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THE ROLE OF PATERNAL ENGAGEMENT IN PHENYLKETONURIA: EXPLORING PSYCHOLOGICAL OUTCOMES IN CHILDREN

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ABSTRACT **– Objective:** This study investigates the psychological outcomes of children with phenylketonuria (PKU) and their fathers, focusing on the impact of paternal engagement on child psychological well-being, quality of life, and metabolic control.

Patients And Methods: A monocentric prospective observational study was conducted on a cohort of 30 fathers and their children with PKU (aged 6–12 years) at the University Hospital of Padua (Italy). Psychological assessments included the Phenylketonuria – Quality of Life questionnaire (PKU-QOL), the Intolerance of Uncertainty Scale for children, and the Parenting Stress Index Short Form (PSI-SF), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7) for fathers. An *ad hoc* questionnaire was developed to measure paternal engagement in disease management. Correlation and regression analyses were performed to explore associations between paternal involvement, psychological functioning, and metabolic control.

Results: Fathers reported a generally high level of engagement, though some expressed feelings of guilt over the genetic transmission of PKU and perceived their role as secondary to mothers. Higher paternal engagement was associated with lower parental stress, improved child quality of life, and reduced intolerance of uncertainty. Regression analysis revealed that paternal stress and engagement significantly predicted children's quality of life, highlighting the relevance of psychological and family dynamics in disease management.

Conclusions: Encouraging paternal involvement in PKU care positively impacts both children and fathers, contributing to better psychological well-being and adherence to treatment. Healthcare professionals should recognize and support the role of fathers to optimize family-centered care in PKU management.

Keywords: Paternal engagement, PKU, Engagement, Parenting stress, Quality of life.

List of abbreviations: GAD-7: Generalized Anxiety Disorder-7; Phe: phenylalanine; PKU: Phenylketonuria; PKU-QOL: Phenylketonuria – Quality of Life; PSI-SF: Parenting Stress Index Short Form; Tyr: tyrosine.

INTRODUCTION

Phenylketonuria (PKU) is a rare inherited metabolic disorder that is caused by a deficiency in the enzyme phenylalanine hydroxylase, which is responsible for converting the amino acid phenylalanine (Phe) into tyrosine (Tyr). The absence of timely treatment leads to a neurotoxic accumulation of Phe, leading to neurological damage, including intellectual disability and epilepsy[1,2].

PKU is the most common amino acid metabolism disorder, with a global prevalence of approximately 1:23,930 live births[3]. The prevalence varies significantly worldwide, ranging from 1:4,500 in Italy to 1:100,000 in populations, such as Finnish, African and Japanese[4].

Thanks to newborn screening, nowadays, it is possible to achieve an early diagnosis and initiate treatment promptly in the first days of life, thus preventing severe brain damage[1]. There are several forms of hyperphenylalaninemia, from the most severe classical PKU (Phe levels at birth >1200 µmol/l) to the moderate form (Phe levels at birth 600–1200 µmol/l), and finally, a mild form called mild hyperphenylalaninemia (Phe levels at birth 360–600 µmol/l), which typically does not require treatment[5,6].

The mainstay treatment for PKU is generally dietary therapy, which includes controlling protein intake combined with supplementation of amino acid mixtures and vitamins[3]. However, other therapies are now available: sapropterin dihydrochloride, a synthetic form of the cofactor tetrahydrobiopterin, and pegvaliase, a recombinant phenylalanine ammonia lyase enzyme that catalyzes the conversion of Phe through an alternative enzymatic pathway. These therapies aim to allow for better control of Phe levels and greater dietary flexibility, sometimes leading to a completely unrestricted diet[7]; however, these treatments are not suitable for all patients. The management of dietary therapy is reported to have a significant impact on the daily lives of patients and their families, with difficulties arising in social situations due to the need to consume special foods or supplements for taste issues[8]. These difficulties can lead to challenges in adhering to the prescribed treatment[9].

The disease and its management may impact the well-being of patients, putting them at risk for experiencing stress, social anxiety, and depressive symptoms[10,11]. However, literature on the quality of life in PKU patients has yielded conflicting results, with some studies showing levels comparable to the general population[12].

Some studies have suggested that the diagnosis of a chronic illness, such as PKU, during childhood not only affects the well-being of the child but also impacts the entire family system[13]. Parents play a critical role in managing the disease: they are responsible for therapy, monitoring Phe levels, and planning medical visits[14]. Furthermore, some studies suggest that the daily life of parents is significantly affected by the considerable burden of the child's disease and its treatment[15]. Specifically, the most disruptive factor contributing to parental stress, as well as the patient's quality of life, is dietary restriction[16]. Adequate family involvement is essential for the well-being of children; indeed, a significant correlation between family engagement and the physical and psychological well-being of children with PKU was found[11].

However, most studies on the impact of chronic diseases on parents have focused only on mothers, who are typically the primary caregivers and at greater risk for caregiver burden[17,18]. However, the few studies on fathers highlighted that their exclusion from disease management may negatively affect both the well-being of mothers and the paternal identity, making fathers feel less effective in caring for their child and leading to frustration and a sense of helplessness regarding the disease[19].

Fathers strongly contribute to infant development and, in the last years, are spending more time with their children than in many past decades; therefore, assessing and supporting their involvement in family dynamics, particularly in illness conditions, is of primary importance[20]. In order to deeply explore the role of fathers in chronic diseases, in recent years, research has started to explore the concept of paternal engagement, which refers to the level of involvement, active participation, and commitment to managing the child's illness. Some studies have highlighted that greater paternal involvement in managing a chronic illness provides emotional and practical support, which can alleviate maternal anxiety and stress related to therapy management[21]. Furthermore, paternal engagement is associated with better psychological and behavioral outcomes in children[22,23]. One study demonstrated that young individuals with chronic conditions from families with absent fathers showed poorer treatment adherence and lower psychological adaptation and health outcomes[24]. Another study emphasized that treatment adherence decreases with lower paternal involvement[19].

Despite these findings, studies on the role of fathers in chronic diseases remain limited, particularly within PKU populations. For instance, a review by Taylor et al[25], which assessed father involvement in pediatric chronic illnesses, highlighted the need for increased research on this topic across various chronic conditions, emphasizing that paternal engagement is one of the most important challenges for future research in pediatric chronic conditions. Therefore, assessing and supporting paternal involvement in the management of PKU, which requires substantial parental oversight of therapy and biochemical values, is crucial. Therefore, this study aims to investigate the level of paternal involvement in children with PKU, focusing on its associations with the mental well-being of both fathers and children.

PATIENTS AND METHODS

Study design

This is a monocentric prospective observational study. Pediatric patients with PKU in care at the Unit of Metabolic and Hereditary Diseases at the University Hospital of Padua (Italy) and their fathers were invited to participate in the study. The inclusion criteria for patients were a PKU diagnosis confirmed through newborn screening and the patient's age between 6 and 12 years. Exclusion criteria were severe intellectual impairments preventing children from completing questionnaires, language comprehension difficulties, and having changed center of care in the previous year.

METHODS

Sociodemographic information

Sociodemographic and medical information regarding the fathers and children was collected through an *ad hoc* questionnaire specifically designed for this study, completed by the fathers. The following information was requested: the child's age and gender and the father's age, ethnicity, occupation, educational level, and marital status. Moreover, the presence of siblings with PKU and the presence of other diseases were requested.

Phe and Tyr levels

The Phe and Tyr levels of the children were obtained from their medical records. These values were measured in two different ways: analysis of blood spots sent from home by the parents or plasma levels of Phe and Tyr collected through blood draws during outpatient visits. Data from the past year were considered, and an annual mean of each patient's values was calculated.

CHILDREN

Phenylketonuria – Quality of Life

The questionnaire Phenylketonuria – Quality of Life (PKU-QOL)[26] was used to assess the children's quality of life related to their illness. This instrument was designed to evaluate the quality of life related specifically to PKU, assessing four variables of the condition: PKU symptoms, the general impact of PKU (physical, emotional, and social impact), administration of Phe-free protein supplements, and daily dietary restriction.

The PKU-QOL is available in four versions, one for each specific group: Children (age 9–11 years, 40 items), Adolescents (age 12–17 years, 58 items), Adults (65 items), and Parents (assessment of their children's and their own quality of life, 54 items). The questionnaire was primarily created in seven languages: English, French, German, Italian, Dutch, Spanish, and Turkish.

Patients or their caregivers are asked to give their agreement with the sentences on a Likert scale from 0 to 4, where higher scores indicate a greater negative impact on quality of life. A total score and one score for each module can be calculated, ranging from 0 to 100. Scores below 25 indicate little impact of PKU on patients' quality of life; scores between 25 and 50 reflect a moderate impact; scores between 50 and 75 indicate a major impact; and scores above 75 denote a severe impact[12].

Intolerance of Uncertainty Scale-12

The questionnaire Intolerance of Uncertainty Scale-12 was used to assess children's intolerance of uncertainty and the difficulty of a person in tolerating uncertain or ambiguous situations. This scale studies two main components: prospective intolerance of uncertainty and inhibitory intolerance of uncertainty. The first component relates to the need to seek information about an uncertain situation perceived as

threatening and intolerable; the second component involves an avoidance strategy that "freezes" the individual, leading to an inability to act and a tendency to procrastinate decisions[27].

The short version of the scale consists of 12 items, with responses provided on a 5-point Likert scale (from 1 = "strongly disagree" to 5 = "strongly agree"). The first seven items measure the level of prospective intolerance of uncertainty, while the last five items assess the degree of inhibitory intolerance. The sum score of the Intolerance of Uncertainty Scale (ranging from 27 to 135) and each scale's score was used in this study. Higher scores indicate higher intolerance of uncertainty.

The Italian version of the scale has been used with a youth sample in a previous study[28].

FATHERS

Engagement

An *ad hoc* questionnaire, formed of five open-ended questions, was developed to assess paternal involvement. Fathers were asked to answer each question with a short answer and subsequently to score their level of agreement with each statement on a Likert scale from 1 to 10, with lower scores indicating less agreement and higher scores indicating greater agreement. The total score is provided by summing the score of each question.

These questions were specifically designed for this study in collaboration with expert clinicians to examine in detail key aspects of fathers' engagement in managing their child's PKU. The instrument aimed to investigate five factors: control, being a reference figure, management of daily life, level of information, and perception of responsibility.

The questions included were:

- *Do you feel you have control over what happens in your child's life regarding the illness?*
- *Do you feel you are a reference figure for your child in relation to the illness?*
- *Do you feel that you actively contribute to managing your child's illness?*
- *Do you feel adequately informed about the illness?*
- *Do you feel in some way responsible for your child's illness?*

Parenting Stress Index Short Form

The Parenting Stress Index Short Form (PSI-SF)[29] was used to assess the parenting stress of the fathers. The PSI-SF is a self-report questionnaire consisting of 36 items designed to measure the level of stress in the parent-child relationship.

The PSI-SF is divided into three subscales: "Parental Stress", which evaluates the degree of discomfort that parents may feel in fulfilling their parenting role and the manner they approach their parenting responsibilities; "Dysfunctional Parent-Child Interaction", which is based on the expectations parents have of their child and the resulting lack of gratification within the relationship; and "Difficult Child", which is based on the child's temperament or behavioral characteristics that may cause difficulties and tension in managing the child, with higher scores in this subscale may indicate behavioral issues in the child. In addition to these subscales, the questionnaire includes control items that assess the parent's desire to present an idealized image of themselves and their relationship with the child, forming the Defensive Response scale.

The PSI-SF uses a 5-point Likert scale, with the total score obtained by summing the scores across all subscales. A higher total score indicates greater parental stress, more dysfunctional interactions, and greater difficulty in managing the child. As a clinical distress cut-off, we used the 85th percentile based on research norms[30].

Patient Health Questionnaire-9

The Patient Health Questionnaire-9, a nine-item self-report scale, was used to assess depressive symptoms in fathers[31]. The items assess potential depressive manifestations, such as difficulty falling asleep, lack of general interest, fatigue, low mood, reduced appetite, low self-esteem, slowed movements, and thoughts of death. After the nine items, there is a tenth item, which is excluded from the total score,

that specifically determines the level of impairment that depressive symptoms may cause in daily activities. Each item is scored on a Likert scale ranging from 0 to 3. Higher scores are related to higher levels of depressive symptoms; the scores are categorized as follows: 0–4 indicates the absence of symptoms, 5–9 represents subthreshold depression, 10–14 corresponds to mild major depression, 15–19 indicates moderate major depression and a score of 20 or higher denotes severe major depression. These categories help to assess the severity of depressive symptoms and may guide treatment decisions.

Generalized Anxiety Disorder-7

The Generalized Anxiety Disorder-7 (GAD-7), a brief self-report questionnaire, was used to assess anxiety symptoms in fathers[32]. It is composed of seven items, rated on a Likert scale from 0 to 3, and it was designed to identify generalized anxiety disorder and other related conditions. It is one of the few measures specifically aligned with DSM criteria. Higher scores indicate a greater presence of anxiety symptoms (cut off ≥15).

Study procedures

Participants were involved in the study both in person, during outpatient visits, and via e-mail. Families were subsequently re-contacted by e-mail for study participation if they had not responded to the initial e-mail. Consent for the participation of children with PKU was provided in writing by both parents, while fathers individually gave their consent to take part in the study.

Participants completed the questionnaires either on paper or through the online link provided to them.

All participants gave written informed consent before participation. The study was approved by the Local Ethics Committee (Ethics Committee Approval No. 6178AO25, University Hospital of Padua, Italy).

The principles of good clinical practice were adhered to throughout the study in accordance with the Declaration of Helsinki (as amended) and the International Conference on Harmonization/good clinical practice guidelines.

Statistical analysis

In the first section, the mean scores of the PKU-QOL and the Intolerance of Uncertainty Scale for children, as well as the PSI-SF, GAD-7, and Patient Health Questionnaire-9 scores for fathers, were calculated and presented in a table to assess the psychological well-being of the PKU population.

In the second section, paternal engagement scores are reported to highlight the quantitative outcomes of the questionnaire. Additionally, a qualitative analysis of fathers' responses to each open-ended question is provided.

In the third section, correlations between paternal engagement scores (both total scores and individual item scores) and the total scores of the patient and father questionnaires were assessed using Pearson's r correlation coefficient.

In the final section, a correlation model was developed to investigate factors that may predict children's quality of life. Potential predictors were identified by estimating correlation coefficients between the medical dimensions and psychological aspects of fathers and the total PKU-QOL score for patients.

RESULTS

Study Cohort

A total of 48 eligible children with PKU and their fathers were identified, and responses were received from 30 families (response rate = 62.5%). Ultimately, 28 children aged 6–12 years (mean = 9.7, SD = 2.1) were enrolled in the study, while the sample of fathers consisted of 30 participants aged between 32 and 72 years (mean = 45.5, SD = 7.8). Two children were excluded from the study due to lack of parental consent.

Within the patient sample, 17 were male (57%) and 13 were female (43%). The mean blood Phe level over the past year was 259.61 µmol/L (SD = 80.38), and the mean Tyr level was 74.80 µmol/L (SD = 18.62). 86% of the sample achieved adequate mean Phe levels, according to the European guidelines for children under 12 years[3], over the past year, while 14% exceeded this range. Of the children, 43% followed dietary therapy, while 57% did not require dietary treatment.

The sample of fathers was predominantly Caucasian (86.7%). Most fathers had completed high school education (56.7%), with the most common occupation being manual labor (23.3%), followed by administrative work (16.6%) and business ownership (13.3%). Most fathers (87%) reported being married, while 10% were cohabiting, and 3% were divorced. The majority of families had two or more children (86.7%), and in 13.3% of cases, there was another sibling with PKU.

Mean values of children's quality of life and intolerance of uncertainty

The mean scores of the psychological variables in children are reported in Table 1, generally within the normal range, with some exceptions. The average level of total quality of life indicates a perception of moderate impact. Specifically, on the scales "symptoms" and "daily dietary restrictions", the impact on quality of life is little, while on the scales "general impact" and "protein supplements" the average value indicates a moderate impact on quality of life. Total intolerance of uncertainty, as well as the "prospective" and "inhibitory" scales, fall within the normal range.

Table 1. Mean levels of children's quality of life and intolerance of uncertainty.

Psychological dimension	Scale	Mean	Standard deviation
Quality of life	PKU-QOL "symptoms"	22.94	15.56
	PKU-QOL "general impact"	30.09	10.15
	PKU-QOL "protein supplements"	28.68	16.05
	PKU-QOL "daily dietary restrictions"	11.61	22.02
	PKU-QOL "total"	26.26	11.60
Intolerance of uncertainty	IUS "prospective"	19.28	6.61
	IUS "inhibitory"	10.92	5.20
	IUS "total"	30.21	10.75

Mean values of fathers' parenting stress, anxiety symptoms, and depressive symptoms

The psychological variables of fathers showed mean scores within the normal range (Table 2).

Table 2. Mean levels of fathers' parental stress, anxiety and depression symptoms.

Psychological dimension	Scale	Mean	Standard deviation
Parental stress	PSI "difficult child"	22.63	7.62
	PSI "parent-child dysfunctional interaction"	19.33	7.09
	PSI "parental distress"	20.43	8.32
	PSI "total"	62.40	20.65
Anxiety	GAD-7 "total"	4.66	4.86
Depression	PHQ-9 "total"	3.70	3.67

Total parental stress, as well as the "difficult child," "parent–child dysfunctional interaction," and "parental distress" scales, show results fully within the normal range. The scores on the Defensive Response scale were within normal limits for all participants.

Similarly, the total mean scores on the anxiety and depression symptom scales fall within the normal range.

Paternal engagement

The data emerging from the quantitative responses are generally adequate in the total score and in almost all domains. Overall, a good level of perceived engagement is observed in the engagement domains "control", "reference figure", "disease management" and "information", while lower involvement is perceived by fathers in engagement responsibilities.

The mean score (score range 0–10) for each domain, total paternal engagement scores, and the number of responses in the low (scores 0–5) or high (scores 6–10) range of response are reported in Table 3.

Table 3. Mean levels and range of response of paternal engagement.

Scale	Mean (SD)	Range of response
Engagement "control"	7.37 (2.76)	0–5: *n*=7/30 (23.3%) 6–10: *n*=23/30 (76.7%)
Engagement "reference figure"	7.77 (2.38)	0–5: *n*=5/30 (16.7%) 6–10: *n*=25/30 (83.3%)
Engagement "disease management"	7.53 (2.40)	0–5: *n*=7/30 (23.3%) 6–10: *n*=23/30 (76.7%)
Engagement "information"	7.70 (2.00)	0–5: *n*=5/30 (16.7%) 6–10: *n*=25/30 (83.3%)
Engagement "responsibility"	4.37 (3.51)	0–5: *n*=20/30 (66.7%) 6–10: *n*=10/30 (33.3%)
Engagement "total"	34,73 (8,59)	0–25: *n*=5/30 (16.7%) 26–30: *n*=25/30 (83.3%)

The results of a more in-depth analysis of each question addressed to fathers regarding their perceived engagement in child management is presented below.

Do you feel you have control over what happens in your child's life regarding the illness?

The responses highlight that the majority of fathers (83.3%) report feeling they have adequate control over the disease, despite some emphasizing the effort required from parents to enable their child to lead a "normal life". However, some fathers (16.7%) report not feeling they have full or partial control over their child's PKU; in particular, concerns arise regarding the management of administrative issues related to the disease and the presence of other medical conditions in the child. Additionally, one parent explained relying on the sense of responsibility of their preadolescent daughter due to difficulties in managing the disease.

Do you feel you are a reference figure for your child in relation to the illness?

A generally positive perception emerged among the majority of fathers (73.3%), who perceive themselves as a primary reference figure for their child, often reporting that they share this role with the mother. Conversely, a notable proportion of fathers (26.7%) do not consider themselves a central figure in the management of the disease; some of these fathers identify the mother as the principal caregiver, with themselves assuming a more peripheral role. Other fathers indicate that their contribution is

primarily limited to providing emotional support regarding the disease, with less involvement in the practical management of the condition.

Do you feel that you actively contribute to managing your child's illness?

A large proportion of fathers (83.3%) report feeling that they actively contribute to the management of their child's disease, while a smaller group (16.7%) indicates that they contribute little or less than they would like. Some of these fathers further stated that it is primarily the mother who plays the dominant role in the management of the PKU.

Do you feel adequately informed about the illness?

In the majority of cases (83.3%), fathers reported feeling "adequately informed," although some expressed feeling poorly informed and uncertain about the disease's progression and future management. The remaining 16.7% indicated that they do not feel sufficiently informed about the characteristics of their child's condition. One father reported coping with this lack of information by independently seeking to supplement his knowledge through personal research despite having limited trust in self-directed learning in this area.

Do you feel in some way responsible for your child's illness?

The final question addressed the sense of responsibility that a father may feel, and nearly all fathers responded by considering responsibility in relation to the transmission of the disease, particularly its genetic component.

Regarding the responses, 70% of fathers indicated that they do not feel responsible for the transmission of the disease, while the remaining 30% expressed feelings of guilt for having genetically transmitted the condition to their children. Some of these fathers specified that they feel responsible despite acknowledging that it is not their fault and recognizing the impossibility of identifying the risk of transmission beforehand. One father, however, stated that he feels responsible for managing the disease but not for the transmission of PKU.

Correlations

Several correlations were observed between paternal engagement and both fathers' and children's psychological variables (Table 4).

Table 4. Correlation between paternal engagement and biochemical levels and fathers' and children's psychological functioning.

	Engagement TOT	Engagement "control"	Engagement "reference figure"	Engagement "disease management"	Engagement "information"	Engagement "responsibility"
Mean Phe	*r*=-0.222 *p*=0.248	*r*=-0.383* *p*=0.040	*r*=-0.353 *p*=0.060	*r*=-0.119 *p*=0.537	*r*=-0.159 *p*=0.410	*r*=0.086 *p*=0.658
IUS	*r*=-0.461* *p*=0.014	*r*=-0.223 *p*=0.253	*r*=-0.456* *p*=0.015	*r*=-0.280 *p*=0.149	*r*=-0.377* *p*=0.048	*r*=-0.172 *p*=0.382
PKU-QOL	*r*=-0.479* *p*=0.010	*r*=-0.417* *p*=0.027	*r*=-0.493* *p*=0.008	*r*=-0.429* *p*=0.023	*r*=-0.389* *p*=0.041	*r*=-0.128 *p*=0.517
PSI-SF	*r*=-0.490* *p*=0.006	*r*=-0.440* *p*=0.015	*r*=-0.470* *p*=0.009	*r*=-0.505* *p*=0.004	*r*=-0.317 *p*=0.088	*r*=-0.016 *p*=0.934
GAD	*r*=-0.328 *p*=0.077	*r*=-0.355 *p*=0.054	*r*=-0.357 *p*=0.053	*r*=-0.431* *p*=0.018	*r*=-0.051 *p*=0.791	*r*=0.108 *p*=0.570
PHQ	*r*=-0.303 *p*=0.104	*r*=-0.212 *p*=0.260	*r*=-0.384* *p*=0.036	*r*=-0.566* *p*=0.001	*r*=-0.005 *p*=0.979	*r*=0.166 *p*=0.381

*p-value < 0.05

Total paternal engagement was found to be moderately negatively correlated with parenting stress, child quality of life, and intolerance of uncertainty.

Specifically, moderate negative correlations were also observed between the engagement in control and both the parenting stress variable and children's quality of life. Engagement with the reference figure was negatively correlated with both the child's quality of life and intolerance of uncertainty, as well as with paternal stress.

Engagement in disease management showed moderate correlations with paternal depression symptoms and parenting stress. The final significant correlations were found between the engagement in information and both child quality of life and intolerance of uncertainty.

Linear regression

The linear regression model was used to test if predictors (mean Phe levels, total parenting stress score, and paternal engagement total score) could significantly predict the child's quality of life.

The results show that the independent variables significantly predict the child's total PKU-QOL score, F (3, 25) = 9.008, $p<0.001$, indicating that the model is significant. Furthermore, the Adjusted $R^2=0.480$ suggests that the model explains 48.0% of the variance in the dependent variable. Specifically, higher levels of parental stress are associated with a greater negative impact on the child's quality of life, while mean Phe levels and paternal engagement do not emerge as significant predictors. The main results of the regression model are reported in Table 5.

Table 5. Linear regression for children quality of life.

	PKU-QOL total			
	B	**Std. β**	**t**	***p*-value**
Intercept	17.227		1.424	0.168
Mean Phe	0.028	0.194	1.314	0.202
PSI total	0.261	0.463	2.877	0.009*
Engagement total	-0.418	-0.310	-1.976	0.060
Model fit	F (3, 25) = 9.008; $p<0.001$			
Adjusted R^2	0.480			

*p-value < 0.05

DISCUSSION

PKU is a condition that significantly impacts patients and their families, not only through the medical challenges of managing a strict low-Phe diet but also through the psychological burden it imposes, affecting emotional well-being, social dynamics, and overall quality of life. The management of PKU requires strict and continuous monitoring, and during childhood, the burden of managing the condition primarily falls on the caregivers. However, despite previous studies in other chronic illnesses highlighting the importance of both parents' involvement in a child's psychological well-being[22], the engagement of fathers in the care of children with PKU has been overlooked.

This study aims to examine the psychological functioning of children with PKU and their fathers, with a specific focus on the paternal perspective on their engagement in disease management.

The first objective was to assess the impact of the disease on the psychological well-being of children and fathers. The results confirmed, in line with the study of MacDonald et al[33], that PKU has a moderate impact on the daily life of children with this condition. This suggests that children with PKU can lead a largely fulfilling life, maintaining adequate levels of quality of life[34].

Regarding fathers, the literature presents conflicting evidence, partly due to the limited research focused on paternal well-being in caregiving. The findings of this study did not reveal any values outside the normative range for parenting stress, anxiety, or depression symptoms. These results are consistent with those of Fidika et al[10], which found that parents of children with PKU do not experience higher stress due to the condition; however, it contrasts with other studies that suggest a

psychological impairment resulting from the challenges of managing PKU[11,35]. Our results can be attributed to the medical and psychological support provided by the hospital's metabolic team, which includes various healthcare professionals, including psychologists. Addressing multiple aspects of the patients' and their families' needs can facilitate better adaptation to the condition and reduce stress, anxiety and impact on quality of life.

The second objective of this study was to analyze paternal engagement both quantitatively and qualitatively in order to explore the paternal perspective on their involvement in disease management.

From a quantitative perspective, fathers report relatively good levels of engagement across almost all aspects of engagement, except for the "responsibility" component; in this section, fathers were asked whether they felt responsible for their child's illness, and a large part of them stated that they feel little responsibility for their child's PKU. The quantitative results on paternal engagement seem to show that fathers perceived themselves as adequately engaged and involved in PKU management; these findings are in contrast with a study on diabetes, which highlighted fathers' tendency to assume less responsibility than mothers[23]. Despite that, a smaller but considerable group of fathers (16.7–33.3%) reported difficulties in different aspects of paternal engagement.

Qualitative analysis of open answers helped with a deeper investigation of fathers' points of view on their engagement. Coherent with previous quantitative analysis, a small number highlighted a high burden and difficulties in daily management that seemed to undermine their sense of involvement. In particular, almost a quarter of fathers (20–23%) expressed insecurity about the future progression of the disease, fear of losing control over managing disease-related tasks, and uselessness in practical and daily support; also, 10% expressed feeling that their parental role was secondary to that of the mother in disease management, with mothers taking on a more prominent role. In the responsibility component, fathers focused mainly on their responsibility regarding their guilt in the genetic transmission of the disease rather than their responsibility in managing their son's PKU: almost a third of them (30%) reported that they felt highly responsible for their child's PKU, and qualitative analysis permitted to deepen that this perception is due to the genetic transmission of the illness.

These results show that, despite the larger part of fathers reporting adequate levels of engagement, there is a smaller but considerable number of fathers who perceive themselves as unhelpful in daily support and that their role as parents is secondary to that of the mother in disease management. Moreover, they reported fear of losing control over disease-related tasks and guilt for the transmission of PKU. The responses are partially consistent with studies on other chronic illnesses that reported that fathers often perceive themselves to be less involved, more insecure and less satisfied due to difficulties in balancing illness management with work and personal responsibilities[21,35].

These findings highlight the need to give attention and further improve both practical and psychological support from the hospital team, with particular attention to involving both parents. As suggested by the studies of Phares et al[22] and Wysocki and Gavin[19], such involvement has positive consequences not only for behavioral factors, such as treatment adherence but also for a child's psychological well-being.

The third objective aims to analyze the correlations between paternal engagement and metabolic control, as well as the psychological variables of both children and fathers, in order to deepen the understanding of the relationship between these dimensions.

The results reveal a negative correlation between Phe level and the "control" component of paternal engagement perceived in relation to the child's illness. This suggests that the two components may influence each other, with a greater sense of fathers' control being associated with lower Phe levels. Since blood Phe levels reflect treatment adherence, it can be hypothesized that greater paternal involvement in managing the child's PKU may promote better therapy adherence. The findings of Wysocki and Gavin[19] support this result, highlighting that increased paternal involvement was associated with better maintenance of treatment adherence and a more favorable quality of life.

Moreover, it has been highlighted that higher levels of paternal involvement are associated with lower levels of parental stress, as well as fewer anxiety and depressive symptoms in fathers. These findings suggest that greater involvement of the father in managing the child and their illness is linked to better mental well-being and lower stress levels in the father. In particular, the father's sense of involvement in managing the child's disease appears to be an important factor, as it is related to all variables of the father's psychological well-being. Despite the literature on the relationship between these factors is largely limited, it appears that adequate paternal involvement in caring for the child's illness may serve as a protective factor against experiencing psychological distress in fathers themselves.

Moreover, higher levels of paternal engagement have been found to be associated with lower levels of intolerance to uncertainty in children and a reduced impact of the illness on their quality of life. These findings suggest that fostering strong paternal involvement can enhance the children's quality of life while also increasing their confidence in managing the uncertainty they may experience due to their condition. These results are consistent with studies that confirm that greater paternal involvement, alongside maternal involvement, promotes stronger family relationships, reduces perceived stress in the couple, and improves the quality of life for children with chronic illnesses[23,25].

The final goal of this study was to analyze the medical and psychological factors capable of predicting the child's quality of life. We expected, consistent with previous studies, that the medical and psychological factors of both the child and the father[11,33] significantly influence the quality of life of children with PKU. The results highlight that average Phe concentration, parental stress, and paternal involvement together are significant predictors of the child's quality of life.

A higher level of blood Phe is associated with a greater impact of PKU on the patient's quality of life, as it may lead to a sense of failure due to non-adherence to treatment and foster negative thoughts about the disease, preventing the child from feeling equal to their peers. Although the medical component has an important impact, parental-related variables are even more determinant: parental stress and paternal involvement emerge as the most influential predictors of the child's quality of life.

Indeed, higher levels of paternal involvement and lower father's parenting stress are predictive of a better child's quality of life; as a matter of fact, stress and engagement are closely interrelated and together influence the child's psychological well-being. An absent father may struggle to manage the disease effectively or to adopt effective coping strategies to address the challenges associated with the condition[36]. A father who is adequately involved in taking care of his child with PKU and perceives less stress in managing the condition seems to be able to ensure a higher level of psychological well-being for the child, potentially mitigating the negative impact of the disease.

Based on these results, and consistent with previous studies[23], the importance of further exploring the father's role in the family balance of families with children affected by chronic conditions becomes crucial. Fathers prove to be fundamental resources not only for disease management but also for reducing the impact that a chronic condition such as PKU may have on the child's quality of life.

Limitations

In our study, we investigated paternal engagement among fathers of children with various forms of PKU. Future research could explore potential differences across PKU subtypes, considering that different forms of the condition may necessitate distinct therapeutic approaches, which, in turn, may influence coping mechanisms and psychological challenges faced by parents.

Additionally, an *ad hoc* questionnaire was employed to assess paternal engagement. While this choice was driven by the need for a brief condition-specific instrument suitable for fathers of children with PKU, the use of a non-standardized measure poses limitations. Specifically, it complicates comparisons with normative populations and may reduce the generalizability of the findings.

CONCLUSIONS

This study demonstrated that fathers of children with PKU perceive themselves as not experiencing significant psychological distress and feel generally adequately involved in the management of the disease. However, some fathers reported feeling responsible for transmitting the genetic mutation causing PKU to their child, feeling less helpful in managing the disease-related issues, and perceiving their parental role as secondary to that of the mothers. Moreover, it was shown that greater paternal involvement may contribute to better metabolic control, improved quality of life, and reduced intolerance to uncertainty in the children, as well as being a protective factor for the fathers' own mental health.

These findings suggest that increasing paternal involvement in the management of pediatric PKU, given the challenges and burden it places on the entire family, may promote the child's well-being, both in terms of treatment adherence and the child's psychological health.

Clinicians should, therefore, ensure greater attention to the paternal role in disease management, from the time of diagnosis through to daily PKU treatment.

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Study conception and design: G.G, A.G.; collection and interpretation of data: G.G, A.G.; statistical analysis: G.G.; manuscript drafting: G.G, A.G.; manuscript editing: G.G, A.G.; approval to submit: G.G, A.G.

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The authors declare that they have no conflict of interest to disclose.

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