UNIVERSITÀ DEGLI STUDI DI MILANO

Scuola di Dottorato in Scienze fisiopatologiche,

neuropsicobiologiche e assistenziali del ciclo della vita

PARENTAL PSYCHOLOGICAL ISSUES, QUALITY OF LIFE AND CORRELATIONS WITH PATIENTS' DIETARY COMPLIANCE IN PHENYLKETONURIA

Tesi di Dottorato di Ricerca di:

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Relatore:

Chiar.ma Prof.ssa Elena Vegni

Anno Accademico 2014-2015

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(Ciclo XXVIII)

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TABLE OF CONTENTS

ABSTRACT

Background. Phenylketonuria (PKU) is an inherited metabolic disease that can be diagnosed and successfully treated early from birth with a phenylalanine-restricted dietary regimen. Nevertheless, PKU parents are found to be at risk for psychological and quality of life (QoL) maladjustments. In chronic illness, parental disturbances are found to influence adherence to treatments of their children.

Objectives. The study aimed to: 1) evaluate the psychological issues and the quality of life of parents of PKU patients distinguishing the disease load from the treatment load; 2) assess if parental psychological functioning is related to blood phenylalanine (Phe) levels of their children, as indicators of metabolic control in relation to dietary compliance.

Methods. The study is a cross-sectional study involving 146 parents of both patients with PKU (who need a phe-restricted dietary regimen) and patients with a mild form (mild hyperphenylalaninemia - MHP) who do not require a dietary treatment. Socio-demographic data of both parents and patients together with patients' clinical data (patient's phenotype and patient's Phe level) were retrieved. Self-report measures of psychological distress and symptoms (SCL-90-R), anxiety (STAI-Y), depression (BDI-2), anger (STAXI-2) and quality of life (SF-36) were collected. For aim 1, the means scores of all scales were compared to the appropriate normative samples; then, differences in SCL90-R, STAI, BDI-II, STAXI-II subscales and SF-36 dimensions mean scores between parents of PKU vs parents of MHP patients were tested through MANCOVA analyses, with socio-demographic variable as covariates in order to control for potential confounders. For aim 2, to assess if the parental psychological issues and quality of life can predict the dietary compliance, logistic regressions with a block entry method were performed.

Results. Globally, parents showed psychological characteristics and quality of life comparable to the normative sample; nevertheless, out of the normative cut off were the following (in brackets, percentage of parents): psychological distress (11,5%), state (25,3%) and trait (29,1%) anxiety, depressive symptoms (16,0%), hyper-control of anger expression (16,1%) and, as concern quality of life, Bodily pain (32,6%), General health (17,4%), Vitality (14,2%), Social functioning (27,7%), Emotional functioning (14,9%), and Mental health (20,6%). Mothers (vs fathers) and parents with a low (vs high) educational level showed statistically significant poor emotional outcomes. Parents of PKU (vs MHP) patients reported statistically higher values of depressive symptoms on the somatic-affective side and lower values of Physical activity and General health QoL scales. Patients optimal Phe levels were found to be predicted (R^2=0,34, p=0.031) by the following parental psychological characteristics: high levels of depressive complaints on the somatic-affective side (β=1.52, p=0.011) and low levels on the cognitive side (β=0.59, p=0.050), high level of anger control (β=0.77, p=0.043) and low level of anger expression outward (β=1.35, p=0.032). Optimal Phe levels were predicted also by the following parental quality of life dimensions (R^2=0,25, p=0.05): a lower Vitality (β=0.93, p=0.035), a lower Social functioning (β=0.94, p=0.027) and a higher Mental health (β=1.07, p=0.043).

Conclusions. Parenting patients with phenylketonuria do not generally affect psychological wellbeing and quality of life. Specific socio-demographic conditions are more at risk of disturbances; maladjustments are also related to the dietary management load and to the effort of maintaining an optimal adherence to diet of their children. Help children to remain adherent to the diet seems to affect the parents' social functioning.

Results are useful to help clinicians to identify specific situations at risk for non adherence and may have implications for setting up interventions to improve compliance to diet, together with parental and family wellbeing.

1. BACKGROUND

1.1. Phenylketonuria: definition, causes, and consequences before the newborn screening

Phenylketonuria (PKU) (PKU; OMIM 261600) is an autosomal recessive inborn error of metabolism, caused by mutations in a gene located on the long (q) arm of chromosome 12 (Fig. 1.1). The gene codifies for the enzyme phenylalanine hydroxylase (PAH), which converts the amino acid phenylalanine to other essential compounds in the body.

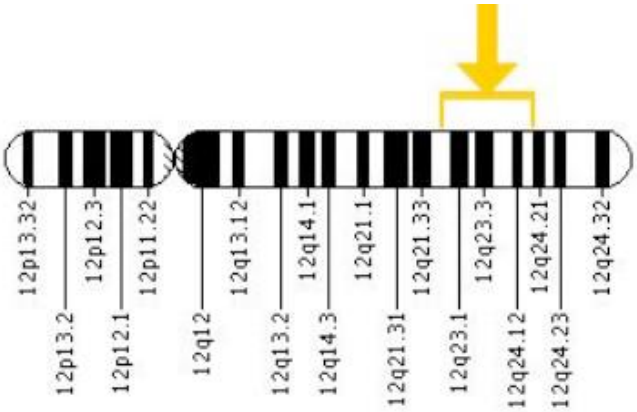

Figure 1.1. PAH gene locus

More than 400 disease-causing mutations have been found in the PAH gene, leading to PAH deficiency and causing different spectrums of disorders, including classic phenylketonuria (PKU) and hyperphenylalaninemia (a less severe accumulation of phenylalanine).

Phenylketonuria is classified as a metabolic disorder because of the deficient activity in the enzyme PAH responsible for converting the aminoacid phenylalanine (Phe) to tyrosine (Tyr) (Fig. 1.2).

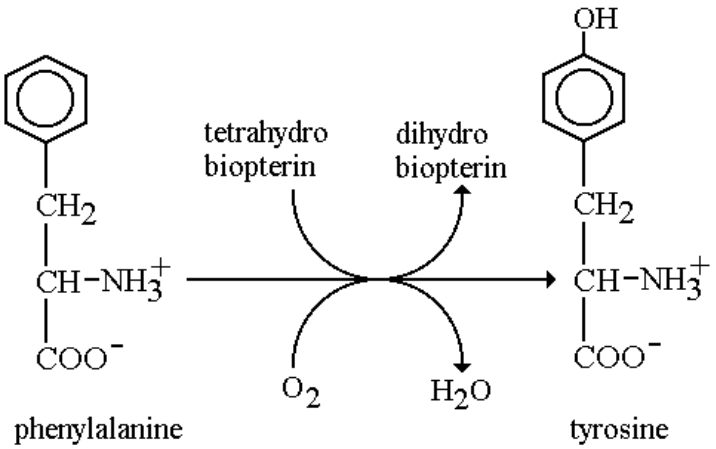

Figure 1.2. Phenylalanine to Tyrosine conversion

This enzyme is responsible for the majority of the catabolism of dietary phenylalanine and is located mainly in the liver (Fig. 1.3).

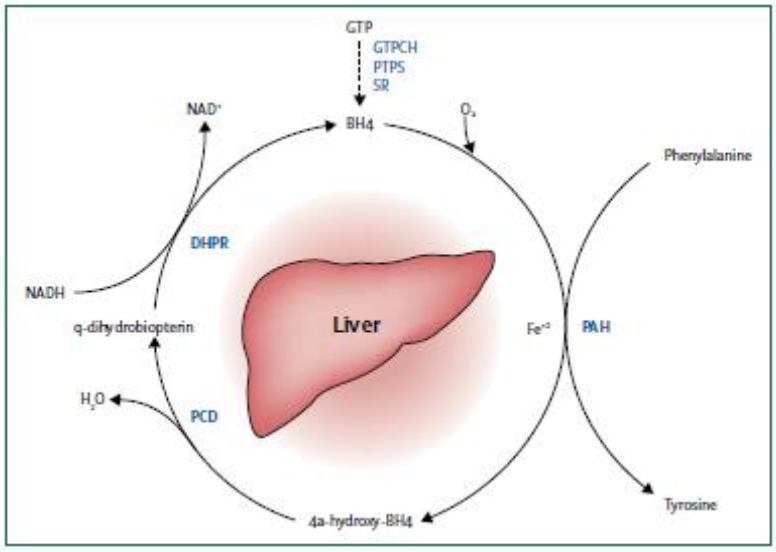

Figure 1.3. Phenylalanine hydroxylating system (Blau et al., 2010)

Loss of PAH activity, with consequently little or no conversion of phenylalanine to tyrosine, results in increased concentrations of phenylalanine in the blood and fluids throughout the body and toxic concentrations in the brain (Nussbaum et al., 2007), thus the catabolism of phenylalanine is blocked and serum levels of phenylalanine rise (hyperphenylalaninemia).

For individuals with PKU, elevated levels of Phe leads to damages of the central nervous system that can result in intellectual disability, seizures and spasticity. Several amino acids, including Phe, are important precursors used by the brain to create neurotransmitters (i.e. dopamine) (Figure 1.4).

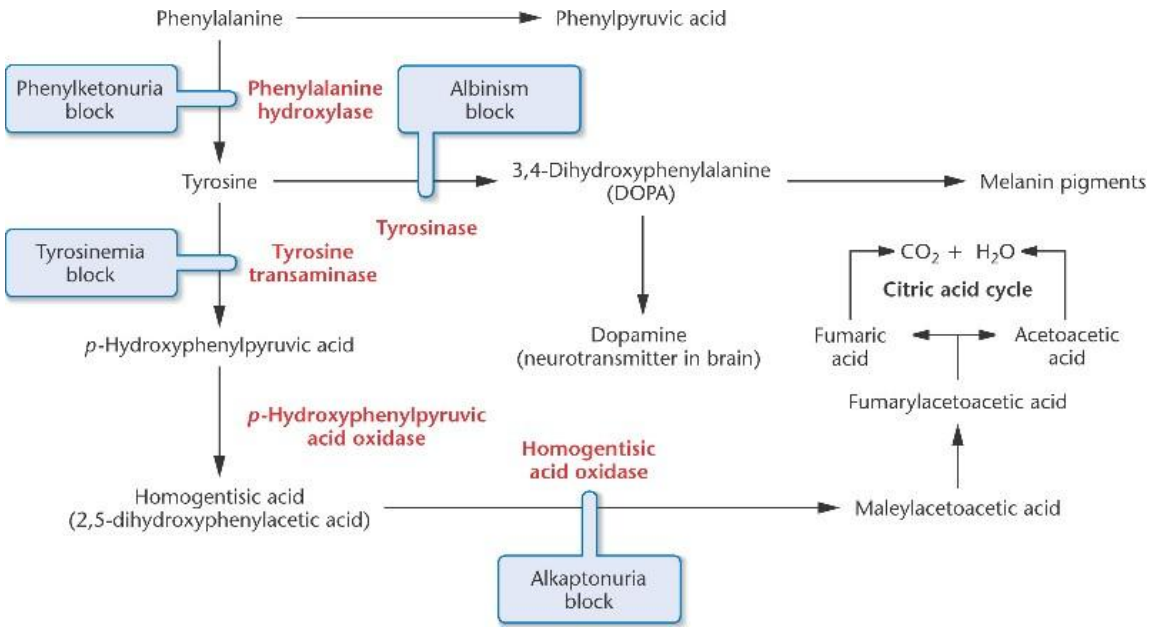

Figure 1.4. Phenylketonuria.

Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine. Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones. Excess phenylalanine also inhibits formation of melanin from tyrosine.

For these amino acids to reach their destination, they must cross over the blood-brain barrier (BBB). To cross the BBB specific amino acid transporters are shared by a variety of amino acids. As the blood Phe level increases, Phe saturates the transporter, increasing the amount of Phe crossing the BBB as well as decreasing the amount of other amino acids that use the same transporter (Pardridge, 1998). Although it is understood how Phe builds up in the body, the process by which it causes damage to the central nervous system has not yet been clarified (Nussbaum et al., 2007).

In any case, depending on the molecular genetics (see chapter 1.3), phenotypes can vary from a very mild increase in blood phenylalanine concentrations to a severe classic phenotype with pronounced hyperphenylalaninaemia, which, if untreated, results in profound and irreversible mental disability (Tab.1.1). In particular, untreated phenylketonuria is associated with progressive intellectual impairment, leading to progressive mental retardation, accompanied by a constellation of additional symptoms, which can include eczematous rash, albinism (excessively fair hair and skin) and hypopigmentation, a "musty odor" of baby's sweat and urine (due to phenylacetate, one of the ketones produced), autism, and motor deficits. Developmental problems and severe learning disabilities, aberrant behaviour and psychiatric symptoms (as hyperactivity or psychotic and depressive disorders) and seizures often become apparent as the child grows, and are the major clinical problems later in life.

Untreated PKU consequences	
Microcephaly with progressive impairment of cerebral function	Mental Disability with progressive intellectual impairment
EEG abnormalities	Seizures
Fail to obtain early developmental milestones	Autism
"Musty odor" of baby's skin, hair, sweat and urine (due to phenylacetate accumulation)	Aberrant behaviour and psychiatric symptoms
Albinism with excessively fair hair and skin	Eczematous rash and tendency to hypopigmentation
Motor Deficits	Hyperactivity

Table 1.1. Clinical features of untreated PKU

1.1.1 The newborn screening

Until the 1960s, most children born with phenylketonuria became profoundly mentally disabled, often spending their lifetime in institutional care. The foundations for the early detection and modern management of phenylketonuria were laid by three key findings: Asbjorn Fölling (1934) identified raised levels of phenylalanine in the blood (hyperphenylalaninaemia) as the underlying cause of the neuropsychological deficits; Horst Bickel (1954) introduced a low-phenylalanine diet to treat Phenylketonuria; and in 1962 Robert Guthrie introduced a diagnostic test suitable for mass screening for hyperphenylalaninaemia, in order to detect PKU before it become clinically symptomatic (the Guthrie test) (Fig. 1.5).

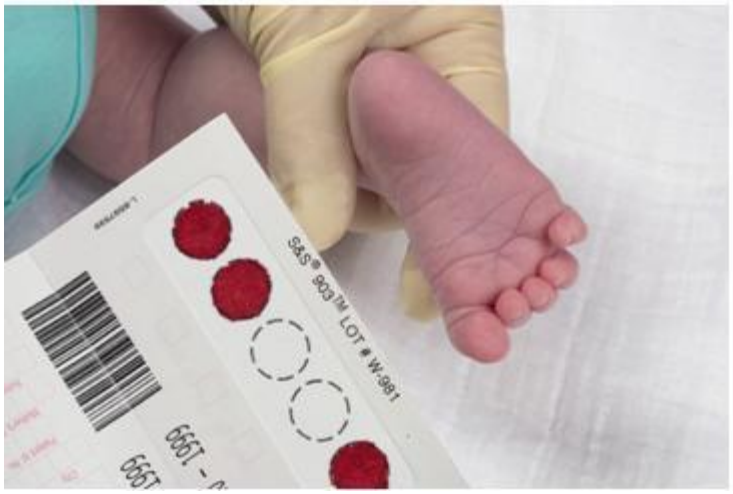

Figure 1.5. The Guthrie Test

Since the '60s , the newborn screening was gradually introduced in several countries (starting from the USA and Europe); most babies in developed countries are today screened for PKU soon after birth; PKU is in fact commonly included in the newborn screening panel of most countries, with varied detection techniques. Screening for PKU is performed on a newborn’s blood sample and done with bacterial inhibition assay (Guthrie test), immunoassays using fluorometric or photometric detection, or amino acid

measurement using tandem mass spectrometry (MS/MS). Measurements done using MS/MS determine the concentration of Phe and the ratio of Phe to tyrosine, both of which will be elevated in PKU.

In most cases, after the routine newborn screening test (typically performed 2-7 days after birth, using samples drawn by neonatal heel prick), a repeat test is done at approximately two weeks of age to verify the initial test and uncover any phenylketonuria that was initially missed.

If a child is not screened during the routine newborn screening test, the disease may present clinically with the characteristics previously described.

In contrast, early diagnosis and prompt intervention with a dietary restriction has undoubtedly allowed most individuals with phenylketonuria to avoid severe mental retardation (Demirkol et al., 2011; Giovannini et al., 2012), though such clinical disorders in a mild form are still possible.

1.1.2 The consequences after the newborn screening: early-treated PKU outcomes

As said above, in PKU children, severe neurological and functional disorders can be prevented through an early strict dietary regimen aimed to reducing blood Phe to nontoxic levels (ranging from 120–360 μmol/L). However, minor structural changes in the brain have been shown in otherwise well-treated children with hyperphenylalaninemia, as well as neurocognitive, psycho-emotional and behavioural disturbances (Sullivan, 2001; van Spronsen et al., 2011; Bone et al., 2012; Sharman et al., 2012).

Neurocognitive outcomes. Although the reasons are unknown, there are still individuals with PKU who exhibit some degree of neuropsychological dysfunction, even though they have had careful nutritional management (De Groot et al., 2010). For example, a meta-analysis of neuropsychological studies showed that adolescents and adults with

PKU perform significantly more poorly than matched controls without PKU on tests of both executive and nonexecutive functions (attention, inhibition, motor control and fine motor skills, perception/ visual spatial abilities and processing speed) with processing speed having the largest effect size (Moyle et al., 2007; Christ et al., 2010; Gentile et al., 2010; Janzen & Nguyen, 2010).

Educational achievement. Children with PKU span the full range of educational achievement but often perform less well at school than children without PKU, especially when metabolic control is suboptimal (Gassio et al., 2005). Poor performance in arithmetic/mathematics (Azen et al., 1991) and impaired ability to copy letters and geometrical designs, for example, are common.

Behavioral, emotional, social disturbances and psychiatric disorders. Behavioral impairments and psychiatric symptoms are well documented across the lifespan of individuals with PKU, even those treated from infancy. Disturbances such as hyperactivity, anxiety, low self-esteem, and social withdrawal have been noted in children with PKU (Sharman et al., 2012; Sullivan & Change, 1999; Sullivan 2001;; van Spronsen et al., 2011; Weglage et al., 1992, 1994, 2000). Depressed mood, generalized anxiety, phobias, decreased positive emotions, social immaturity, agoraphobia, panic attacks, and social isolation have been reported especially during adulthood (Bone et al., 2012; Brumm et al., 2010). Studies have reported rates of psychiatric issues among patients with PKU that were up to twice that of the general population (Burgard et al., 1994; Pietz et al., 1997).

The etiology of the elevated rate of psychosocial maladjustment in phenylketonuria is not still clear; three hypotheses has been formulated to explain it: one based on biological factors, one on psychological considerations, and the other on the interaction between those two class of factors.

From the biological point of view, increased levels of phenylalanine may lead to a reduced synthesis of dopamine and serotonin in the brain of PKU patients, resulting in an imbalance of neurotransmitters and thus contributing to the pathogenesis of psychiatric disturbances (Jusiene & Kucinskas, 2004). Supporting studies showed a positive correlation between the degree of metabolic control and the severity of emotional disorders (Smith et al., 1988; Anjema et al., 2011; Sharman et al., 2012).

The psychological perspective hypothesized that these problems are a consequence of living with a chronic condition rather than a biological effect of increased Phe levels. This perspective stresses the impact of an abnormal developmental condition and the burden of a strict and continuous dietary treatment (Feldmann et al., 2002; Weglage et al., 2000). Beyond the intra-child focus of most organic models, contemporary frameworks for studying child development increasingly emphasize the importance of interacting biological, social and psychological factors. Central to these current perspectives is the recognition of the family as the critical context of development for the young child. Parental involvement in PKU treatment is essential, because the parents are mostly responsible for the child maintaining a proper diet. In addition to the usual strain associated with caring for a newborn child, the parents of PKU children have to deal with two additional demands: 1) the grief and disappointment of having given birth to a sick child (i.e. parental feelings of guilt), 2) demands associated with learning to manage the diet. Distress and anxiety, common in PKU families especially in the first year, and a restrictive-controlling style of parenting is believed to contribute to the development of psychosocial maladjustment (Sullivan & Chang, 1999; Weglage et al., 2000).

The third hypothesis tries to gather the other two perspectives pointing out the importance of the interaction between biological and environmental factors (Feillet et al., 2010), for example how the parental and family features and strategies influence, predict or

protect PKU patients against the risk of developing mental and emotional difficulties due to their genetic predisposition.

1.2 Epidemiology

The occurrence of PKU varies worldwide. In Europe, the incidence is about 1/10,000 births, but ranges from 1/4,000 in Turkey, to 1/100,000 in Finland. In Asia, the rates vary from 1/15,000 to 1/105,000 within China, to less than 1/200,000 in Thailand. The rates in Latin American range from 1/25,000 to 1/50,000, and the incidence in the United States is about 1/15,000 live births (Blau et al., 2010). In Italy the incidence is about 1/17,000 (Williams et al., 2008).

1.3 PKU genetics and classification

PKU is known to be an autosomal recessive genetic disorder. This means both parents must have at least one mutated allele of the PAH gene and the child must inherit both mutated alleles, one from each parent. Therefore, it is not impossible for a parent with the disease to have a child without it if the other parent possesses one functional allele of the gene for PAH. The risk for two carriers to have an affected child is 25%, which leaves a 75% chance with each pregnancy that their child will not be affected. Yet, a child from two parents with PKU will inherit two mutated alleles every time, and therefore the disease (Fig. 1.6).

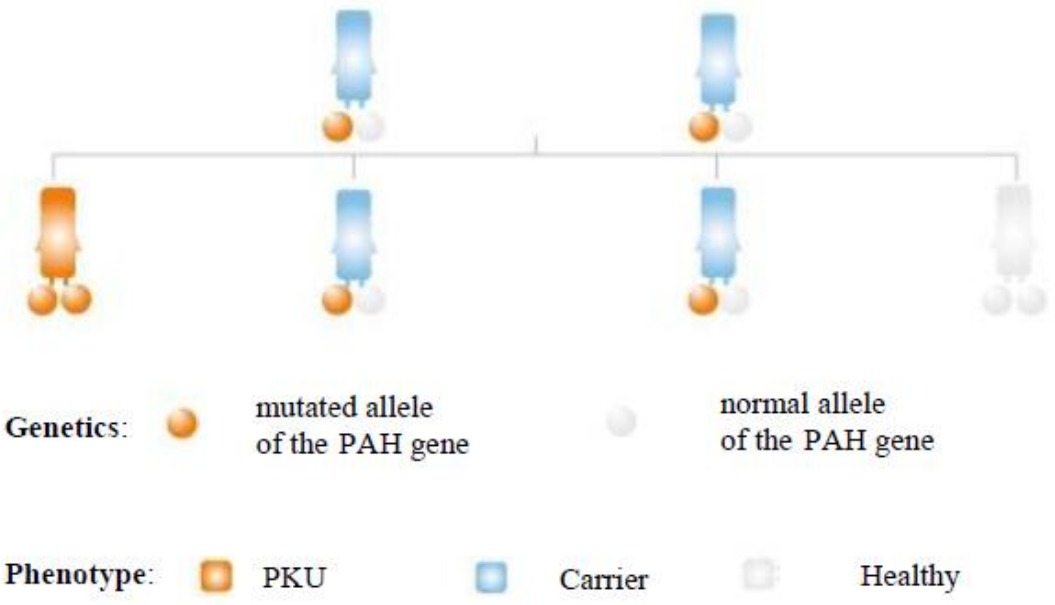

Figure 1.6. Phenylketonuria inheritance by an autosomal recessive way

The Human PAH Mutation Knowledgebase (PAHdb,) a database of naturally occurring mutations in the human PAH gene, was summarised in 2007 (Scriver, 2007) and includes a total of 548 separate mutations. The position and nature of the mutation dictates its effect on the activity of the PAH enzyme, which determines the severity of hyperphenylalaninaemia and the patient's phenotype classification (Tab. 1.2). Various combinations of mutations result in a full spectrum of metabolic phenotypes, in which the three different classifications of PKU are dependent upon the severity and the amount of Phe within an individual's blood before treatment has been started. The normal range of Phe in the blood is 50-110 μmol/L. Individuals with values of 120-360 μmol/L are considered to have mild hyperphenylalaninemia (MHP); these patients do not require dietary treatments. Individuals with a value of 360- 600 μmol/L are considered to have mild PKU, with a value of 600- 1200 μmol/L moderate PKU, and with values above 1200 μmol/L classic PKU; all of these three phenotypes require dietary treatments.

PKU CLASSIFICATION		
Metabolic phenotypes	**Blood Phe**	**Treatment**
Classic	PKU >1200 µmol/l	Dietary treatment
Moderate PKU	600–1200 µmol/l	Dietary treatment
PKU mild	360 – 600 µmol/l	Dietary treatment
Mild Hyperphenilalaninemia (MHP)	(HPA) < 360 µmol/l	No need to treat

Table 1.2. Metabolic Phenotypes of PKU based on blood Phe levels and treatment indication

1.4 Treatment: the dietary management

As just said, individuals who are diagnosed with PKU must follow a low Phe diet to prevent clinical disease manifestations from occurring, and to have optimal growth, development, and mental functioning while providing a nutritionally complete diet. The diet that individuals with PKU have to abide by is restrictive. Foods such as grain products, and all food derived from animals, need to be avoided, while others must be weighed before consumption, especially starchy vegetables. The diet does not only include making sure there are low levels of Phe being ingested, but also that proper levels of vitamins, minerals and essential fatty acids are being consumed.

The goal of the diet is to maintain plasma concentrations of Phe within an acceptable range. The acceptable, or target, range for Phe levels varies throughout the world and across ages (Blau et al., 2010) (Tab. 1.3).

	<2 years	2–6 years	7–9 years	10–12 years	13–15 years	>16 years
Australia	100–350	100–350	100–350	100–450*	100–450*	100–450*
Austria	40–240	40–240	40–240	40–900	40–900	40–1200
Croatia	130–240	130–360	130–360	130–600	130–600	130–960
Denmark	120–300 (<4 years)	120–400 (4–8 years)	120–600 (8–10 years)	120–700	120–900	120–900
France	120–300	120–300	120–300	120–600	120–900	120–1200
Germany	40–240	40–240	40–240	40–900	40–900	40–1200
Hungary	120–360	120–360	120–480	120–480	120–480 (7–14 years)	120–600 (>14 years)
Italy	120–360	120–360	120–360	120–360	120–600	120–600
Japan	120–240	120–360	180–360	180–480	180–600	180–900
Netherlands	120–360	120–360	120–360	120–360	120–600	120–600
Poland	120–360	120–360	120–360	120–720	120–720	120–720
Portugal	120–360	120–360	120–360	120–360	120–480	120–480
Spain	<360	<360	<480	<480	<720	<720
Switzerland	100–300	100–400	100–400	100–600	100–600	100–600
Turkey	60–240	60–240	60–240	60–240	60–240	60–240
UK	120–360	120–360	120–480	120–480	120–700	120–700
USA	120–360	120–360	120–360	120–360	120–600	120–900

*Some phenylketonuria centres accept a concentration of less than 700 µmol/L.

Table 1.3. Target blood phenylalanine concentrations (µmol/L) as recommended for treatment of phenylketonuria in different countries, by age grousp (Blau et al., 2010)

The National Institutes of Health has recommended Phe blood levels for individuals with PKU who are younger than twelve and those who over twelve years of age. The normal value of Phe in an adult ranges from 43-80 µmol/L, the amount of Phe recommended for those under twelve is 120-360 µmol/L, and for those over twelve it is 120-900 µmol/L, even if for adolescents Phe levels ranging between 120-600 µmol/L are recommended (National Institutes of Health Consensus Development Panel, 2001).

For individuals who are on a low Phe diet, it is important to monitor their Phe levels to make sure they are remaining within their target zones. The monitoring of blood Phe levels is typically done through blood spot analysis. While there are recommended ranges, the ideal range for an individual will depend on their age, height and weight, and their bodies'

ability to handle Phe. During infancy adjustments to an individual's diet may need to be assessed weekly, whereas later, assessments will not have to occur as close together. Then again a low dietary compliance leads to cognitive and psycho-emotional disturbances (Sullivan & Change, 1999).

Although there is data and support for the diet in individuals with PKU, there is limited knowledge on whether or not the diet is needed throughout their life. Those with PKU who were started early on with a low Phe diet are just now reaching middle age. The large majority of these individuals are neurologically healthy, but the possibility of neurological decline cannot be ruled out (Cleary, 2010). Among adult patients with PKU that claimed to be following their diet, 53% were found to be above the target level (Modan-Moses et al., 2007); and those with Phe levels above target showed significantly improved reaction time and sustained attention after four to five weeks of strict diet control (Schmidt et al., 1994).

The full impact of adhering to the diet in adulthood may not yet be understood, but for women who are pregnant, the importance of maintaining the diet is well known, as Phe can be transported across the placenta to the developing fetus, resulting in severe birth defects and developmental delay (Committee on Genetics, 2008). For women who have PKU, it is ideal for pregnancies to be planned, for them to have Phe levels under control before becoming pregnant, and maintaining a blood Phe level of 120-360 μmol/L for the duration of the pregnancy (Koch et al., 2010).

Dietary restriction of phenylalanine remains the mainstay of treatment, thus an active area of research focuses on factors facilitating/preventing adherence to treatment; among them some are related to patients but many regard parents and family characteristics and functioning. In fact, patients and their families has to face various challenges across the lifespan, that vary as a function of the children's developmental phases and the way they cope with them can influence compliance to diet and patients' psychological well-being.

1.5 PKU management through the lifespan: patients and parents challenges

The patient outcome is much more complex than the sole consequences of Phe levels on the brain. PKU will induce many disturbances in the family structure, and diet treatment by itself may have some specific burden to the individual with PKU and their family. The overall consequences of PKU extend beyond the disease itself. A recent review has explored and summarized the consequences and challenges of PKU throughout the lifespan (Feillet et al., 2010).

Diagnosis announcement: from initial shock to reality

The first step in PKU management following neonatal screening is the announcement of diagnosis. This is always a traumatic experience for parents, who have to come to terms with their baby's health challenges ahead. Even after many years, when the child's PKU is well managed and everyone in the family has adjusted to the new lifestyle, parents can still describe the terrible moment when the diagnosis was first announced (Lord et al., 2008). This initial shock of diagnosis is heightened since the baby with PKU initially appears to be in good health. The diagnosis may seem like a complete intrusion of the medical world into a family who was otherwise unprepared with no prior signals of a disturbance.

From infancy and to the early school years

The quality of metabolic control during infancy is strongly related to the children IQ, which is why a strict diet is recommended for the first 10 years of life. Nevertheless, even when metabolic control is maintained, some children experience attention deficit hyperactivity disorder (ADHD), which can lead to poor academic performance (Kalverboer et al., 1994; Salardi et al., 1992). The onset of ADHD may be due to a modifying gene known as MAO-B, which can trigger the increase of phenylethylamine (a toxic metabolite of Phe) when it is impaired (Ghozlan et al., 2004). Moreover,

neuropsychological studies have shown that children with PKU face some difficulties in mathematics (Pennington et al., 1985).

Failure of PKU treatment may be related to parents' inability to administer a low-Phe diet to their child. Reasons for failure can be attributed to parents and family functioning and backgrounds (Olsson & Montgomery, 2007; Shulman et al., 1991). Some parents cannot bring themselves to impose the diet on their child (Jusiene & Kucinskas, 2004). The success of parents in enforcing adherence to the diet often appears to parallel their general parenting skills. Those parents who are themselves accepting of the diet and view it as non-negotiable with the child typically exhibit the greatest success. The stress of having to administer the diet can be worse on the family than the risk on the child's health.

During adolescence

The main challenge in this view during the period of adolescence is the typical relaxation of the diet that occurs in this age group, regardless of the guidelines proposed by the medical team. There is an absence of perception of any immediate harm linked with a relaxed diet, and the benefit and pleasure of food becomes more important to the individual. The primary obstacles often cited to better adherence are time constraints and stress associated with food preparation and record-keeping, and the restrictions imposed on social life (Bilginsoy et al., 2005). These obstacles can be amplified by parental maladjustment to chronic illness (Jusiene & Kucinskas, 2004).

Many studies have reported psychological disturbances in older children or adolescents with PKU (Weglage et al., 1992; Burgard et al., 1994; Weglage et al., 2000; Sullivan, 2001; Jusiene et al., 2001). Internalizing problems such as depressive mood, anxiety, physical complaints, or social isolation are significantly more common in individuals with PKU, whereas externalizing problems are not (Burgard et al., 1994; Jusiene et al., 2001). Weglage et al. (1992; 2000) also showed that patients are characterized by less autonomy, more negative evaluation of their scholastic ability, less achievement motivation, low

frustration tolerance, more negative self-description, less extroversion and impulsiveness, a feeling of not being quite healthy, and feeling that they are less independent. Individuals with PKU may see their social situation as being distinctly restricted. These psychological attributes have been found equally in patients with diabetes and may be related to the burden of a chronic condition (Jusiene et al., 2001).

During adulthood

In adulthood, individuals with PKU face challenges that involve interpersonal relationships associated with the maintenance of their PKU diet, as well as the basic incompatibility between the PKU diet and many lifestyle demands (Frank et al., 2007). In women, one of the main behavioral goals, as explained above, is the prevention of an unplanned pregnancy.

1.6 Phenylketonuria in families: the impact of PKU on parents

Since PKU is an autosomal recessive disorder, it can be inferred that the parents of affected individuals are obligate carriers. Those who have only one PAH mutation (e.g., parents of a child with phenylketonuria, unaffected sibling) are carriers (Figure 1.7).

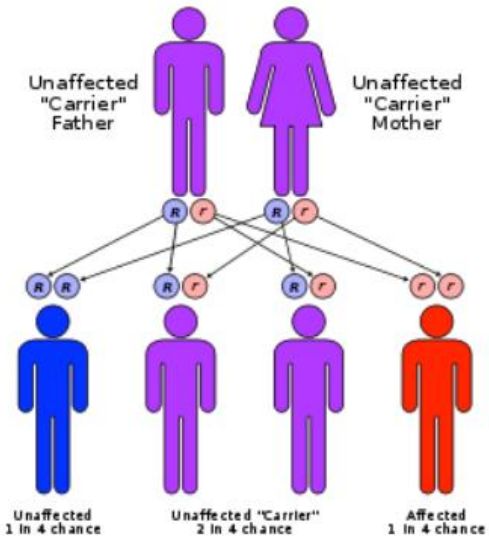

Figure 1.7. Parents of PKU children are obligate carriers for PAH mutated allele

It is presumed that such individuals have below normal phenylalanine hydroxylase levels since it has been repeatedly demonstrated that carriers have a reduced tolerance to a phenylalanine load. Whether or not these persons share other biochemical characteristics with the homozygous phenylketonuric, such as reduced serotonin and catecholamine levels, has currently not been clarified. It has been suggested, that persons heterozygeous for phenylketonuria are more apt to suffer from psychopathology than other individuals (Penrose, 1935). However, the studies on psychological wellbeing of parents of PKU patients showed inconsistent results: various has found psychological and quality of life disturbances among parents and unaffected siblings of PKU patients (Fisch et al., 1981; Jusiene & Kucinskas, 2004; Kuznetsova, 1972; Lord et al., 2005, 2008; Mahmoudi-Gharaei et al., 2011); but others highlighted that parents have a good psychological adjustment (Blumenthal, 1967; Fidika et al., 2013; ten Hoedt et al., 2011).

It could be important to evaluate the impact of PKU on families and to clarify what can be the origin of these disturbances. Within this clarification effort, a theoretical model base on the perspectives used to explain patients' psychological disorders could be applied also to parents.

Within a biological perspective, if we think of PKU as an autosomal recessive disorder, parents are carriers, so it would be important to study the presence of emotional and behavioral problems related to being biologically heterozygous for PKU gene (a gene that altered the neurotransmitters involved in emotional and behavioral regulation, i.e. dopamine). This perspective would be coherent to a specific psychiatric literature that has focused on studying families who include individuals with psychiatric disorders (as schizophrenia, bipolar disorder or autism) to detect relatives who are carriers of the genes (or polymorphisms) involved in those disorder, and who showed smoothed manifestations of the clinical symptoms, traits associated with the clinical disorder (called endophenotypes). For example, a recent meta-analysis (Lavoie et al., 2013) has highlighted

that social cognition (mentalizing, emotional processing, social perception, social knowledge and/or attributional style, theory of mind) is globally affected in first-degree relatives of people with schizophrenia (who are carrier of specific polymorphisms), suggesting that social cognition deficits in schizophrenic families may be related to a genetic vulnerability for the disorder.

From a psychosocial point of view, PKU can be seen as a chronic disease that requires a rigorous therapeutic treatment in which parental involvement is very heavy and burdensome, with potential implications for parents' emotional distress and quality of life. Reoccurring health-related concerns or treatment adherence problems, together with feeling of guilty for transferring PKU gene (Eiser, 1985) and trauma reactions to the diagnosis or grief response to the loss of a normal healthy child (Ashton & Ashton, 2000) may constitute chronic stressors for parents (Streisand & Tercyak, 2004), challenge parents self efficacy, psychological wellbeing and quality of life. This perspective would be consistent with previous research showed that parents of chronically ill children (diabetes, asthma, cancer, etc) are at risk of developing psychological disorders and psychosocial problems and to have poorer health than parents of healthy children (Cohen, 1999)

A systematic review of the literature regarding psychological issues among parents of PKU children has been conducted[1]. Here we illustrate the main thematic areas emerging from all the included studies (n=17) (Fig. 1.8).

[1] Borghi et al. (2015). Psychological issues in parenting children with phenylketonuria. A systematic narrative review of the existing literature. Submitted manuscript.

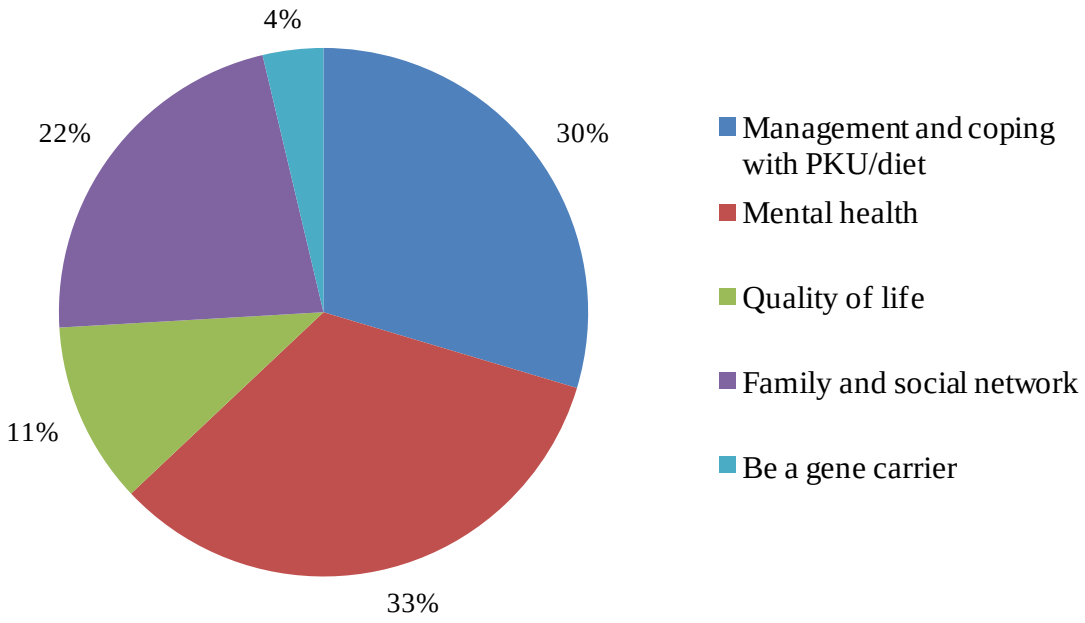

Figure 1.8. Thematic issues emerging from a systematic review of the literature regarding psychological issues among parents of PKU patients

We did not set any time constrain, in order to collect all the studies on the topic of interested; included studies ranged from 1967 to 2013. To note that the more dated studies regarded parents' mental health within a biological perspective; then, studies focused mainly on parental relationships both in family and social networks; only recently, studies concerned parental strategies to manage and cope with PKU/diet and parental quality of life, shifting the focus towards a psycho-social perspective.

2. OBJECTIVES

2.1 Need for this Study

As regards parents of PKU children, there is only little knowledge about psychological adjustment and about the etiology of these potential disturbances, either they are considered to be manifestations of being a PKU carrier or reactions to have a child with a chronic disease.

The information that will be learned from these families will help medical professionals provide a higher standard of care to these families by providing relevant information and by setting up interventions that are tailored to their needs.

As regard PKU patients, the benefits of newborn PKU testing and being on a low Phe diet are known and understood. It is also known that patients with PKU may shows psychological maladjustment, that are partially related to non adherence to diet and resulting higher phenylalanine levels. Only a few studies, however, have explored the compliance to treatment of PKU children in the context of parent-related factors. Such investigations could shed some light on environmental factors that influence the patients' blood phenylalanine levels and may covary with measures of psychological functioning across the lifespan (Sullivan & Chang, 1999).

2.2 Hypothesis and Study Objectives

This study seek to answer three main questions. The first is to determine if parents of children with phenylketonuria suffer from any psychological maladjustment compared to the general population. The second is consequent to the first, that is: if parents show psychological disturbances are them related to be a PAH gene carrier or to the stress of having a child with a chronic disease. This could be clarify comparing psychological issues

of parents of PKU children who need a chronic management of the illness (dietary treatment along the lifespan) with parents of MHP children that are always heterozygote for the mutated gene but whose children do not need dietary treatment. Finally, we would evaluate the role of parental psychological issues on blood phenylalanine levels, that are the results of compliance to diet and that could be related to patients psychological wellbeing.

The study aims therefore are to:

1) evaluate parents psychological issues and quality of life with two focus:

a) among the whole population of PKU parents (compared to the normative scores for the general population)

b) comparing those measures between parents of PKU children (who have to follow a phe-restricted dietary regimen) vs parents of MHP children (who not need to be treated)

2) evaluate if parental psychological issues and quality of life predict blood Phe levels (dietary compliance) of their sons/daughters.

3. MATERIALS AND METHODS

3.1 Participants

Participants were consecutively recruited at the Clinic of Metabolic Disorder, Department of Paediatrics, San Paolo Hospital, Milan, from July 2013 to April 2015.

The neonatal screening for HPA is obligatory by law in Italy since 05/02/1992, but executed in Lombardy up from 01/01/1977. Therefore, every newborn screened for hyperphenylalaninemia, if found to be positive, is sent to our centre for diagnosis confirmation; thus our centre is one of the main centres that provides management for children with PKU in Italy.

The sample consisted of one or both parents from families with a child with PKU o MHP with no age limits. If families had more than one child with PKU within the age range, data were collected in relation to the younger child with PKU.

Exclusion criteria were: parents' psychiatric history and inability to understand Italian.

3.2 Data collection

Participants were recruited in the waiting room at the time of their children's clinic visit at the outpatient for metabolic disorders of the Paediatric Department by a qualified psychologist researcher. Participating parents attended a single assessment session lasting about 60 min in which they were provided with a packet of self-report measures which they were asked to fully complete and return.

Self-reported psychological data included measures of: psychological distress (Symptom Check List 90-R; State-Trait Anxiety Inventory; Beck Depression Inventory-II); aggressiveness and modality of anger management (State-Trait Anger Expression Inventory-II - STAXI), and quality of life (Short-Form Health Survey 36 - SF-36). Parents

and children socio-demographic were collected through a specific form; patients' blood phenylalanine level of the visit in which parents filled out the questionnaires were retrieved from the medical records.

The study protocol was approved by the San Paolo Hospital Ethics Committee. All participants gave informed written consent before entering the study.

3.3 Measures and instruments

- *Parents socio-demographic data*: parents' age, relational status, educational level and professional condition were collected in order to control for possible confounders or to identify risk factors for the psychological assessment.
- *Patients' data*: patients' age, gender and phenotype classification were also collected from medical records. Patients were divided in two groups:
  - Group 1: **PKU patients** who are individuals periodically monitored at our Department from diagnosis and who have started the dietary treatment within first six weeks of life based on Phe-free protein substitutes and vegetal foods with a low Phe content, according to their dietary requirements.
  - Group 2: **MHP patients** who were allowed to follow an unrestricted dietary regimen and recommended routine dietary advice as used for healthy children.

Psychological issues - psychological distress, anxiety and depressive symptoms, aggressiveness and modality of anger management – and quality of life were evaluated by means of the following self-report scales.

- *Psychological symptoms and distress (SCL-90-R)*

  Parents' psychological distress was measured using **Symptom Checklist-90-Revision (SCL-90-R)**, which is a multidimensional, self-report symptom inventory developed by Derogatis et al.(1976; 1994). The SCL-90-R (Derogatis et al., 1994: Sarno et al., 2011) is a 90 items questionnaire rated on a five-point Likert scale (ranging from "0=no problem" to "4=very serious"). It evaluates a broad range of psychological problems and symptoms of psychopathology clustered in 9 primary scales (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism). It also includes 3 Global Indices: Global Severity Index (GSI), designed to measure overall psychological distress; Positive Symptom Distress Index (PSDI), measuring the intensity of symptoms; Positive Symptom Total (PST), i.e. number of self-reported symptoms. Higher scores on scales and indexes of the SCL-90-R indicate higher distress. The Italian version of the questionnaire showed good internal coherence for all subscales (Cronbach alpha values between 0.70 and 0.96) (Prunas et al., 2012).

- *Anxiety (STAI-Y)*

  Parents anxiety issues were assessed using the Italian version (adapted by Pedrabissi & Santinello, 1989) of the State-Trait Anxiety Inventory-Form Y (STAI-Y) (Spielberger et al., 1983). The questionnaire differentiates between temporary or emotional state anxiety and long standing personality trait anxiety in adults. The STAI-Y is therefore divided into two sections, each composed of twenty four-point Likert items: STAI-Y1 assesses state anxiety, that is the current psychological condition of each subject, whereas the STAI-Y2 investigates the trait anxiety, that is the subject's usual state of mind. The Italian version of the STAI-Y has shown a

good internal consistency (Cronbach's alpha coefficient ranges from 0.91 to 0.95 for the Y1 subscale and from 0.85 to 0.90 for the Y2 subscale) and a good test-retest reliability (0.49 for the Y1 and 0.82 for the Y2 subscale) (Spielberger et al., 2012).

- *Depression (BDI-2)*

Parents depressive symptoms were evaluated using the Italian adaptation (Beck et al., 2006) Beck Depression Inventory-2nd Edition (BDI-2) (Beck et al., 1996), a 21-item self-report inventory designed to assess the presence and severity of depressive symptoms in the past 2 weeks in clinical and nonclinical samples. It is rated on a 4-point Likert-type scale ranging from 0 to 3 based on severity of each item. Scores range from 0 (no symptoms) to 63 (very severe symptoms); total scores can be categorized as minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63) (Beck et al., 1996). In the Italian version, a score of 12 has been identified as an optimal cut-off to discriminate individuals with and without problems of depression in the Italian population (Beck et al., 2006).

The BDI-2 possesses excellent internal reliability (α = 0.90–0.92) and test-retest reliability (r=0.93) (Beck et al., 1996; Beck et al., 2006).

The psychometric properties of the scale are supported in clinical and nonclinical samples by an extensive literature (Arbisi, 2001); its structure has been examined using factor analysis (Ward, 2006), revealing a two-factor solution that comprises a cognitive factor and a somatic-affective factor in non-clinical individuals (Beck et al., 2006). Separate scores for each factor were calculated for each participant.

- *Anger and aggressiveness (STAXI-II)*

  Participants' state and trait anger and aggressiveness were evaluated using the State-Trait-Anger-Expression-Inventory-2nd Edition (STAXI-2; Spielberger, 1999), which is a self-report questionnaire composed of 57-items on a 4-point scale. The instrument is composed of six scales, five subscales, and an Anger Expression Index, and they measure five different dimensions: how a person feels angry at a given moment (State-Anger), how frequently, easily, and intensely the person feels angry (Trait-Anger) and what the person does when feeling angry (e.g. express or control the anger) (Anger Expression-In, Anger Expression-Out, Anger Control-In, Anger Control-Out). Higher scores indicating higher levels of state and trait anger, and a prevalence on the modality to cope with anger. The Italian version has shown good validity and internal consistency (Cronbach's alpha coefficient ranges from 0.74 to 0.95) (Comunian, 2004).

- *Quality of life (SF-36)*

  Parents' quality of life (QoL) was assessed using the Italian version of the MOS 36-Item Short Form Health Survey (SF-36) (Ware & Sherbourne, 1992; Apolone & Mosconi, 1998), a widely used and validated instrument containing a total of eight subscales, namely Physical Functioning (activity), Physical Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Functioning and Mental Health. The subscales scores range between 0 and 100, with lower scores indicating poorer QoL and a higher concern in the specific domain. The questionnaire shows good internal consistency for all the subscales (Cronbach's alpha values range from 0.77 to 0.93). In addition, the subscales are combined to yield two summary health status measures, the Physical Sum scale and the Psychological Sum scale (Ware & Sherbourne, 1992; Apolone et al., 2000).

- *Dietary compliance indicator*

  Patients' blood phenylalanine levels of the day in which parents complete the self-report scales were collected from medical records. Blood phenylalanine levels were determined by the Guthrie bacterial inhibition assay. Compliance was evaluated according to age adjusted reference threshold values of plasma Phe as suggested by Scriver; in particular, blood phenylalanine levels of PKU patients under dietary regimen (group 1) were considered indexes of compliance to diet if levels were <360 (for children under 13 yrs) and <600 (for children older than 13 years). Patients current Phe levels were considered as a representative index of metabolic control (Antshel et al., 2004) and an indicator of dietary compliance.

3.4 Data analysis

Preliminary analysis included a description of parents' socio-demographic characteristics, patients socio-demographic and patients' clinical data. Frequencies and percentages were used for discrete variables; means, standard deviations, and variances for continuous variables.

Descriptive statistics were also performed to describe the parents' psychological and QoL characteristics; t-tests and one-way ANOVA were used to compare psychological and QoL outcomes between different socio-demographic and clinical conditions.

For all the continuous variables, Skewness e Kurtosis were used to assess the normality of the distribution. When either the indexes were suboptimal, the removal of outliers was conducted until Skewness and Kurtosis values have reached sufficiently acceptable in order that parametric tests can be applied; when it was not possible to normalize the scales non-parametric tests were used.

For aim 1, differences in SCL90-R subscales, STAI, BDI-II, STAXI-II subscales and SF-36 dimensions mean scores between parents PKU patients vs parents of MHP patients were tested through MANCOVA analyses. Parents socio-demographic characteristics were used as covariates, in order to control to potential confounders. Patients' phenotypes (divided in two groups: PKU vs MHP) and patients' age were insert as independent variables.

MANCOVA were performed for STAI, BDI, STAXI expression Subscales, ANCOVA were used for GSI SCL-90-R index and trait-STAXI, Kruskal-Wallis test was used for state-STAXI.

For aim 2, to assess if the parental psychological issues and quality of life can predict the dietary compliance logistic regressions with a block entry method were conducted; Durbin-Watson test were performed in order to verify that the residual were not correlated (values has to range 1,5-2,5).

Two-tailed statistical analysis was performed using SPSS for Windows 21.0 software (SPSS Inc., Chicago, IL, USA) with statistical significance set at a level of $p \leq 0.05$.

4. RESULTS

4.1 Preliminary analysis

Parents contacted for the study were n=217, of which 88% (n=190) accepted the initial proposal and n=146 completed and returned all the questionnaires, resulting in a 68% response rate. Participating families involved 146 parents of 101 children. The non participating parents (n =27) did not differ significantly from the study sample when compared on available demographic data (patient age, patient gender, patient's phenotype: PKU/MHP); fathers refuse more than mothers. Reasons for refusals were mostly the time commitment required for the study and the parents time constraints; another reason was the personal nature of the information sought.

4.2 Socio-demographic and clinical characteristics of the sample

The total sample consisted of n=146 parents of patients with phenylketonuria (n=101).

The Parent Sample

From 101 families, data were available for 86 mothers and 60 fathers.

The mean age of mothers was 40.5 years (SD = 6.8, range 23–62 years), and the mean age of fathers was 43.6 years (SD=7.5, range 30–63 years). Mothers mean age was significantly lower than father one (t=2.5, p=0.012). Parents were mainly cohabiting or married, but 20% of them were single or divorced.

Most of the mothers (76%, n=62) and fathers (97%, n = 58) had a professional condition; the majority had a high or graduate educational level (69%, n=57 of mothers and 64%, n = 35 of fathers). While mothers and fathers did not differ for educational level (χ^2=1.01, p=0.6), mothers were more frequently unemployed compared to fathers (χ^2=11, p=0.001). Parents came from various regions of Italy.

The patient sample

Of the 101 patients, 52 were male and 49 were female. The mean age of the patients was 8.8 years (SD=7.01, range = 1 month – 37 years).

All children had a form of phenylketonuria. Just over half of patients (60%) had a diagnosis of classic/moderate PKU requiring phe-restricted dietary regimen and regular blood tests (group 1); 40% had MHP requiring monitoring but no diet restriction (group 2).

4.3 Socio-demographic comparison between parents of PKU and of MHP patients

There are no differences between parents of children requiring dietary treatment and parents of children requiring only to be monitored for the socio-demographic characteristics (Table 4.1).

	Parents of PKU patients	**Parents of MHP patients**	***p***
Relationship status, % (n)			0.44
Single/divorced	19 % (16)	24 % (13)	
Cohabiting/married	81 % (70)	76 % (41)	
Educational level, % (n)			0.15
Primary	30 % (25)	38% (20)	
High school	49 % (40)	32 % (17)	
Graduate	21 % (17)	30 % (16)	
Profession, % (n)			0.73
Professional conditions	85 % (73)	83 % (43)	
Non professional conditions (housewives, students, unemployed)	15 % (13)	17 % (9)	

Table 4.1 Comparison of socio demographic characteristics between parents of PKU patients and parents of MHP patients

4.4 Parents psychological issues and quality of life compared to the normative sample

Parents' mean scores of SCL-90-R, STAI, BDI-II and STAXI-II subscales and indexes were all within the normal ranges; nevertheless, some of them reported clinical psychological distress (GSI > 1), state and trait anxiety, depression and an extreme tendency to control the anger expression outward (Table 4.2).

Psychological distress	Anxiety	Depression	Anger control
Gobal Severity Iindex 11,5%	State Anxiety 25,3% Trait Anxiety 29,1%	BDI 16%	Control out 16,1%

Table 4.2 Clinical psychological features of parents

All the parents' mean scores of the SF-36 subscales were also within the normal ranges; but some of them reported a poor quality of life in different domains, both on the physical and on the emotional field (Table 4.3).

Bodily pain	General health	Vitality	Social functioning	Emotional functioning	Mental health
32,6%	17,4%	14,2%	27,7%	14,9%	20,6%

Table 4.3 Altered quality of life domains among parents

Mothers reported more psychological distress, were more anxious, depressed and angry and more frequently presented an altered quality of life in the domains of emotional well-being than fathers (Figure 4.4-4.6)

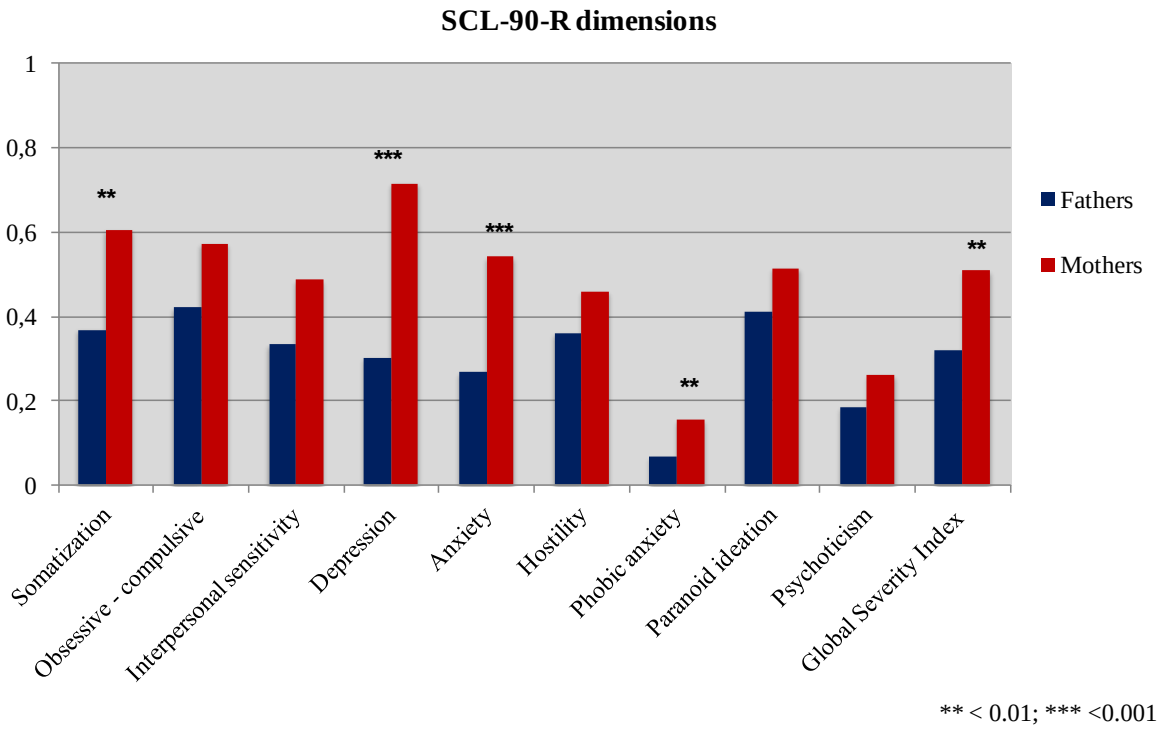

Figure 4.4 Psychological disturbances among mothers and fathers

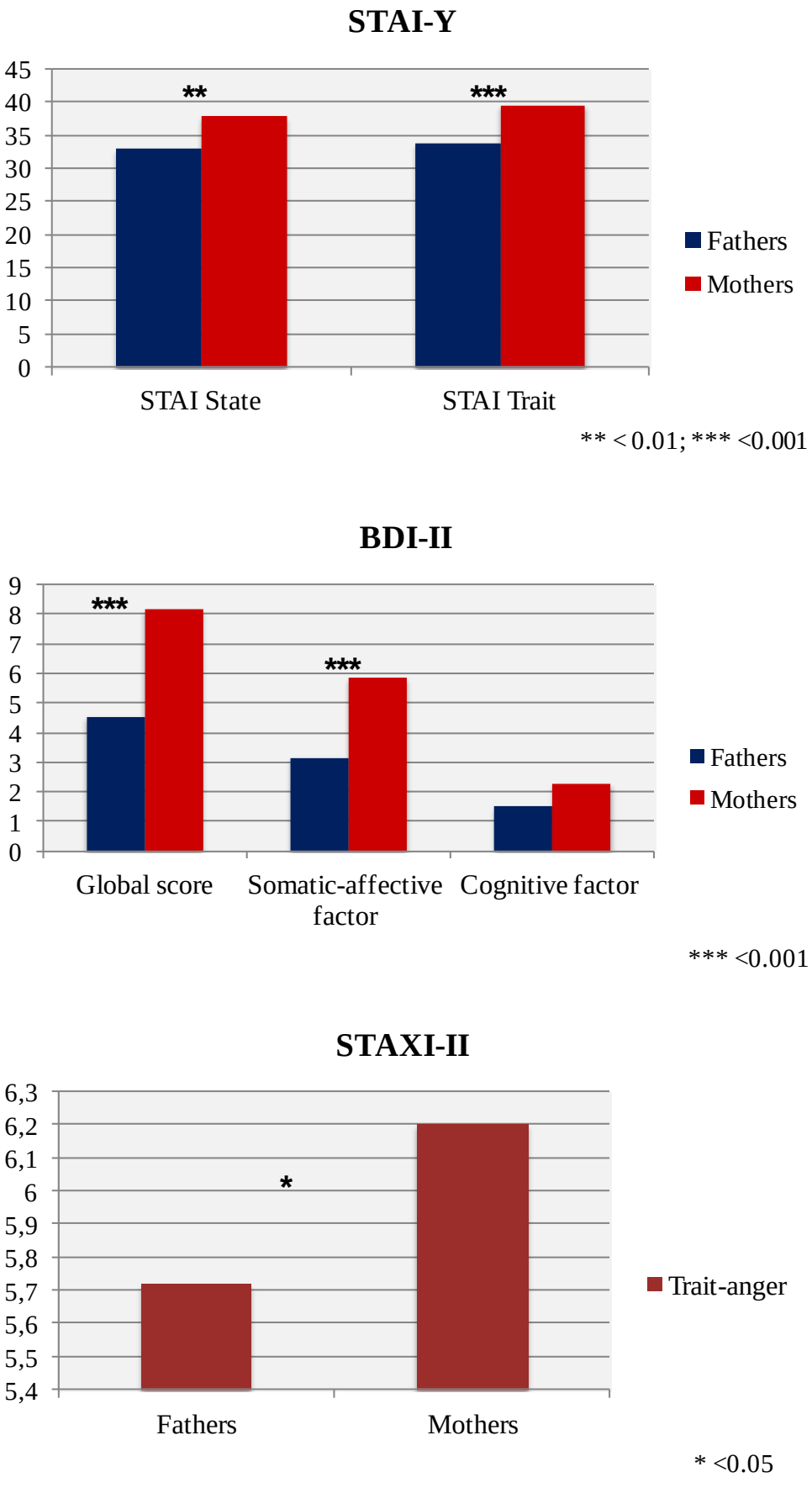

Figure 4.5 Anxiety, depression and anger among mothers and fathers

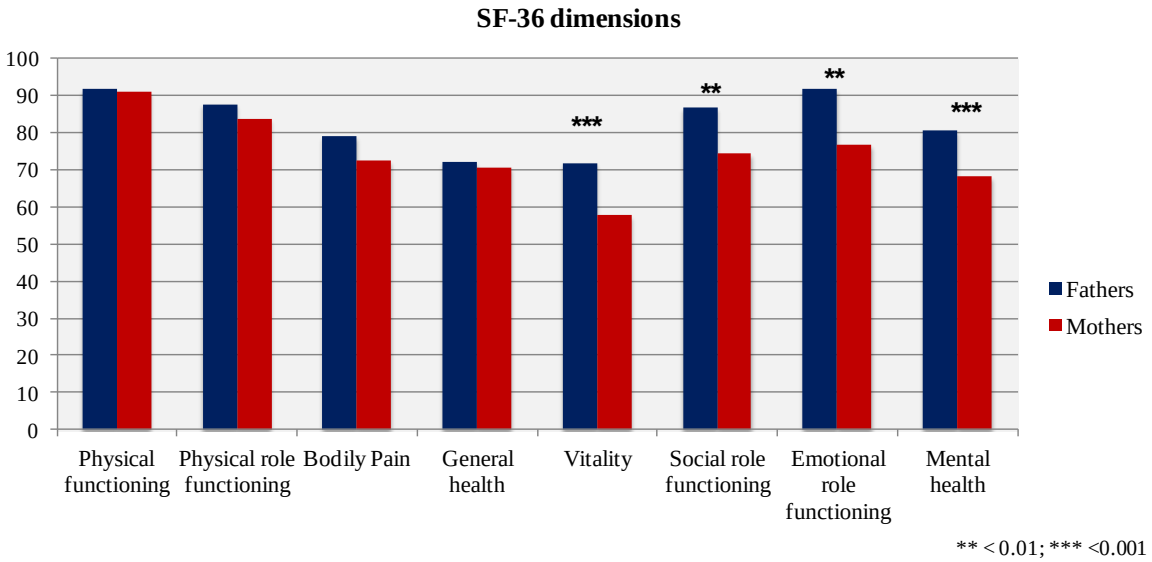

Figure 4.6 Quality of life among mothers and fathers

4.5 Comparison between parents of PKU patients and parents of MHP patients

To evaluate differences in psychological issues and quality of life between parents of PKU patients (with a dietary regimen) and parents of MHP patients (without a diet restriction) MANCOVA analyses were performed; the patient's phenotype (PKU vs MHP) and the patient's age were set as independent variables, while parental socio-demographic characteristics as covariates.

MANCOVA analyses, one with SCL-90-R subscales and one with SCL-90-R indexes as dependent variables, revealed no effects of socio-demographic characteristics (except for gender, in the direction described above), nor of the patient's phenotype, the patient's age or their interaction.

MANCOVA analysis with STAI scales as dependent variables confirmed the effect of gender; no effect of the patient's phenotype, the patient's age and of their interaction was found.

MANCOVA analysis with BDI subscales as dependent variables confirm the effect of gender, and found a significant effect of the educational level on the cognitive factor (lower-educated parents reported more depressive symptoms on the cognitive side compared to high-educated and graduated) and of the patient's phenotype on the somatic-affective factor of parental depression (Tables 4.4 – 4.7).

Table 4.4 Multivariate tests

Effect		Value	F	Hypothesis df	Error's df	Sig.	Partial eta squared
Intercept	Pillai's trace	0,037	2,144(a)	2,000	111,000	0,122	,037
	Wilks' lambda	0,963	2,144(a)	2,000	111,000	0,122	,037
	Hotelling trace	0,039	2,144(a)	2,000	111,000	0,122	,037
	Roy's largest root	0,039	2,144(a)	2,000	111,000	0,122	,037
Gender	Pillai's trace	0,064	3,777(a)	2,000	111,000	**0,026**	,064
	Wilks' lambda	0,936	3,777(a)	2,000	111,000	0,026	,064
	Hotelling trace	0,068	3,777(a)	2,000	111,000	0,026	,064
	Roy's largest root	0,068	3,777(a)	2,000	111,000	0,026	,064
Age	Pillai's trace	0,019	1,090(a)	2,000	111,000	0,340	,019
	Wilks' lambda	0,981	1,090(a)	2,000	111,000	0,340	,019
	Hotelling trace	0,020	1,090(a)	2,000	111,000	0,340	,019
	Roy's largest root	0,020	1,090(a)	2,000	111,000	0,340	,019
Marital status	Pillai's trace	0,009	0,516(a)	2,000	111,000	0,598	,009
	Wilks' lambda	0,991	0,516(a)	2,000	111,000	0,598	,009
	Hotelling trace	0,009	0,516(a)	2,000	111,000	0,598	,009
	Roy's largest root	0,009	0,516(a)	2,000	111,000	0,598	,009
Educational level	Pillai's trace	0,091	5,547(a)	2,000	111,000	**0,005**	,091
	Wilks' lambda	0,909	5,547(a)	2,000	111,000	0,005	,091
	Hotelling trace	0,100	5,547(a)	2,000	111,000	0,005	,091
	Roy's largest root	0,100	5,547(a)	2,000	111,000	0,005	,091
Patient's phenotype	Pillai's trace	0,065	3,852(a)	2,000	111,000	***0,024***	,065
	Wilks' lambda	0,935	3,852(a)	2,000	111,000	0,024	,065
	Hotelling trace	0,069	3,852(a)	2,000	111,000	0,024	,065
	Roy's largest root	0,069	3,852(a)	2,000	111,000	0,024	,065
Patient age	Pillai's trace	0,096	1,878	6,000	224,000	0,086	,048
	Wilks' lambda	0,906	1,879(a)	6,000	222,000	0,085	,048
	Hotelling trace	0,103	1,881	6,000	220,000	0,085	,049
	Roy's largest root	0,084	3,132	3,000	112,000	0,028	,077
Patient's phenotype * Patient age	Pillai's trace	0,037	0,711	6,000	224,000	0,641	,019
	Wilks' lambda	0,963	0,705(a)	6,000	222,000	0,646	,019
	Hotelling trace	0,038	,699	6,000	220,000	0,651	,019
	Roy's largest root	0,021	,788	3,000	112,000	0,503	,021

a Exact statistics

Bold = effect of covariate variables; ***bold italic*** of independent variables

Table 4.5 Levene's test	F	df1	df2	Sig.
BDI-II somatic-affective factor	0,802	7	116	0,587
BDI-II cognitive factor	0,774	7	116	0,610

Table 4.6 Tests of Between-Subjects Effects

	Dependent variable	Sum of squares type III	df	Mean square	F	Sig.	Partial eta squared
Correct model	BDI-II somatic-affective factor	344,981(a)	11	31,362	2,083	0,027	,170
	BDI-II cognitive factor	38,396(b)	11	3,491	,886	0,557	,080
Intercept	BDI-II somatic-affective factor	64,766	1	64,766	4,302	0,040	,037
	BDI-II cognitive factor	8,132	1	8,132	2,063	0,154	,018
Gender	**BDI-II somatic-affective factor**	112,921	1	112,921	7,501	**0,007**	,063
	BDI-II cognitive factor	8,520	1	8,520	2,162	0,144	,019
Age	BDI-II somatic-affective factor	24,393	1	24,393	1,620	0,206	,014
	BDI-II cognitive factor	,192	1	,192	,049	0,826	,000
Marital status	BDI-II somatic-affective factor	5,811	1	5,811	,386	0,536	,003
	BDI-II cognitive factor	,209	1	,209	,053	0,818	,000
Educational level	BDI-II somatic-affective factor	11,593	1	11,593	,770	0,382	,007
	BDI-II cognitive factor	14,776	1	14,776	3,749	**0,050**	,032
Patient's phenotype	**BDI-II somatic-affective factor**	51,018	1	51,018	3,389	***0,050***	,029
	BDI-II cognitive factor	,791	1	,791	,201	0,655	,002
Patient age	BDI-II somatic-affective factor	60,992	3	20,331	1,350	0,262	,035
	BDI-II cognitive factor	11,436	3	3,812	,967	0,411	,025
Patient's phenotype * Patient age	BDI-II somatic-affective factor	32,997	3	10,999	,731	0,536	,019
	BDI-II cognitive factor	7,509	3	2,503	,635	0,594	,017
Error	BDI-II somatic-affective factor	1686,140	112	15,055			
	BDI-II cognitive factor	441,443	112	3,941			
Total	BDI-II somatic-affective factor	4237,000	124				
	BDI-II cognitive factor	796,000	124				
Correct total	BDI-II somatic-affective factor	2031,121	123				
	BDI-II cognitive factor	479,839	123				

a R^2=0,17 (R^2 adj=0,09); b R^2 =0,08 (R^2adj = 0,01)

Bold = effect of covariate variables; ***bold italic*** effect of independent variables

Parents of PKU patients, requiring a phe-restricted diet, showed significant higher depressive symptoms on the somatic-affective side compared to parents of MHP patients.

Table 4.7 Effect of being a parents of PKU or MHP patient on BDI factors

Dependent variables	Patient's phenotype	Means	Std. error	C.I. 95%	
		Inferior limit	Superior limit	Inferior limit	Superior limit
BDI-II somatic-affective factor	MHP	3,625	0,660	2,317	4,933
	PKU	5,256	0,602	4,065	6,448
BDI-II cognitive factor	MHP	1,567	0,338	,898	2,236
	PKU	1,364	0,308	,754	1,974

As regard STAXI, the scale of state-anger could not be normalized; thus, to evaluate the effect of the patient's phenotype and the patient's age on it non-parametric test was performed; Kruskal-Wallis Chi-Squared test was not significant. ANCOVA analysis with STAXI Trait-anger scale as dependent variable revealed no effects of socio-demographic characteristics, nor of patient's phenotype, patient's age or their interaction. MANCOVA analysis with STAXI anger expression and control scales as dependent variables revealed an effect of educational level on Anger Control-In and Anger Control-Out; no effect of patient's phenotype group, patient's age or their interaction was found. Means evaluation revealed that parents with a primary educational level had a less control of anger expression, while graduate parents more frequently tend to control anger.

MANCOVA analyses with SF-36 dimensions (one with physical and one with mental dimensions) were performed. As concern physical dimensions (Physical Functioning (activity), Physical Role Functioning, Bodily Pain, General Health) an effect of educational level, of the patient's phenotype, and of the interaction between patient's age and patient's phenotype were found (Tables 4.8 – 4.9); of these, the tests of between-subjects effects confirmed the role of educational level on Physical functioning (in which parents with a

primary educational level showed a lower physical activity) and the interaction effect (Table 4.10).

Table 4.8 Multivariate tests $_{(a)}$

Effect		Value	F	Hypothesis df	Error's df	Sig.	Partial eta squared
Intercept	Pillai's trace	0,603	34,918[b]	4,000	92,000	0,000	0,603
	Wilks' lambda	0,397	34,918[b]	4,000	92,000	0,000	0,603
	Hotelling trace	1,518	34,918[b]	4,000	92,000	0,000	0,603
	Roy's largest root	1,518	34,918[b]	4,000	92,000	0,000	0,603
Gender	Pillai's trace	0,065	1,586[b]	4,000	92,000	0,185	0,065
	Wilks' lambda	0,935	1,586[b]	4,000	92,000	0,185	0,065
	Hotelling trace	0,069	1,586[b]	4,000	92,000	0,185	0,065
	Roy's largest root	0,069	1,586[b]	4,000	92,000	0,185	0,065
Age	Pillai's trace	0,065	1,608[b]	4,000	92,000	0,179	0,065
	Wilks' lambda	0,935	1,608[b]	4,000	92,000	0,179	0,065
	Hotelling trace	0,070	1,608[b]	4,000	92,000	0,179	0,065
	Roy's largest root	0,070	1,608[b]	4,000	92,000	0,179	0,065
Marital status	Pillai's trace	0,078	1,943[b]	4,000	92,000	0,110	0,078
	Wilks' lambda	0,922	1,943[b]	4,000	92,000	0,110	0,078
	Hotelling trace	0,084	1,943[b]	4,000	92,000	0,110	0,078
	Roy's largest root	0,084	1,943[b]	4,000	92,000	0,110	0,078
Educational level	Pillai's trace	0,114	2,953[b]	4,000	92,000	**0,024**	0,114
	Wilks' lambda	0,886	2,953[b]	4,000	92,000	0,024	0,114
	Hotelling trace	0,128	2,953[b]	4,000	92,000	0,024	0,114
	Roy's largest root	0,128	2,953[b]	4,000	92,000	0,024	0,114
Patient's phenotype	Pillai's trace	0,225	1,907	12,000	282,000	***0,033***	0,075
	Wilks' lambda	0,788	1,915	12,000	243,701	0,033	0,076
	Hotelling trace	0,253	1,909	12,000	272,000	0,033	0,078
	Roy's largest root	0,137	3,215	4,000	94,000	0,016	0,120
Patient age	Pillai's trace	0,036	0,848[b]	4,000	92,000	0,499	0,036
	Wilks' lambda	0,964	0,848[b]	4,000	92,000	0,499	0,036
	Hotelling trace	0,037	0,848[b]	4,000	92,000	0,499	0,036
	Roy's largest root	0,037	0,848[b]	4,000	92,000	0,499	0,036
Patient's phenotype * Patient age	Pillai's trace	0,215	1,818	12,000	282,000	***0,045***	0,072
	Wilks' lambda	0,795	1,836	12,000	243,701	0,043	0,073
	Hotelling trace	0,244	1,843	12,000	272,000	0,042	0,075
	Roy's largest root	0,175	4,111	4,000	94,000	0,004	0,149

a. Design: Intercept + gender + age + Marital status + Educational level + Patient age + Patient's phenotype + Patient age * Patient's phenotype - b. Exact statistics. **Bold** = effect of covariate variable; ***bold italic*** effect of independent variables or their interaction.

Table 4.9 Levene's test

	F	df1	df2	Sig.
SF36 Physical activity	1,707	7	99	0,116
SF36 Physical role functioning	3,794	7	99	0,001
SF36 Bodily pain	1,192	7	99	0,315
SF36 General Health	,912	7	99	0,501

Table 4.10 Tests of Between-Subjects Effects

	Dependent variable	Sum of squares type III	df	Mean square	F	Sig.	Partial eta squared
Correct model	SF36 Physical activity	1628,860[a]	11	148,078	2,788	0,003	0,244
	SF36 Physical role functioning	4887,216[b]	11	444,292	1,593	0,113	0,156
	SF36 Bodily pain	9338,306[c]	11	848,937	2,006	0,036	0,189
	SF36 General Health	4421,188[d]	11	401,926	1,652	0,097	0,161
Intercept	SF36 Physical activity	7568,035	1	7568,035	142,484	0,000	0,600
	SF36 Physical role functioning	7603,938	1	7603,938	27,268	0,000	0,223
	SF36 Bodily pain	9832,345	1	9832,345	23,239	0,000	0,197
	SF36 General Health	8532,429	1	8532,429	35,063	0,000	0,270
Gender	SF36 Physical activity	22,189	1	22,189	,418	0,520	0,004
	SF36 Physical role functioning	365,615	1	365,615	1,311	0,255	0,014
	SF36 Bodily pain	2626,569	1	2626,569	6,208	0,014	0,061
	SF36 General Health	196,890	1	196,890	,809	0,371	0,008
Age	SF36 Physical activity	273,370	1	273,370	5,147	0,026	0,051
	SF36 Physical role functioning	75,497	1	75,497	,271	0,604	0,003
	SF36 Bodily pain	28,725	1	28,725	,068	0,795	0,001
	SF36 General Health	4,252	1	4,252	,017	0,895	0,000
Marital status	SF36 Physical activity	163,266	1	163,266	3,074	0,083	0,031
	SF36 Physical role functioning	98,934	1	98,934	,355	0,553	0,004
	SF36 Bodily pain	2394,735	1	2394,735	5,660	0,019	0,056
	SF36 General Health	1153,980	1	1153,980	4,742	0,032	0,048
Educational level	**SF36 Physical activity**	565,022	1	565,022	10,638	**0,002**	0,101
	SF36 Physical role functioning	793,632	1	793,632	2,846	0,095	0,029
	SF36 Bodily pain	551,296	1	551,296	1,303	0,257	0,014
	SF36 General Health	101,098	1	101,098	,415	0,521	0,004

Patient age	SF36 Physical activity	198,635	3	66,212	1,247	0,297	0,038
	SF36 Physical role functioning	3062,496	3	1020,832	3,661	0,015	0,104
	SF36 Bodily pain	3353,968	3	1117,989	2,642	0,054	0,077
	SF36 General Health	2660,008	3	886,669	3,644	0,015	0,103
Patient's phenotype	SF36 Physical activity	94,023	1	94,023	1,770	0,187	0,018
	SF36 Physical role functioning	202,653	1	202,653	,727	0,396	0,008
	SF36 Bodily pain	1252,588	1	1252,588	2,961	0,089	0,030
	SF36 General Health	94,184	1	94,184	,387	0,535	0,004
Patient age * Patient's phenotype	**SF36 Physical activity**	757,673	3	252,558	4,755	***0,004***	0,131
	SF36 Physical role functioning	1748,482	3	582,827	2,090	0,107	0,062
	SF36 Bodily pain	1733,592	3	577,864	1,366	0,258	0,041
	SF36 General Health	2167,606	3	722,535	2,969	***0,036***	0,086
Error	SF36 Physical activity	5045,906	95	53,115			
	SF36 Physical role functioning	26491,289	95	278,856			
	SF36 Bodily pain	40193,881	95	423,093			
	SF36 General Health	23117,784	95	243,345			
Total	SF36 Physical activity	973300,000	107				
	SF36 Physical role functioning	924375,000	107				
	SF36 Bodily pain	671675,000	107				
	SF36 General Health	584822,000	107				
Correct total	SF36 Physical activity	6674,766	106				
	SF36 Physical role functioning	31378,505	106				
	SF36 Bodily pain	49532,187	106				
	SF36 General Health	27538,972	106				

a. R^2 = 0,244 (R^2 adj = 0,156); b. R^2 = 0,156 (R^2 adj = 0,058); c. R^2 = 0,189 (R^2 adj = 0,095); d. R^2 = 0,161 (R^2 adj = 0,063) - **Bold** = effect of covariate variables; ***bold italic*** of independent variables or their interaction.

The interaction was significant for Physical functioning (activity) and General health SF-36 subscales (Figures 4.7 and 4.8). While quality of life of parents of MHP patients fluctuated a little until the scholar stage and then markedly improve, quality of life of PKU parents slightly decreased.

Figure 4.7 Effect of the interaction between patient's phenotype group and patient's age on Physical functioning SF-36 subscale

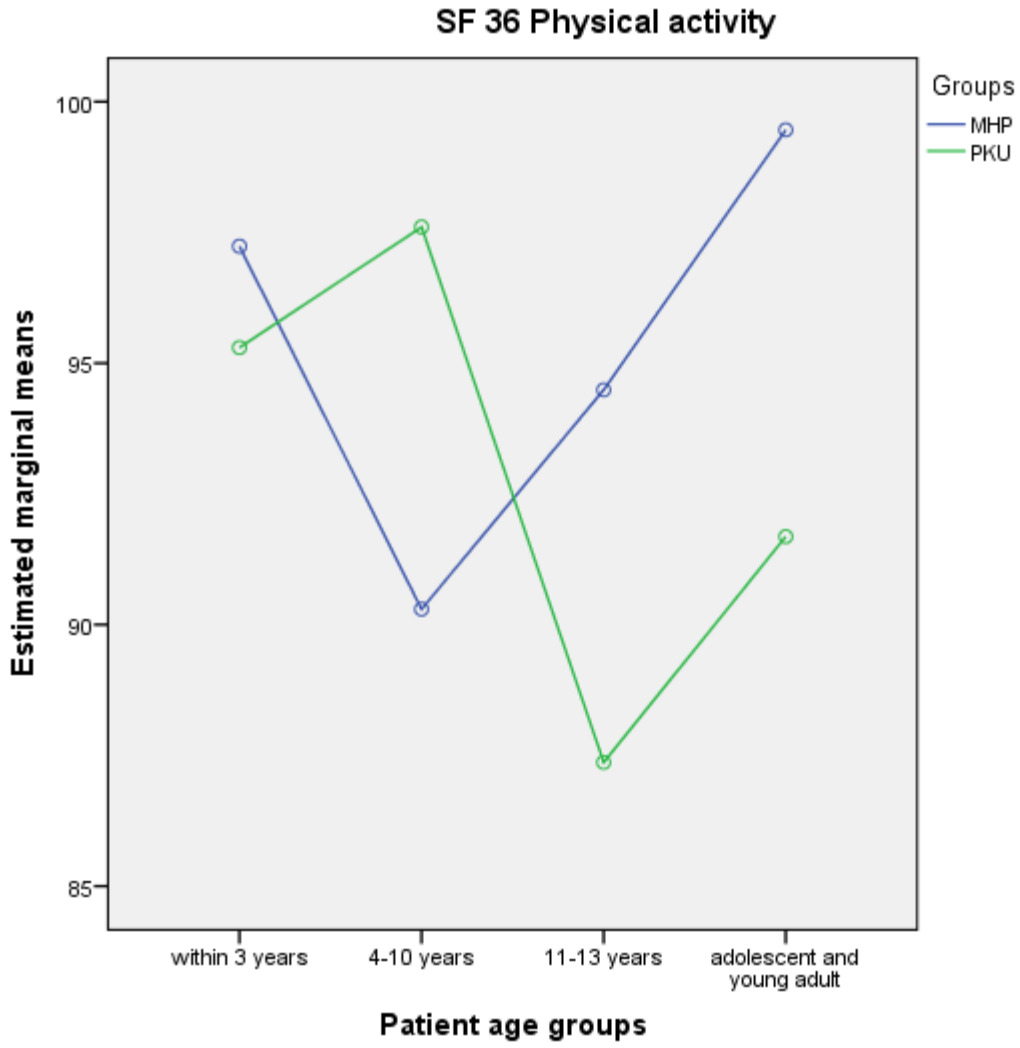

Figure 4.8 Effect of the interaction between patient's phenotype group and patient's age on General health SF-36 subscale

As concern the SF-36 dimensions regarding the emotional wellbeing (Vitality, Social Functioning, Emotional Role Functioning and Mental Health), the MANOVA analysis revealed no effects of socio-demographic characteristics (except for gender, in the direction already described above), nor of patient's phenotype group, patient's age or their interaction (Table 4.11).

Table 4.11 Multivariate tests [(a)]

Effect		Value	F	Hypothesis df	Error's df	Sig.
Intercept	Pillai's trace	0,165	5,576[b]	4,000	113,000	0,000
	Wilks' lambda	0,835	5,576[b]	4,000	113,000	0,000
	Hotelling trace	0,197	5,576[b]	4,000	113,000	0,000
	Roy's largest root	0,197	5,576[b]	4,000	113,000	0,000
Gender	Pillai's trace	0,129	4,173[b]	4,000	113,000	**0,003**
	Wilks' lambda	0,871	4,173[b]	4,000	113,000	0,003
	Hotelling trace	0,148	4,173[b]	4,000	113,000	0,003
	Roy's largest root	0,148	4,173[b]	4,000	113,000	0,003
Age	Pillai's trace	0,004	0,104[b]	4,000	113,000	0,981
	Wilks' lambda	0,996	0,104[b]	4,000	113,000	0,981
	Hotelling trace	0,004	0,104[b]	4,000	113,000	0,981
	Roy's largest root	0,004	0,104[b]	4,000	113,000	0,981
Marital status	Pillai's trace	0,017	0,485[b]	4,000	113,000	0,747
	Wilks' lambda	0,983	0,485[b]	4,000	113,000	0,747
	Hotelling trace	0,017	0,485[b]	4,000	113,000	0,747
	Roy's largest root	0,017	0,485[b]	4,000	113,000	0,747
Educational level	Pillai's trace	0,035	1,017[b]	4,000	113,000	0,402
	Wilks' lambda	0,965	1,017[b]	4,000	113,000	0,402
	Hotelling trace	0,036	1,017[b]	4,000	113,000	0,402
	Roy's largest root	0,036	1,017[b]	4,000	113,000	0,402
Patient's phenotype	Pillai's trace	0,067	0,659	12,000	345,000	0,790
	Wilks' lambda	0,934	0,652	12,000	299,261	0,797
	Hotelling trace	0,069	0,645	12,000	335,000	0,803
	Roy's largest root	0,040	1,144[c]	4,000	115,000	0,339
Patient age	Pillai's trace	0,006	0,182[b]	4,000	113,000	0,947
	Wilks' lambda	0,994	0,182[b]	4,000	113,000	0,947
	Hotelling trace	0,006	0,182[b]	4,000	113,000	0,947
	Roy's largest root	0,006	0,182[b]	4,000	113,000	0,947
Patient's phenotype * Patient age	Pillai's trace	0,036	0,348	12,000	345,000	0,979
	Wilks' lambda	0,964	0,345	12,000	299,261	0,980
	Hotelling trace	0,037	0,343	12,000	335,000	0,980
	Roy's largest root	0,032	0,915[c]	4,000	115,000	0,458

a. Design: Intercept + gender + age + Marital status + Educational level + Patient age + Patient's phenotype + Patient age * Patient's phenotype

b. Exact statistics

Bold = effect of covariate variable

4.6 Compliance to diet in PKU patients

In the 86 parents of PKU patients (on a phe-restricted diet), means of blood phe levels were 378,19 μmol/L (s.d. 246,85, range 77-1247 μmol/L). With the cut-off of the target blood phe levels by age group (Blau et al., 2010), 73% (n=63) were adherent to diet while 27% (n=23) had high phe levels indicating a poor metabolic control in relation to a poor dietary compliance.

Patients' phe level positively correlated with patient age ($r=0.67$, $p<0.001$): that is, adolescent and young adult showed the worse compliance to diet (Figure 4.12).

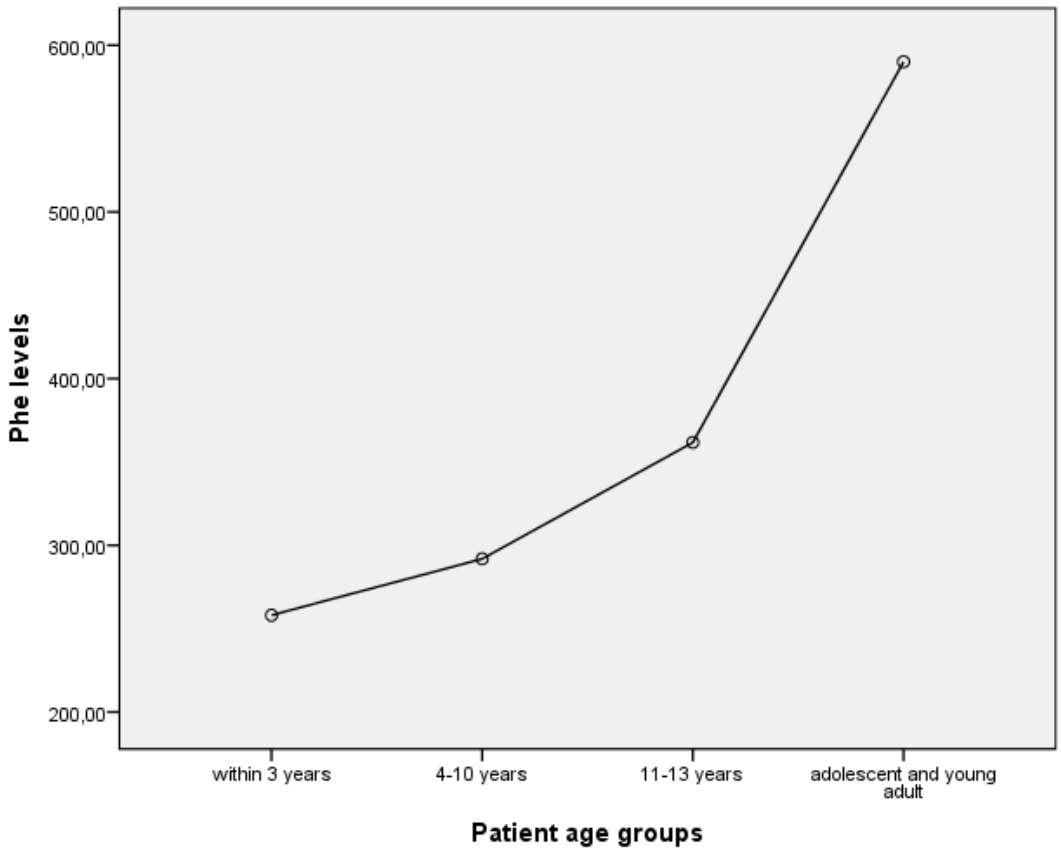

Figure 4.12 Blood phenylalanine levels increase with patient age

There were no differences between parents of adherent patients and parents of non-adherent patients for the socio-demographic characteristics.

Logistic regressions were performed to test if parental psychological and QoL outcomes predict PKU patients' compliance to dietary regimen; the results are summarized below.

4.6.1 Relationship between parental psychological issues and patients' Phe levels

Patients optimal phe levels and thus patients' good compliance to the dietary regimen was found to be predicted by specific parental psychological characteristics, that globally explained the 34% of variance. In particular, parents how showed high levels of somatic-affective component (β=1.52, p=0.011) and low levels of cognitive component (β=0.59, p=0.050) of depressive complaints, high level of anger control (β=0.77, p=0.043) and low level of anger expression outward (β=1.35, p=0.032) more frequently had adherent sons/daughters (see tables below).

Omnibus Tests of Model Coefficients

		Chi-squared	df	Sig.
Step 1	Step	19,836	10	0,031
	Block	19,836	10	0,031
	Model	19,836	10	0,031

Model summary

Step	-2 Log likelihood	Cox & Snell R^2	Nagelkerke R^2
1	66,772	0,225	0,335

Classification table (a)

Observed			Predicted		
			Adherence 01		Percentage correct
			0	1	0
Step 1	Adherence 01	0	7	12	36,8
		1	3	56	94,9
	Overall percentage				80,8

a The cut value is 0,500

Variables in the equation

		B	E.S.	Wald	df	Sig.	Exp(B)
Step 1(a)	SCL90_GSI	2,628	1,607	2,674	1	0,102	13,846
	STAY_State	0,003	0,051	0,003	1	0,954	1,003
	STAY_Trait	-0,041	0,065	0,398	1	0,528	0,960
	BDI_II_Somatic_Affective	0,420	0,165	6,510	1	0,011	1,522
	BDI_II_Cognitive	-0,519	0,267	3,783	1	0,050	0,595
	STAXI_RT	0,216	0,137	2,478	1	0,115	1,241
	STAXI_ER_OUT	-0,259	0,128	4,103	1	0,043	0,772
	STAXI_ER_IN	-0,109	0,103	1,133	1	0,287	0,897
	STAXI_CR_OUT	0,299	0,140	4,580	1	0,032	1,349
	STAXI_CR_IN	-0,284	0,128	4,894	1	0,057	0,753
	Costante	2,806	2,991	0,880	1	0,348	16,547

a Variables entered in step 1: SCL90_GSI, STAY_State, STAY_Trait, BDI_II_Somatic_Aff, BDI_II_Cognitive, STAXI_RT, STAXI_ER_OUT, STAXI_ER_IN, STAXI_CR_OUT, STAXI_CR_IN.

4.6.2 Relationship between parental quality of life and patients' Phe levels

Patients optimal phe levels was found to be predicted also by some of the parental quality of life dimensions, which globally explained the 25% of variance. In particular, parents how showed a lower Vitality (β=0.93, p=0.035) and a lower Social functioning (β=0.94, p=0.027) and a higher Mental health (β=1.07, p=0.043) more frequently had adherent sons/daughters (see tables below).

Omnibus Tests of Model Coefficients

		Chi-squared	df	Sig.
Step 1	Step	15,223	8	0,055
	Block	15,223	8	0,055
	Model	15,223	8	0,055

Model summary

Step	-2 Log likelihood	Cox & Snell R^2	Nagelkerke R^2
1	81,434	0,171	0,246

Classification table (a)

			Predicted		
			Adherence 01		Percentage correct
	Observed		0	1	
Step 1	Adherence 01	0	8	15	34,8
		1	2	56	96,6
	Overall percentage				79,0

a The cut value is 0,500

Variables in the equation

		B	E.S.	Wald	df	Sig.	Exp(B)
Step 1[a]	SF36 Physical activity	-0,028	0,027	1,074	1	0,300	0,973
	SF36 Physical role functioning	-0,003	0,017	0,028	1	0,867	0,997
	SF36 Bodily pain	0,010	0,018	0,314	1	0,575	1,010
	SF36 General health	0,030	0,020	2,189	1	0,139	1,030
	SF36 Vitality	-0,066	0,031	4,469	1	0,035	0,936
	SF36 Social functioning	-0,053	0,024	4,898	1	0,027	0,948
	SF36 Emotional role functioning	0,015	0,015	0,928	1	0,335	1,015
	SF36 Mental health	0,068	0,034	4,081	1	0,043	1,071
	Costante	3,368	2,222	2,298	1	0,130	29,024

a. Variables entered in step 1: SF36_AF, SF36_RF, SF36_DF, SF36_SG, SF36_VT, SF36_AS, SF36_RE, SF36_SM.

5. DISCUSSION

The current investigation focused on psychological wellbeing and quality of life among parents of patients with phenylketonuria. The first aim of the study was to describe the parental psychological characteristics and quality of life; the second aim was to evaluate the influence of parental psychological issues on patients' compliance to dietary regimen.

Globally, parents showed psychological characteristics and quality of life comparable to the normative sample. This finding is remarkable because of the potential substantial burden of the disease on the family (Kazak et al. 1988), due to the stress and the added responsibilities associated with a metabolic disorder and its treatment. As a whole parents under study were functioning quite well, showing a good psychological adaptation and a positive perception of their quality of life, which is consistent to previous studies showing that mental wellbeing and health related quality of life of the parents are almost normal (Bosch et al., 2015; Blumenthal, 1967; Fidika et al., 2013; Fisch et al., 1981; ten Hoedt et al., 2011;). Several explanations for the relatively high reported wellbeing of the parents are conceivable. Compared to other pediatric chronic or life threatening conditions (diabetes, congenital heart disease, lysosomal storage diseases, etc.), PKU is highly responsive to treatment. Therefore the course and the life expectancy are very promising. Another considerable fact could be that the participating parents are selected from one of the main referenced centres that provides management for PKU children, that have a medical team specifically trained in counselling and include a psychologist who follows all the developmental stages of children and goes along with parents.

Despite the general good adaptation observed, a percentage of parents reported critical issues: clinical psychological distress, state and trait anxiety, depressive symptoms, and an impact on various quality of life domains both in the psychical and in the emotional fields. Moreover, parents showed a tendency to hyper-control the expression of anger. As yet

little attention has been paid to the feeling of anger and aggressiveness in parents of PKU children; this gap in knowledge is of concern, given the common parental reactions of anger towards their child's chronic illness. So the evaluation of anger and anger reactions conducted in our research is a strength-point.

These maladjustments seem to be related to specific parents' socio-demographic or patients' clinical conditions.

Mothers are more at risk of developing psychological maladjustment as they scored higher on almost all the scales evaluating the emotional well-being. The results are consistent with previous studies both on PKU (Kazak, 1987; Lord et al., 2005, 2008) and other chronic illness showing a greater impact on mothers than fathers (Barlow & Ellard, 2006). This discrepancy may reflect gender differences on self-reporting emotional issues in the general population or may due to the fact that mothers are the main caregiver of children and so are the most frequently burdened by the disease and treatment management.

Lower educational level is associated with higher depressive symptoms on the cognitive domains, a lower control of anger expression and a lower physical functioning. These data are consistent with previous literature exploring the role of educational level on emotional wellbeing: lower-educated individuals may be less able to deal with psychological stress and burdens because they have a weaker internal locus of control, lower levels of social support, and more passive coping strategies (Kristenson et al., 2004; Schieman & Plickert, 2008).

The dietary regimen plays a burdening role on the emotional wellbeing of parents. We have highlighted the load of dietary treatment comparing parents of PKU children (who have to follow a phe-restricted diet) and parents of MHP children (who not need to be treated). Parents of PKU patients reported more depressive symptoms on the somatic-affective side (also with the parent gender as a covariate; that is, the effect is not due to

mothers) and showed a lower quality of life, in particular in later developmental stages of their sons/daughters (pre-adolescence, adolescence and young adulthood). That is, a good emotional wellbeing is acquired earlier by parents of patients whose disease phenotype do not impact on the dietary management. To our knowledge, the effort we have done trying to distinguish the impact of having the diagnosis of phenylketonuria from the load of the dietary management on parental wellbeing comparing PKU and MHP is the first attempt and is a strength-point of our research.

The second aim of the present study was to evaluate (obviously only among parents of PKU patients) the role of parental psychological issues on blood phenylalanine levels, that reflect the metabolic control and the dietary compliance. First of all, the majority of PKU patients showed an optimal compliance to the diet; nevertheless, a non marginal percentage (27%) of them resulted non adherent. Moreover, a robust positive correlation between age and phenylalanine levels was found, that in other words means that adherence to diet decrease with age; this trend has also been found in the diabetes literature (Anderson et al., 1997). The need to be part of a peer group is a salient developmental phenomenon during adolescence and this need can conflict with dietary regimen; in fact a great part of adolescents with chronic health conditions fail to adhere to treatment recommendations (Kyngäs et al., 2000).

Our data pointed out an association between parental psychological issues and the metabolic control that reflects a dietary compliance. Few studies has previously tried to link parents' functioning to metabolic control in phenylketonuria but they have led to inconclusive data (Olsson et al., 2007; Reber et al., 1987). These results are similar to other studies in the field diabetes that have shown that family factors play a role in adherence behaviors, with family conflict and self-management competence emerging as important predictors of non-adherence to treatment and metabolic control (Anderson et al., 1999; Hauser et al., 1990; Miller-Johnson et al., 1994). What we have found is partially in

agreement and partially in discordance with the hypothesis that a parental emotional maladjustments are associated to lower adherence. In fact, we found that a good adherence to diet is predicted by a good mental health and less depressive symptoms on the cognitive side together with a tendency to control and repress anger expression outward; surprisingly, optimal compliance was also predicted by more depressive symptoms on the somatic side, less vitality and a lower social functioning.

These results convey various reflections.

First, psychological adjustment of parents seems to be important for children to follow the diet prescriptions, as similar to the literature on other chronic conditions (Chaney & Peterson, 1989; Christensen et al., 1992; Davis et al., 2001; Hauser et al., 1990; Miller-Johnson et al., 1994).

Second, expressing anger does not pay in terms of adherence to treatment. Parents probably repress their feeling of anger adopting a controlling modality of anger expression outward. Perhaps, the same controlling-modality grounds a successful management of the dietary treatment leading to an optimal adherence.

Third, in some way, adherence to the diet appears to be an emotional cost for parents. In fact, adherence is maintained optimal at the expense of parental vitality, social activities and the possibility to express emotional feelings (including angry) that results in somatisations.

Finally, our study seems to pointed out the role and the impact on parents' social functioning, but in a new perspective. Previous studies has stressed the importance of social support and social network as protective factors for the emotional wellbeing of parents of PKU children (Lord et al., 2005; ten Hoedt et al., 2011) if not even a signal of successful adaptation to the disease and treatments (Kazak, 1987). In our study parents of adherent patients are those who showed a great impact on social activities; that is, the cost

that parents pay to help their sons/daughters to remain adherent to dietary regimen is the reduction of social activities.

As already pointed out directly from patients words in a previous study (Vegni et al., 2009), PKU seems to be like a disease that is not visible except for the social occasions in which the illness becomes manifest, presenting itself as a social disease. The paradox that PKU patients', and probably their parents, has to face is therefore between either being healthy and normal (maintaining an optimal adherence to diet) but isolated from the social context, or being seen as different if they do not decide to give up the convivial aspects that profoundly characterize the social relations.

5.1 Practice implications

The findings of the present study have several implications for clinical practice.

Results are useful to help clinicians to identify specific situations at risk for non adherence and may have implications for setting up interventions to improve compliance to diet.

A relationship exists between children metabolic control and parental wellbeing; the higher depressive symptoms on the cognitive side, anger expression outward and mental stress in parents, the more likely their children showed phenylalanine level reflecting non adherence. Parents at risk for psychological or quality of life disturbances should be referred to psycho-educational group programs to take a survey of the problems and to empower parents to set up or maintain an adequate well-being, child adherence but not at the expense of social activities and functioning.

Parental mental functioning influences not only compliance to diet but also the health, development and adjustment of their children (Prince et al., 2007), and this is particularly important with children with chronic disorders that are vulnerable to develop adjustment

problems when compared to their healthy peers (Pless & Nolan, 1991; Wallander & Varni, 1998); moreover, blood phenylalanine levels are related to patients psychological wellbeing, since high levels are associated with mood and behavioural disorders. Therefore, it is important that physicians involved in the care of children with PKU also pay attention to the well-being of the parents.

5.2 Limits

There are a few limitations of the current study which should be acknowledged. For example, our sample size was relatively small. Moreover, the fact that no data on reasons for declining participation were available might conceal a self-selection of less or more stressed parents within the study group. The study is monocentric and participants were all selected in one of the referred centre in Italy for PKU: potentially we gather parents coming from different cultural context and regions but probably are parents a little bit more adapted to their child disease because of the quality of care provided.. Notwithstanding these limitations, our study group has a considerable sample size and is representative to a certain extent for all parents of children with PKU. The absence of a comparison group of parents with children with other chronic conditions does not allow drawing any conclusion about the specificity for the group of parents of children with PKU.

5.3 Future directions

As we have highlighted the role of phenylketonuria on parents wellbeing, it could be important to consider also some relational aspects of these parents; new areas of interest could be the relationship with the partner and the relationship with the ill child, in terms of attachment.

Because of previous inconstant results, it would be interesting to examine the impact of parenting a child with phenylketonuria on marital relationship and on parental social networks, both within and outside family.

As far as attachment research, the literature has stressed the importance of parental psychological adjustment as an essential factor both for the structuring of a secure parent-child relationship and for chronically ill child's psychological adjustment. In fact, parental psychological adjustment, that is coping abilities, emotional state and attitudes toward a sick child and the illness, can influence children's psychological adjustment through relations with a child. It could be very interesting to evaluate the effect of parents' psychological wellbeing on parent-child relationship, in term of the type of the developed attachment relation exploring which factors are associated with a secure attachment in phenylketonuric families.

6. CONCLUSIONS

Parenting children with phenylketonuria do not affect psychological wellbeing or quality of life. Maladjustments arise in specific socio-demographic conditions, and are mainly related to the dietary management load and to the effort of maintaining an optimal adherence. Help children to remain adherent to the dietary seems to affect the parents' social functioning.

Our data seem to point in the direction of seeing psychological disturbances in parents of PKU patients from a psychosocial perspective (one of the possible perspective stated in the first chapter): PKU amounts to a chronic disease that requires a rigorous therapeutic treatment in which parental involvement is very heavy and burdensome, with implications for parents' psychological wellbeing and quality of life.

We can conclude that parental psychological wellbeing and quality of life is of utmost importance to consider when dealing with patients with phenylketonuria. On the one hand, children learn to adjust and cope from their parents. On the other hand, parental disturbances can restrict their ability to satisfy children's social and emotional needs. Moreover, parental distress can negatively affect adherence to treatment requirements. Increase of the concentration of phenylalanine in child's organism, as a result, may directly influence child's mental health, that is cognitive and emotional functioning. Thus, the evaluation of the impact of parenting a PKU child could provide useful insights to set up prevention programs and to improve parents wellbeing, parent-child relationships and patients adjustment, in particular in specific critical conditions.

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