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Health Related Quality of Life of Caregivers of Children and Adolescents With Phenylketonuria: A Systematic Review

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Abstract

Introduction. Caregivers of children with chronic illness are at risk of having impairment in their quality of life (QOL). We systematically reviewed the available literature related to the Health Related Quality Of Life (HRQOL) of caregivers of children with Phenylketonuria (PKU). *Methods.* We comprehensively searched in electronic databases including Scopus, Science Direct, CINAHL, Medline, PubMed, Google scholar, and ProQuest. The search criteria included studies with samples more than one, children suffering from PKU, exploring parents or primary caregiver's HRQOL, published from 2010 to 2020, full article available for download and published in English. Eight studies including 5 cross sectional studies, 1 open label trial, and 2 surveys were systematically reviewed. *Results.* Seven out of 8 studies have established a negative correlation between PKU and parent's HRQOL in at least 1 of the domains. In one study, the HRQOL of parents is higher than their population norms. *Conclusion.* Most of the caregivers had poor to moderate HRQOL. More studies are required to explore HRQOL of caregivers of children with PKU using similar tools and outcome measures addressing all the domains of HRQOL in order to have more clarity on the impact of PKU on caregiver's HRQOL. Interventional studies might help in improving the HRQOL of caregivers.

Keywords

phenylketonuria, parents, caregivers, children, adolescents, Health Related Quality of Life

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Research Highlights

- Parental HRQOL was poor to moderate and HRQOL decreases when stress level increases.
- Child's age, dietary factors, and parent's demographics influences HRQOL of caregivers.
- Parent's age, education level, child's age, and income are predictors of HRQOL of caregivers.
- Designing strategies to improve the HRQOL of caregivers is essential.

Introduction

Inborn Errors of Metabolism (IEM) are genetic disorders that affect the metabolic pathways resulting in an accumulation of toxic metabolites.[1] IEM is a significant cause of morbidity and mortality among young children. These disorders result from genetic mutations; causing defects in a specific enzyme interfering with normal metabolism of exogenous or endogenous protein, carbohydrate or fat.[2] The change in the metabolism can affect all organs and can result in a variety of symptoms. Involvement of the central nervous system could result in psychomotor retardation, epilepsy, and movement disorders.[3]

There are more than 600 IEM's described so far and the number is increasing with progressing genetic studies.[4] The incidence of IEM is estimated to be as high as 1 in 800 live births but it varies depending on the population (eg, Phenylketonuria) and is highest in Caucasians

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1/10 000 live birth).[5] The highest prevalence of IEM is seen in Eastern Mediterranean region due to consanguineous marriage among parents.[6] Phenylketonuria (PKU) is an autosomal recessive disorder and is a most prevalent IEM of amino acids which is characterized by accumulation of phenylalanine (Phe) in the blood and body fluids due to defective Phe hydroxylase activity.[7] PKU affects 1:15 000 people in the United States.[8] In the Mediterranean region, Bahrain reported at least 10 PKU cases in 100 000 live births, Qatar has 8 cases/100 000, UAE has 5 cases/100 000 and Oman has 2.4 cases/100 000 live births.[9]

If PKU is not treated, the higher levels of Phe concentration in the blood can result in severe cognitive impairment, seizures, features of autism, and behavioral problems.[10] These irretrievable complications could be prevented through early detection and management with low Phe diet from the beginning after diagnosis[11,12] and throughout life.[10,13-15] Dietary management of PKU can be achieved through a low Phe diet that limits the intake of natural protein to reduce the blood Phe concentrations.[16,17] Low Phe foods including fruits, few vegetables, fats, oil, low protein flour, pastas, and bread are considered beneficial in controlling the blood Phe levels.[14] The dietary management in children with PKU is very essential. Thus, it requires careful planning, dietary preparation, and regular monitoring.[18]

PKU impacts the lives of caregivers as caring children with PKU is time consuming. In addition to preparing the meals for the family members, the caregivers of children with PKU are required to organize, prepare and cook low phenylalanine meals, which is a time consuming task.[14] The caregivers also have to constantly liaise with other family members as well as with school teachers to keep them informed about the suitable dietary management. The time consuming nature of PKU diet represents an extra burden for caregivers every day.[19] The caregivers are required to visit the hospital more frequently for regular medical check-up and continuous treatment.[20,21] Parents of children with PKU face serious threat to their child's development during the initial months and years after the diagnosis. Chronic stress is created in the caregivers due to the health related concerns and treatment adherence problems of their children.[22]

It has been reported in previous studies that the parents report posttraumatic reactions even years after the diagnosis of PKU.[23] In general, the parents of children with chronic illness are at increased risk of developing psychological problems and psychological disorders and have poor health.[24] Parental Health related Quality of life (PHRQOL) is the most important and appropriate indicator of parental adjustment to children with chronic illness.[25] "HRQOL is an individual's perception of their position in life in the context of the culture and value systems in which they live in relation to their goals, expectations, standards and concerns."[26] "HRQOL is the person's perception of the impact of the disease and treatment on functioning in a variety of dimensions, including physical, psychological and social domains."[27]

Although research related to HRQOL in the context of children with chronic illness is on the rise, so far, it is not fully understood why some caregivers of children with chronic illness cope well and others do not. Moreover, very little is known on HRQOL of caregivers of children and adolescents with PKU. Therefore, this review is designed to summarize the available literature related to the HRQOL of caregivers of children and adolescents with PKU in an attempt to recommend strategies to improve the HRQOL of caregivers.

Methods

The authors completed a systematic review of literature through a systematic process in an attempt to understand the HRQOL of caregivers of children and adolescents with PKU. With the available qualitative and quantitative literature, a systematic review was completed. The literature search was done in databases including Scopus, Science Direct, CINAHL, Medline, PubMed, Google scholar, and ProQuest. The search terms used were *Phenylketonuria and health related quality of life, PKU and HRQOL, Parents HRQOL and PKU, Caregivers HRQOL and PKU, and Children and adolescents with PKU.* The peer-reviewed literature published in English between January 1, 2010 and December 30, 2020 were reviewed.

Study Selection

All longitudinal studies, prospective studies, cross sectional studies, and the trials matching the search terms were included in the review. Three reviewers did an independent search initially resulting in 50 articles and the additional records identified through other sources were (n = 5). The articles found suitable after removing duplicates were (n = 48) and the articles screened based on title and abstract were (n = 48). The records excluded after title and abstract screening were (n = 22). The full-text articles assessed for eligibility were (n = 26) and the full-text articles excluded, with reasons were (n = 18). Finally, 8 articles were included in the review. The studies included 5 cross sectional studies, 1 open label trial and 2 surveys. The studies were from Dutch (1), Denmark (1), Brazil (1), Australia (1), Amsterdam and Groningen (1), Japan (1), France, Germany, Italy, The

Netherlands, Spain, Turkey and the UK (1) and Brazil, Colombia, Germany, Spain, and Turkey (1). The summary of the articles is appended in an article review matrix. (Table 1). PRISMA flow diagram is attached as Figure 1 and it explains the process of systematic review.

Inclusion Criteria

The search criteria included studies with samples more than one, children suffering from PKU, exploring parents or primary caregivers HRQOL while having a child with PKU, published from January 1, 2010 to December 30, 2020, articles published in English language, and articles published in peer- reviewed journals.

Exclusion Criteria

Parents and children suffering from IEM other than PKU, and untreated PKU patients and their parents were excluded.

Data Extraction

The data extracted from the study includes author and year, type of study, sample size, setting and period of time, age of the patients, and type of IEM, tool used, and findings on HRQOL. This review had 897 parents or the primary caregivers involved in the assessment of HRQOL. The mean age of the children with PKU ranged from 6.5 ± 4.6 to 12.4 and the mean age of parents ranged from 35.63 ± 8.82 to 42.4 ± 6.0.

Outcome Measures

The primary outcome measures were HRQOL of parents of children and adolescents with PKU and secondary outcome was to identify the predictors of HRQOL of parents of children and adolescents with PKU.

Risk of Bias of the Studies

Three reviewers independently reviewed the studies using "ROBINS-I tool of risk of bias in non-randomized studies" developed by Cochrane bias Methods group. The domains in the tool included confounding and selection of participants, classification of interventions, deviations after the start of the interventions such as missing data, measurement of outcomes, and selection of reported results. Risk of bias was scored as critical risk = 4, serious risk = 3, moderate risk = 2, and no information = 0.[29]

Quality Appraisal

Three authors independently assessed the quality of the included articles using a quality assessment tool for observational, cohort, and cross-sectional studies. The tool marked CD as cannot be determined, NA as not applicable, NR as not reported, N as no, and Y as yes.[30]

Results

In this section, we present a detailed evaluation of our results. Eight studies have provided the finding that has measured the HRQOL of caregivers of children with PKU. Seven out of 8 studies have established a negative relationship between phenylketonuria and parents' QOL in at least 1 domain. In the remaining one study, the QOL of parents is higher than their population norms. The findings are arranged under 3 headings: Overall PHRQOL, Factors influencing PHRQOL, and the predictors of PHRQOL.

Overall PHRQOL

The most substantial observation of overall PHRQOL was found in 6 studies where the PHRQOL was recorded at a lower range. The PHRQOL scores in all dimensions demonstrated no significant differences in the mean scores between mothers and fathers. PHRQOL scores were at the highest level for "family satisfaction" and at the lowest level for "self-development." The remaining domains of the PHRQOL ["physical and daily functioning," "well-being," and "emotional stability"] scored within a small and similar range.[31] Likewise; most parents perceived their overall QOL as average and perceived a low state of health in comparison with the community population. The mean scores for physical, psychological, social and environmental domains were lower than average. The highest level was found in the physical wellbeing and the lowest average was seen in environmental dimension.[32] The mean score of QOL of parents is lower than the average level and the maximum mean score in the different domains of QOL has been related to physical functioning and the lowest to emotional problems.[33] Majority of caregivers' partners had some concerns about raising a child with IEM, and the distribution was similar to that of primary caregivers.[34]

In relation to the parental mental health variables, the relationship between QOL of parents and stress and anxiety of parents was studied in one study. The caregivers of children with PKU had poorer expectations of QOL compared to the community population and a high degree of stress and anxiety among caregivers is one of the most associated variables with their QOL.[35] In contrast, 2 studies showed a conflicting result to the above findings. Major association was found between QOL of parents and PKU of their children. Stronger HRQOL of parents of children with PKU was reported in 8 out of 12

Table 1. Article Review Matrix Showing Health Related Quality of Life (HRQOL) of Caregivers of Children and Adolescents With Phenylketonuria.

Sl. no.	Author	Setting and time period	Research design	Sample size	Sampling method	Mean age of the parent	Age of the child	Instrument	Major findings
1	ten Hoedt et al[36]	Dutch, December 2008 and February 2009	Cross sectional study	185 parents (116 PKU and 69 Galactosemia)	Letter of invitation to patients via treating physician	PKU = 40.7 ± 6.3, Galactosemia = 42.5 ± 6.5	PKU = 8 ± 0.7 5, Galactosemia = 9.8 ± 5.1	TNO-AZL Questionnaire for Adult's Health related Quality of Life (TAAQoL)	Parents of children with PKU or galactosemia reported a HRQOL comparable to parents of healthy children and a significantly better HRQOL than parents of children with other metabolic disorders.
2	Yamaguchi et al[34]	Japanese families from August to October 2015	Cross-sectional study	143 primary care givers	Purposive sampling	42.4 ± 6.0	12.0 ± 3.1	World Health Organization QoL (WHOQoL-26)	Lower parental distress, higher family empowerment, and higher household income contributed to higher QOL in primary caregivers. Higher household income, lower anxiety about childrearing, and higher satisfaction in the relationship with the child and entire family contributed to higher QOL of partners.
3	Morawska et al[37]	Queensland Lifespan Metabolic Medicine Service at the Queensland Children's Hospital, Brisbane, Australia	Cross-sectional study	18 Parents	Parents of children with PKU is invited to participate	38.67 ± 5.96	6.89 ± 3.68	PKU Impact and Treatment Quality of Life Questionnaire (PKU-QOL). Child Adjustment and Parent Efficacy Scale	There were no significant changes on measures of impact of PKU on HRQOL, parenting stress, general child emotional and behavioral adjustment, or parent self-efficacy for managing general child behavior. Higher parental stress rates are related to higher PKU symptoms and higher levels of PKU cognitive, social and overall effects.
4	Fidika et al[31]	Germany 2008 to 2009	Cross sectional study	89 Parents	Parents of children with PKU is invited to participate	35.9 ± 4.7	6.5 ± 4.6	The Ulm Quality of Life Inventory for Parents of chronically ill children	Parents reported that their PHRQOL was highest in the domain "satisfaction with the family" and lowest in "self-development." The remaining domains of the PHRQOL ["physical and daily functioning," "wellbeing" and "emotional stability"] scored within a small and similar range.

(continued)

Table 1. (continued)

Sl. no.	Author	Setting and time period	Research design	Sample size	Sampling method	Mean age of the parent	Age of the child	Instrument	Major findings
5	Etemad et al[32]	Iran March to December 2015	Cross sectional study	240 Parents	Census sampling	36.82 ± 7.8	8.73 ± 8.1	World Health Organization Quality of Life- Brief (WHOQOL-BREF)	Most of the participants reported an average level of overall QOL and had little satisfaction with their health status. Quality of life in parents with psychological, social and environment aspects were lower than average.
6	Mahmoudi-Gharaei et al[35]	Tehran, time not specified	Cross sectional study	49 parents	Convenience sampling	35.63 ± 8.82	9.84 ± 6.62	WHOQOL-BREF	Found lower levels of QOL in caregivers of children with PKU than the general population. The results of the study also showed that depression, anxiety and stress levels of these parents are higher than the general population.
7	Irannejad et al[33]	Kerman province in Iran in 2017	Cross sectional study	124 parents	Consensus method	39.63 ± 10.62	<18 years	Quality of life (SF36)	The mean score of QOL is lower than the average level. When stress increases, the QOL decreases and parents with lower education level had higher stress scores than parents with higher education level.
8	Feldmann et al[38]	Germany 2012-2015	Cohort study	49 parents	consensus method	Not mentioned	12.4 (6.6-18.7)	Ulm Quality of Life Inventory for Parents (ULQIE)	Before the start of therapy, the parents of the sapropterin group and the control group (classic diet) did not differ on the scales of QOL, except for the self-development scale. After 6 months, the QOL was generally higher in parents of the treatment group patients. The differences after 6 months were only significant for the emotional stability scale, in favor of the treatment group.

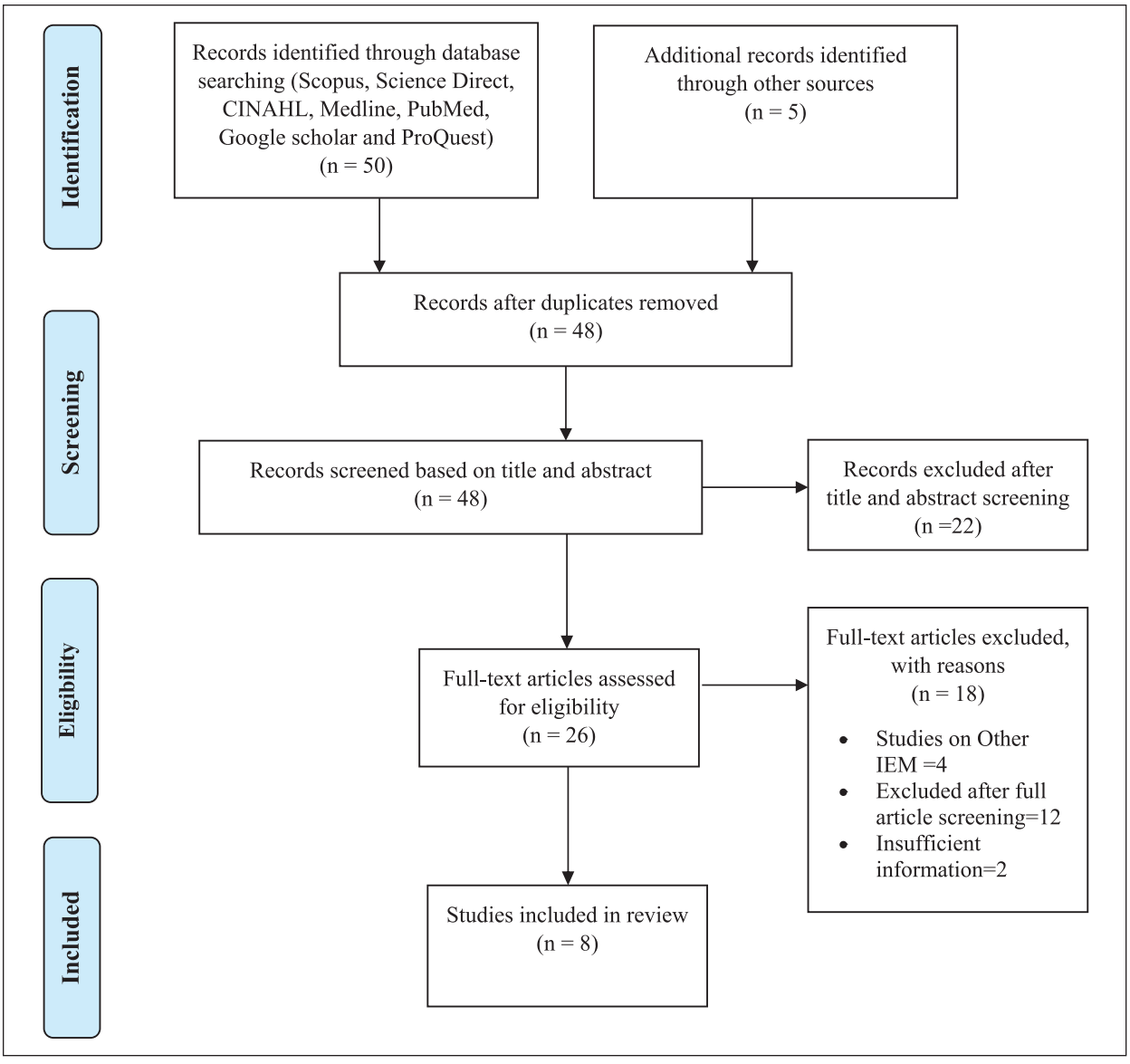

Figure 1. Schematic representation of review process. The figure demonstrates the analytical process.
Source: Adopted from Moher et al.[28]

domains than those with other metabolic disorders.[36] In addition, higher satisfaction with family relationships led to the higher QOL of partners. Lower parental distress scores ($P < .001$), and higher scores on the J-FES family subscale ($P < .001$), contributed to higher QoL of primary caregivers.[34]

Three studies have analyzed the association between QOL and the age of the parent. Age of parents was significantly associated with PHRQOL in the dimensions of "emotional stability," "self-development," and the total score. Low family stress ($P < .001$) and parental coping were identified as possible predictors of QOL.[31] In a study, there was a significant relationship found between psychological dimension, social relationships dimension and parent's age.[32] However, in contrast, another study reported that it was hard to determine whether primary caregiver's age had an impact on the QOL.[34] A significant relationship was found between higher parent stress rates with higher PKU symptoms and higher levels of cognitive, social and overall effects related to PKU. It is noted that the overall impact of PKU on the HRQOL of mothers were worse in these families.[37] Likewise, negative correlation between QOL and perceived stress has been reported. Therefore, it can

be concluded that the QOL of parents decreases when the stress level increases.[33]

Factors Influencing PHRQOL

Child's Age

Four studies assessed the influence of child's age on the PHRQOL. Mental HRQOL (MCS) of parents was significantly influenced by their child's age. A stronger MCS has been related to a higher child's age ($P < .05$) and more social support ($P < .05$); also in the predecessor year, parents who found the child's disease development stable reported stronger MCS ($P = .071$).[36] The mean "self-development" score varies substantially ($P < .001$) in parents of children less than 6 years of age, than the parents of elderly children (6-12). Families of pre-school children recorded lowest overall PHRQOL values than the families of schoolchildren ($P = .011$) and teenage parents. This indicates that the PHRQOL was in the lowest range in parents of pre-school children relative to parents with school-aged children and teenage parents.[31] There has been a major relationship between the psychological dimension, social dimension and the environmental dimension of PHRQOL with the age of the infant. However, there was no significant association between the QOL domain and the parent's relationship to the child, the child's sex and the number of PKU children in the family.[35] The correlation between the child's age and PKU, the number of children, number of children with PKU as well as the age of diagnosis and parents' QOL were considered as important ($P < .05$).[33]

Dietary Characteristics of the Child

A further substantial result shows the relationship between the dietary characteristics of children with PKU and the poor QOL of their parents. Mothers of children with classical PKU have reported greater (severe) impact of guilt due to dietary constraints and Phe-free amino acid supplementation relative to low PKU and hyper-Phe supplementation (low/no control and high impact, respectively).[36] The parents of sapropterin group and control group (the standard diet) had shown no difference on the scale of QOL before initiation of sapropterin therapy except for the self-development scale. In parents of the treatment group, QOL was generally higher in the emotional stability scale after 6 months.[38]

Parent's Demographic Factors

The parent's age, education level and QOL are significantly related ($P < .05$). The psychological dimension was significantly related to the level of parental education ($P = .015$). The social interactions factor and employment ($P = .002$) were significantly linked with household income ($P = .025$). The environmental dimension was substantially related to the residence ($P = .034$), household earnings ($P = .002$), and parent schooling ($P = .007$). There were no major relations between QOL domains and hospitals, and employment. The level of parental education and the perceived stress were significantly related. The mean stress level in parents with higher education was lower.[37] With regard to the demographic characteristics; the best-related indicator with QOL was the occupation of caregivers. The occupation of caregivers was associated with the physiological subscale, social subscale and the environment subscale. Across different occupations, employed participants had the highest QOL subscales and the lowest QOL was found in unemployed participants and those with other jobs were in the middle range.[20] It has been reported that the primary caregivers and their partners had some anxieties related to raising a child with IEM.[34]

Predictors of HRQOL of Parents

Many demographic variables were identified as the predictors of PHRQOL in 5 studies. In the physical dimension of QOL, parent's age; in the psychological and social dimension of QOL, parent's educational level and child's age; and in the environmental dimension, household income was found to be the predictor of QOL.[32] These findings are in line with results reported by Mahmoudi-Gharaei et al[35] where the most correlated factors with the physiological subscale were caregiver's occupation and anxiety. In the psychological subscale, depression and in the social subscale, caregivers' occupation and depression showed the most positive correlation. Caregiver's occupation and anxiety were the most correlated factors for the environmental subscale. The employed participants had highest scores of QOL and the unemployed samples had the lowest QOL. This is consistent with the findings of Fidika et al[31] which suggest that age of parents, age of children, social support, family stress, and parental coping as the most powerful predictors of PHRQOL. Unlike data from previous studies, one of the study showed that lower parental distress scores, higher scores on the J-FES family subscale, and higher levels of household income contributed to higher QOL of primary caregivers and their partners.[34]

Discussion

We undertook a systematic review to summarize the evidence of HRQOL of caregivers of children and

adolescents with PKU. The literature published from January 1, 2010 to December 30, 2020 were included in this review. After careful review of the eligible articles, 8 articles were included in the final analysis. The analysis resulted in 3 important outcomes. It includes overall PHRQOL, factors influencing PHRQOL and predictors of HRQOL of parents.

Having a child or adolescent with PKU negatively influences the lives of caregivers. Caring for a child or adolescent with PKU is time consuming, as the caregivers are required to prepare a low Phe diet. In addition to that, frequent hospital visit of the child for regular treatment adds on to the caregiver burden. Having a child with PKU, which is a chronic illness, increases the psychological stress among caregivers. With such a high stress and difficulties arising from caring children with PKU, it not only affects the psychological state of the caregivers, but it greatly affects the HRQOL of caregivers most importantly mothers, as they are the primary caretakers.[39]

The overall PHRQOL was poor in caregivers of children and adolescents with PKU. It was reported that lowest level of QOL was found in "self-development" domain.[31] Furthermore, most parents perceived their overall QOL as average and perceived a low state of health. The parents also reported average QOL scores in physical, psychological, social and environmental domains. The lowest average QOL was seen in environmental dimension.[32] The QOL is found to be lowest to emotional problems.[33] The caregivers of children with PKU have poorer expectations of QOL and experienced high degree of stress and anxiety.[35]

Though the studies mentioned here reported average to poor HRQOL among caregivers of children and adolescents with PKU, 2 studies showed a conflicting result to the above findings. A study conducted by ten Hoedt et al,[36] showed a stronger HRQOL among parents of children with PKU in 8 domains. Another study also reported higher satisfaction with family relationships which led to higher QOL of partners.[34] These results could be due to the presence of supportive family and support systems for the management of children with PKU. However, more studies are recommended to confirm these findings as most of the studies reported poor HRQOL among the caregivers.

Low family stress and parental coping are considered to be the possible predictors of QOL.[31] It is noted in another study that higher parental stress rates are related to higher PKU symptoms and higher levels of PKU cognitive, social, and overall effects.[37] Furthermore, another study showed that there was a significant negative correlation between QOL and perceived stress.[33] Therefore, it can be concluded that if the caregivers experience less stress and have better coping abilities, they would be able to have better HRQOL. Studies have reported that there was a significant relationship between psychological, social relationships dimension, and parent's age.[32] However; in another study, it was informed that it is hard to determine the relationship between the age of the caregiver and their QOL.[34] Therefore, further research is needed to determine age as a predictor for HRQOL of the caregivers of children with PKU.

Few other factors have been found to influence the PHRQOL. It includes child's age, dietary characteristics of the child and parent's demographic factors. Child's age has an impact on the HRQOL of parents. ten Hoedt et al found that mental HRQOL (MCS) of parents was significantly influenced by their child's age. A stronger MCS has been related to a higher child's age ($P < .05$) and more social support ($P < .05$).[36] In another study, families of pre-school children with PKU recorded the lowest overall PHRQOL compared to families of school children and teenage children.[31] It is interesting to note that there is a major relationship between the psychological, social, and the environmental dimension with the age of the infant.[35] It is mentioned in a study that the child's age, number of children in the family, number of children with PKU, and the age of diagnosis of PKU determines the PHRQOL.[33] Therefore, it can be assumed that the HRQOL of caregivers improves as the age of the child increases. In addition, if the social support is more, the HRQOL of parents of children with PKU will be better.

This review identified that the dietary characteristics of the child influences the HRQOL of caregivers of children with PKU. The caregivers reported poor HRQOL, as they could not adequately prepare Phe-free amino acid food.[36] Similarly, another study showed that the parents' QOL was generally higher in the emotional stability scale after 6 months of Sapropterin treatment.[38] Therefore, it is well evident that if the caregivers could prepare the Phe-free amino acid food, they will have improved HRQOL as they are able to satisfy the needs of the child.

The parent's demographic factors including parent's age and education level are significantly related to their HRQOL. Relationship could be found between the level of parental education and the psychological health of the parents. In addition, the level of parental education is related to the perceived stress. Furthermore, it is noted that the stress level is lower in parents with higher education.[37] The occupation of caregivers is associated with their QOL. The review identified that employed participants had the highest QOL subscales.[20] Also, it is found that the primary caregivers and their partners had some anxieties related to raising a child with IEM.[34] Thus, this review concluded that the demographic characteristics

influences the HRQOL of caregivers of children and adolescents with PKU.

Our review also identified the predictors of HRQOL of parents of children and adolescents with PKU. Age of the parents, their educational level and the age of the child were considered as predictors of the physical, psychological and the social relationships dimensions of QOL respectively. Another predictor of QOL is the household income.[32] Caregiver's occupation was associated with the anxiety of parents. In addition, caregivers' occupation and depression showed a positive correlation. The employed participants had the highest scores of QOL and unemployed participants had the lowest QOL.[35] Fidika et al[31] also reported that the age of parents, age of children, social support, family stress, and parental coping as the potential predictors of PHRQOL. Yamaguchi et al[34] showed that higher levels of household income contributed to higher QOL of primary caregivers and their partners.

Having limited data on HRQOL of caregivers of children and adolescents with PKU, the authors could summarize the HRQOL in terms of overall parental HRQOL, factors influencing parental HRQOL and the predictors of parental HRQOL. The authors recommend further studies to explore more on this topic to design required interventions for the caregivers of children and adolescents with PKU.

Conclusion

Though most of the studies reported poor to moderate HRQOL in caregivers of children and adolescents with PKU, further research is needed to confirm these findings. The authors recommend interventional studies targeting the strategies to improve the HRQOL of caregivers of children and adolescents with PKU.

Author Contributions

Deepa Shaji Thomas and Divya K.Y conceptualized and designed the study and conducted the literature review. Judie Arulappan helped in resolving classification disagreements between Deepa Shaji Thomas and Divya K.Y and when differences were encountered in assessing the study quality. Deepa Shaji Thomas and Divya K.Y led the initial interpretation of the findings and drafted the manuscript. Judie Arulappan critically reviewed the manuscript for important intellectual content and revised it to ensure it met required scientific rigor. All authors approved the final manuscript and agree to be held accountable for the entire work.

Declaration of Conflicting Interests

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