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Dietary Adherence in Children with Amino Acid Metabolism Disorders and its Impact on Caregivers' Quality of Life

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ABSTRACT

This study explored the relationship among socio-demographic factors, patients' dietary adherence, and the Quality of Life (QoL) experienced by their caregivers. A cross-sectional study was carried out, involving 66 caregivers of pediatric patients in Malaysia diagnosed Amino Acid Metabolism Disorders (AAMDs). Dietary adherence was assessed using a modified version of the Malaysia Medication Adherence Assessment Tool (MyMAAT-12), and the caregiver's QoL was evaluated using the 36-Item Short Form Survey (SF 36) questionnaire. Majority of the patients were Malay (75.76%), and female (59.1%). Statistical analysis found that caregivers with a higher education level were associated with a higher dietary adherence (rs=0.382, p=0.002) and better mental health (rs=0.281, p=0.022). The age of patients had negative significant correlation with the physical function and general health (rs=0.287, p=0.019) of their caregivers. Besides that, dietary adherence was negatively correlated with social functioning (p=0.010), role limited due to physical health (p=0.018), role limited due to emotional problems (p=0.022), vitality (p=0.021), mental health (p=0.014) and pain (p=0.011). Conclusion: Dietary adherence had a significant impact on the QoL for caregivers of patients with amino acid metabolism disorders. Therefore, it is crucial to explore appropriate treatment strategies and provide support to enhance patients' adherence to their dietary requirements, simultaneously improving the caregivers' QoL.

Keywords: amino acid metabolism, caregivers, inborn errors, mental health, quality of life

INTRODUCTION

Amino Acid Metabolism Disorders (AAMDs) include a spectrum of conditions, such as Organic Acidaemias (OA) including Methylmalonic (MMA), Propionic (PA), Isovaleric Acidaemias (IVA), Glutaric Aciduria (GAT1), and others; aminoacidopathies such as Maple Syrup Urine Disease (MSUD), Phenylketonuria (PKU), Homocystinuria (HCS), and Tyrosinemia (TYS) type 1; as well as Urea Cycle Disorders (UCD), which are rare Inherited Metabolic Disorders (IMD) that occur due to a defect in amino acid catabolism (Saudubray *et al.* 2013; Ezgu 2016). Most of these conditions are inherited autosomal recessive traits, with the exception of Ornithine Transcarbamylase (OTC) deficiency, which follows an x-linked genetic disorder (De Meirleir & Rodan 2017). These disorders lead in the accumulation of toxic intermediary metabolites and deficiencies in various essential metabolites (Boyer *et al.* 2015).

Generally, individuals with amino acid metabolism disorders require an individualised dietary treatment that includes stringent limitations on natural protein intake and supplementation

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with synthetic amino acid formulas. The main goal of dietary therapy is to reduce the accumulation of toxic substances, while ensuring an adequate supply of energy, protein, vitamins, and minerals for optimal growth and development (Boyer *et al.* 2015; Dixon *et al.* 2014).

However, the strict adherence of lifelong dietary and medical treatment for pediatric patients with AAMDs imposes a considerable burden for caregivers, requiring exclusive dedication that could also potentially compromise their well-being (Lim *et al.* 2022; Zeltner *et al.* 2019; Martianto *et al.* 2011). Research demonstrates that adhering to these specialized diets can contribute to higher perceived stress and a lower Quality of Life (QoL) among the caregivers (Fabre *et al.* 2013). Parents reported notable burdens and challenges, including in the preparation of meals with specific weighing requirements, time constraints, and restrictions on social life (Bilginsoy *et al.* 2005; Fabre *et al.* 2013). These complications have been linked to increased mental, emotional, and interpersonal stress among caregivers (Yamaguchi *et al.* 2018). In fact, several studies have indicated that dietary management is the leading cause of caregivers' poor QoL (Rohde *et al.* 2015; Ford *et al.* 2018). Other relevant factors associated with caregivers' QoLs (Fidika *et al.* 2013) include the child's age, household income, educational level (Tejada-Ortigosa *et al.* 2019), and parental stress (Morawska *et al.* 2020) .

Specifically, the decline in caregivers' QoL is primarily linked to dietary supervision, particularly when caring for patients with restrictive diets due to amino acid metabolism disorders (Carpenter *et al.* 2018). However, to the best of the author's knowledge, there is a lack of research investigating the relationship between dietary adherence and the QoL of caregivers for patients with disorders of amino acid metabolism in Malaysia. As such, this present study aimed to address this literature gap by examining the relationships between socio-demographic factors, dietary adherence of pediatric patients with these disorders, and the QoL of their caregivers in the Malaysian context.

METHODS

Design, location, and time

This study employed a cross-sectional design to examine the relationship between socio-demographic factors, the dietary adherence of pediatric patients with AAMDs, and the QoL of their caregivers. A total of 66 eligible caregivers of affected patients participated in the study, which was conducted between October and December 2020.

This study received approval and registration from both the National Medical Research Register (NMRR-20-138-52694) and the Research Ethics Committee UKM (JEPUKM-615 2021-765). Informed consent was obtained from the parents or legal guardians of participating patients, as well as from caregivers.

Sampling

Purposive sampling was used, for which the inclusion criteria were Malaysian citizen, patients aged under 18 years with disorders of amino acid metabolism their caregivers aged above 18 years who were receving treatment at the Genetic Clinic in Hospital Kuala Lumpur, the national referral centre for the treatment of patients with genetic diseases.

Using a combined sampling strategy, all eligible caregivers of patients with AAMDs attending the Genetic Clinic at Hospital Kuala Lumpur during the period October-December 2020 were invited to participate. This approach was necessitated by the limitations in readily available data regarding the precise population size of AAMD patients in Malaysia, which estimated to range from 74 to over 100 patients (Shafie *et al.* 2020).

Study measurement. Data collection included questionnaires evaluating participants' socio-demographic details, dietary adherence, and the caregivers' QoL. The questionnaires underwent a meticulous back-translation process to ensure their cultural and linguistic equivalence. Initially translated from English to Malay by two experienced bilingual researchers, the questionnaires were then subsequently retranslated back into English. These translated versions were presented at a research meeting to identify and address any potential ambiguities or discrepancies in wording, sentence structure, and intended meaning. Following reviews and adjustments, as well as unanimous consensus by all research team members, the socio-demographic questionnaire were finalized. It comprehensively assessed subject-specific information, such

as gender, age, ethnicity, education level, occupational status, marital status, parental consanguinity, monthly household income, and other pertinent details. Dietary adherence was assessed using the adapted Malaysia Diet Adherence Assessment Tool (MyDAAT-12). This tool, derived from the MyMAAT-12, was constructed by the Faculty of Pharmacy UKM and the Ministry of Health Malaysia (Hatah *et al.* 2020). My DAAT-12 scores reflect the likelihood of patients adhering to their prescribed diets, with higher scores indicating greater adherence and vice versa. The tool utilizes a 5-point Likert scale (1=Strongly disagree; 2=Disagree; 3=Meutral; 4=Agree; 5=Strongly agree). A total score of 54 (90%) and above indicated good adherence, reflecting its clinical importance of strict adherence due to the nature of the disorder. Scores below 54 were classified as poor adherence. The modified questionnaire exhibited robust internal consistency reliability, with a Cronbach's alpha of 0.826.

The caregivers' QoL was assessed using the widely utilized 36-Item Short Form Survey (SF-36) questionnaire. The questionnaire is a preferred measure for evaluating Health Related Quality of Life (HrQoL) among IEM's patients (Pascoal *et al.* 2018). It includes eight domains: physical functioning, physical role, pain, general health, vitality, social function, emotional role, and mental health. Higher scores on each domain indicate netter QoL.

Data collection

Following the provision of a detailed information sheet outlining the study's objectives, benefits, risks, and data confidentiality measures, participants provided informed consent and proceeded to complete self-administered questionnaires. The questionnaires, requiring an estimated 30–60 minutes to complete, were designed to collect primary data on participants' socio-demographics, dietary adherence, and quality of life.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., 2015). Descriptive statistics were employed to characterize the socio-demographic profiles of both patients and caregivers. Normally distributed continuous variables were presented as mean and standard deviation, while skewed data was reported as median and interquartile range. Categorical variables were summarized by frequency (n) and percentage (%). Spearman's rank correlation coefficient was used to determine the potential associations between socio-demographic variables, dietary adherence, and the QoL of the caregivers. Statistical significance was established if $p<0.05$.

RESULTS AND DISCUSSION

The study included 66 caregivers, categorized based on the underlying disorders of the patients they cared for. Among these, 36.4% (n=24) were caregivers of patients with OA, including Propionic Acidemia (PA; n=9), Glucose Transporter Type 1 deficiency (GLUT1; n=7), Methylmalonic Acidemia (MMA; n=4), Isovaleric Acidemia (IVA; n=2), and Hydroxymethylglutaryl-CoA (HMG-CoA) lyase deficiency (n=2). The remaining participants cared for patients with either aminoacidopathies (37.9%, n=25) – encompassing Maple Syrup Urine Disease (MSUD; n = 18), Phenylketonuria (PKU; n=3), Tyrosinemia Type 1 (TYS; n=3), and Homocystinuria (HCS; n=1) – or Urea Cycle Disorders (UCD) (25.8%; n=17). The mean ages of patients with OA, aminoacidopathies, and UCD were 6.42±4.75, 9.46±4.41 and 8.38±4.96 years, respectively. An analysis of patient ethnicity revealed a majority of Malay individuals across all groups: 58.3% (OA), 76% (aminoacidopathies), and 100% (UCD). This finding aligns with prior research conducted in the Malaysian context (Pei *et al.* 2014; Thong & Yunus 2008). However, further research is warranted to investigate the potential reasons for this observed higher prevalence of amino acid metabolism disorders among the Malay population. Regarding education, the majority of OA patients (62.5%) did not attend school, while 16.7% received special education.

Parental consanguinity rates varied across the groups, observed in approximately one-fifth of OA (20.8%) and UCD (23.5%) cases, and exceeding one-third (32.0%) in MSUD cases (Table 1). There findings align with previous studies reporting a higher prevalence of parental consanguinity among patients with IMDs (Kong *et al.* 2014; Thong & Yunus 2008; Najafi *et al.* 2016). A prior cross-sectional study among Malaysians

with IMDs found a parental consanguinity rate of 40.9% in MSUD patients (Kong & Roslee 2015). Consistent with these findings, the present study observed a relatively high prevalence of parental consanguinity in patients with AAMDs, with about one-third of taminoacidopathies and one-fifth of OA and UCD patients exhibiting this characteristic. An Iranian study reported a prevalence of parental consanguinity at 84.7% among OA patients (Najafi *et al.* 2016). Notably, in this study, the majority of the caregivers were mothers, a trend consistent with (Khangura *et al.* 2016).

It was found that most caregivers in the most possessed a secondary school education (54.55%), followed by individuals who graduated from college or university (36.36%). Majority of the caregivers were married (OA: 83.3%, aminoacidopathies: 88.0%, UCD: 94.1%). Regarding employment, most OA caregivers were full-time housewives (66.7%), followed by working people (29.2%), and retirees (4.2%). In contrast, a higher portion of caregivers in the aminoacidopathies (64.0%) and UCD (52.9%) cohorts were employed (Table 2). In fact, more than half of the caregivers for patients with aminoacidopathies and UCD in this study were still working, contrasting with findings from studies in Spain and the UK. Tejada-Ortigosa *et al.* (2019) reported that 77.4% of the caregivers in Spain needed to reduce their working hours or quit their jobs to care for their children with IMD.

Table 1. Sociodemographic profile of the patients with disorders of amino acid metabolism (n=66)

Variables	OA (n=24)	Aminoacidopathy (n=25)	UCD (n=17)
Age of patients, years, mean±SD	6.42 (4.75)	9.46 (4.41)	8.38 (4.96)
Gender, n (%)			
Male	13 (54.2)	11 (44.0)	3 (17.6)
Female	11 (45.8)	14 (56.0)	14 (82.4)
Ethnicity, n (%)			
Malay	14 (58.3)	19 (76.0)	17 (100)
Chinese	6 (25.0)	3 (12.0)	-
Indian	1 (4.2)	1 (4.0)	-
Others	3 (12.5)	2 (8.0)	-
Stage of onset, n (%)			
Early onset (≤28 days)	11 (45.8)	13 (52.0)	7 (41.2)
Late onset (>28 days)	13 (54.2)	12 (48.0)	10 (58.8)
Education level for patients, n (%)			
Preschool	-	2 (8.0)	1 (5.9)
Kindergarten	-	4 (16.0)	1 (5.9)
Primary school	4 (16.7)	7 (28.0)	2 (11.8)
Secondary school	1 (4.2)	3 (12.0)	2 (11.8)
Special education school	4 (16.7)	5 (20.0)	5 (29.4)
Informal education	1 (4.2)	-	-
Not schooling	14 (58.3)	4 (16.0)	6 (35.3)
Type of treatment			
Diet and medical treatment	24 (100)	25(100)	17(100)
Family history, n (%)			
Yes	1 (4.2)	3 (12.0)	2 (11.8)
No	20 (83.3)	18 (72.0)	14 (82.4)
Does not know	3 (12.5)	4 (16.0)	1 (5.9)
Parental consanguinity, n (%)			
Yes	5 (20.8)	8 (32.0)	4 (23.5)
No	16 (66.7)	16 (64.0)	13 (76.5)
Does not know	3 (12.5)	1 (4.0)	-

OA: Organic Acidaemias; SD: Standard Deviation; UCD: Urea Cycle Disorders

More than half of the OA patients in this study did not attend school or received special education, aligning with findings from a cross-sectional study by Najafi *et al.* (2016), where only 9.7% of OA patients were enrolled in mainstream education. This pattern may be attributed to the frequent association of OA with both convulsions and developmental disorders (Thomas *et al.* 2017). The substantial proportion of OA patients not attending school potentially contributes to the observation that most OA caregivers were full-time housewives (66.7%), facilitating childcare at home. This aligns with reports indicating that one-third of OA patients may experience developmental delays, potentially requiring additional caregiving support (Najafi *et al.* 2016).

Among the participants, 40 patients (60.61%) displayed good adherence to their prescribed diet (Table 3). This adherence was primarily motivated by the patients' desire to prevent neurological problems and metabolic crises, while balancing the need for sufficientenergy and protein intake. These findings align with previous study by Bilginsoy *et al.* (2005), who reported that 72% of the PKU families in Utah maintained adequate energy consumption, indicative of successful dietary management. A UK cross-sectional study involving 106 PKU patients reported only 8% with poorly controlled blood phenylalanine status, indicating that most of the patients had good adherence to a low-natural-protein diet

Table 2. Sociodemographic profile of the caregivers of the patients with disorders of amino acid metabolism (n=66)

Variables	OA (n=24)	Aminoacidopathy (n=25)	UCD (n=17)
Age of caregivers, years (Mean±SD)	37.08±11.83	39.32±8.31	40.00±7.17
Relationship, n (%)			
Mother	21 (87.5)	20 (80.0)	12 (70.6)
Father	1 (4.2)	4 (16.0)	5 (29.4)
Grandparents	1 (4.2)	-	-
Others	1 (4.2)	1 (4.0)	-
Ethnicity, n (%)			
Malay	14 (58.3)	19 (76.0)	17 (100)
Chinese	6 (25.0)	3 (12.0)	-
Indian	1 (4.2)	1 (4.0)	-
Others	3 (12.5)	2 (8.0)	-
Education level for caregivers, n (%)			
Does not go to school	1 (4.2)	1 (4.0)	-
Primary school	3 (12.5)	-	1 (5.9)
Secondary school	13 (54.2)	15 (60.0)	8 (47.1)
Diploma/Degree (Bachelor/Master/PHD)	7 (29.2)	9 (36.0)	8 (47.1)
Marital status, n (%)			
Single	1 (4.2)	3 (12.0)	1 (5.9)
Married	20 (83.3)	22 (88.0)	16 (94.1)
Divorced	3 (12.5)	-	-
Number of children dependant	2.4 (1.2)	3.3 (1.5)	2.9 (1.9)
Range	1 to 5	1 to 6	1 to 6
Employment status, n (%)			
Working	7 (29.2)	16 (64.0)	9 (52.9)
Retirees	1 (4.2)	-	-
Retired but still working	-	-	-
Unemployed/housewife	16 (66.7)	9 (36.0)	8 (47.1)
Monthly household salary (Mean±SD) (MYR)	4,366.67 (3,856.77)	6,228.0 (7,334.59)	5,135.29 (5,197.35)
Monthly food budget (Mean±SD) (MYR)	1,293.75 (1,229.73)	1,413.40 (1,110.76)	1,485.29 (1,089.12)

MYR: Malaysian Ringgit; OA: Organic Acidaemias; SD: Standard Deviation; UCD: Urea Cycle Disorders

Table 3. Dietary adherence of the patients with disorders of amino acid metabolism (n=66)

Dietary adherence	OA (n=24)	Aminoacidopathy (n=25)	UCD (n=17)	Total
Good adherence, n (%)	14 (58.3)	14 (56.0)	12 (70.6)	40 (60.6%)
Poor adherence, n (%)	10 (41.7)	11 (44.0)	5 (29.4)	22 (33.3%)

OA: Organic Acidaemias; UCD: Urea Cycle Disorders

(MacDonald *et al.* 2016). This contrasts with a Brazilian cross-sectional study of 56 PKU patients, where only 18 (32.1%) were classified as treatment adherent (Vieira *et al.* 2018). Notably, no significant differences in any of the QoL domains were observed between groups (Table 4).

A statistically significant, albeit weak positive correlation was found between caregiver education level o and dietary adherence (rs (64)=0.382, p=0.002). This finding suggests a potential association between higher caregiver education levels and improved dietary adherence among pediatric patients.

Table 5 shows the correlations between socio-demographic variables, dietary adherence, and quality of life domains. Caregiver education level oexhibited a significant positive correlation with mental health (rs (64)=0.281, p=0.022) (Table 5). However, dietary adherence displayed a weak negative correlation with various QoL domains, including role limitations due to physical health (rs (64)=-0.290, p<0.05), role limitations due to emotional problems (rs (64)=-0.282, p<0.05), bodily pain (rs (64)=-0.309, p<0.05), vitality (rs (64)=-0.284, p<0.05), mental health (rs (64)=-0.300, p<0.05) and social functioning (rs (64)=-0.314, p<0.05). Dietary adherence was found to negatively correlated with all QoL domains.

In the present study, association between higher caregiver education levels and improved dietary adherence, reflecting enhanced knowledge of the treatment regimen (Tejada-Ortigosa *et al.* 2019). This finding aligns with previous studies demonstrating the link between lower education level attainment and poorer knowledge of the treatment, leading to lower dietary adherence (Adam *et al.* 2013; Öztürk *et al.* 2022). However, our findings diverge from a previous study by Zeltner *et al.* (2019), which reported a decline in dietary compliance with advancing age, particularly around 10 years old.

Caregivers of female patients reported lower role limitations due to emotional problems. It was found that Malay caregivers had lower scores in various domains, including role limitations (physical and emotional), bodily pain, vitality, and mental health. However, the generalizability of these findings may be limited due to the high proportion of Malay participants (over two-thirds) within the sample. Further studies are needed to explore the associations between gender, ethnicity, and QoL while considering diverse demographic representation. Additionally, our findings suggest an association between higher caregiver education and better mental health. This could be attributed to enhanced

Table 4. Quality of life of caregivers of the patients with disorders of amino acid metabolism (n=66)

Categories of disorders of amino acid metabolism	Physical function	Role limitations due to physical health	Role limitations due to emotional problems	Bodily pain	General health	Vitality	Mental health	Social functioning
				Median (IQR)				
OA	80.00 70.00–95.00	75.00 25.00–100.00	100.00 33.00–100.00	88.75 57.50–100.00	72.50 60.00–80.00	65.00 55.00–75.00	68.00 56.00–84.00	81.25 62.50–100.00
Aminoacidopathy	85.00 70.00–90.00	75.00 25.00–100.00	100.00 50.00–100.00	77.50 51.25–100.00	70.00 62.50–80.00	65.00 50.00–77.50	68.00 50.00–84.00	75.00 62.50–87.50
UCD	90.00 77.50–95.00	100.00 87.50–100.00	100.00 83.33–100.00	80.00 56.25–90.00	80.00 47.50–95.00	70.00 52.40–80.00	80.00 68.00–90.00	75.00 62.50–93.75
p	0.287	0.135	0.454	0.670	0.811	0.785	0.215	0.405

IQR: Interquartile Range; OA: Organic Acidaemias; SD: Standard Deviation; UCD: Urea Cycle Disorders; p-value tested by using Kruskal-Wallis test at p<0.05

knowledge of treatment regimens, leading to improved patient management and ultimately, caregiver well-being. It is important to note that the link between low education and depression (Niemeyer *et al.* 2019) highlights the potential for broader mental health considerations among caregivers with lower education attainment.

This study identified a negative correlation between patients' age and caregivers' QoL, aligning with findings from a German cross-sectional study of 89 PKU parents (Fidika *et al.* 2013). The study found that parents with children under six years old had significantly lower mean scores for "self-development" compared to parents of older children. Younger children, being unable to independently manage their own diets, required increased parental support and supervision. Hence, it can be inferred that caregivers experienced a higher QoL due to the greater parental freedom available when their child attended school from the age of six and above (Fidika *et al.* 2013). Contrary to our current findings, parents with higher monthly income and younger age showed higher quality of life (Thomas *et al.* 2017). Nevertheless, this discrepancy might be attributed to the fact that medical visits and medical food are fully reimbursed by the Ministry of Health in Malaysia.

Table 5. Correlation of socio-demographic parameter and dietary adherence with quality of life

Variables	Physical function	Role limitations due to physical health	Role limitations due to emotional problems	Bodily pain	General health	Vitality	Mental health	Social functioning
	rs, Sig.	rs, Sig.	rs, Sig.	rs, Sig.	rs, Sig.	rs, Sig.	rs, Sig.	rs, Sig.
Type of IEMs	-0.027, 0.829	-0.014, 0.910	-0.205, 0.099	-0.216, 0.082	-0.027, 0.829	-0.160, 0.198	-0.240, 0.052	-0.149, 0.232
Age of patients	-0.287*, 0.019	-0.039, 0.757	-0.004, 0.976	-0.110, 0.379	-0.287*, 0.019	-0.238, 0.054	-0.205, 0.098	-0.099, 0.431
Gender	-0.048, 0.702	-0.240, 0.053	-0.277*, 0.024	-0.231, 0.062	-0.048, 0.702	-0.075, 0.551	-0.166, 0.184	-0.139, 0.267
Ethnicity	-0.181, 0.146	-0.286*, 0.020	-0.269*, 0.029	-0.254*, 0.040	-0.181, 0.146	-0.261*, 0.034	-0.252*, 0.041	-0.202, 0.103
Stage of onset	0.016, 0.898	0.016, 0.200	0.083, 0.506	-0.077, 0.536	-0.006, 0.959	-0.077, 0.536	0.126, 0.313	0.242, 0.051
Education level of patients	0.134, 0.284	0.056, 0.654	0.041, 0.743	0.120, 0.338	0.134, 0.284	0.059, 0.637	0.081, 0.518	0.206, 0.097
Age of caregivers	-0.120, 0.336	-0.082, 0.514	-0.033, 0.793	-0.091, 0.468	-0.120, 0.336	-0.174, 0.162	-0.053, 0.675	0.044, 0.724
Relationship	0.144, 0.247	-0.067, 0.591	-0.152, 0.222	-0.101, 0.421	0.144, 0.247	-0.105, 0.400	0.017, 0.893	-0.131, 0.296
Number of children	-0.098, 0.433	-0.149, 0.232	0.070, 0.577	-0.094, 0.453	-0.098, 0.433	-0.103, 0.411	-0.065, 0.605	0.033, 0.793
Marital status	-0.177, 0.156	-0.015, 0.904	-0.040, 0.750	0.097, 0.441	-0.177, 0.156	-0.027, 0.831	0.012, 0.926	0.092, 0.464
Educational level of caregiver	0.178, 0.152	0.229, 0.064	0.161, 0.197	-0.094, 0.452	0.178, 0.152	0.001, 0.991	0.281*, 0.022	0.086, 0.493
Working status	-0.186, 0.135	-0.078, 0.536	-0.019, 0.881	0.006, 0.963	-0.186, 0.135	-0.040, 0.749	-0.018, 0.889	0.003, 0.979
Household salary	0.009, 0.945	0.091, 0.465	0.170, 0.173	0.111, 0.374	0.009, 0.945	-0.041, 0.746	-0.213, 0.086	0.101, 0.420
Food budget	-0.070, 0.574	0.083, 0.510	0.137, 0.271	0.013, 0.918	-0.070, 0.574	0.073, 0.560	-0.006, 0.962	0.023, 0.857
Dietary adherence	-0.178, 0.153	-0.290*, 0.018	-0.282*, 0.022	-0.309*, 0.011	-0.183, 0.141	-0.284*, 0.021	-0.300*, 0.014	-0.314*, 0.010

rs: Spearman correlation coefficient ; Correlation (*) is significant at 0.05 level (2 tailed)

Among the barriers to dietary adherence are burden of dietary treatment, diet and dietary behavior, parenting challenges, limited knowledge related to dietary treatment, and challenges in healthcare system delivery (Lim *et al.* 2022). Our study supports the hypothesis that increase in dietary adherence leads to a lower QoL. This aligns with findings from MacDonald *et al.* (2016), who reported that caregivers managing PKU in the UK experienced time-related stress. This stress emanated from the constant need for caregivers to engage with other families and nursery teachers, ensuring ongoing communication, supervision, and maintenance of appropriate dietary management. Furthermore, caregivers of children with PKU identified meal planning, reparation, and cooking of low-phenylalanine meals as the most time-consuming aspects of dietary management. This burden was further amplified in social settings due to the limited availability of suitable low-protein options, necessitating additional meal preparation efforts. Bilginsoy *et al.* (2005) reported that these factors, along with the stress of record-keeping and social life limitations, were the primary obstacles to dietary adherence. Both caregivers and patients expressed frustration with the dietary restrictions imposed by PKU, particularlythe inability to share certain foods (Fabre *et al.* 2013). Morawska *et al.* (2020) identified several factors contributing to a lower QoL among caregivers, includin parental guilt, the financial burden of a low-protein diet and supplements, as well as the emotional stress caused by their child's anxiety during blood tests. Additionally, the demands of preparing specialized meals significantly impact the daily lives of caregivers, reducing their opportunities for social interaction (Thomas *et al.* 2017).

This study faced the challenge of a limited sample size due to the COVID-19 pandemic, which restricted travel for patients from outside of Kuala Lumpur, especially those residing on the West Coast of Malaysia. Despite this limitation, the study holds significant value. This is the first study in Malaysia to examine the differences between the socio-demographic profiles, dietary adherence levels, and QoL across three distinct categories of pediatric patients with AAMDs and their caregivers. This broader scope, encompassing various conditions beyond the commonly studied PKU or MSUD, offers valuable insights into the diverse experiences and potential needs of this population within the Malaysian context.

CONCLUSION

This study revealed a correlation between dietary adherence in pediatric patients with AAMDs and their caregivers' QoL. Specifically, greater dietary adherence was associated with lower QoL among the caregivers, likely due to the increased time burden associated with managing the low-protein diet, including meal planning and preparation. Socio-demographic factors also played a role. Caregivers with higher levels of education showed a positive association with increased dietary adherence in their children and their own mental health.

Consequently, further research efforts should prioritize a qualitative study to gain a comprehensive understanding of the specific challenges impacting caregivers' QoL within this context. Identifying these challenges can reveal previously unidentified factors affecting their well-being.

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DECLARATION OF CONFLICT OF INTERESTS

All the authors declared that they have no conflict of interest.

REFERENCES

Adam S, Almeida MF, Assoun M, Baruteau J, Bernabei SM, Bigot S, Champion H, Daly A, Dassy M, Dawson S *et al.* 2013. Dietary management of urea cycle disorders: European practice. Mol Genet Metab 110(4):439–445. https://doi.org/10.1016/j.ymgme.2013.09.003

Bilginsoy C, Waitzman N, Leonard CO, Ernst SL. 2005. Living with phenylketonuria: Perspectives of patients and their families.

J Inherit Metab Dis 28(5):639–649. https://doi.org/10.1007/s10545-005-4478-8

Boyer SW, Barclay LJ, Burrage LC. 2015. Inherited metabolic disorders: Aspects of chronic nutrition management. Nutr Clin Pract 30(4):502–510. https://doi.org/10.1177/0884533615586201

Carpenter K, Wittkowski A, Hare DJ, Medford E, Rust S, Jones SA, Smith DM. 2018. Parenting a child with Phenylketonuria (PKU): An Interpretative Phenomenological Analysis (IPA) of the experience of parents. J Genet Couns 27(5):1074–1086. https://doi.org/10.1007/s10897-018-0227-7

De Meirleir L, Rodan LH. 2017. Approach to the Patient with a Metabolic Disorder. Swaiman's Pediatric Neurology: Principles and Practice: Sixth Edition. Amsterdam (NL): Elsevier Inc.

Dixon M, MacDonald A, White F, Stafford J. 2014. Disorders of Amino Acid Metabolism, Organic Acidaemias and Urea Cycle Disorders, Clinical Paediatric Dietetics: Fourth Edition. New Jersey (USA): John Wiley & Sons Ltd.

Ezgu F. 2016. Inborn errors of metabolism. Advances in Clinical Chemistry. 1st Edt. Cambridge (USA): Elsivier Inc.

Fabre A, Baumstarck K, Cano A, Loundou A, Berbis J, Chabrol B, Auquier P. 2013. Assessment of quality of life of the children and parents affected by inborn errors of metabolism with restricted diet: Preliminary results of a cross-sectional study. Health Qual Life Outcomes 11:1–8. https://doi.org/10.1186/1477-7525-11-158

Ferreira CR, Rahman S, Keller M, Zschocke J, ICIMD Advisory Group, Abdenur J, Ali H, Artuch R, Ballabio A, Barshop B et al. 2021. An International Classification of Inherited Metabolic Disorders (ICIMD). J Inherit Metab Dis 44(1):164–177. https://doi.org/10.1002/jimd.12348

Fidika A, Salewski C, Goldbeck L. 2013. Quality of life among parents of children with Phenylketonuria (PKU). Health Qual Life Outcomes 11(1):1–9. https://doi.org/10.1186/1477-7525-11-54

Ford S, O'Driscoll M, MacDonald A. 2018. Living with phenylketonuria: Lessons from the PKU community. Molecular Genetics and Metabolism Reports 17:57–63. https://doi.org/10.1016/j.ymgmr.2018.10.002

Hatah E, Rahim N, Makmor-Bakry M, Shah NM, Mohamad N, Ahmad M, Haron NH, Hwe CS, Wah ATM, Hassan F, Rahmat SS, Robert SA, Abdullah N. 2020. Development and validation of Malaysia Medication Adherence Assessment Tool (MyMAAT) for diabetic patients. Plos One 15(11):e0241909. https://doi.org/10.1371/journal.pone.0241909

Khangura SD, Tingley K, Chakraborty P, Coyle D, Kronick JB, Laberge AM, Little J, Miller FA, Mitchell JJ, Prasad C, Siddiq S. 2016. Child and family experiences with inborn errors of metabolism: A qualitative interview study with representatives of patient groups; Child and family experiences with inborn errors of metabolism: A qualitative interview study with representatives of patients. J Inherit Metab Dis 39:139–147. https://doi.org/10.1007/s10545-015-9881-1

Kong JP, Roslee R. 2015. Growth and nutritional status of children with Maple Syrup Urine Disease (MSUD): A 6-months follow up study in Institute of pediatric, Hospital Kuala Lumpur (HKL). Nutr Food Sci 45(2):286–301. https://doi.org/10.1108/NFS-08-2014-0077

Lim JY, Rajikan R, Amit N, Ali NM, Hamid HA, Leong HY, Mohamad M, Koh BQ, Musa A. 2022. Exploring the barriers and motivators to dietary adherence among caregivers of children with disorders of Amino Acid Metabolism (AAMDs): A qualitative study. Nutrients 14(12):2535. https://doi.org/10.3390/nu14122535

Lim MT, Ab Rahman N, Teh XR, Chan CL, Thevendran S, Ahmad Hamdi N, Lim KK, Sivasampu S. 2021. Optimal cut-off points for adherence measure among patients with type 2 diabetes in primary care clinics: A retrospective analysis. Ther Adv Chronic Dis 12:2040622321990264. https://doi.org/10.1177/2040622321990264

MacDonald A, Smith TA, de Silva S, Alam V, van Loon JM. 2016. The personal burden for caregivers of children with phenylketonuria: A cross-sectional study investigating time burden and costs in the UK. Molecular Genetics and Metabolism

Reports 9:1–5. https://doi.org/10.1016/j.ymgmr.2016.08.008

Martianto D, Riyadi H, Ariefiani R. 2011. Pola asuh makan pada rumah tangga yang tahan dan tidak tahan pangan serta kaitannya dengan status gizi anak balita di Kabupaten Banjarnegara. J Gizi Pangan 6(1):51–58. https://doi.org/10.25182/jgp.2011.6.1.51-58

Morawska A, Mitchell AE, Etel E, Kirby G, McGill J, Coman D, Inwood A. 2020. Psychosocial functioning in children with phenylketonuria: Relationships between quality of life and parenting indicators. Child: Care Health Dev 46(1):56–65. https://doi.org/10.1111/cch.12727

Najafi R, Hashemipour M, Mostofizadeh N, Ghazavi M, Nasiri J, Shahsanai A, Famori F, Najafi F, Moafi M. 2016. Demographic and clinical findings in pediatric patients affected by organic acidemia. Iran J Child Neurol 10(2):74–81. https://doi.org/10.22037/ijcn.v10i2.10410

Niemeyer H, Bieda A, Michalak J, Schneider S, Margraf J. 2019. Education and mental health: Do psychosocial resources matter?. SSM-Population Health 7:100392. https://doi.org/10.1016/j.ssmph.2019.100392

Öztürk FÜ, Bülbül SF, Alpcan A. 2022. Assessment of parents knowledge regarding phenylketonuria and its affecting factors: A cross-sectional study. Pan Afr Med J 41(1).

Pascoal C, Brasil S, Francisco R, Marques-da-Silva D, Rafalko A, Jaeken J, Videira PA, Barros L, dos Reis Ferreira V. 2018. Patient and observer reported outcome measures to evaluate health-related quality of life in inherited metabolic diseases: A scoping review. Orphanet J Rare Dis 13:1–16. https://doi.org/10.1186/s13023-018-0953-9

Pei KJ, Rajikan RB, Hock NL, Jamil K. 2014. Growth and nutritional status of children with Urea Cycle Defects (UCD): A 6-months follow up study in Institute of Pediatric, Hospital Kuala Lumpur. Int J Clin Nutr 2(3):41–52. https://doi.org/10.12691/ijcn-2-3-1

Rohde C, Thiele AG, Och U, Schönherr K, Meyer U, Rosenbaum-Fabian S, Maddalon C, Matzken S, Blessing H, Lang F, Jörg-Streller M. 2015. Effect of dietary regime on metabolic control in phenylketonuria: Is exact calculation of phenylalanine intake really necessary?. Molecular Genetics and Metabolism Reports 5:36–41. https://doi.org/10.1016/j.ymgmr.2015.09.006

Shafie AA, Supian A, Ahmad Hassali MA, Ngu LH, Thong MK, Ayob H, Chaiyakunapruk N. 2020. Rare disease in Malaysia: Challenges and solutions. Plos One 15(4):e0230850. https://doi.org/10.1371/journal.pone.0230850

Saudubray JM, Matthias R, Baumgartner, Walter J. 2016. Inborn Metabolic Diseases: Diagnosis and Treatment. 6th edition. Berlin (GM): Springer.

Tejada-Ortigosa EM, Flores-Rojas K, Moreno-Quintana L, Muñoz-Villanueva MC, Pérez-Navero JL, Gil-Campos M. 2019. Health and socio-educational needs of the families and children with rare metabolic diseases: Qualitative study in a tertiary hospital. An Pediatr 90(1):42–50. https://doi.org/10.1016/j.anpede.2018.03.005

Thomas DS, Shakman LMW, Saraswathy K, Arulappan J. 2017. Parenting a child with metabolic diseases: Impact on health related quality of life of parents. Diabetes Metab Syndr Clin Res Rev 11(1):25–29. https://doi.org/10.1016/j.dsx.2016.07.002

Thong MK, Yunus ZM. 2008. Spectrum of inherited metabolic disorders in Malaysia. Ann Acad Med Singap 37(Suppl 3):66–70.

Vieira E, Maia HS, Monteiro CB, Carvalho LM, Tonon T, Vanz AP, Schwartz IVD, Ribeiro MG. 2017. Quality of life and adherence to treatment in early-treated Brazilian phenylketonuria pediatric patients. Braz J Med Biol Res 51. https://doi.org/10.1590/1414-431x20176709

Yamaguchi K, Wakimizu R, Kubota M. 2018. Quality of life and associated factors in japanese children with inborn errors of metabolism and their families. J Inborn Errors Metab Screen 6:2326409818755799. https://doi.org/10.1177/2326409818755799

Zeltner NA, Welsink-Karssies MM, Landolt MA, Bosshard-Bullinger D, Keller F, Bosch, AM, Groenendijk M, Grünert SC, Karall D, Rettenbacher B, Scholl-Bürgi S. 2019. Reducing complexity: Explaining inborn errors of metabolism and their treatment to children and adolescents. Orphanet J Rare Dis 14(1):1–9. https://doi.org/10.1186/s13023-019-1236-9