43.4 (7.4)	Mother (84), Father (14), Other key relative (2)	12.8 (5.6); range 4–25 years	Multiple	Fair
McMullan et al., 2021 (UK)	57 (84.2%)	14% 25–34 years; 24.6% 35–44 years; 49.1% 45–54 years; 12.3% 55+ years	Family member – not specified (98.2), Other (1.8)	35.7% >18 years; 16.1% 18–24 years; 7.1% 25–34 years; 7.1% 35–44 years; 14.3% 45–54 years; 19.6% 55+ years; 1.8% prefer not to say	Not reported	Fair
Miodrag & Peters, 2015 (USA)	124 (>90%)[h]	Mean age (depending on genotype of disorder): Mothers 35.56–39.29 (*SD* 6.42–10.02), Fathers 37.7–42.32 (*SD* 6.45–8.99) Overall Mothers ranged from 23.1 to 55.8 years; Fathers ranged from 23.1 to 59.8 years.	Mother (>90%), Father (remaining)	Mean age (depending on genotype of disorder): 5.07–5.39 (*SD* 5.16–4.14) Children – young adults; overall range 0.9–27 years	Individual	Fair
Moretti et al., 2021 (Italy)	105 (≥65.7%)[h]	Mothers 2.9% 20–29 years; 24.6% 30–39 years; 44.9% 40–49 years; 24.6% 50–59 years; 2.9% 60+ years Fathers 23.5% 30–39 years; 47.1% 40–49 years; 23.5% 50–59 years; 2.9% 60+ years; 2.9% not reported	Mother (65.7), Father (32.4), Not specified (1.9)	Median 9.98 years (*SD* 6.8)	Multiple	Fair
Mori et al., 2017 (Australia)[c]	149; but 192 in total for the study (≥ 88.6%)[h]	Parental age ($n = 160$) 38.2 (7.0), ($n = 160$)	Biological mother (87.9), Biological Father (10.7), Foster Mother (0.7), Grandparent (0.7) ($n = 149$)	Median 5.2 years (range 0.2–34.1 years)	Individual	Good
Pelentsov et al., 2016a (Australia)[d]	301 (91%)[h]	2.7% 15–24 years; 27.9% 25–34 years; 43.5% 35–44 years; 21.9% 45–54 years; 4% 55+ years	Mother (91.4), Father (8.6)	Children (< 18 years)	Multiple (and undiagnosed = 3.97%)	Fair
Picci et al., 2015 (Italy)	55 (54.5%)[h] *and* 56 in control group[g] (53.6%)[h]	42.52 (5.79); control group 42.56 (6.59)	Mother (54.5), Father (45.5); control group Mother (54.6), Father (46.4)	Children	Multiple	Fair
Pohlig et al., 2017 (Germany)	58 (77.6%)	Mean ages of depending on RD type: 47.5 (6.8) and 47.7 (7.7)	Mother (77.6), Father (22.4)	Not reported	Multiple	Fair
Qi et al., 2021 (China)	49 (not reported)	Not reported	Primary caregiver – not specified (100)	38.9% 0–4 years; 10.2% 5–7 years; 24.5% 8–12 years; 4.1% 13–14 years; 22.5% 15+ years	Individual	Good

Table 3 (continued)

First Author, year (location)	Sample size, *n* (% women)	Mean age, years (*SD*) or other	Relationship to person with RD (%)	Mean age of person with RD, years (*SD*) or other	Number of diseases	Quality Assessment
Rodríguez et al., 2021 (Spain)	110 (82.8%)	Women 44.67 (7.25); Men 47.42 (11.07)	Parents (100)	12.75 (6.56)	Multiple	Fair
Rozensztrauch et al., 2021 (Poland)	23 (not reported)	Not reported	Parents (100)	7.22 (3.57); range 2–12 years	Individual	Fair
Save et al., 2013 (France)	47 (30 families) (63.8%)[h]	Not reported	Mother (63.8), Father (36.2)	19.8 (range 2–56 years), 3 deceased	Individual	Fair
Schadewald et al., 2018 (USA)	82 (not reported)	25% 25–34 years; 50% 35–44 years; 22.6% 45–64 years	Primary caregiver – not specified (100)	Women 8.7 (4.8); Men 8.2 (4.5); all <18 years ($n = 100$; some parents >1 child with disorder)	Multiple	Fair
Silibello et al., 2016 (Italy)	154 (70.1%)[h]	Mothers 39.08 (6.6); fathers 42.38 (7.19)	Mother (70.1), Father (29.9)	7.04 (4.69)	Multiple	Fair
Stewart et al., 2018 (USA, Spain)[e]	32 (68.8%)	55.9 (12.8)	Spouse/Partner (72.4), Mother (10.3), Father (3.4), Child (10.3), Other (3.4)	Not reported	Individual	Fair
Witt et al., 2019 (Germany)	73 (76.7%)	Not reported	Parents (100)	9.75 (3.02); range 5–14 years	Individual	Fair
Xu et al., 2021 (China)	49 (73.5%)	51% ≤30; 20.4% 31–39 years; 28.6% ≥40	Mother (67.4), Father (22.5), Spouse (10.2)	11.81 (12.26); range 2–45 years; 79.6% <18 years.	Individual	Good
Yoo et al., 2019 (USA)	80 (98%)	Median 34 years (range 23–62 years)	Caregiver – not specified (100)	Children	Multiple	Fair

RD rare disease

[a]Participants based in nine countries (including 90% USA, 5% Australia, 2% Canada)

[b]Participants based in five European countries (France, Germany, Italy, Spain, UK)

[c]Participants based worldwide, with 92% from Europe (14% Italy, 12% UK, 12% Germany, 11% France, 10% the Netherlands, 10% Spain, and 7% Poland)

[d]Participants based in Australia and NZ

[e]Participants based in USA and Spain

[f]Control group consisted of mothers of children with a chronic severe illness

[g]Control group consisted of parents of a child with chronic diseases

[h]Based on information provided in paper in relation to relationship of participants to person with RD

Table 4 Psychosocial Subthemes Reported on in Each of the Eligible Studies

First Author (year)	Emotions/MH	QoL/ HRQoL	Work/ Occupation	Burden	Social/ Relationships
Anderson et al. (2013)	X				X
Berrocoso et al. (2020)	X	X	X	X	
Boettcher et al. (2020)	X	X			
De Stefano et al. (2020)			X	X	
Dellve et al. (2006)	X				
Duncan et al. (2020)			X		
Hiremath et al. (2018)	X			X	
Khair & Pelentsov (2019)	X				
Kim et al. (2010)	X	X		X	
Kolemen et al. (2021)	X				
Lagae et al. (2019)	X		X		X
Li et al. (2021)	X	X			
Magliano (2014)	X				
McMullan et al. (2021)	X				
Miodrag & Peters (2015)	X				
Moretti et al. (2021)	X				
Mori et al. (2017)		X			
Pelentsov et al. (2016a)	X		X		X
Picci et al. (2015)	X				
Pohlig et al. (2017)	X				
Qi et al. (2021)	X	X		X	
Rodríguez et al. (2021)			X		
Rozensztrauch et al. (2021)		X			
Save et al. (2013)	X		X		X
Schadewald et al. (2018)	X				
Silibello et al. (2016)	X		X		X
Stewart et al. (2018)	X	X	X	X	
Witt et al. (2019)		X			
Xu et al. (2021)	X	X			
Yoo et al. (2019)	X				X
Total	24	10	9	6	6

In terms of stress, findings suggested that having a family member with a rare disease led to increased levels of stress for the whole family (Anderson et al., 2013; Moretti et al., 2021). Dellve et al. (2006) found that mothers showed more stress than fathers and compared to a group of mothers of young children. In one study (Hiremath et al., 2018), caregivers reported seeking help from a professional in relation to their emotional stress. Rare disease subtype (Miodrag & Peters, 2015) was found to impact participants' perceived level of stress.

In two studies (Li et al., 2021; Xu et al., 2021), caregivers reported higher levels of depression and anxiety than national norms. Parents of children with a rare disease were found to experience greater subjective depression, and have a significantly higher prevalence of depression, than mothers of children with a chronic illness or disease (Kim et al., 2010; Picci et al., 2015). Similarly, parents of children with a rare disease were found to have considerably higher anxiety scores than parents of children with a chronic disease (Kim et al., 2010; Picci et al., 2015) and many participants (39–67%) were found to have clinical levels of anxiety (Kim et al., 2010; Xu et al., 2021). As well, Stewart et al. (2018) found that caregivers in the USA reported more symptoms of anxiety and depression than Spanish caregivers. In relation to anxiety, two studies (Boettcher et al., 2020; Kolemen et al., 2021) reported that mothers experienced higher levels of anxiety than fathers, however, Picci et al. (2015) found no significant difference in anxiety scores between mothers and fathers of children with a rare disease. Kolemen et al. (2021) found that receiving a diagnosis for their family member, significantly decreased participants' state anxiety levels, but not their long-term

levels of anxiety. And, in several studies, participants reported experiencing worries (Lagae et al., 2019; Pohlig et al., 2017; Save et al., 2013; Silibello et al., 2016) and fear (Pohlig et al., 2017) in relation to their family member's rare disease and future.

As well as anxiety, fear and worry, participants reported a wide spectrum of other emotions including anger and frustration (Khair & Pelentsov, 2019; Pelentsov et al., 2016b), grief and sadness (Khair & Pelentsov, 2019), uncertainty (Pelentsov et al., 2016b; Yoo et al., 2019), helplessness and vulnerability (Pelentsov et al., 2016b), and optimism (Dellve et al., 2006; Xu et al., 2021). Save et al. (2013) found that at the time of diagnosis families experienced disorientation and concern, and that these were followed by sadness and fear. In contrast, Silibello et al. (2016), found that within the family, happiness and compassion were the most expressed emotions, with loneliness, aggression, and sadness less frequently expressed. Dellve et al. (2006) found that the majority of participants reported high life satisfaction whilst Picci et al. (2015) reported that parent's satisfaction with life ranged from slightly satisfied to satisfied. Additionally, Magliano et al. (2014) found that the majority participants reported that caregiving had a positive impact on their lives.

QoL and HRQoL Impacts

A third of the studies ($n = 10$, 33%) reported on QoL or HRQoL. The most frequently used instrument to measure QoL/HRQoL was the Medical Outcomes Study Short Form Health Survey, of which three studies used the Short Form 36 (SF-36) version, two utilised the Short Form 12 (SF-12) and one study used the Short Form 8 (SF-8). Two studies used the World Health Organization's Quality of Life Questionnaire (WHOQOL), and one study each used the Beach Center Family Quality of Life Scale (BCFQOL), the Pediatric Quality of Life – Family Impact Module (PedsQL-FIM) and the Ulm Quality of Life Inventory for Parents (ULQIE). In one study, two measures of QoL/HRQoL were utilised (Mori et al., 2017). In total, participants in three studies (Berrocoso et al., 2020; Li et al., 2021; Xu et al., 2021) reported lower QoL across all QoL domains (including those in relation to emotional wellbeing/psychological and social relationships) in comparison to healthy population norms. In additional, while some studies did not find lower QoL across all domains, participants reported significantly lower scores on the domains relating to emotional wellbeing and mental health domain (Mori et al., 2017; Qi et al., 2021; Witt et al., 2019), compared to the healthy population. However, when compared to a primary care population, no significant difference in participants' QoL was found within the psychological and social relationship domains (Berrocoso et al., 2020). Mothers reported significantly lower QoL compared to fathers (Boettcher et al., 2020) and having a child with a rare disease was found to lead to lower QoL compared to having a child with a chronic illness (Kim et al., 2010). One study (Mori et al., 2017) reported that while family QoL was generally rated as satisfactory, emotional wellbeing scores were the lowest. Stewart et al. (2018) found no difference in participants' QoL based on location, with participants from both Spain and USA reporting poor QoL mental health scores. Rozensztrauch et al. (2021) investigated the impact of quality of life on the family and found a large impact on the worry dimension and the least impact in relation to family relationships and cognitive function.

Work and Occupational Impacts

A total of nine studies (30%) assessed the impact of having a family member with a rare disease on participants' work and occupation. A variety of measures were utilised, none of which solely measured work and occupational impacts. Three studies used disease-specific measures (Epidermolysis Bullosa Burden of Disease, eB-BoD; Glanzmann's Thrombasthenia Patient/Caregiver Questionnaire; Dravet syndrome caregiver survey, DISCUSS), two used an author-developed questionnaire, and one study used the Economic costs questionnaire, the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SH). One study (Silibello et al., 2016), used a modified questionnaire from a previous study, however the questionnaire was unable to be located in English. Having a family member with a rare disease was found to negatively impact work or occupation of participants in all nine studies. Due to their family member's rare disease, participants across a number of studies reported giving up their employment or reduced or adjusted their work hours (Berrocoso et al., 2020; De Stefano et al., 2020; Lagae et al., 2019; Pelentsov et al., 2016b; Rodríguez et al., 2021; Save et al., 2013); missing or taking time off work (Duncan et al., 2020; Lagae et al., 2019); and changing their employment activity or choice of career (Lagae et al., 2019; Save et al., 2013). Save et al. (2013) found that mothers more frequently modified their professional lives than fathers, and Stewart et al. (2018) reported that the impact of having a family member with a rare disease, varied between countries. In one study (Pelentsov et al., 2016b) participants reported that their partner's work hours were also been impacted.

Caregiver Burden

Six studies (20%) reported on caregiver burden. The majority (four studies) measured burden using the Zarit Burden Interview (ZBI), of the other two studies, one used

an author-developed measure and the other utilised a disease-specific measure (Epidermolysis Bullosa Burden of Disease; eB-BoD). The amount of burden reported by participants was variable. Qi et al. (2021) reported that, on average, participants experienced a moderate to severe caregiver burden, whereas Berrocoso et al. (2020) found that over 95% of participants were not deemed to be overburdened. Mothers of a child with a rare disease reported significantly higher caregiver burden compared to mothers of children with a chronic illness (Kim et al., 2010) and parents reported significantly greater burden when their child had a more debilitating form of a rare disease (De Stefano et al., 2020). While most studies did not specify the type of burden caregivers experienced, Hiremath et al. (2018) found that having a child with a rare disease placed emotional burden on family members and caregivers and De Stefano et al. (2020) found that families with a child with a more debilitating form of a rare disease, experienced a greater impact on their family and social life. One study (Stewart et al., 2018) found differences in caregiver burden based on location, and that in comparison to Spanish caregivers, caregivers from the USA experienced greater burden in the relationship with their family member, lower emotional wellbeing, worse social and family life and greater loss of control over life.

Social and Relationship Impacts

Six studies (20%) investigated the impact of having a family member with a rare disease on family, partner, and social relationships. The impact on relationships was predominantly measured using author-developed surveys (four studies), while one study utilised a disease-specific survey (Dravet syndrome caregiver survey; DISCUSS), and another study used a modified version of a previously developed questionnaire, which the authors could not be locate in English. Five of the six studies (Anderson et al., 2013; Lagae et al., 2019; Pelentsov et al., 2016b; Save et al., 2013; Yoo et al., 2019) found that having a family member with a rare disease impacted relationships, whilst one study (Silibello et al., 2016) found no significant change in partner, family, or social relationships. The majority of impacts reported by participants were negative and included seeing family and friends less often than desired (Anderson et al., 2013), a reduction in the number of friends and social network (Pelentsov et al., 2016b; Save et al., 2013), having difficulty communicating with others about their child with a rare disease (Lagae et al., 2019), experiencing strained personal relationships (Yoo et al., 2019) and having limited time to engage in social and leisure activities (Lagae et al., 2019; Save et al., 2013). Some participants also reported increased conflict with their partner and a small number reported that their child's illness caused them and their partner to separate (Save et al., 2013). Conversely, some participants indicated that they have become closer and have a better relationship with their family or partner (Anderson et al., 2013; Save et al., 2013) and better communication with their partner (Save et al., 2013). Save et al. (2013) also found that a loss of friends was infrequently reported by participants and that a fifth of participants did not observe any substantial impact in their partner relationship. Of the studies that looked at the impact on siblings of a child with a rare disease, some parents and caregivers reported that siblings missed leisure activities and time at school (Lagae et al., 2019), were asked to assume more familial responsibility and received less parental attention (Pelentsov et al., 2016b; Save et al., 2013). In two studies (Khair & Pelentsov, 2019; Pelentsov et al., 2016b) parents reported feeling lonely, and in three studies it was reported that parents (Khair & Pelentsov, 2019; Pelentsov et al., 2016b; Save et al., 2013) and siblings (Save et al., 2013) felt socially isolated.

Discussion

This systematic review attempted to synthesise the literature on psychosocial impacts associated with having a family member with a rare disease. The findings identified a range of psychosocial impacts which were categorised into five subthemes: (1) emotional and psychological health, (2) Quality of Life (QoL) and Health-Related Quality of Life (HRQoL), (3) caregiver burden, (4) social and relationships, and (5) work and occupational impacts. Overall, family members of an individual with a rare disease reported experiencing a range of psychosocial impacts, including psychological distress, lower quality of life, higher caregiver burden and changes to their social support. While it appears that some of these impacts are also experienced by families of children with chronic diseases, others seem to be unique to, or amplified by, the rarity of the disease.

Emotional and Psychological Health

One of the most salient psychosocial impacts of having a family member with a rare disease was the psychological distress that family members experienced. The majority of the included papers discussed the impact of the rare disease on family members' psychological health and emotions. Increased levels of psychological distress were frequently reported by family members, with anxiety being most commonly reported, followed by depression and stress. These findings are in line with the qualitative research in the area (Baumbusch et al., 2018; Boettcher et al., 2020; Pelentsov et al., 2016a) and highlight the importance of providing psychological support to family members.

Additionally, mothers of children with rare diseases have been found to experience higher rates of anxiety and depression in comparison to mothers of children with a more common but chronic illness (Kim et al., 2010; Picci et al., 2015). This supports the suggestion that rarity of the disease poses some unique challenges beyond those encountered by parents of children with other illnesses (Kim et al., 2010; Picci et al., 2015). Based on previous research (Beaulieu et al., 2014; Boettcher et al., 2021; Rice et al., 2020; Zurynski et al., 2008), the often-prolonged diagnostic odyssey, lack of information and available support is likely contributing to the increased rates of psychological distress experienced by family members. As overall positive mental wellbeing has been found to have wider implications for individuals, such as healthier lifestyles, greater productivity, improved relationships, and improved quality of life (Friedli, 2009) the development of interventions to address the psychological distress experienced by family members is vital.

Whilst studies found that family members experienced a range of emotions, the most commonly reported were negative in nature, such as fear and grief (Khair & Pelentsov, 2019). However, when participants were asked how frequently they expressed different emotions, Silibello et al. (2016) found that positive emotions were expressed more often than negative ones. One explanation for these contradictory findings is that measures used in studies may be more focused on the experience of negative emotions, and less frequently ask participants about positive emotions. Alternatively, it may be explained through the theory of emotional bias, which suggested that we have a bias towards remembering, and reporting, negative emotions (Shrout et al., 2018; Vaish et al., 2008). To more clearly understand the emotions experienced by family members, future research should ensure family members have the opportunity to report on a range of both positive and negative emotions, and that they are asked at different time points, which has been found to help reduce negative emotion bias (Shrout et al., 2018). More contextual and longitudinal research would also allow greater understanding of how family member's emotional experiences change over time alongside the disease trajectory.

Quality of Life

Similar to the results of the systematic review conducted by Boettcher et al. (2021), the data synthesised in this review suggests that family members of individuals with a rare disease have a lower quality of life compared to the healthy population, in particular with regards to the emotional wellbeing and mental health domains. Additionally, whilst parents of children with more common but chronic illnesses have been found to experience poorer quality of life compared to parents of healthy children (Cohn et al., 2020; Puka et al., 2018), Kim et al., (2010) found that rare diseases led to larger impacts on parents' quality of life than did more common diseases. This is not surprising given that family members of individuals with rare disease face additional challenges during the course of the disease, in comparison to those who have a family member with a more common disease.

Work and Occupational Impacts

Only a third of studies explored the impacts of having a family member with a rare disease on work and occupational activities. In the majority of these studies, the work and occupational impacts were rarely the focus of the paper, and there were no measures dedicated to exploring these. All work and occupational impacts reported on were negative; family members reported having to reduce or adjust their work hours, take time off work, give up their employment or change their type of employment. This supports the view that having a child with a rare disease has far-reaching implications on the lifestyle of family members (Boettcher et al., 2021) and likely reflects the burden of care family members experience (Baumbusch et al., 2018). As the reduction and changes in work hours is likely to have financial impacts, increasing the complexity of caring for the individual, it is important that these impacts are well understood and addressed.

Caregiver Burden

There were only a small number of studies that reported the burden experienced by families, and results were mixed. However, most family members reported experiencing caregiver burden, which typically appeared to increase in relation to the severity of the disease. This supports previous research suggesting that family members often take on the burden of rare disease (Baumbusch et al., 2018). Additionally, of the studies that specified the type of burden experienced, it was found that rare disease placed an emotional burden on families and impacted their family and social life, which is in line with other synthesised literature in this review, and demonstrates the multifaceted outcomes as would be expected when applying biopsychosocial framework.

Social Impacts and Relationships

Few included papers described aspects of social consequences for family members of individuals with a rare diagnosis. Of those that looked into relationships, having a family member with a rare disease was found to impact relationships in all but one study (Silibello et al., 2016). The majority of effects were reported as negative, including a reduction in the number of friendships, strained personal

relationships and seeing family and friends less frequently than desired. On the other hand, several studies indicated having a family member with a rare disease improved their family and partner relationships (Anderson et al., 2013; Save et al., 2013). These findings emphasise the need for further research investigating the factors that are more likely to lead to the development of stronger relationships, for example coping or communication styles. As social support has been found to offer the possibility for individuals to share experiences, as well as receive crucial emotional support, having less social support may be impacting on the psychological distress individuals experience (Ozbay et al., 2007). Therefore, improving social support could be an avenue for reducing feelings of social isolation as well as symptoms of anxiety, depression and stress experienced by family members.

Clinical and Practical Implications

The results of this review found that many of the psychosocial impacts were found to be worse for mothers than fathers (e.g., lower quality of life, and more often modifying their personal lives). These results are supported by other research, which has found that in relation to providing care, women experience greater mental strain, caregiver burden, and higher levels of psychological distress (Sharma et al., 2016; Yee & Schulz, 2000). Whilst there appear to be some changes in household patterns over the past few decades, women still frequently shoulder the primary responsibility for household tasks and childcare (Cunha et al., 2016) and are often the main providers of informal care for family members with chronic medical conditions or disabilities (Sharma et al., 2016). Therefore, whilst the lower response rate of fathers, compared to mothers, may be leading to possible bias in the results, it also supports the idea that women may also be bearing the burden of care of children with rare disease, and therefore participating more. Based on this, it is important that healthcare professionals are aware that mothers may be carrying more caregiver burden and experiencing increased psychosocial impacts, and as such might require increased support.

Additionally, Stewart et al. (2018) found differences between psychological health and work productivity between Spanish and USA participants. These results may indicate how differences in health systems, social systems, and resources available to participants are impacting psychosocial wellbeing of family members of individuals with a rare disease. Individuals in Spain have access to free public healthcare however, this is not the case in the USA. Whilst this may impact all individuals, it is likely to be particularly impact those with a in rare disease, who often face a prolonged diagnostic odyssey involving many medical appointments and tests (Rice et al., 2020; Schieppati et al., 2008; Zurynski et al., 2017). To understand these cultural differences further, future research could investigate the role of cultural differences on psychosocial impacts experienced by family members of those with rare disease. As well, in the context of most research in this review being conducted in the USA, it should be recognised that the results of this review may not present an accurate picture globally.

From the literature presented in this review, it can be seen that psychosocial impacts are consistently experienced across different rare diseases, most of which are negative. Based on this, it is recommended that healthcare professionals start to draw on these findings by considering the additional challenges this cohort faces and providing family members with information regarding a range of psychosocial support options. At a broader service level, as suggested in previous research (Simpson et al., 2021), the introduction of a role of a care coordinator is likely to be beneficial in reducing some of the burden experienced by family members and help them access needed resources. Additionally, promoting family member education and the development of support groups in which family members can meet others in the same position, and access a wealth of information, is also advocated for.

Strengths, Limitations, and Future Research

The current review has a number of strengths. To our knowledge, this is the first systematic review to explore a wide range of psychosocial impacts of having a family member with a rare disease. Whilst a previous systematic review synthesised evidence on quality of life of parents of children with a rare disease (Boettcher et al., 2021), it did not look at the broader psychosocial impacts and examine each of these individually. Additionally, this systematic review applied a thorough search strategy; we utilised a broad date range, explored a wide range of psychosocial impacts across a range of rare diseases, and included studies with a range of designs. This was based on a biopsychosocial framework and as such these theoretical and methodological decisions enabled us to be comprehensive in our review of psychosocial impacts. However, despite our broad search strategy, it possible that some key outcome studies may have been overlooked for inclusion in this review. Firstly, as we did not search every specific rare disease due to the feasibility of including over 6000 terms in the search, papers that did not refer to the condition as a ‘rare disease’ in either title, abstract or key terms of a paper may have been missed. Additionally, due to time constraints, hand searching of grey literature and reference lists for relevant papers was not performed. To ensure inclusions in reviews such as this, and to build the literature on experiences shared across different rare diseases in the

future, it is recommended that researchers investigating individual rare diseases state that the disease is 'rare' within the commonly searched fields of the paper (i.e., abstract, title or key terms). In line with the findings of this review, this will also allow the researchers to acknowledge the unique challenges that the participants are likely to face due to the rarity of the disease.

Whilst the overall quality of the included studies was deemed to be 'fair or 'good,' there was large heterogeneity in the measures used across studies to assess psychosocial impact, making it difficult to compare results and draw succinct conclusions. Interestingly, there was no study, or individual measure, that assessed all aspects of psychosocial impacts. This could be, in part, due to the ambiguous definition of the term 'psychosocial impacts,' and suggests a need for the term to be operationalised and contextualised within a theoretical framework. Whilst there is some research that has attempted to operationalise the term within health literature (Fu et al., 2013), little consistency exists in the definition and measurement of psychosocial impacts. Consequently, further research should prioritise defining and operationalising this term. This will aid the development of measures that span the breath of psychosocial impacts, which could be used in both research and clinical practice to understand how family members are being impacted and address these as needed. Furthermore, future research may benefit from interpreting findings through a theoretical lens. We used a biopsychosocial model to capture the diverse nature of effects, but future studies may find incorporating a theory such as the health belief model useful to guide question formulation and methodology.

Another limitation of previous research is the difficulty in compiling a large enough data set to draw accurate conclusions. A number of the included studies have small sample sizes, owing to the rarity of the diseases, which result in there being a greater risk of error. Additionally, whilst we aimed to investigate the psychosocial impacts experienced by range of family members, it should be noted that, with a few exceptions, the majority of participants were parents, most of whom were mothers. Therefore, whilst there were other family members included in the results presented, the overall conclusions drawn from the data may best apply to mothers, rather than all family members. As well, although several papers investigated the impacts experienced by siblings (Lagae et al., 2019; Save et al., 2013) and spouses (Stewart et al., 2018; Xu et al., 2021), research looking at the range of psychosocial impacts that siblings and other family members experience remains very limited. For example, we were unable to find any papers that considered the psychosocial impacts experienced by children of people with rare disease. As the results of the existing studies suggest that siblings and other family members experience significant psychosocial impacts, understanding these impacts in more detail should be a priority for the future. This could allow more tailored supports to be developed to meet their needs. Furthermore, the studies reviewed for this review were, with a few exceptions, from English speaking countries and thus it has to be acknowledged that the research presented may represent a particular set of cultural understandings and systems.

While this review aimed to consolidate the knowledge across a range of rare diseases, and highlight shared psychosocial impacts, it is important to note that there appeared to be some factors that influenced family members' experience of psychosocial impacts. Whilst beyond the scope of this systematic review, it would be helpful for future reviews to identify the protective and risk factors for experiencing psychosocial impacts of having a family member with a rare disease (e.g., severity of disease, family structure, medical intervention required, symptomatology, impact on sleep). It is anticipated that this knowledge could then be used to identify family members who are more like to be at risk of experiencing more severe psychosocial impacts, and ensure they are well-supported through their journey. Furthermore, whilst we identified a broad range of psychological and social outcomes, an exploration of mediating and moderating factors such as coping strategies and access to social support could provide a more nuanced understanding (Chen et al., 2022; Wen & Chu, 2020).

Despite the limitations in this study, the synthesis of the literature brought out several important insights and allows for a number of recommendations for further research, most of which have already been mentioned. Ultimately, it is anticipated that having a clearer understanding of the psychosocial impacts experienced by family members of individuals with a rare disease, specific and tailored interventions can be developed to address and reduce these and to better support family members.

Summary and Conclusions

This review highlights that family members of an individual with rare disease experience a wide range of psychosocial impacts, some of which appear to be unique to, or amplified, by the rarity of the disease. Family members have been found to experience increased psychological distress, lower quality of life, higher caregiver burden and a lack of social support, as compared to those whose lives are impacted by more common diseases. However, to fully understand how different family members are impacted, and the role that risk and protective factors play, further research and more comprehensive studies would be a welcome addition to the rather limited body of literature currently available. Future research would also benefit from employing a theoretical

framework to guide research questions and aid in interpretation of findings. It is hoped that this review offers a broad overview of the psychosocial impacts currently experienced by family members, and that following further research, interventions can be developed to improve the lives of family members of individuals with a rare disease.

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