



## The PKU & ME study: A qualitative exploration, through co-creative sessions, of attitudes and experience of the disease among adults with phenylketonuria in Italy



Lidia Borghi<sup>a,\*</sup>, Carlotta Moreschi<sup>a</sup>, Alessandra Toscano<sup>b</sup>, Peter Comber<sup>b</sup>, Elena Vegni<sup>a</sup>

<sup>a</sup> *Clinical Psychology, Department of Health Sciences, University of Milan, Via A. di Rudini 8, 20142 Milan, Italy*

<sup>b</sup> *Atstrat, Consulting Company focused on Co-creation sessions, Patient Support Programmes Design, Via Gallarate 105, 20151 Milan, Italy*

### ARTICLE INFO

#### Keywords:

Adherence  
Adulthood  
Co-creation sessions  
Engagement  
Patient experience  
Phenylketonuria  
Psychological factors  
Qualitative research

### ABSTRACT

**Background:** Phenylketonuria (PKU) is a hereditary metabolic disease that can be diagnosed and successfully treated from birth with a lifelong phenylalanine-restricted dietary regimen. However, optimal adherence to diet remains an issue and often progressively decreases after adolescence. The study aimed to explore the experience of adults living with PKU in order to gain insights related to their adherence to diet and engagement in managing their condition.

**Methods:** The study adopted a qualitative methodology in sessions that combined specifically designed co-creation exercises with focus group discussion. Adults with early-treated classic PKU were enrolled for 2 different sessions - one for adherent and one for non-adherent patients. The verbatim notes of both sessions and focus group were analyzed using content analysis.

**Results:** Twelve adherent and nine non-adherent adults with PKU participated. Besides the behavioral dictates of following a strict diet, adherent adults reported a positive mental approach and organizational rigor; they seemed aware of the consequences of high-phenylalanine levels, reporting that it can affect mood and consequently social interactions which they value highly. In the non-adherent group, the individuals seemed to not fully accept their disease: they were aware of the consequences of non-adherence in children but not in adults, they felt the management of PKU was an individual burden and they experienced a feeling of 'diversity' in the social context (related to eating) that caused emotional distress. PKU seemed a very influential element of the identity both for adherent and non-adherent adults, but with different consequences for the two groups. Finally, all participants reported the desire to be assisted in a healthcare setting dedicated to adults.

**Conclusions:** The findings expand the understanding of the psychological experience of adult patients with PKU in relation to their disease and its dietary requirements, highlighting specific factors that might drive tailored educational or psychological intervention to improve adherence and engagement in the care process.

### 1. Introduction

Phenylketonuria (PKU; OMIM #261600) is a rare (incidence in Europe around 1/10,000–1/15,000 births) autosomal recessive disorder of phenylalanine (phe) metabolism caused by a deficiency of the phenylalanine hydroxylase enzyme (PAH; EC 1.14.16.1), which results in increased blood concentrations of Phe and toxic accumulation in the brain [1]. While untreated infants showed severe intellectual disability and neurological abnormalities, the introduction of mandatory newborn screening tests, enabling the early detection and treatment, allows individuals who adhere to a low-phe diet to lead healthy lives [2].

Because there is currently no strong evidence regarding the safety of

discontinuing the dietary treatment in adulthood it is recommended that PKU patients follow the diet lifelong. However, as the treatment is based on a strict dietary management [3] it is acknowledged to be associated with significant patient burden [4,5], like the majority of chronic disease and treatments [6], adherence is often an issue and progressively decreases after adolescence [7,8].

A recent review has explored and summarized the consequences and challenges of PKU throughout the lifespan that seem to extend beyond the disease in itself [9]. While a huge amount of studies has been conducted on neurocognitive, behavioral, psychological and psychosocial outcomes in children, the literature has only recently highlighted some critical areas of management also in adulthood [10–12].

\* Corresponding author.

E-mail addresses: [lidia.borghi@unimi.it](mailto:lidia.borghi@unimi.it) (L. Borghi), [alessandra@atstrat.com](mailto:alessandra@atstrat.com) (A. Toscano), [peter@atstrat.com](mailto:peter@atstrat.com) (P. Comber), [elena.vegni@unimi.it](mailto:elena.vegni@unimi.it) (E. Vegni).

**Table 1**  
The eight principles behind co-creation methodology.

1. Emotional-based	Creative activities are less mediated by logic than discussions, thus facilitating the exploration of less rational, emotional aspects.
2. Multi-perspective	Different creative activities allow any subject to be explored with various approaches.
3. Targeted	Each co-creation session has a clear and defined subject and objective.
4. Tailored	The exercises of each session are specifically devised for the participants to maximize the relevance of the creative stimuli.
5. Repetitive	Each creative activity follows a similar repetitive sequence.
6. Subgroups activities	Participants are divided into subgroups who perform the creative activities simultaneously, but separately. This approach allows different ideas to emerge in the respective subgroups; this mitigates the risk of group-thinking and makes the discussion of the ideas produced by each team a rich source of information, insights, emotions, and clarifications.
7. Groups debriefing	Each session ends with a brief group discussion. It is worthwhile to notice that the last point is really not educational but behavioral.
8. Informal setting	The sessions are not recorded. Covert recording is unethical and overt recording can have a significant impact on participant spontaneity. The moderators both take verbatim notes and collect all the worksheets produced by the participants

First, the dietary management is shown to be challenging also for adults, because it is extremely restrictive: the sourcing and preparation of appropriate food is time consuming and is a significant daily burden [11,13] which has not been found to ease with increasing age [8,14].

Another critical aspect appears to be the management of interpersonal relationships associated with the maintenance of their PKU diet. As eating is also a social activity, the need to have specific and diverse food exposes the patients to frustration and exclusion [11]. These feelings may induce lack of spontaneity within social situations in the PKU adult population [10].

Third, adults with PKU are found to report high levels of depression and anxiety [11,12,15].

Finally, for women, another challenge is avoiding hyperphenylalaninemia (HPA), a maternal-fetal syndrome consisting in the teratogenic effect of high phenylalanine levels during pregnancy in PKU women [16]. While a child born with PKU can be treated with an early dietary intervention, once the damage has occurred, it is irreversible. For this reason, women with PKU have to undergo radical treatments during pregnancy that allow the PKU levels to be reduced, in order to protect the fetus [17].

These studies shed light on the importance of adherence to dietary regimen and also its costs in terms of management, psychosocial and psychological wellbeing. However, these studies are mainly grounded on quantitative research which explores the experience of PKU patients from a top-down perspective, with a priori hypothesis and areas of interest driven by the researchers or by the clinical issues. To our knowledge, no study has yet explored the experience of adults with PKU adopting a qualitative bottom-up approach starting from individuals' perspective to identify the determinants of adherence behaviors.

The present study aimed to explore the experience of adults living with PKU in order to gain insights related to their adherence to diet and engagement in managing their condition.

## 2. Materials and methods

The study adopted Co-creation sessions (CCS), a qualitative bottom-up approach, with the main focus of reaching a gradually increasing involvement of the target group in the research work by active participation [18]. Co-creative sessions combine participatory techniques and active learning, with co-authorship through group collaborative creativity and empathic transference. In this way, the target groups improve co-learning and empowerment [19].

The importance of understanding people's thoughts, drivers, challenges and ideas that are not only cognitive but also emotionally driven was the reason for choosing a methodology that combines sessions of creative exercises together with focus group discussion. Two CCS were used to explore the experience of being an adult with PKU: the first session with individuals who were strictly adherent to treatments and the second session with individuals who were non-adherent to treatments. The exercises of the second session were modulated on the target based on the findings of the first session.

### 2.1. Participants

Enrollment was conducted accessing the registers of four patient associations in Italy (AMMeC, A.P.M.M.C., Associazione IRIS, Cometa A.S.M.M.E.) and PKU Centers in various Italian regions. All subjects respecting the following inclusion criteria were potentially eligible: 1) having being diagnosed with PKU (moderate or classic) at birth; 2) requiring a life-long dietary treatment with supplementations; 3) being in an age range from 18 to 40 years old. Exclusion criteria were: 1) having children; 2) taking drug treatments such as sapropterin or others alternative treatments. For 'Adherent' group, participants had to meet the following further criteria in the previous 24 months: good (< 600  $\mu\text{mol/L}$ ) levels of blood phenylalanine for 100% of the time of the previous two years; referred adherence to diet and engagement in their care process (assessed through regular Guthrie tests and presence at the scheduled check-up visits). For 'non adherent' group, participants had to meet the following further criteria in the previous 12 month: high levels of blood phenylalanine (consistently > 600  $\mu\text{mol/L}$ ) for 100% of the time of the previous year; non-adherence to diet and a lack of engagement in their care process (assessed through irregularity of Guthrie tests and absence at scheduled check-up visits). The sampling was conducted adopting a convenience approach and trying to involve individuals with a maximum variation of socio-demographic (age, gender, region of Italy) variables.

### 2.2. Procedures

Sessions were conducted following the principles of co-creation methodology (see Table 1 for a detailed description).

Subjects decided to participate voluntarily and gave their written informed consent; participants received a fee for their participation. In each CCS, participants were divided into three subgroups (teams); each team was heterogeneous with respect to gender and geographic provenance. Two moderators facilitated the groups by presenting the creative exercise and coordinating the activity of the group.

Both of the one-day sessions had the same structure: four creative exercises were performed in succession and the session concluded with a focus group discussion. For each creative exercise: the creative activity was explained to the group; the activity was conducted autonomously and in parallel by the subgroups using the worksheets provided; each subgroup then presented their work to the group; in conclusion a discussion regarding the output was conducted with the whole group. During the presentations the two moderators autonomously took notes of what was said and occasionally asked questions to the presenter and/or the group.

The exercises are fully described in Table 2.

At the end of each session a 1-h session of focus group was conducted with all participants. The focus group made use of the worksheets from the creative exercises to discuss the specific areas of interest and aimed at:

- seeking clarification regarding any incongruence that may have

**Table 2**  
Description and characteristics of the 4 co-creation sessions divided by adherent and non-adherent groups.

Exercise	Duration	Areas of interest	Adherent group	Non-adherent group
1	30 min	<i>The 'rules' (experience and constraints) of living with PKU</i>	<b>THE 9 COMMANDMENTS OF PKU</b> Identify which are the nine commandments of PKU.	
2	20 min	<i>The motivating and de-motivating factors of adherent PKU patients</i> <i>Emotional experience and attitudes of non-adherent PKU patients</i>	<b>TIRED &amp; WIRED</b> Identify the factors that motivate you and those that get you down in relation to PKU. Choose an image, draw something or describe in a few words the image you have in mind.	<b>PKU &amp; ME</b> Choose an image that represents your emotional experience of PKU and another image that represents your attitude towards PKU. You are also free to draw something or describe in a few words the image you have in mind.
3	40 min	<i>Needs and wishes regarding communication and information in the PKU healthcare setting</i> <i>Emotional and practical issues of PKU</i>	<b>THREE TAPS</b> Identify which are three fundamental needs and wishes regarding the engagement with the healthcare setting along with the practical solutions	<b>HAMMER BLOWS</b> Decide which are the strongest "blows" that PKU gives to your life in terms of: <ul style="list-style-type: none"><li>● emotional issues</li><li>● practical issues</li></ul>
4	40 min	<i>Identify adherence and engagement facilitators for those struggling to manage PKU</i>	<b>LIFEBELT</b> Each team had to complete a poster in which a lifebelt is depicted: participants had to identify the factors which could help engage non-compliant PKU patients. The lifebelt is divided into four themes:  Practical help Motivation Information Special resources	

emerged from the work.

– giving space to spontaneous declarations regarding the subject.

As with the exercise presentations, during the focus group the two moderators autonomously took verbatim notes.

### 2.3. Data analysis

Within 24 h of the conclusion of the CCS, the two researchers who also moderated the sessions (AT, PC) separately transcribed their notes in a document that described in chronological order the events of the workshop. The two moderators then worked together following the conventional content analysis method [20], a qualitative research method of deriving results directly from data in an inductive manner, rather than from an existing predefined coding scheme, and organizing them into main themes [20]. First, the transcripts were compared and the contents examined. Both the researchers read the transcripts in order to identify the main labels of contents. In this process, a code was assigned to a text chunk of any size that represented a single requirement that was mentioned. The collection of these codes resulted in a coding scheme. Subsequently, an analytical session between the two researchers was organised to compare, discuss, fine-tune and align these two coding schemes to make sure the codes were clear, mutually exclusive and that both researchers had the same understanding of each code. In case of difference, discussion was used to reach consensus. To ensure data integrity and validity, triangulation with another researcher (LB) was adopted, and a final list of subordinate and superordinate contents were created. The final step was to summarise the main superordinate contents in themes for each of the areas of interest (exercises). The presentation of the results follows the 4 areas of interest and is split into the adherent and non-adherent groups.

## 3. Results

The study enrolled 21 young adults with PKU, divided into two groups: "Adherent" ( $n = 12$ ) and "non-adherent" ( $n = 9$ ). See Table 3 for the socio-demographic characteristics of participants. All the subjects were in full-time employment except for 3 individuals of the adherent group who were students.

The results are presented separately for the two groups, and in the order in which they were performed. Some extracts that exemplify the main themes are reported in Table 4.

**Table 3**  
Socio-demographic characteristics of participants.

Characteristics	Adherent group ( $n = 12$ )	Non-adherent group ( $n = 9$ )
<b>Gender, n (%)</b>		
Male	3 (25%)	5 (56%)
<b>Age</b>		
Mean (SD), range	25 (3.8), 21–33	22 (5.5), 22–36
<b>Geographical provenance</b>		
Northern Italy	6 (50%)	2 (22%)
Central Italy	3 (25%)	4 (44%)
Southern Italy and Islands	3 (25%)	3 (33%)

### 3.1. Adherent group

Regarding the first area of interest, i.e., the experience and constraints of living with PKU, explored by the '9 Commandments of PKU', the fundamental priorities appeared to be related to behavioral dictates: undergoing periodic visits at a PKU Center, performing regular phlebotomies, and following the diet, without skipping meals and supplements. These were felt to be essential and in adherent adults were attained through a self-imposed positive mental approach and organizational rigor.

In the second area of interest – i.e. the motivating and de-motivating factors that adherent adults experience regarding PKU - the majority of participants reported a positive relationship and approach towards food.

Some of them, however, felt some regret for what they had to forgo; while the majority reported deriving satisfaction from the food they are allowed to eat. It appears that, for this group, the mental stress of giving up a type of food is less difficult than managing the practical and social aspects of the diet, because it is a source of organizational stress and diversity. One of the motivations to be adherent to the diet was the desire to preserve important relationships, as they identified irritability and fatigue as symptoms of non-adherence which negatively affected social interactions (e.g., one participant chose an image of a couple drowning in the middle of the sea and said "When I don't follow the diet I get stressed and drown and drag down my boyfriend who tries to help me but can't and I feel sorry for him").

In fact, participants recognized that family and friends were fundamental, as mentors and support: being in a social group where there

**Table 4**  
Exemplar quotes of the themes emerged from the 4 co-creation sessions divided by adherent and non-adherent groups.

Exercise	Type of exercise	Areas of interest	Adherent group	Non-adherent group
1	The 9 commandments of PKU	The 'rules' (experience and constraints) of living with PKU	<p>"Don't let it limit you"</p> <p>"Discipline, tenaciousness and self-awareness"</p> <p>"PKU must not make you feel different"</p> <p>"Accept it, with psychophysical and psychological balance"</p>	<p>"[PKU] is not accepted, because it is difficult to manage"</p> <p>"... to see that the [Phe] values are always good for a period of time even if you aren't strictly on the diet"</p> <p>"[You] are so used to the management of the diet that now you [feel autonomous] and then, to attend a clinic seems useless and maybe makes you feel like a sick person and you do not want that feeling"</p> <p>"After years it's all the same and there's no room for improvement except, obviously, diet"</p>
2	Tired & wired	The motivating and de-motivating factors of adherent PKU patients	<p><b>Resources</b></p> <p><i>Family and social support:</i></p> <p>"The help of others (family and friends) and equilibrium"</p> <p>"The love and support of friends and family"</p> <p><i>Precision and harmonic equilibrium:</i></p> <p>Choosing an image portraying a watch "The watch is the precision of the mechanism (me doing everything right) and time passing while always trying to do better"</p> <p>Choosing an image portraying an astronaut "The astronaut represents when I'm feeling good and do everything right and I am in harmony with everyone else"</p> <p><b>Limits</b></p> <p><i>Hidden consequences:</i> "Invisibility and hiding – PKU sometimes stops me from participating in something."</p> <p><i>Critical phases:</i> "The struggle and angst of adolescence"</p> <p><i>Consequences of non-adherence:</i></p> <p>"The room in ruins is the risk associated with high Phe levels"</p> <p>"A couple drowning because when I don't follow the diet I get stressed and drown and drag down my boyfriend who tries to help me but can't and I feel sorry for him"</p>	<p><b>PKU</b></p> <p>"PKU is dangerous for children and you have to eat only vegetables"</p> <p>"I ate anything, I didn't accept PKU"</p> <p>"I concentrate on eating what is allowed"</p> <p>"PKU is a problem in social contexts, I feel judged by others, I feel different, alien, insecure and sick"</p> <p>"PKU is a lion and I am the prey, if I eat wrong it attacks me"</p> <p><b>ME</b></p> <p>"I am free and active, I don't let PKU stop me"</p> <p>"I am confused, I don't fully understand PKU and the diet (like a Picasso painting)"</p> <p>"I am a fighter, a lone wolf howling at the moon, a dragon, but also shy like a flower. Sometimes I want to run away but I don't know from what"</p> <p>"I must transform the lion into a kitten by being precise and then I can become a winner (gold medalist)"</p>
3	Three taps	Needs and wishes regarding communication and information in the PKU healthcare setting	<p>"Personal webpage with [phe] test results and tailored therapeutic indications"</p> <p>"Creation of a network at a national level"</p> <p>"The PKU clinics should periodically reserve a half-day exclusively for adult PKU patients and concentrate all the appointments of PKU adults on that occasion. This would make the ambience less pediatric and allow PKU adults to meet and share experience and moral support on PKU management"</p>	<p><b>Practical</b></p> <p>"travel is complicated because protein-free food is hard to locate and supplements are complex to transport"</p>
3	Hammer blows	Emotional and practical issues of PKU		

(continued on next page)

Table 4 (continued)

Exercise	Type of exercise	Areas of interest	Adherent group	Non-adherent group
4	Lifebelt	<b>Identify adherence and engagement facilitators for those struggling to manage PKU</b>	<p>"Learn to cook, make your own protein-free tasty food"</p> <p>"Properly manage your PKU today to be healthy in the future"</p> <p>"To manage PKU you have to be creative and resilient"</p> <p>"You should manage your PKU for those who you love and who love you"</p> <p>"Get psychological help"</p> <p>"Learn how to adapt the diet/supplements to your life not only the other way round"</p>	<p>"social occasions often involve eating and if you want to stay on diet this is always difficult"</p> <p><b>Emotional</b></p> <p>'fear of not being understood'</p> <p>'anger at always having to give explanations'</p> <p>"being singled out and bullied for being different"</p> <p>"Not eating what others eat you get isolated"</p> <p>"I do not know if I am the problem, or if it is the hasty and 'omnipotent' attitude of the doctors I have to talk to get my Phe exam results."</p> <p>"... following the diet without help, alone, feeling different, caged in a rigid diet without having physical reactions that make you sick - well, refusing food you shouldn't eat is difficult"</p> <p>"You think you have learned to manage and understand the disease, so the clinic check-ups are useful but not essential to feel good."</p> <p>"Sometimes I get angry because it seems they experimenting with me, not curing me."</p>

is no need to explain the disease, was recognized by adherent subjects as a source of well-being and normality. Equilibrium and control are felt to be essential for their wellbeing; one participant associated the image of a watch to the precision of his/her coping mechanisms "this is me while doing everything right and the time passes while I am always trying to do better".

Conversely, the demotivating and negative factors reported by adherent patients seemed to be more related to the inner emotional experience: participants reported distress, anger or a looming feeling of ruin; moreover, PKU seemed to act as an invisible force preventing the subject from doing something or interacting in social contexts (see Fig. 1 as an example).

It is of note that the negative aspects associated with PKU seemed to be more emotionally driven, and in particular linked to feeling of anxiety and powerlessness, while the solutions seemed to be predominantly rational.

Some extracts that exemplify the above-mentioned themes are reported in Table 3.

As for the third area of interest - i.e. needs and desires regarding communication and information in the PKU healthcare setting-, adherent adults reported a strong desire to feel treated as adults (leaving the pediatric centers). Moreover, participants demand greater speed and ease of obtaining the answers of their Phe test levels. Other themes that emerged were the desire for an App to calculate Phe values (Fenilometer) in food, and the need for more information (e.g., collaboration between clinics, information for aiding travel, information on protein-free products, pipeline therapies). Finally, a desire to socialize with other PKU patients for support, exchange tips/recipes and "tricks" (live and on Facebook) was commonly reported.

Regarding the fourth area of interest - i.e. perceived facilitators for adherence and engagement in PKU management adherent adults identified psychological help as the decisive factor in helping individuals who are not adherent. Others important factors that might be used to motivate the non-adherent patients were: a "shock" through exposure to the consequences of uncontrolled Phe; having more choices in terms of different types of drugs/supplements, flexibility in their use. Learning to cook and knowledge of good food recipes that respect the diet were also considered important. Finally, adherent adults reported that a crucial aspect might be the promise of feeling better and feeling better with others; they thought this promise would be more believable if non-adherent PKU adults had the opportunity to confront and compare experiences with adherent PKU adults.

### 3.2. Non-adherent group

Regarding the first area of interest - i.e. the experience and constraints of living with PKU, explored by the '9 Commandments of PKU' - non-adherent adults seem to know what they should do, they are all aware of the basic aspects of PKU management even if they choose not to respect them. The management of PKU emerged unequivocally as being a solitary burden, while the consequences, for adults, of not managing PKU correctly were unknown. The majority of non-adherent adults reported to follow a diet but not strictly (though some declared they did not make any attempt to follow a diet): for non-adherent PKU adults the meaning of "following a diet" is very subjective. They claimed to do periodic checks but admit they are not punctual and regular ("I forget to do the Guthrie tests"). Phe levels seemed to be considered as an indicator they used to look at (as children) because they perceive PKU to be a dangerous condition for infants and children but not dangerous for adults. Some participants reported that even with high values of Phe they do not follow the diet because they do not experience symptoms.

In the second area of interest - i.e. the emotional experience and attitudes towards PKU - non-adherent adults described their relationship with PKU most commonly as a conflict or a fight; the condition is experienced as an internal enemy. As reported in Table 3, a subject



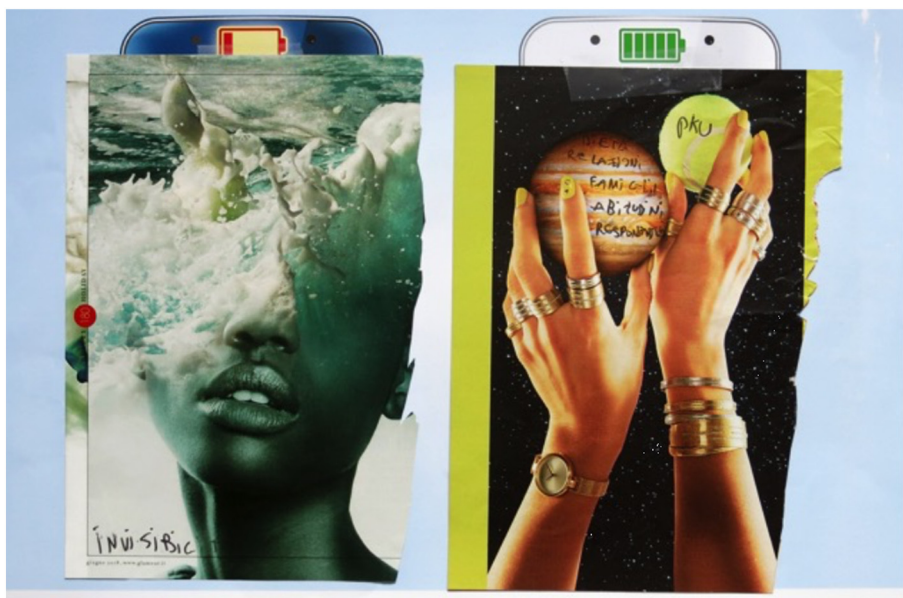


Fig. 1. Exemplar image of the co-creation exercise ‘Tired & wired’ on the motivating and de-motivating factors of adherent PKU patients.

described his/her relation with PKU in terms of “PKU is a lion and I am the prey, if I eat wrongly, it attacks me”, while the representation of PKU seemed to have to go through a sort of devaluation in order that the subject could adapt to the disease: “I must transform the lion into a kitten by being precise and then I can become a winner (gold medalist)”.

Please see Fig. 2 for the co-creative material.

Family, social networks and relationships were not perceived as a source of support (except for family members also with PKU), and the management of the condition was perceived as entirely and solely an individual responsibility.

Finally, this group of participants reported a widespread sense of uncertainty and confusion regarding PKU as a condition in advanced adulthood. As reported in Table 4, one participant choosing an image of a Picasso painting, stated “I am confused, I don’t fully understand PKU and the diet”.

As for the third area of interest - i.e. perceived emotional and practical issues concerning PKU - non-adherent adults reported that the main practical issues were related to the management of diet restriction, especially when in relation with other aspects of life.

In fact, one of the most oppressing problems seemed to be related to the possibility to travel safely and autonomously (travel meaning any place outside familiar local territory): participants reported a strong difficulty in managing the diet outside the home due to the fact that the information about the nutritional values of foods are often difficult to find and calculate. Other difficulties involving the diet management emerged: protein-free foods are available only in pharmacies; restaurants are not prepared for the provision of protein-free food. Another aspect that emerged is the perception of being obliged to continuously plan life. Simple things like where to have lunch but also bigger decisions like a pregnancy, (the female members of all three teams referenced and understood the need to plan pregnancy to avoid fetus



Fig. 2. Exemplar image of the co-creation exercise ‘PKU & me’ on the emotional experience and attitudes of non-adherent PKU patients.

development issues), at the expense of spontaneity and impulsivity.

Regarding the emotional issues of PKU, discomfort and embarrassment for the diversity caused by the disease, seemed to be the most relevant concerns. It is interesting to note that individuality and diversity was reported as a positive value for many but only in the sense of standing out and being unique for things they control and PKU, being an imposed diversity, was frequently described as a negative diversity.

Dietary restrictions seemed to affect social life, including love life – being a carrier of a hereditary genetic disorder also complicated serious amorous relationships. The difficulty in explaining their own condition (“nobody has heard of it, we always have to explain”), the fear of not being understood (“people sometimes think we are just annoying vegans, but for us it is not a choice”), the anger in having to always justify dietary needs were perceived as the more exhausting emotional issues of PKU, along with the fear of the unidentified potential consequences of the disease. Some individuals expressed the idea that the diet could become.

‘an obsession’ and being obliged to eat things they did not want to eat caused demoralization, sadness and depression. See [Table 4](#) for some examples.

Regarding the fourth area of interest - i.e. perceived facilitators for adherence and engagement in PKU management – an absence of motivation was highlighted. The part of the exercise dedicated to motivation remained empty. It was not possible to discriminate how much of their low motivation was an adverse symptom of the condition or just an indigent attitude to their condition; the absence of motivation in non-adherent adults should be further explored. As far as practical help, non-adherent PKU adults also request PKU clinics for adults (out of pediatric departments). Another crucial point is the ambivalence in the perception of doctor-patient communication and relationship with the healthcare system. On one side, the non-adherent adults expressed the impression of being disengaged from the care system, feeling left alone: this resulted in adherence problems (“... following the diet without help, alone, feeling different, caged in a rigid diet without experiencing physical reactions that make you sick - well, refusing food you shouldn't eat is difficult”), in negative feelings of impotence (“I do not know if I am the problem, or if it is the hasty and ‘omnipotent’ attitude of the doctors I have to talk to get my Phe exam results.”) and anger towards the healthcare providers (“Sometimes I get angry because it seems they are experimenting with me, not curing me.”)

Some reported the desire to be better served by the healthcare system for his/her care: for example, through immediate measurement of Phe levels to understand in real-time how diet affects blood levels.

Regarding information, non-adherent PKU adults reported a need for more information on food, concerning nutritional values and also protein-free recipes, along with more information on scientific research on PKU. Some expressed the desire for a dialogue with other adult patients both live and on digital media to exchange advice.

#### 4. Discussion

The different outcomes of the two groups - optimal versus poor adherence - seemed to be related to two aspects: one practical and the other more emotional. On the practical side, adherent adults described a meticulous organization and planning of PKU management that guaranteed a precise and strict compliance to the treatments. This optimal adherence seemed to be driven by a very tenacious mental approach in which the concept of “non-adherence” to PKU management was almost inconceivable. The same mental disposition seemed to be lacking in non-adherent adults. On a more inner level of interpretation, it could be claimed that non-adherent adults with PKU do not fully accept their disease. This finding is consistent with the study by Cazzorla and colleagues [10] who conducted a survey aimed at identifying how Italian adult patients actually experience PKU and related dietary treatment. As regards the symptoms awareness, while adherent individuals reported to perceive the disease symptoms when they had

missed to adhere to diet, the non-adherent subjects failed to perceived and recognize the symptoms. Despite anxiety and depression symptoms were not systematically recorded, from the co-creation sessions and the focus group discussion emerged that anxiety was reported in both the adherent and non-adherent group, while depression was reported only by some of the individuals in the non-adherent group. Consequently, efforts should be made to improve the disease and symptoms awareness in particular in non-adherent patients. For example, non-adherent patients might benefit of interventions aimed to organize coherent representations or beliefs about the disease and the diet, and to understand the link between the disease, the treatment and the somatic or emotional symptoms. Indeed, there is an extensive literature that highlighted the role of illness perception in treatment adherence and outcomes in medical conditions [21]. Coherently, in our study the adherent group appeared to be more aware of the need to achieve better control to help them function better in life; on a performance level, the facilitators noted that the subjects in the adherent group were more focused, faster and smarter than the non-adherents in doing the co-creation exercises.

Another difference between the two groups regards the role of social support. For adherent adults the family is perceived as the main source of influence and support in the understanding and management of PKU, while for non-adherent individuals PKU is felt to be a personal, individual burden. The role of family and social networks has been emphasized in the recent literature [22] on parents and children with PKU as they appear to be key factors for the wellbeing of the whole family, with some evidences of the link to the child's outcomes in terms of metabolic control. It is also worth noting that the views and dietary practices of adherent subjects are formed in childhood care and persist in adulthood, while non-adherent subjects tend to have a perception of PKU as a pediatric issue. It is evident that greater efforts need to be made to instill in adult PKU patients that their condition is life-long and requires life-long management. Individual tailored counselling or psychoeducational group interventions should be offered to adults with PKU in order to adapt the awareness about the disease and the diet to adulthood functioning and needs, and to change their behaviors accordingly, with a dedicate attention to the phase of transition from pediatric to adult care. In fact, regarding the needs and wishes related to the healthcare setting, the need for a non-pediatric, adult PKU clinical setting was voiced unanimously. This was also highlighted in another study [10] on adults with PKU. The fact that adults in Italy always remain the responsibility of pediatric departments is a source of psychological, emotional and also practical and organizational discomfort that can lead to inconstant care or discontinuation.

PKU appears to be a strong identifier of the self, both for adherent and non-adherent adults, but in opposite directions. While adherent adults reported they manage to live the diversity in a positive way, as a value of “uniqueness” and to be proud of how they manage the disease while pursuing their life goals, for non-adherent individuals PKU was something that makes them different (even bullied), something that is ‘other than me’ and a strong factor of emotional distress and psychological burden. Our results seem to suggest that PKU is an influential and cumbersome element for the identity of adults and that adherent patients successfully integrate the disease in their identity while non-adherent patients do not.

Adopting the transtheoretical model of the stages of change by Prochaska and di Clemente [23], it could be assumed that tailoring psychological interventions that help patients to reconstruct their identity by integrating PKU in a harmonious way might have benefit on achieving adherent behaviors.

As already highlighted, non-adherent patients reported more emotional issues related to PKU and, compared with adherent patients, seemed to be lacking either organizational and planning ability or attitude. This finding is, to our knowledge, new for the field while similar results have been found in adults with other chronic conditions perceived as ‘invisibles’.

[24]. Similar to others conditions, the PKU adults might lack to recognize symptoms associated with their condition but they still claim for new therapies. We hypothesized that this apparent incongruity might be specifically linked to the ‘invisibility’ of the PKU condition, in which the dictate of following a life-long diet is the evidence of having the disease and, in this sense, all the subjects (both the adherents and the non-adherents to diet) still wanted new therapies able to cure them, in order to have less strict dietary regimens.

Another major issue is related to the feeling of ‘diversity’ experienced in the social context, due to the difficulty in explaining their own condition, the fear of not being understood, the anger in having to always justify dietary needs. This finding is in line with a recent study [11] on parents/caregivers of children and adults with PKU showing that the perception of social isolation and the dietary stigma are the major obstacles for PKU management.

Other factors also emerged that contribute to a lack of follow up. Self-management of PKU seems viable to non-adherent adults who believe there is nothing new to learn from their (pediatric) healthcare providers. Non-adherence to diet and high Phe levels are reported by many to be asymptomatic. Moreover, even the most knowledgeable patients seemed to be unaware of the long-term consequences of not controlling phenylalanine levels in adulthood. Again, this finding has also been reported by Cazzorla and colleagues [10]. However, even though the long-term consequences are unknown and easily discounted they still create anxiety about the future as is shown by the universal desire for new therapies.

#### 4.1. Limits

Although the study has reached its goals on gaining insights and new understanding of the experience of living with PKU in adulthood, some limitations should be taken into account. Firstly, only participants from Italy were included in the study which might preclude generalization because other countries might have different practices in place regarding PKU care or social needs. Moreover, the Italian context may exacerbate certain experiences and attitudes to food due to eating being perceived as an important bonding and social activity in this country. Thus, further studies in different countries (e.g., Western and non-Western, or developed and underdeveloped countries) should be conducted in order to evaluate if the present findings are generalizable or are context-related. Secondly, the study did not examine differences in cognitive ability between adherent and non-adherent groups, which could influence certain attitudes and expectations.

Thirdly, the small number of participants further reduces the possibility to generalize; however, the qualitative methodology adopted tempers this limit and the innovative use of CCS remain a strong-point.

## 5. Conclusions

In conclusion, the present study expands the understanding of how adult patients with PKU psychologically experience their disease and the related dietary treatment, with a specific focus on adherence and engagement to the care process.

One of the most relevant findings seems to be the importance of viewing PKU as a very influential element for the identity of the people who are affected, and their ability to integrate the disease in a harmonious view of the Self seems to be crucial to achieve adherent behaviors. For this reason, psychological interventions that help individuals with PKU in understanding, integrating, or reconstructing their sense of self to include a realistic and grounded view of the disease might be effective in achieving an optimal adherence to treatment and engagement in the care process.

Finally, our findings call for a restructuring of the healthcare services for PKU care in Italy, highlighting the importance of a dedicated multidisciplinary care for PKU adults, in order to address the specific needs of adult care. So far, the majority of adults with PKU are still

treated in pediatric centers worldwide [25]). Some countries have recently tried to transit the adult care to internal medicine outpatients [26,27], while only very few medical centres offer special medical care for adult patients with inborn metabolic diseases or specifically with PKU [25,28]. Thinking of a renovation of the Italian PKU care offering will mean paying particular attention to the transition phase (i.e. adolescence) that we presume to be a crucial and bridging phase [29].

## Ethics approval and consent to participate

Subjects decided to participate voluntarily and gave their written informed consent.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Funding

None to declare.

## Authors' contributions

All Authors contributed to conception and design of the work; AT and PC contributed to the acquisition of data; LB, AT, and PC contributed to the data analysis; all authors contributed to the interpretation of data. LB and CM contributed to the draft of the work; all authors revised it critically for important intellectual contents and gave their final approval of the version to be published.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

## Acknowledgements

We thank patients and staff from all the participating sites and patients' associations for their kind collaboration and help.

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