



## Living with Phenylketonuria: Lessons from the PKU community

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### ABSTRACT

**Introduction:** We report the practical, social and psychological issues of living with phenylketonuria (PKU) from one of the largest surveys that has been completed by both adults with PKU and parents/caregivers of children. **Methods:** In the UK, parents/caregivers of children and adults with PKU were invited to complete an online survey between November 2017 to January 2018 by the NSPKU (National Society for Phenylketonuria).

**Results:** 631 participants (adults,  $n = 338$ ; parents/caregivers of children,  $n = 293$ ) with PKU completed the questionnaire. Problems experienced by children with PKU were: difficulty with maintaining focus (48%,  $n = 114/236$ ), educational difficulties (28%,  $n = 67/236$ ), anxiety or depression (29%,  $n = 68/236$ ), and gastrointestinal symptoms (34%,  $n = 97/282$ ). Fifty one per cent ( $n = 120/236$ ) described social exclusion; 17% ( $n = 41/236$ ) had relationship issues with friends or family. Problems experienced by adults were: depression or anxiety (52%,  $n = 148/286$ ), difficulty maintaining focus (54%,  $n = 154/286$ ), and low mood (54%,  $n = 180/334$ ). Difficulties were experienced with relationships (34%,  $n = 96/286$ ); social exclusion (44%,  $n = 126/286$ ); and gastrointestinal issues ( $n = 34%$ ,  $n = 112/334$ ). Common medications used included antidepressants (40%,  $n = 131/331$ ) and anxiolytics (18%,  $n = 60/334$ ).

**Discussions:** Adults with PKU or caregivers/parents of children identified significant neurocognitive, mental health and general health issues. Limits on socialisation, perception of social isolation and dietary stigma are major obstacles which are difficult to overcome with conventional dietary management.

### 1. Introduction

Phenylketonuria (PKU) is a rare, metabolic disorder, caused by an enzyme deficiency (phenylalanine hydroxylase) that catalyses the hydroxylation of phenylalanine (Phe) to tyrosine. Untreated, brain Phe accumulation occurs, leading to global intellectual disability, significant delays in developmental milestones, with hyperactive behaviour and autistic features. If treatment is started within the first four weeks of life, people with PKU fall within the broad normal range of general ability and adults should lead independent lives, although outcome is dependent on metabolic control. The first successful dietary treatment for PKU was initiated in the UK in 1952. Initially the necessity for treatment in PKU was contested beyond childhood but in 1993 [1], lifelong dietary treatment was recommended, and subsequently endorsed by the National Society for PKU (NSPKU). The case for lifelong treatment was further strengthened by the recent European Guidelines for PKU published in 2017 [2].

A low Phe diet consists of four main principles: 1) exclusion of high protein/high Phe foods e.g. meat, fish, eggs, cheese, bread, flour, pasta,

nuts, seeds and aspartame; 2) measured amounts of Phe according to individual tolerance from food sources such as potatoes and peas (exchange foods), 3) replacement of most of the natural protein with a synthetic protein (protein substitute or medical food) with added vitamins and minerals, and 4) use of very low protein foods (exchange free) from fruits, some vegetables, butter, oil, sugar and manufactured low protein special foods. All the Foods for Special Medical Purposes are prescribed by the NHS and approved by the Advisory Committee for Borderline Substances, and on the instruction of specialist hospital dietitians they are then prescribed by community GP services and dispensed by local pharmacies or home pharmaceutical delivery services. In England, adults in employment (except during pregnancy) pay a nominal prescription charge for each item, but children, and people with PKU in Wales and Scotland are all exempt from any payment charges.

It is accepted that dietary management is challenging, adds significant daily burden, and does not ease with advancing age [3]. Stringent blood Phe control is recommended throughout life, although it is well established that it deteriorates from adolescence and only one

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in four adults achieve satisfactory blood Phe control [4,5]. In the UK, with the exception of pregnancy, the health systems do not reimburse the use of sapropterin for BH4 responders and so diet is the only treatment.

In 1973, the NSPKU was formed to help and support individuals with PKU, their parents and families. For some time, the society has been concerned that the outcome in adults with PKU is suboptimal, with deficits in neurocognitive and psychosocial functioning, nutritional status and brain pathology. The Society is aware that many adults are not following dietary treatment, standards of care vary, and many adults are lost to follow up. The Society considers it a priority that patients are offered access to all available treatments to enable more patients to adhere to treatment. The NSPKU conducted an online survey, open to all people with PKU in the UK or their parents / caregivers. The aim was to describe the experiences of the UK PKU population and explore issues around living with the condition and its treatment.

## 2. Material and methods

An online questionnaire was voluntarily completed and submitted by adults with PKU or parents/caregivers of children or adults unable to complete the survey themselves. The questionnaire was placed on the UK NSPKU website, Facebook and Twitter accounts between 9th November 2017 and 31st January 2018. Additional promotion of the survey was conducted by the NSPKU at patient and family meetings. We requested that only one questionnaire was completed for each person with PKU.

This non-validated questionnaire was comprised of 61 questions, including single choice, multiple choice and 4 open-ended questions on all aspects of PKU: dietary management, drug treatments, blood phenylalanine control, knowledge of treatment, type of clinic (specialist vs non-specialist), educational and work issues, mental and physical symptoms, frequency of follow-up, adherence with treatment and issues affecting ability to adhere to diet. Demographic information was also collected. There were specific questions for women aged 18 years and over, on pre-conception, pregnancy and post-natal pregnancy experiences and these results are discussed in a separate paper. This questionnaire was developed by using questions adapted from other national patient surveys on PKU that had been conducted by European patient groups.

Two open ended questions were selected for in-depth thematic analysis and these were analysed jointly (a common set of nodes was created as there was a large amount of overlap in the codes generated from the responses). The questions and number of useable responses (useable meaning that there was some content in the response which could be understood as a meaningful response to the question) are described below.

If you don't stick to a low protein diet or struggle with your diet, please describe why you.

find it hard in your own words. (Your answer may be included in published materials but.

you will not be identified by name): 255 useable responses.

“Is there anything else about your experience of having PKU (or the person with PKU under your care) which you would like to share? (Your answer may be included in published materials but you will not be identified by name): 240 usable responses.

We have excluded reporting on two open questions. One open question on pregnancy has been described elsewhere; one open question on experience with sapropterin was excluded as only a few respondents had short term access to this treatment, mainly through clinical trials.

The whole survey dataset was imported into ‘NVIVO v.11 pro’ software, a programme for qualitative data analysis. Each survey response was created as a case (allowing responses to be filtered by any characteristics or response which was captured in the survey). Each

open-ended question was created as a node, and the individual response to each question was read individually and coded at a very fine level of detail according to one or more nodes created in response to emerging patterns in the data.

## 3. Data cleaning and recoding

There was particular interest in how responses might vary by child/adult status as there has been little work comparing dietary practices and general and mental health issues within adults and children with PKU. The age variable in the survey was recoded into two groups (using SPSS) which corresponded to children (aged  $\leq 18$ y) and adults (aged  $\geq 19$ y) and this variable was part of the survey dataset imported into NVIVO. Using the matrix coding query in NVIVO, a breakdown by adult / child was provided for each node (i.e. how many coding references in each node for children and how many for adults). This enabled some assessment of the extent to which each node (and each theme) were relevant to adults and children respectively although this is of course only indicative.

## 4. Analysis

The closed questions (multiple choice and single choice) were analysed using descriptive statistics only. The two open ended questions identified above were analysed using inductive thematic analysis [6] which identified patterns in the text which seem most relevant to the research objectives (ie understanding the experiences of people with PKU and their families, friends and carers). Ideas, comments or statements which recurred were coded in NVIVO and these codes were organised into a hierarchical pattern of nodes with the top-level parent nodes being considered as themes. Codes and themes were reviewed and refined throughout the analysis process (e.g. merging and splitting codes).

## 5. Ethics

Ethical consent was not sought as it was clarified at the beginning of the questionnaire that the primary purpose of the survey was to gain information to support NHS procedures considering future treatments for PKU in England, Scotland, Wales and Northern Ireland. Potential respondents were also advised that the NSPKU may publish data from the survey in an anonymised form. Adults with PKU and caregivers gave their consent by their voluntary completion and submission of the online questionnaire. If names or hospitals were mentioned in verbatim abstracts, these were removed.

## 6. Results

Results from the quantitative analysis of the survey data and qualitative thematic analysis of two open-ended questions are summarised below. The structure is provided by the themes and the quantitative data which is most relevant to each theme is presented under those headings. Themes with five or more coding references are identified and in total 9 met this criterion. These were: 1) dietary treatment, 2) mental health, effects, symptoms and co-morbidities of PKU 3) social isolation, 4) support and low awareness of PKU by health professionals, 5) quality of life, 6) alternative treatments, 7) pregnancy, 8) explaining PKU to others, and 9) blood tests. The number of responses to each theme are given in Table 1. Pregnancy data obtained from this questionnaire is discussed in another publication. There was only a small number of responses to alternative treatment as sapropterin is not routinely reimbursed through the UK health services and is not discussed in this publication. The verbatim extracts about ‘explaining PKU to others’ and ‘blood tests’ are not discussed as they form only 2% and 1% of the total responses.

**Table 1**The number of coding references for top themes for people with PKU aged  $\leq 18$  and  $\geq 19$  years with PKU.

Theme ranking	Themes	Number (n) and % of coding references for each theme				Total number (n) and % of coding references for each theme	
		Respondents aged $\leq 18$ years		Respondents aged $\geq 19$ years		n	%
		n	%	n	%		
1	PKU diet	89	51	139	50	228	50
2	Mental health, symptoms, effects and co-morbidities of PKU	37	21	61	22	98	22
3	Social isolation	15	9	16	6	31	7
4	Support and low awareness of PKU by health professionals	6	3	24	9	30	7
5	Quality of life impacted by PKU	12	7	12	4	24	5
6	Treatments	7	4	11	4	18	4
7	Pregnancy	2	1	7	3	9	2
8	Explanations of PKU to others	3	2	6	2	9	2
9	Blood tests	2	1	3	1	5	1
	Total number of coding references	173		279		452	

## 7. Demographic profile of respondent

Six hundred and thirty-one respondents participated in the survey, including 338 adults (54%), and 293 (46%) caregivers of children. Five hundred and ninety-seven respondents lived in the UK (451 [71%] from England, 74 [12%] Scotland, 30 [5%] Wales, 42 [7%] Northern Ireland), 1 [0.002%] Isle of Man and 33 [5%]) were non-UK residents. Two hundred and ninety-three (46%) respondents were 18 years old and younger (children); and 338 (54%) were adults (300 female), 202 (32%) respondents were aged 19 to 35 years, 88 (14%) aged 36 to 45 years, 38 (6%) aged 46 to 55 years and only 10 (2%) were aged  $\geq 56$  years. Eighty-six per cent ( $n = 540$ ) of respondents attended a specialist metabolic clinic, 11% ( $n = 70$ ) a shared care service and 3% ( $n = 16$ ) a non IMD specialist clinic.

## 8. Theme 1: dietary treatment

Most caregivers (89%,  $n = 260/293$ ) said their children followed a low Phe diet supervised by their dietitian (with 80%,  $n = 233/293$  tolerating 10 g/day or less of natural protein each day). The number of respondents following a low Phe diet decreased with age and only 57% ( $n = 191/338$ ) of adults said they were on a prescribed low Phe diet. Seventy-three per cent of both adults ( $n = 209/286$ ) and caregivers of children ( $n = 173/236$ ) said they found dietary management difficult.

Diet accounted for 50% of the thematic analysis coding references in both adults and children as diet was clearly a very central focus for people with PKU and their parents / caregivers. Parents described dietary adherence struggles with their children from school age onwards.

Verbatim extracts from parents' and caregivers' responses about dietary treatment.

*My daughter seems to find it difficult now she's at high school to stick to her diet. She hasn't told many of her friends and eats lots of things she shouldn't. She doesn't seem to recognise how it affects her mood, concentration etc. But the rest of her family know immediately if her blood Phe is high.*

*My daughter, as a teenager, does not stick to the diet. She is often grumpy and resents having a disorder that other people do not understand nor afford adequate understanding to just how much of her life is restricted particularly in social situations.*

Adults also described their psychological challenges in maintaining the low Phe diet. If they deviated from their dietary treatment, they found it hard to return to treatment.

Verbatim extracts from adults about the low Phe diet.

*Sticking to the diet all the time requires a tremendous amount of discipline and self-control. If phe levels are raised, then your ability to stick to the diet is diminished leading to a vicious circle scenario.*

*As you get older you learn more and at least you start to understand the importance of it, but by this point you've gotten so used to fighting against it, it is hard to get back to a proper PKU diet.*

Thirty-nine per cent ( $n = 133/338$ ) of adults and 11% ( $n = 31/293$ ) of children either did not take protein substitute or they took less than the prescribed amounts. From the low Phe diet theme, parents described the daily labours of administering the protein substitute at least three times every day. Sometimes, protein substitute was associated with nausea and stomach ache.

Verbatim extracts from parents and caregivers describing difficulties of administering protein substitute to their children when following a low Phe diet.

*Our greatest struggle is getting our son taking his supplements. He refuses to take it and it can take up to 45 min for him to finish one with a lot of upsets.*

Most adults and caregivers of children said significant effort was associated with dietary management (86% [ $n = 291/338$ ] adults and 89% [ $n = 260/293$ ] of caregivers of children) and with some adults (14%,  $n = 48/338$ ) saying they could not manage this independently. The top 5 issues affecting the ability to follow diet in adults were: 1) limited food choices 2) diet is too time consuming to manage, 3) unpleasant protein substitute, 4) unpleasant food choices and 5) inconvenience. In children the top 5 issues were: 1) limited food choices, 2) unpleasant protein substitute, 3) unpleasant food choices, 4) diet is time consuming and 5) expense of diet.

Parents and adults supported these findings when discussing their barriers to adherence in the low Phe diet theme.

Verbatim extracts from parents and caregivers describing the barriers in adhering to dietary treatment.

*My son does not like most of the free foods and those available on prescription therefore making his diet extremely limited and not very appealing to him.*

*You have to work out what foods they are allowed to eat. And*

then work out how much they need per meal. And then picking it all up off the floor and chair and counting what they haven't eaten so you have an accurate amount of what is left to eat for the day to meet the required amounts.

As the caregiver I struggle to find the time to cook enough low protein food for my PKU daughter. Consequently, her diet is further restricted by a lack of choice. When I run out of something, she's deprived of it until I can find the time to make it again and when I have made it I have to ration it so I don't run out too quickly.

Verbatim extracts from adults describing the barriers in adhering to dietary treatment.

Practicality; extremely difficult/not possible to weigh foods. I find the overwhelming majority of PKU foods/recipes, completely unappealing. In addition, working shifts or being on the road a lot with your job makes adhering to the diet even more difficult.

The diet is stressful and time consuming and with two children to raise, a full-time job and normal life stresses I just can't manage it successfully no matter how hard I try.

Some respondents described the practical issues and their frustrations at trying to access low protein foods and protein substitutes.

Verbatim extracts from parents and caregivers and adults describing the difficulties in accessing low protein foods and protein substitutes.

This diet is so difficult, and the doctors have had me in tears on a number of occasions when I need prescriptions and protein substitute and I've been treated like I shouldn't be having it.

Prescriptions are difficult and unreliable to obtain, and we have to deal with two delivery companies, the local pharmacy the dietitian and the GP to obtain them.

## 9. Theme 2: mental and general health issues and co-morbidities of PKU

Results of the quantitative survey indicated common mental and general health effects of PKU in adults and children were: depression, low mood and anxiety, recurrent indigestion problems such as heart burn and stomach ache (Table 2). In addition, parents / caregivers reported that 28% ( $n = 67/236$ ) of children had educational difficulties at school, with 19% ( $n = 51/272$ ) receiving school intervention for educational or behavioural issues. In adults 28% ( $n = 79/286$ ) had difficulties gaining qualifications or with career progression and 15% ( $n = 42/286$ ) employment issues.

Overall, this theme received 22% ( $n = 98/452$ ) of comments from adults and parents/ caregivers from the two open-ended questions. Some of the mental health problems could be directly due to PKU or because of trying to adhere to dietary treatment.

Verbatim extracts from parents and caregivers about children's health issues.

My daughter is never at peace with the world ..... She gets angry at home for no reason and with my younger children. She also gets upset easily. She often cries and is sad at bedtime. I am considering seeking medical help for this. She also loses focus at school very quickly.

Anxiety about going to school, nervous about new situations, angry when gets answers wrong, struggling at school needs extra help.

Verbatim extracts from adults about their health issues.

I have mood swings, extremely tired and want to sleep all the

**Table 2**

Results from the quantitative survey reporting mental and general health issues for people with PKU aged  $\leq 18$  and  $\geq 19$  years.

Mental and general health issues	$\leq 18$ years		$\geq 19$ years	
	n = 236 respondents	%	n = 286 respondents	%
Difficulty with focus	114	48	154	54
Depression/anxiety	68	29	148	52
Eating disorder	35	15	40	14
	n = 282 respondents	%	n = 334 respondents	%
Digestive problems e.g. stomach ache, reflux	97	34	112	34
Frequent headaches	52	18	106	32
Low mood/sadness	68	24	180	54
Feeling tired all the time	64	23	178	53
	n = 272 respondents	%	n = 331 respondents	%
Use of anti-depressants	15	6	131	40
Use of anxiolytics	10	4	60	18
Use of laxatives	50	18	47	14
Medicines for recurrent digestive problems e.g. reflux	28	10	81	24
Use of psychology services	56	21	74	22
Use of psychiatric services	11	4	42	13

time and feels like this is a grey cloud hanging over my head, but not depression.

I find it difficult to plan, be organised and find that I lack energy, enthusiasm and motivation. I have blank moments where I can't think or get my words out that I am trying to say. I experience anxiety and I get paranoid. All this impacts my work life as my job is very fast paced.

I get "brain fog" tend to become irritable and uneasy in social settings.

### 9.1. Body weight and eating patterns

Adults made several comments about the impact of the low Phe diet on weight and their eating patterns.

Verbatim extracts from adults about overweight and disordered eating (from the theme health issues).

I have not been on the diet since my early teens. I overeat a lot, and feel food is a reward for everything in my life - good and bad. I am a foodie and eat everything I want. I have no self-control for the PKU diet and have never been back on it since my teens.

I also have a horrible relationship with food but no counselling is available to me unless I pay out of pocket, which I can't afford. It's also extremely restrictive and I get stressed, fed up and upset about food very easily. I don't have an eating disorder, but I do have disordered eating patterns.

I was bullied for having PKU in school and so I struggled with the food intake and even now I find it hard also.

Some adults reported having an abnormal relationship with food. The quantitative data showed that many have difficulty controlling weight gain (55%,  $n = 158/286$ ), suffer with eating disorders or disordered eating patterns (14%,  $n = 40/286$ ) and 4% ( $n = 12/331$ ) had received therapy for eating disorders.

## 10. Theme 3: social isolation

Almost half of parents and caregivers (51% [ $n = 120/236$ ] and 44% of adults ( $n = 126/286$ ]) described social exclusion because of the diet. From the theme of social isolation, respondents identified this as a source of upset, frustration, embarrassment and major barrier to adherence and how it made them feel different from their friends and colleagues. Inability to access suitable food in restaurants, at work and related social activities was common. One respondent had to leave a restaurant because of a refusal to cook low protein food which she had brought with her. Some people with PKU were also bullied because of eating their own food in social settings.

*Verbatim extracts from parents, caregivers and adults describing the impact of diet on social isolation.*

*My daughter gets extremely upset in social situations. She gets very panicky about the food and what she can and cannot have. I still haven't been able to leave her at a party.*

*Restaurants are impossible, and the diet is so rare that most waiters will actually argue with you about your requirements.*

*I do find it difficult having PKU. I would love to just say 'Let's go out for dinner!' and not have to sit there thinking of where to go that will cater for me well. It makes me feel like a burden within my friendship group.*

*I was never invited to parties because the PKU food was too hard to accommodate or didn't want me to bring my own food. Medication was poured in my hair and food was stolen as well as the PKU food being mocked.*

## 11. Theme 4: support and lack of health professional awareness of PKU

Many adults expressed frustration that the symptoms or issues which maybe a direct or indirect consequence of PKU, were not always taken seriously by health professionals. Only one in five adults (22%,  $n = 74/331$ ) and children (21%,  $n = 56/272$ ) were referred to psychology services.

*Verbatim extracts from adults about their symptoms and not being listened to by health professionals.*

*I have always been treated as if "blaming" my PKU is an excuse. It feels odd to now see that maybe my thinning hair, maybe my flaky nails, maybe my weight-difficulties, anxiety, fear and emotional sensitivity are all affected by PKU and how my body is coping.*

*To be good at diet you need full support-home & medical - If one part is missing you fall off wagon.*

*People don't seem to realise the mental and physical toll it takes on you as a person having PKU, they seem to think, 'Oh it's just a food thing, I'm sure it can't be that bad' ...*

*Clinical treatment falls so short. Most GPs aren't familiar with the diet so you can't turn to them for help, and the GP and the clinic don't talk to each other so health issues that might be related to your PKU aren't treated holistically.....*

*.....being released from diet at 16 and not being informed by anyone that I needed to return to diet at time of discovery and being left to eat normally for a long period of time making it so much harder to revert back to diet.*

## 12. Theme 5: quality of life

There was overlap with themed comments in this section and impact of treatment on socialisation but also included frustrations about adults not fulfilling their full potential at work, issues with personal relationships, and lack of spontaneity with social situations. The quantitative data indicated that 36% ( $n = 117/327$ ) of adults felt guilt and self-blame. Seventeen per cent ( $n = 41/236$ ) of children and 34% ( $n = 96/286$ ) of adults had difficulties with relationships with friends, family or partners.

*Verbatim extracts from adults about impact of PKU on the quality of their life*

*I feel that I am not able to realise my potential at work and in relationships with friends and family.*

*My working relationships are temporary, friendships are short lived and my relationships with family members are distant at times.*

*Some employment opportunities are restricted due to the nature of requiring prescription foods in addition to supplements.*

*I conform to the diet. I take all my medication. I manoeuvre my whole life around it. I STILL SUFFER.*

There were many comments about the 'overwhelming' impact of PKU and 'all consuming' responsibility for caregivers. Having a child or person with PKU considerably impacted on the life of caregivers. The mother was the main carer in 84% ( $n = 226/270$ ) of cases, and care was shared jointly by parents in 11% ( $n = 31/270$ ). PKU caused considerable worry and strain which affected the wellbeing of 75% ( $n = 191/253$ ) of parents and caregivers. They describe the constant pressure of dealing with dietary management and how this is a daily struggle in their lives. It was clear that the burden of care lasts over many years with parents being equally as concerned about their teenagers as they are with infants and young children.

*Verbatim extracts from parents/caregivers about their quality of life.*

*When you can cause irreversible brain damage to your child, it causes a lot of worry, stress and even panic.*

*As a carer for a child of PKU and having had 2 other children I have found that having a child with PKU has been the most difficult thing I have experienced in my life because of my child's continual rebellion against the condition and the fact that it will never go away has had a massive detrimental impact on my mental health and wellbeing.*

*There's never a break - home, school, social events it's a cloud that hangs over her.*

*It takes so much time and planning every day that at times it is hard to sustain. Difficult as a parent to be always saying no and having to be so controlling over what he eats, where he goes etc for fear of noncompliance.*

*PKU rules our lives.*

Fifty-nine per cent ( $n = 149/253$ ) of caregivers stopped working, changed job or working pattern to take care of a person with PKU with 77% ( $n = 194/253$ ) finding it difficult to organise any childcare due to challenges in others understanding PKU management.

Over half of the caregivers said their ability to socialise or do certain activities decreased (56%;  $n = 141/253$ ), almost one third said that their relationship with their partner had been affected (31%,  $n = 78/253$ ), and 40% ( $n = 100/253$ ) said that having a child with PKU affected the decision about having more children.

*Verbatim extracts from parents/caregivers about the impact of PKU on future children.*

*The battle of trying to stick to the very restrictive diet day in day out plus the addition of monitoring blood has been extremely hard work. It has made myself and my husband make the decision to not have any more children.*

Thirty-seven per cent ( $n = 94/253$ ) of caregivers said that taking care of their child had affected their ability to give attention to other children in their family.

### 13. Discussion

We report the results from one of the largest surveys completed by people living with PKU. Many respondents struggled with long term dietary management and they were only able to adhere to this with variable success. Thematic analysis of open-ended questions from this survey particularly identified issues with the practical application and acceptability of dietary treatment, effect on socialisation, and the burden of care associated with dietary management. In addition, PKU affected physical, psychological and emotional health, social wellbeing, interpersonal relationships [7,8] as well as education and work.

A diagnosis of PKU in an infant fundamentally changes the lives of parents and caregivers and it has a significant psychological impact. The knowledge that their actions can affect the neurocognitive outcome of their children is a heavy responsibility. From their personal accounts, it appears that parents / caregivers carry an onerous workload associated with protein substitute administration, thinking continuously about diet, maintaining strict dietary routines, ensuring maintenance of 'home-made' food supplies, worrying about teenage rebellion, and meticulously planning every family activity [9]. Parents found balancing their own work and PKU care challenging and some mothers stopped work or reduced their working hours to take care of their child with PKU, with personal career ambitions taking a low priority. Fear of neglecting non PKU siblings was a significant concern. Some of the parents said they found PKU very difficult to accept and wanted their child to experience normality.

Stigmatisation, misconceptions and the feeling of social exclusion were common issues in both children and adults, and eating away from the home was a huge barrier to adherence. The general public do not have an understanding of protein restrictions and for people with PKU having to eat different food caused unwanted attention. Some respondents said they did not disclose their diagnosis as the implications of PKU can be difficult to explain to others. Bullying, mainly in the form of verbal abuse, tended to occur at mealtimes when children with PKU were viewed as 'different'. As a result, some children withdrew from social situations or refused to attend school. Some adults described how bullying in childhood remained with them throughout their life and affected their relationship with food, leading to a lifetime of disordered eating. The latter has previously been reported in PKU [10–12]. Adults in this survey also described how they withdrew from social situations and became socially isolated.

It was clear that maintaining a lifelong low Phe diet is not a realistic option for many in adulthood. Some adults described how they found dietary management complex and impractical and abandoned treatment, with some withdrawing from medical care. Some of the adults had stopped dietary treatment in childhood and the thought of diet recommencement was almost inconceivable. Some adults who remained on diet said they maintained higher blood Phe levels than target ranges and had lifelong feelings of self-failure. Adults who received support from partners or family appeared to cope with dietary treatment better. Some described how they received ambivalent messages from health professionals about the need to follow dietary treatment so

were not fully committed to it. Others described moving 'in and out' of dietary treatment and if their daily routine was disrupted they would then struggle to recommence diet. Previous research has shown that half of adult patients interrupt their dietary treatment at least once over four years [13] but reinstatement of dietary therapy is associated with a low success rate [14]. Our group of adult respondents described themselves as going into a 'downward spiral' if they disrupted dietary management and this 'was hard to climb out of.' They described associated symptoms such as inability to think, depression, low motivation, tiredness and some would 'binge eat' at this time leading to guilt and self-shame. Even individuals who said they achieved acceptable blood Phe control, still reported having to adapt and compromise some of their dietary standards to cope with holidays, work and social events.

Amongst both adults and children, cognitive and executive function deficits, mental health, general and gut health issues were identified from our survey. Both groups commonly described issues of inattention, depression, anxiety, behavioural issues, irritability, poor memory, and headaches. All of these problems have been well described in PKU [15–19]. Adults mentioned that they had 'brain fog' affecting their ability to think. Many of the participants who identified anxiety or depression had been prescribed medication. Some recognised that their poor organisation and planning affected their daily life, their ability to follow a low Phe diet or maintain employment. Many respondents described a lack of psychological support within their clinics and only one in five patients were referred to a psychologist.

Some respondents described their frustrations with their local health care teams (rather than specialist care) poor knowledge of PKU and their attitudes to treatment. Some highlighted inefficiencies, delays and even refusal of access to Foods for Special Medical Purposes (low protein foods and protein substitutes), and lack of communications between local health care and specialist teams. Some adults stated their distress when their symptoms were not believed or were trivialised and commonly dismissed as being unrelated to PKU, or they felt ignored or belittled by health professionals. It was commonly regarded that the negative responses of health professionals represented a significant barrier to successful application of care.

Although this is a UK survey, it is likely that the findings from this survey are relevant to PKU populations in other countries. Almost all societies will find a low Phe diet challenging as food and culture are inextricably linked, with food providing an important foundation for hospitality and comfort. In the UK, PKU services do not meet the expectations and needs of people with PKU, particularly as they observe that non-dietary treatments are available to others within Europe. This survey indicates that dietary management is particularly challenging for those living in poverty, poor housing, with low access to suitable 'Foods for Special Medical Purposes' and limited and uncoordinated health professional support. It will be particularly arduous for those disadvantaged to achieve life-long acceptable blood Phe control on dietary management alone.

### 14. Limitations

Our sample of adults with PKU or parents/caregivers of children were self-selected rather than drawn from a random sample, and it is unknown to what extent the sample matches the demographic characteristics of the general population or the PKU population. A high proportion of adult respondents were women (maybe because more women remain in PKU follow-up care). It is also possible that the survey respondents were more informed about PKU than the general PKU population as many were users of the NSPKU website. Adults lost to follow-up, who are a more likely to be in a negative situation, would probably have been unaware of this survey on the NSPKU website and therefore are probably under-represented in the survey, as are people without easy access to the internet. Responses were not collected directly from teenagers. We also did not match the health effects identified in our survey with the general population or other conditions

treated by diet. Our questionnaire was non-validated, and it was unclear if all the questions were understood by respondents. The experience of living with PKU is a complex one and qualitative research methods (such as one to one interviews) would be appropriate for a deeper understanding of these experiences. We did not collect any control data for the general, neurocognitive and mental health issues in the general population.

## 15. Conclusions

The results of this large survey indicate that many people with PKU and their caregivers struggle with dietary treatment. People with PKU identified significant neurocognitive, mental health and general health issues although the symptoms are not always monitored or acknowledged as PKU related. Limits on socialisation, perception of social isolation and dietary stigma are major obstacles which are difficult to overcome with conventional dietary management. The NSPKU believe it is time for UK health professionals to explore alternative or adjunct PKU treatments such as sapropterin and address the psychological support needs of people with PKU.

## Conflicts of interest

Suzanne Ford has received either funding to attend conferences or honoraria from Nutricia, Vitaflo International, Biomarin, and Mevalia. She is a member of a Nutricia Advisory Board on PKU.

Mike O'Driscoll has no conflicts of interest.

Anita MacDonald has received research funding and/or honoraria from Nutricia, Vitaflo International, Biomarin, Galen Pharmaceuticals and Mevalia. She is a member of the European Nutrition Expert Panel (Biomarin), member of Sapropterin Advisory Board (Biomarin), member of the Advisory Board entitled ELEMENT (Danone-Nutricia), and member of an Advisory Board for Arla and Applied Pharma Research.

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